

15. Commercial whole drug, same as No. 9, above, except cleaned by motor brushing and powdered, No. 30.....	4.13	0.42
	4.17	0.47
16. Commercial whole drug, same as No. 8, above, except cleaned by motor brushing and powdered, No. 30.....	3.74	0.33
	3.76	0.35

DEPARTMENT OF PHARMACOGNOSY,
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THE VOLATILIZATION OF ETHYL NITRITE FROM SPIRIT OF NITROUS ETHER.*

BY J. G. ROBERTS.

An investigation to determine the cause of the deterioration of spirit of nitrous ether was instituted on account of the frequent prevalence of low strength samples which had, supposedly, been stored under normal conditions.

As shown by the following results deterioration is due to either the decomposition of, or to the volatilization of the ethyl nitrite. Decomposition is due to the action of light and volatilization to the action of heat, to the imperfect sealing of containers or to insufficiently filled containers. Carelessness or slowness in mixing the ethyl nitrite and alcohol is also a contributing factor. The latter cause can, however, be eliminated, particularly when a small quantity is prepared, by using the sealed tubes which contain sufficient ethyl nitrite, which when mixed with one pint of alcohol will produce spirit of nitrous ether of official strength.

Ethyl nitrite or nitrous ether as it was first named is a well-established product which has been well known for a considerable period. It was discovered by Kunkel as early as 1681 and was obtained by the reaction of nitric acid, alcohol and copper. It is a yellowish volatile liquid of a pleasant, ethereal odor, has a specific gravity of 0.990 at 15.5° C. and boils at 17° C. It is readily miscible with alcohol from which it is easily dissipated when not properly stored.

In the present method of manufacture, ethyl nitrite is produced by the reaction of sodium nitrite, sulphuric acid and alcohol. It is preferably made in a stoneware vessel of convenient size which is provided with a mechanical stirrer. The resulting gaseous ethyl nitrite is passed through a well-cooled condenser and collected in an ice-packed receiving vessel. As it is decomposed in the presence of water, particular care is taken to render it anhydrous.

Spirit of nitrous ether is a very popular article and judging from the attention given it, it has the greatest popularity among the various national, state and municipal authorities, who have made it a very frequent cause of investigation and examination. That their vigilance is justified is proven by the large number of cases of low quality sweet spirit of nitre that they have found. The ready volatility of its ethyl nitrite content has always been a disturbing factor and is a matter of deep concern to all those who take pride in the quality of the preparations they dispense.

According to modern chemical classification ethyl nitrite is an ester and not an ether. Its ethereal quality was probably the reason for the name or possibly on account of the discarded, inaccurate term "compound ether" that was formerly

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applied to this class of products. This inaccuracy should be corrected in the next revision of the United States Pharmacopoeia and the name "Spirit of Ethyl Nitrite" adopted. It would then be consistent and in uniformity with Spirit of Glyceryl Trinitrate which has been adopted for spirit of nitroglycerin.

With the object of determining the factor most responsible for the deterioration in quality, a number of experiments were conducted and the following results noted.

Experiment No. 1.

One-ounce flint and amber bottles were completely filled and placed in a refrigerator.

	Flint bottle, %.	Amber bottle, %.
Original strength.....	5.25	5.25
After keeping 4 weeks.....	5.22	5.23

Practically no change occurred in contents of either style of bottle when kept for this period under the above condition.

Experiment No. 2.

One-ounce flint and amber bottles were completely filled and kept in a dark closet at room temperature for four weeks.

	Flint bottle, %.	Amber bottle, %.
Original strength.....	5.25	5.25
After keeping 4 weeks.....	5.20	5.19

Very little change occurred in contents of either style of bottle.

Experiment No. 3.

One-ounce flint and amber bottles were completely filled and kept on shelf for four weeks.

	Flint, %.	Amber, %.
Original strength.....	5.25	5.25
After 1 week.....	5.24	5.25
After 2 weeks.....	5.24	5.23
After 3 weeks.....	5.24	5.22
After 4 weeks.....	5.07	5.19

Only a little change occurred in the amber containers and practically none in the flint containers until between the third and fourth weeks when a perceptible decrease in strength occurred. This peculiarity has been noted at various times and may be due to the presence of a foreign substance.

Experiment No. 4.

One pint was placed in a one-pint glass-stoppered bottle and examined weekly.

Original strength.	After 1 week.	After 2 weeks.	After 3 weeks.	After 4 weeks.
5.25%	5.1%	4.99%	4.96%	4.86%

This bottle was kept on a shelf under ordinary conditions. A progressive loss of about 0.4% for this period is noted.

Experiment No. 5.

A one-quart cork-stoppered bottle was filled and placed on shelf. Two ounces were taken out each day and the strength noted. The following results, given in order of their testing, were obtained on succeeding days: 5.22%, 5.22%, 5.22%, 5.18%, 5.16%, 5.1%, 5.07%, 5.11%, 5.01%, 4.95%, 4.90%, 4.7%, 4.57%, 4.62%, 4.04%. As the original strength was 5.25%, it is shown that a loss of 1.21% was suffered during that period. This test was conducted in order to parallel the conditions that exist when a large number of orders are filled from the same container.

Experiment No. 6.

Four ounces were placed in a pint bottle and kept on a shelf under ordinary conditions.

Original strength.	After keeping 1 day.	After keeping 21 days.
4.58%	3.92%	2.71%

The loss of 1.87% of ethyl nitrite during this period shows the inadvisability of placing a small quantity in a container that allows a large air space above the liquid.

Experiment No. 7.

One-ounce bottles were completely filled, then exposed to direct sunlight, and assayed weekly.

	Flint, %.	Amber, %.
Original strength.....	5.25	5.25
After one week.....	4.10	5.24
After two weeks.....	2.62	5.20
After three weeks.....	1.89	5.18
After four weeks.....	1.18	5.19

Results show surprisingly little change in the contents of amber bottles, and that the contents of the flint bottles show marked deterioration.

Experiment No. 8.

Desiring to determine the relative volatility of ethyl nitrite and alcohol when in admixture, 16 ounces were heated on a steam-bath. When a quantity equal to the amount of ethyl nitrite present had been driven off it was found to contain 2.5% ethyl nitrite which was a loss of 2.08%. Upon continuing the evaporation until all of the ethyl nitrite had been eliminated, it was found that 2.5 ounces had been vaporized, about 1.75 ounces of which were alcohol.

Experiment No. 9.

Exposure to the atmosphere in a porcelain evaporating dish.

Original strength.	After 1/2 hour.	After 1 hour.	After 1 1/2 hours.
4.58%	1.4%	0.275%	0.038%

The pronounced volatility of the ethyl nitrite is well illustrated in this test which shows the elimination of practically all of it in 1 1/2 hours.

Experiment No. 10.

Exposure to the atmosphere and agitation in a porcelain dish.

Original strength.	After stirring 1 minute.	After stirring 3 min.	After stirring 5 min.
4.56%	3.58%	2.19%	1.54%
	After stirring 10 minutes.	After stirring 15 minutes.	
	0.57%	0.19%	

The rate of elimination was substantially increased by stirring, as most of the ethyl nitrite was dissipated in 10 minutes and practically all in 15 minutes.

As a result of this study we¹ find that ethyl nitrite is easily dissipated from an alcoholic solution; that the action of direct sunlight is very destructive to it in flint glass containers; that partly filled containers are objectionable and that it is bad practice to dispense numerous orders from the same container. The ideal method of storage is in small *completely filled*, amber bottles kept in a refrigerator or ice-box.

ANALYTICAL LABORATORY OF
SMITH, KLINE & FRENCH CO.

A CONTRIBUTION TO THE HISTORY OF THE DEVELOPMENT OF THE ENTERIC CAPSULE.

BY A. G. DUMEZ.

During the years 1914 and 1915, at least four articles concerning the hardening of gelatin capsules with formaldehyde appeared in American journals,

¹ The writer desires to express his appreciation of the services rendered by Mr. T. R. Singer in this investigation.