

TECHNICAL DRUG STUDIES: II. ON THE STABILITY OF SPIRIT OF NITROUS ETHER.*

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The stability of spirit of nitrous ether under various conditions of preparation and storage has been studied by a number of investigators.¹ It has been generally found that by observing certain very ordinary precautions, it is possible to keep this product for a considerable length of time without material change and that its alleged unstability has been exaggerated. Yet notwithstanding the general conclusions arrived at and published in various pharmaceutical and chemical journals, an examination of a large number of samples collected from retailers and manufacturers has disclosed a great many which varied from the legal standard. It was, therefore, deemed advisable to make an investigation of the keeping qualities of this product under conditions obtaining in most drug stores, as well as under modified conditions suggested by previous investigators.

The series of experiments was formulated to test out the following points:

1. Does the water and other foreign material commonly present in U. S. P. alcohol materially hasten the decomposition of the spirit of nitrous ether?
2. Does the use of absolute alcohol increase its stability?
3. Is refrigeration necessary?
4. Does potassium bicarbonate by neutralizing the acidity retard decomposition?
5. Are small (individual) containers preferable to large stock bottles?
6. Does frequent opening of large stock containers and a large air space above the spirit hasten deterioration?
7. What time limit ought to be set on the keeping of this product?

Twelve sets of samples of two general types were prepared: (a) seven made up with U. S. P. alcohol (95.5 percent) and (b) five made up with U. S. P. absolute alcohol. In view of the fact that a very large percent of the spirit of nitrous ether is made by diluting concentrated ethyl nitrite (90 percent), this was used as a basis for the experiments. The entire quantity for each type of experiment was prepared in a large container by diluting the concentrated ethyl nitrite in the one case with U. S. P. alcohol and in the other with absolute alcohol U. S. P. These were then assayed by the U. S. P. method and bottled. In order to avoid loss by evaporation when distributing the product into the various containers, a syphon with a ground-glass stop-cock was prepared and each container then filled from the large container by means of this syphon.

The following sets of experiments were prepared from the U. S. P (95.5 percent) alcohol (Type A):

No. 1. Ten 30 mil, amber-colored bottles, kept on a shelf in the laboratory, exposed to diffused light.

No. 2. Ten 30 mil, amber-colored bottles, containing a small quantity of potassium bicarbonate, kept on a shelf, exposed to diffused light.

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¹J. E. Stacy, Proc. Mass. Pharm. Assoc. (1899), 53. Farr and Wright, Trans. Brit. Pharm. Conf. (1901), 447. D. Gilmore, Pharm. Jour., 66, 54 (1901). B. O. Leubner, Merck's Report, 11, 344 (1902). G. E. Shaw, Pharm. Jour., 71, 236 (1903). L. A. Brown, Amer. Drug, 59, 215 (1911). J. R. Rippetoe, Amer. Drug, 59, 307 (1911). C. B. Jordan, Proc. Ind. Pharm. Assoc. (1912), 53. F. L. Shannon, Jour. Amer. Pharm. Assoc., 2, 83 (1913).

- No. 3. Ten 30 mil, flint bottles kept in diffused light.
- No. 4. Ten 30 mil, flint bottles kept in a refrigerator.

No. 5. One 360 mil, amber-colored bottle, exposed to diffused light.

No. 6. One 360 mil, amber-colored bottle containing some potassium bicarbonate, kept in diffused light.

No. 7. One 360 mil, flint bottle kept in a refrigerator.

The following sets were prepared from the absolute alcohol, U. S. P. (Type B) :

No. 8. Ten 30 mil, flint bottles kept in a refrigerator.

No. 9. Ten 30 mil, flint bottles kept in diffused light.

No. 10. One 30 mil, amber-colored bottle kept in diffused light.

No. 11. One 360 mil, flint bottle kept in a refrigerator.

No. 12. Ten 360 mil, amber-colored bottles exposed to diffused light.

As no hydrolytic action was expected in the sets of Type B, it was not thought necessary to try any experiments using KHCO_3 to counteract any acid formed.

All bottles were stoppered with paraffined corks. The temperature of the refrigerator in which Nos. 4, 7, 8, and 11 were stored ranged from about 8° to 15° C., and that of the room in which the other samples were kept from about 20° to 32° C.

The assay before bottling showed A to contain 4.56 percent of ethyl nitrite and B, 4.68 percent. Inasmuch as the purpose of the experiments was to study the deterioration of the product, it was not thought necessary to dilute it to 4 percent, the minimum U. S. P. strength. In fact, the test would seem to be all the more rigid when using a product of higher strength.

The following table shows the results of the assays of the various samples, made from time to time. In all cases the U. S. P. method was used.

INFLUENCE OF STORAGE ON SPIRIT OF NITROUS ETHER.

	A (U. S. P. 95.5 percent Alcohol).							B (U. S. P. Absolute Alcohol).				
	1	2	3	4	5	6	7	8	9	10	11	12
Type of container	Small amber	Small amber	Small white	Small white	Large amber	Large amber	Large white	Small white	Small white	Large amber	Large white	Small amber
Condition of storage	Light	Light KHCO_3	Light	Refrig.	Light	Light KHCO_3	Refrig.	Refrig.	Light	Light	Refrig.	Light
1914												
May 27.....	4.56	4.56	4.56	4.56	4.56	4.56	4.56	4.68	4.68	4.68	4.68	4.68
June 30.....	4.52	4.51	4.57	4.53	4.58	4.60	4.58	4.69	4.64	4.71	4.65	4.74
July 30.....	4.39	4.10*	4.27	4.51	4.59	4.51	4.39	4.55	4.64	4.67	4.76	4.50
Aug. 31.....	4.41	4.62	4.34	4.35	4.31	4.59	4.42	4.51	4.47	4.6	4.68	4.57
Nov. 28.....	4.46	4.57	4.19	4.43	3.08*	4.39	4.32	4.50	4.31	4.61	4.71	4.46
1915												
July 22.....	4.15	4.48	3.79	4.35	0.26*	3.97	4.35	4.58	3.10	4.62	4.60	4.48
Aug. 22.....	3.67	4.28	3.58	4.38	0.23*	4.01	4.06	4.59	3.77	4.21	4.61	4.46
Sept. 28.....	3.06	4.22	3.54	4.4	0.25*	3.19	3.98	4.56	3.64	4.17	4.51	2.93
Nov. 2.....	3.07	4.20	3.50	4.54	**	**	3.82	4.60	4.10	3.76	4.59	4.65
Nov. 28.....	**	**	3.83	4.53	**	**	3.96	4.56	3.84	**	4.60	4.14

* Cork loose.
** Material exhausted.

The results can perhaps best be appreciated by considering the different intervals of time that elapsed during the experiment. For the first three months it might be said that all samples kept well whether U. S. P. (95.5 percent) or

absolute alcohol was used; whether kept in diffused light at ordinary temperature or in a refrigerator; with or without potassium bicarbonate; in small filled (individual) bottles or in large bottles. The material in the large amber bottle kept in diffused light showed the greatest loss, but this was only 0.25 percent of ethyl nitrite. In this case it was found that the cork did not fit tightly, and still later in the experiments it was found to be quite loose.

When kept for six months, it might be said that all, with the exception of No. 5 (which had the cork loose) and Nos. 3 and 9 kept very well. The greatest deterioration (in Nos. 3 and 9) was 0.37 percent, or about 8 percent of the original ethyl nitrite.

When kept for somewhat over a year (fourteen months in these experiments), under conditions observed in Nos. 2, 4, and 7 of Type *A* and Nos. 8, 10, 11, and 12 of Type *B*, the results showed that the losses came within a reasonable variation. Both small and large amber bottles of Type *B* stored under ordinary conditions of temperature and light kept well. This was also true of the small amber containers of Type *A* with potassium bicarbonate. However, it is not believed to be desirable to keep the product a year before dispensing.

When kept for a period of over eighteen months, of Type *A* only those stored in small bottles and kept in a refrigerator remained practically unchanged; of Type *B*, both small and large bottles kept in the refrigerator were not subject to any material change, and there seems to be no doubt that the product kept under those conditions would have stood much longer without change. Lack of material prevented the continuation of the experiments to verify this belief.

Quite in accord with the results obtained by earlier experimenters, these observations show that *properly prepared* spirit of nitrous ether is comparatively stable and can be kept without material change much longer than the average pharmacy would ordinarily keep it.

The conclusion might therefore be reached from these experiments, that for all ordinary purposes the U. S. P. spirit of nitrous ether does not offer any great difficulties in order to be kept up to the standard strength, provided it is made up to the proper strength to begin with, carefully bottled and stoppered with paraffined corks. If the spirit is prepared with 95 percent alcohol, it is best to store it in a refrigerator or in small amber containers kept in diffused light. If stored in large amber bottles kept in diffused light, it is best to use absolute alcohol in its preparation.

Concentrated Spirit of Nitrous Ether.—Since spirit of nitrous ether is usually made by diluting concentrated (90 percent) ethyl nitrite with alcohol, it is interesting to note the ethyl nitrite content of four samples, after being stored in a refrigerator for three years. Each sample was obtained from a different manufacturer and was stated to contain 90 percent ethyl nitrite. Samples I, II, and III kept well and presented no difficulty in opening. When diluted and assayed by the U. S. P. method, they yielded 89.6 percent, 92.0 percent, and 93.4 percent, respectively. Sample IV, however, although sealed in amber glass tubes, had partially decomposed. Of the four tubes at hand, three exploded violently when an attempt was made to open them, although they had been cooled in an ice-salt freezing mixture. A strong odor of nitrous acid was also given off. The third tube was less decomposed, although the pressure was such, even after cooling, that some of the contents were expelled. The assay showed only 81.0 percent of ethyl nitrite. The data so far obtained are insufficient to draw any conclusions as to the keeping quality of the concentrated spirit.