SCIENTIFIC SECTION

FLUIDEXTRACT OF ERGOT.*

BY L. W. ROWE AND WILBUR L. SCOVILLE.

The present paper is a continuation of the work reported to this Section two years ago.

In January 1932, a second series of fluidextracts was made from a defatted ergot by the repercolation process. No heat was used in making these fluidextracts.

Three menstrua were used, *viz.*, Diluted alcohol, 77% alcohol (alcohol 4 vols., water 1 vol.) and 87% alcohol (alcohol 9 vols., water 1 vol.).

For Series A, 750 cc. of Fluidextract was made using Diluted Alcohol. This was divided into three parts, to one of which—labeled "A"—was added sufficient hydrochloric acid to produce a p_H of 2.85. To a second portion—"A 1"—was added enough tartaric acid to produce a p_H of 3.15. To the third portion—"A 2"—was added sufficient 50% hypophosphorous acid to produce a p_H of 2.97.

Each of the above was filled into (8) 1-oz. amber-glass bottles, two of which were stored in a refrigerator, and the rest on the laboratory shelf at room temperatures.

The second series corresponds to the first except that the initial fluidextract was made with 77% alcohol as the menstruum, and one-third of the product was adjusted to a p_H of about 3.0 with hydrochloric acid, the second third with tartaric acid, and the third with hypophosphorous acid, being labeled "B," "B 1" and "B 2."

The third series was similarly made with a menstruum of 87% alcohol, and correspondingly adjusted with the same three acids, and labeled "C," "C 1" and "C 2."

The fourth series, of 300 cc., was also made with a menstruum of 87% alcohol and divided into two portions. The first portion was stored (in 1-oz. bottles) without further addition or adjustment and to the second portion was added 0.2% w-v. of cysteine hydrochloride. All were stored in 1-oz. amber-glass bottles.

Since the main purpose of these experiments was to ascertain the relative stability of the preparations, and the effectiveness of the stabilizing materials used, it was deemed unnecessary to assay, at the beginning, more than one sample of each series, it being assumed that all represented the same percolate. Also each of the B series, and the C series and the D series would be of the same strength, since each was a portion of the corresponding percolate.

At the end of about a year a sample of each was assayed, these samples having been stored at room temperature. The Cock's Comb method of assay was employed in all cases.

The following table summarizes the results.

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FLUIDEXTRACT OF ERGOT.

Series.	Menst.	Stabilizing Agent.	p_H.	First Assay.	Second Assay.
A	49% Alc.	HCl	2.85	120 %	110%
A1	.....	H_3Ta	3.15	(120)%	100%
A2	.....	HPH_2O_2	2.97	(120)%	120%
B	77% Alc.	HCl	2.90	75 %	65%
B1	.....	H_3Ta	3.18	(75)%	80%
B2	.....	HPH_2O_2	3.06	(75)%	80%
C	87% Alc.	HCl	2.50	75 %	75%
C1	.....	H_3Ta	3.35	(75)%	75%
C2	.....	HPH_2O_2	3.03	(75)%	65%
D	87% Alc.	None	5.60	75 %	75%
D1	.....	Cryst. hyd.	5.20	(75)%	80%

Two samples made in November 1930, and stabilized with hypophosphorous acid were reassayed, with the following results.

No. 1.—Assay Nov. 1930, 125%; May 1931, 125%; Nov. 1932, 120%.

No. 2.—Assay Nov. 1930, 125%; May 1931, 125%; Nov. 1932, 120%.

One cannot draw positive and final conclusions from so few experiments when all are not in harmony, but the above results indicate with reasonable agreement the following:

Stronger alcoholic menstrua exert a stabilizing influence, but add greatly to the difficulty of extraction. Ergot is a difficult drug to extract, and yields to aqueous menstrua more readily than to alcoholic. This may explain the continued favor of aqueous preparations of ergot. When fresh they may represent the drug in fuller measure than alcoholic extracts.

We may also note that Moir of England claims that ergot has an action upon the uterus which is not due to its alkaloids but is caused by an undiscovered water-soluble substance. While his claims have not yet been confirmed he is too prominent to be ignored, and it may not be wise to shut the official door upon low-alcoholic preparations.

We also have to consider that while ergot contains alkaloids which are not themselves soluble in water, they probably are soluble in an aqueous extract of the drug, particularly when acidulated.

In view of the greater efficiency in extraction, and its probable inclusion of all the active principles, it seems wise to adhere to the present alcoholic strength of menstruum (for this revision).

An acidity equivalent to a p_H of about 3 is generally accepted as adding to stability by most of the workers on this preparation. The above results also confirm the opinion that an acid which has a reducing action is better than one which does not. Thus tartaric and hypophosphorous acids show a greater stabilizing action than does hydrochloric acid. The (new) British Pharmacopœia uses tartaric acid—in rather indefinite amount—in its Liquid Extract of Ergot.

In the above experiments—and those made two years ago—hypophosphorous acid seems to be the more effective stabilizer. Since this is a strong reducing agent its influence is but logical.

It is well to bear in mind that the methods of standardizing ergot are the least satisfactory of any in use. A variation of 20% is not considered unreasonable by the official method.

The assays on the preparations herein reported were all made by one of us (L. W. R.), who has had considerable experience with the official Cock's Comb method as well as with the Broom and Clark method. Some prefer the Broom and Clark method, in which the inhibiting action of ergot is observed on a strip of rabbit-uterus muscle—but a considerable margin of error is acknowledged for it.

The British Pharmacopœia has adopted the colorimetric determination of alkaloids by chemical methods, on the ground that while this includes both the inactive and active alkaloids the error "is probably less" than is found in biological methods.

These facts are mentioned simply to make plain that the activity figures in the above table cannot be taken with the same confidence as in the chemical assays of other alkaloidal drugs. Some of these assays were repeated because the second assay showed a materially higher activity than the first—which is, of course, contradictory. In such cases the lower figure of the (repeated) assays is given. In all tests at least two roosters were used and in several cases three, for each test.

The best prospect seems to be to use diluted alcohol with hypophosphorous acid for this preparation. In the sample prepared two years ago an equivalent of 40 cc. of U. S. P. Hypophosphorous Acid (30%) per liter was needed to produce a p_H of 4.15. In the one made a year ago—and reported in the above table an equivalent of 26 cc. per liter was required.

With tartaric acid, the sample in the table contains 30 Gm. per liter.

Better results in extraction may be expected when the acid is used in the menstruum rather than added to the fluidextract. The amount of acid to be directed will vary with the alcoholic strength of the menstruum—less being needed for high strength alcohol than for low.

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THE STANDARDIZATION OF ERGOT.*[1]

BY ASA N. STEVENS.

A COMPARATIVE STUDY OF THE BRITISH PHARMACOPŒIA ASSAY FOR EXTRACTUM ERGOTÆ LIQUIDUM AND THE MODIFICATION OF SMITH'S QUANTITATIVE COLORIMETRIC ASSAY.

A colorimetric method of assay for Ergot and its preparations is given official recognition in the recently revised "British Pharmacopœia 1932." The close relationship that exists between the British Pharmacopœia assay for Liquid Extract of Ergot and the Modification of Smith's Quantitative Colorimetric (1) Assay, which was outlined by the writer in an earlier paper, has made it desirable to undertake a comparative study of the two methods as they apply to the assay of Fluidextract of Ergot U. S. P.

It is the purpose of this paper, therefore, to present and to compare the results that have been obtained by the use of both methods.

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* Scientific Section, A. PH. A., Madison meeting, 1933.

[1] From the Analytical Laboratories, Eli Lilly & Co.