FINAL REPORT ON THE ALKALOIDS OF GELSEMIUM.*

BY L. E. SAYRE AND G. N. WATSON.

For many years contributions have been offered and published in the Proceedings of this Association by the author and others from the University laboratory upon the subject of the active constituents of Gelsemium.[1] Each one of these investigations has progressively added some new information tending toward solving the problem of separating the various active constituents of the drug. The difficulty involved in the isolation or separation of these constituents has been due largely to the fact that the peculiar intractable resin-like body (a resinoid differing from the ordinary members of its class) permeates the extractive (or alkaloidal) substances which is difficult to separate from the latter without losing these alkaloidal constituents or masking them in a way that leads one to the conclusion of former investigators, that some of these active principles are uncrystallizable.

One of the most noteworthy investigations contributing much to the constitution of the extractives of Gelsemium was that of Charles Watson Moore, published in the *Transactions of the English Chemical Society*, 1910, Volume 97. But this author failed, like others, to separate the component parts of the so-called uncrystallizable material of Thompson, which, the latter author named "Gelseminine."[2] The facts revealed by our investigation seem to show that there does not exist in the drug any such alkaloid as Gelseminine, but that this constituent (so-called) is a compound body consisting of several alkaloids having different properties, as we will attempt to show.

In this report the authors desire to give such details of the separation of the various constituents that others, following same, may be assured of successful results in such separation of Gelsemium active principles. It is hoped it will be a guide to manufacturers who wish to isolate any or all of the principles for the market. The process of isolation will throw some light upon a method of standardization of the drug, which will be the subject of another paper by our colleague, Professor L. D. Havenhill.

SEPARATION OF SEMPERVIRINE (AS NITRATE).

Twenty-five pounds of the drug in No. 20 powder were completely extracted with 70 percent alcohol by re-percolation. The alcohol was distilled off on a water bath. The concentrate, made alkaline with ammonia, was extracted with large excess of chloroform (5 washings) until free from alkaloid. The chloroform extract (washing) was concentrated by distillation on a water bath. The evaporated chlororoformic concentrate was extracted with 0.5 percent hydrochloric acid. The acid solution, containing the alkaloidal hydrochloride was treated with a saturated solution of sodium nitrate (5 mils per 100 mils of acid solution) which resulted in

* Read before Scientific Section, A. Ph. A., New York Meeting, 1919.

[1] Assay of F. E. Gelsemium, Proc. A. Ph. A., 1907, p. 357. A further Study of the Alkaloids of Gelsemium, A. Ph. A. meeting at Hot Springs, Arkansas, Sept. 7–12, 1908. "A Study of the Alkaloids Gelsemine and Gelseminine," Proc. A. Ph. A., 1909. Gelsemium, A. Ph. A., Richmond, Virginia, 1910. "The Composition of Gelseminine," A. Ph. A., Journal, May, 1912. "Further Study of the Alkaloid Gelseminine," A. Ph. A. Journal, March, 1914. "Sempervirine from Gelsemium Root," A. Ph. A. Journal, 1915. "Third Alkaloid from Gelsemium," A. Ph. A. Journal, 1915.

[2] Pharmaceutical Era, 1887, p. 3.

the precipitation of sempervirine nitrate (an alkaloid previously reported). The sempervirine nitrate was separated by filtration, dissolved in hot water and re-precipitated with sodium nitrate. The latter process was twice repeated. The resulting sempervirine nitrate was first washed with water containing sodium nitrate, then with water, small amount (process repeated twice). The salt was then dried and dissolved in hot alcohol and set aside to crystallize from alcoholic solution. About 3 grammes of a somewhat bulky sempervirine nitrate were thus obtained.

REMOVAL OF GELSEMIC ACID.

The acid filtrate from the sempervirine nitrate (representing organic—gelsemic acid—alkaloidal salts, etc.) was extracted with chloroform, the solution before washing being somewhat concentrated and only partly neutralized. This chloroform washing removed gelsemic acid.

SEPARATION OF GELSEMINE.

The above acid solution of the alkaloids was then made alkaline with NH_4OH and extracted, first with ether (3 washings) to remove gelsemine and then with chloroform (3 washings) to remove other alkaloids soluble in chloroform.

The ether extract was concentrated and precipitated in ether solution by means of HCl gas as an impure gelsemine hydrochloride.

The impure gelsemine hydrochloride was dissolved in water. The greater part of the water was evaporated spontaneously, filtered and the residue washed with strong alcohol until colorless. By this method of purification all possible traces of gelsemic acid and the hydrochlorides of other alkaloids were removed leaving the pure white gelsemine hydrochloride. Both the aqueous and alcoholic filtrates were further concentrated and treated in order to remove all alkaloidal material, gelsemine hydrochloride and the hydrochlorides of associated alkaloids.

About 8 grammes of gelsemine hydrochloride were obtained.

EXTRACTION OF REMAINING ALKALOIDS.

The chloroformic solution of alkaloids after extraction of the gelsemine was concentrated by distillation to a soft brown, amorphous extract representing the remaining total alkaloids, *i. e.*, the total alkaloids minus the gelsemine and sempervirine.

This extract was dried, dissolved in the least possible amount of absolute alcohol in a glass stoppered flask, the alcoholic solution treated with hydrochloric acid gas and then with a large excess of absolute ether. The mixture was allowed to stand 24 hours and then filtered. The precipitate of hydrochlorides of the so-called amorphous alkaloids was washed with chloroform, which dissolved an amorphous portion and left on the filter a brown, heavy, granular, crystalline, extremely soluble, hydrochloride of an alkaloid (weighing 1.75 grammes), for which we suggest the name "Gelsemidine"—not "Gelseminine"—since gelseminine, the name formerly given to the amorphous alkaloids of gelsemium, has been proved conclusively to be not a single alkaloid but a mixture of three alkaloids, one of which is crystalline, one capable of forming a crystalline salt and one distinctly amorphous and possibly colloidal.

Weight of Gelsemidine hydrochloride, about 2.5 grammes.

The chloroform-soluble portion of the mixture of hydrochlorides was of a light brown color and amorphous when first precipitated, but soon passed into a

dark brown mass having a resinous appearance. This residue was strongly alkaloidal and in appearance and behavior is very much like Lloyd's Emetoidine, said to be a colloidal alkaloid of Ipecac, and might be very appropriately called "Gelsemoidine."

In order to secure the total gelsemic acid (not important to this investigation) the original chloroform extract was concentrated to a syrupy extract and washed with hot water to remove gelsemic acid which was purified by repeated concentrations and filtrations and finally crystallized from alcohol.

PHYSICAL DESCRIPTION.

Gelsemine.—Gelsemine is the most abundant and only ether-soluble alkaloid of Gelsemium. Its ether residue is a reddish, amorphous mass having a resinous appearance. Its hydrochloride is pure white, crystalline, soluble in water and difficultly soluble in alcohol. The fact that the alkaloid is soluble in ether and its hydrochloride almost insoluble in alcohol makes its separation from the other alkaloids and its final purification very efficient. The aqueous solutions of its salts are precipitated by the general alkaloidal reagents.

Sempervirine.—The free alkaloid crystallizes from chloroform in reddish brown needles. It is slightly soluble in alcohol and water and almost insoluble in ether, benzol and petroleum ether. Its hydrochloride is readily soluble in water and alcohol and is precipitated by nitric, tannic and picric acids; by potassium chromate, platinic chloride, sodium chloride and sodium nitrate giving yellow precipitates. The nitrate is somewhat soluble in water, very soluble in hot water and in hot alcohol. Their solutions give precipitates with Wagner's and Mayer's reagents.

Gelsemidine is an amorphous alkaloid, insoluble in ether, soluble in chloroform and alcohol. Its hydrochloride is insoluble in ether and chloroform, soluble in alcohol and extremely soluble in water. Its crystalline form is granular; its action, purely sedative. Like sempervirine, gelsemidine exists in gelsemium in very small quantity.

COLOR REACTIONS WITH SULPHURIC ACID AND MANGANESE DIOXIDE.

Gelsemidine (hydrochloride)	Purple, bluish green
Gelsemoidine (hydrochloride)	Purple, green
Sempervirine (nitrate)	Green, yellowish green
Gelsemine (hydrochloride)	Crimson, green, yellowish

PHYSIOLOGICAL ACTION OF THE ALKALOIDS OF GELSEMIUM ON FROGS.

Alkaloid.	Respiration.	Behavior.	Paralysis.
Gelsemine Hydrochloride	Slow, irregular 30 per 22–30 sec.	Restless, convulsions	Slight
Sempervirine Nitrate	Slow, irregular 30 per 27–30 sec.	Restless, convulsions	None
Gelsemidine Hydrochloride	Nearly normal, regular 30 per 16–19 sec.	Quiet	Decided
Gelsemoidine Hydrochloride	Normal	Quiet	Present

Physiological study to be continued.

Gelsemoidine is amorphous, insoluble or nearly insoluble in ether, soluble in alcohol, soluble in chloroform and in water. It does not form crystalline salts.

Its hydrochloride is soluble in the same solvents and is hygroscopic. Like sempervirine and gelsemidine, it is in small quantity. It is separated from the ammonia-soluble, resinous matter (once thought to be alkaloid) by means of water or acidulated water in which it is soluble.

As above stated, it is believed that this investigation will aid in the determination of a satisfactory process for the standardization of the drug and its preparations. Conjointly with this work Professor L. D. Havenhill is working out such a process of standardization.

The authors would like to add a word with regard to the importance of our understanding the chemical constitution of such a drug as Gelsemium, as this drug is one that powerfully impresses the nervous system. It is said that small medicinal doses relax the muscles and allay nervous irritation. Therapeutically, Gelsemium is said to act upon the cerebrospinal nervous centers and it has found much favor among the eclectic practitioners who claim that the drug "possesses a perfect control over the nervous system, removing nervous irritability more completely than any other known agent."

Since the habit-producing drugs (of the narcotic and hypnotic group) have caused much alarm, evidenced by legislation, it is wise for chemists and therapeutists to endeavor, as far as possible, to employ a substitute. It is believed that if the drug in question is more thoroughly studied by therapeutists it will be found more valuable, than it is deemed at present, as one of the important agents in the armamentarium of the practitioner.

THE PERMANENCY AND DETERIORATION OF SOME VEGETABLE DRUGS TWENTY-FIVE YEARS OF AGE.*

BY E. N. GATHERCOAL.

Some two years ago opportunity offered for the examination of a collection of crude drugs that had been prepared some twenty-five years ago by W. K. Higley of Northwestern University School of Pharmacy, Chicago. These drugs were placed in glass-stoppered bottles kept in cases more or less exposed to the light. For a number of years, at least, none of the bottles have been opened. While the conditions under which these drugs have been kept are not exactly similar to the conditions met with in drug stores, in many respects they are similar to those in stores where crude drugs are kept in glass. Of course, where drugs are kept in wooden drawers or boxes, or in paper packages, the liability to deterioration is perhaps increased.

This paper is deficient in some respects. It will be noted that a number of assayable drugs have not been assayed. This was due in some cases to an insufficiency of material, in others to lack of time on the part of the author. Despite the fact that spare moments for two years have been devoted to this work, many of the drugs have not received nearly the attention they should have had.

A number of important drugs are omitted because samples of them were not present in the collection examined.

Among the drugs fully U. S. P. there occur, much to the author's surprise, Digitalis, which is of a strength one and a half times the present pharmacopoeial

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