

## THE ALKALOIDS OF SABADILLA.

BY RICHARD FISCHER.\*

Although considerable work has been done by different chemists and pharmacists on the alkaloids of sabadilla seed (*Asagraea officinalis*), still the results obtained have been so contradictory in many respects, that the real character of these alkaloids is as yet unknown. With the view of isolating the various alkaloids if possible, and to try the effect of different ways of extraction of the drug, I entered upon the following work :

The presence of an alkaloid in sabadilla seed was first discovered in 1819 by Meissner, and at about the same time, but independently of him, by Pelletier and Caventon. The latter obtained the alkaloid in the form of an amorphous base (or rather mixture) by boiling the seeds in water acidulated with sulphuric acid and precipitating the aqueous extract with ammonia.

Conerbe, in 1834, isolated from a mixture so obtained three distinct substances, of which one was amorphous, but yielded a crystallizable sulphate and hydrochlorate. It was readily soluble in alcohol or ether, but insoluble in water. To this alkaloid Conerbe gave the name veratrine. The second alkaloid, called by him sabadilline, was insoluble in ether, but soluble in alcohol and water, and crystallizable therefrom. The third was also soluble in alcohol and water, insoluble in ether, was amorphous, and formed non-crystalline salts ; it was regarded by him as the mono-hydrate of sabadilline.

In 1855, Merck obtained from commercial veratrine, by evaporation of a solution in diluted alcohol, a very pure substance which he succeeded in crystallizing. This body, to which he applied the term veratrine, gave upon analysis numbers leading to the formula  $C_{32} H_{52} N_2 O_8$ . Its salts, with the exception of the auro-chloride, failed to crystallize.

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\* Communicated by Albert B. Prescott.

Weigelin, in 1871, separated three alkaloids from sabadilla seeds, of which the one identical with Merck's base, he considers as capable of existing in two different forms, one soluble and the other insoluble in water. The other two alkaloids were obtained by shaking with fusel oil, in the aqueous extract from which ammonia had precipitated the first base.

In 1877, Schmidt and Köppen obtained a crystallizable base from *Asagræa officinalis*, for which they gave the formula  $C_{32}H_{50}NO_9$ . They agree with Weigelin in his conclusion that veratrine can exist in a soluble and an insoluble variety.

In 1878, Wright and Luff, in an extensive research published in the *JOURNAL OF THE CHEMICAL SOCIETY* for that year, found three distinct alkaloids: Firstly, an amorphous base, termed by them veratrine, which furnishes a crystallizable sulphate and hydrochlorate. Secondly, the crystalline alkaloid previously described by Merck, Weigelin and Schmidt and Köppen, but for which they propose the term cevadine. They regard its composition as  $C_{32}H_{49}NO_9$ . Thirdly, cevadilline, an amorphous base, insoluble in ether, but differing in other respects from the alkaloid previously described by Weigelin under that name. The method of extraction of the seeds, as used by these investigators, was, in short, as follows: The coarsely powdered seeds were percolated with alcohol, acidulated with tartaric acid, the percolate was evaporated to a small bulk, the resin precipitated with water and the alkaloids finally precipitated with an alkali and shaken out with ether.

Since then, Bosetti, in 1883, after working on commercial veratrine, concluded that this consists of two isomeric modifications of the same alkaloid,  $C_{32}H_{49}NO_9$ . The first of these (Wright and Luff's cevadine) is crystalline, almost insoluble in water, but readily soluble in alcohol or ether. For this he retains Merck's name, veratrine. The second modification is soluble in water. For this he proposes the name veratridine.

Later than this, I have found hardly any literature on the subject. In the work done I have proceeded as follows:

Two kilos. of the coarsely powdered seeds were macerated for two weeks with 95% alcohol, after which they were expressed; the residue was then packed in a percolator and extracted with alcohol.

The percolate was mixed with the portion expressed and the whole divided into two parts, half of which was evaporated on the water bath while the rest was allowed to evaporate spontaneously with the purpose of seeing whether or not there would be any difference in the yield.

After concentrating the solution to the consistency of a syrup, it was poured into about ten times its volume of acidulated water, when a large quantity of resin and oil separated out. The aqueous solution was then rendered alkaline with sodium carbonate (which I found would precipitate the alkaloid much more readily than ammonia) and repeatedly shaken out with ether, the ethereal solution being agitated with a dilute solution of sulphuric acid and used over again. The acid solution of alkaloids was again precipitated with sodium carbonate and re-dissolved in ether, when, upon separating and spontaneous evaporation of the ether, a resin-like, amber colored mass was left, easily pulverizable, and almost white when powdered. This residue seemed identical with the mass left upon evaporation of an ethereal solution of Merck's so-called "crystalline veratrine."

The alkaloidal mixture so obtained was found to be readily soluble in ether, alcohol, chloroform, amyl alcohol and methyl alcohol, almost insoluble in water, and but slightly soluble in petroleum benzine, the part dissolved out in the latter case being found to be identical with the residue, as subsequent additions of the same quantity of solvents dissolved out exactly the same amounts. It responded to all the tests of the U. S. Ph. for veratrine, such as dissolving in hot hydrochloric acid with a blood-red color, and giving a strong greenish-yellow fluorescence when triturated in a mortar with concentrated sulphuric acid, which color soon passes to a reddish-yellow and finally to an intense scarlet.

Upon dissolving a part of the mass in alcohol and allowing it to evaporate spontaneously, a portion separated out on the sides of the beaker in colorless, transparent masses which under the microscope were of a decided crystalline structure, though not distinct crystals.

Upon dissolving another portion in ether and adding petroleum benzine a precipitate was formed. I therefore added enough

petroleum benzine (previously diluted to prevent too great precipitation) until a very slight cloudiness appeared and allowed the mixture to evaporate spontaneously. The residue for a large part consisted of small, colorless, transparent, bead-like masses, which, when broken up, presented a crystalline appearance, and which I considered as quite pure cevadine (Merck's veratrine). They responded to the same tests as the mixture and perfectly neutralized acids but the salts failed to crystallize. Upon adding auric chloride to the hydrochloric acid solution of the alkaloid, a heavy yellow precipitate formed, almost insoluble in water but readily soluble in alcohol, from which, however, it failed to crystallize. The platinic salt similarly produced was much more readily soluble in water; it, too, failed to crystallize.

I next tried Merck's method for the separation of a crystallizable alkaloid, namely, that of adding enough water to an alcoholic solution of the alkaloidal mixture to cause a slight precipitate, then adding alcohol till this just dissolved and evaporating on the water bath at 50-60° C. A fine white precipitate soon separated, but it was mixed with so much of a resin-like substance as to make it impossible to obtain it pure. I therefore tried another watery alcoholic solution and allowed it to evaporate spontaneously. In a few days, quite large quantities of a substance separated in the form of shining scales, which appeared crystalline under the microscope, and which I think is identical with Merck's veratrine.

The amount of crystalline alkaloids obtained by all of these processes was, however, too small to allow of an elementary analysis.

The resin-like mass left after the separation of the crystalline principle could not be obtained pure enough to warrant the belief that it really is one alkaloid, as it has been regarded by Wright and Luff, who named it veratrine.

In the hope of obtaining Wright and Luff's cevadilline, I shook out with amyl alcohol the alkaline extract from which ether would remove no more alkaloid, and evaporated off the amyl alcohol on the water bath, when a brownish-yellow mass remained, insoluble in ether, but readily soluble in alcohol and slightly, so in water. Upon solution in a small quantity of acidulated

water, and subsequent addition of an excess of sodium carbonate, quite a heavy white, flocculent precipitate was formed, which, after filtering out, was found to be perfectly soluble in a large quantity of water, but could be obtained almost pure white upon washing with ether, in which it is practically insoluble. It was found to be precipitated by the general reagents for alkaloids, but the quantity obtained was too small to admit of any further researches. Wright and Luff in their investigations obtained the brownish residue mentioned above, but did not succeed in obtaining a white alkaloid.

The second portion of the alcoholic extract was treated as follows: After allowing it to evaporate spontaneously to the consistence of a syrup, it was added to about ten times its volume of acidulated water, the aqueous solution was separated from the oil and resin, and the alkaloids precipitated by sodium carbonate. They were then filtered out, washed on the filter until the filtrate ran through colorless, and dried at a gentle heat. The product was a perfectly white powder, for the greater part soluble in ether, the residue being of a yellow color and appearing to be extractive matter that had not been washed out. The soluble portion acted exactly like the substance described above.

To try the effect of extracting the drug with acidulated alcohol, two kilos. of the powdered seeds were extracted in exactly the same manner as described in the previous process, using, however, alcohol containing 0.5% of sulphuric acid as a menstruum. Upon evaporating off the alcohol and precipitating the resin with water, a great difference in the amount of oil separating out was noticed, for while by the former process about 10% was obtained, the yield by the latter did not exceed three per cent.

The alkaloids were now extracted from their aqueous solution, as in the previous process, with the exception that the final ethereal solution was again shaken out with acidulated water, precipitated with sodium carbonate, the precipitate collected and washed on a filter and dried at a gentle heat.

The white alkaloidal powder thus produced, seemed in no way to differ from the products of the other methods and by repeating the processes of evaporation from various solvents the same crystalline residues were formed.

The amount of alkaloids obtained was about the same for either method, varying from seventeen to twenty grms. per kilo. or almost two per cent., which is a much larger yield than I have seen reported by any previous investigator, Wright and Luff obtaining only 0.6%, while Conerbe, Schmidt and Köppen and several others obtained one per cent.

With regard to the term *veratrine*, different authors use it to represent altogether different substances, thereby causing considerable confusion. Thus, the term is used by the U. S. Ph. to represent the mixture of alkaloids as prepared from *sabadilla* seed. Conerbe, who first investigated the composition of this mixture, applied the name *veratrine* to an amorphous alkaloid; later, Merck applied it to his crystalline alkaloid, and this term was used quite generally until Wright and Luff named the crystalline alkaloid *cevadine*, and mentioned an amorphous alkaloid under the name *veratrine*, claiming priority on account of Conerbe's researches. The terms *cevadine*, *veratrine* and *cevadilline* as used by these latter investigators, have been adopted in both the United States and National Dispensatories, Maisch's *Materia Medica*, Beilstein's "*Organische Chemie*," and several other books, while Richter's *Organic Chemistry* still applies the name *veratrine* to Merck's base, and mentions *cevadine* as identical with it.

In conclusion, to summarize my results in this work, I would say that for extracting the drug, I regard the use of any acid whatsoever in the menstruum as entirely superfluous; and extraction by percolation to be the most satisfactory, as long maceration and expression and subsequent percolation, though perhaps just as thorough, takes up much more time with no visible advantages. The use of heat (the temperature of the water bath) in evaporating off the alcohol seems to be without objection, and has the advantage that the alcohol can be recovered.

With regard to the yield of total alkaloids, it seems to me that the amount usually stated is too low, for although I did not attempt a quantitative estimation, yet the results obtained by ordinary procedure warrant me in coming to the above decision. Whether this difference is due to a superior quality of drug in my case, or to a difference in the method of extraction, I am unable

to state. It appeared to me, however, that the method of extraction with ether would be preferable, for by it I obtained a larger yield, because in washing the precipitate according to the other method considerable goes into solution. Besides this, the product obtained in the former case is much purer and the method, for that reason alone, deserves preference.

Concerning the chemical composition of commercial veratrine, I accomplished practically nothing on account of lack of time. The great difficulty is in obtaining alkaloids pure enough, because all but one are amorphous and the presence of even a minute quantity of amorphous alkaloid prevents the other from crystallizing. The subject is certainly an interesting as well as an important one, and would furnish a large field of work for any investigator.

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UNIVERSITY OF MICHIGAN.