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XLI.—*The Alkaloïds of the Veratrums.* Part I. *The Alkaloïds of Veratrum Sabadilla* (Asagrœa officinalis).

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§ 1. *General History of the Alkaloïds.*

The alkaloïdal constituents of *Veratrum Sabadilla* seeds have been partially investigated by various chemists and pharmacists, with results in many respects contradictory of each other. On examining the methods of manipulation adopted by most of these experimenters for the purpose of isolating the alkaloïds contained in the seeds, it is at once manifest that if any alkaloïd be naturally present which is capable of splitting up by saponification, like the aconite alkaloïds, this base must inevitably have been more or less decomposed during extraction by the reagents employed in many instances; consequently there is room for some doubt as to how far the substances isolated and examined by different investigators were normal constituents of the seeds, and how far they were alteration-products or mixtures. On subjecting a specimen of commercial so-called "veratria" from saba-

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dilla seeds, obtained from Messrs. Hopkin and Williams, to the action of alcoholic soda at 100°, or of water in sealed tubes at 140°, we found that considerable quantities of *two* different acids were formed, one identical with the *dimethylprotocatechuic acid* obtained by us from pseudaconitine (this Journal, 1878, i, 151), and therefore identical with the *veratric acid* obtained by E. Merck from sabadilla seeds (Körner, *Deut. Chem. Ges. Ber.*, 1876, 937), the other apparently identical with the *methylcrotonic acid* synthesised by Frankland and Duppa (this Journal, 1865, 133), and with the *cevadic acid* of Pelletier and Caventou (*Ann. Chem. Phys.* [2], 14—69), from which it is probable that the so-called "veratria" of commerce is a mixture containing two different saponifiable alkaloïds (and possibly others besides), so that a ready explanation is offered as to why such divergent results have been obtained by different experimenters hitherto.

Thus Pelletier and Caventou obtained in 1819 an amorphous base (mixture ?) melting at 50° (*Ann. Chim. Phys.* [2], 14, 69), whilst Couerbe obtained in 1834 (*ibid.* [2], 52, 352) three alkaloïdal bodies, of which one was amorphous, but yielded a crystallisable sulphate and hydrochloride. This was insoluble in water, melted at 115°, and was termed by him *veratrine*. The second was soluble in water and crystallisable therefrom, and fusible at 200°: this he termed *sabadilline*. The third was soluble in water, and non-crystalline, and was viewed by him as a *hydrate of sabadilline*. In 1855 Merck isolated from the amorphous mixture then sold as "veratria" a small quantity of a crystallisable alkaloïd, the salts of which, with the exception of the aurochloride, did not crystallise. To this Merck applied the term *veratrine*, although it in no way corresponded with the base previously described by Couerbe under that name. He ascribed to it the formula $C_{32}H_{52}N_2O_8$ (*Liebig's Annalen*, xcv, 200).

In 1871 Weigelin, working in Dragendorff's laboratory, described three alkaloïds as obtainable from *V. Sabadilla* (*Untersuchungen über die Alk. der Sabadillsamen*, Dissert. Dorpat, 1871; also Dragendorff, *Beiträg. z. ger. Chemie*, 1872, 94; *Wigger's and Husemann's Jahresber. der Fortschr. der Pharmacie*, 1871, 28; *N. Jahresber. Pharm.*, xxxvii, 94). One of these fused at 150°, and was regarded by Weigelin and Dragendorff as Merck's base; they obtained numbers leading to the formula, $C_{52}H_{86}N_2O_{15}$. The other two were obtained by shaking with fusel-oil the liquid from which ammonia had precipitated the first base; of these one was almost insoluble in ether, but crystallised from benzene; as it was somewhat soluble in water, and fused at 200°, they viewed it as Couerbe's sabadilline; the other was amorphous, and more soluble in water than sabadilline; it formed only amorphous salts; to this they applied the term *sabatrine*, regarding it as a simple

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substance. The analytical numbers led to the formulæ, $C_{41}H_{66}N_2O_{13}$ and $C_{51}H_{86}N_2O_{17}$ for these bases respectively. Moreover, Weigelin regarded the first base, the veratrine of Merck, as being capable of existing in more than one modification, one soluble in water, one insoluble therein, or nearly so.

Recently (*Liebig's Annalen*, clxxxv, 224) Schmidt and Köppen have obtained from sabadilla seeds a base crystallisable from alcohol, and melting at 205°; this they regard as identical with Merck's base, but they assign to it the formula, $C_{32}H_{50}NO_9$; they conclude with Weigelin, that this base can exist as a modification soluble in water, as well as in two insoluble forms, one crystalline, one amorphous.

On comparing together the analytical data and general collateral evidence contained in these various papers, it is evident that whilst Merck had obtained the base described by him as "veratrine," in a state of tolerable purity, this body was not identical with that previously described by Couerbe, under the same name; and that his formula was incorrect, the single nitrogen determination on which it was founded being erroneous: for Schmidt and Köppen had evidently the same body in their hands, and all Merck's analyses (with the exception of this solitary nitrogendetermination) agree sharply with those of Schmidt and Köppen, which again agree well with their formula, and equally well with the almost identical formula, *à priori* more probable, which, as shown below we deduce from our experiments, together with those of these chemists, viz., $C_{32}H_{49}NO_9$.

Next it is evident from Weigelin's statement as to the melting point of his "veratrine," and his analytical numbers, that, whilst he had obtained the same alkaloïd as Merck, and Schmidt and Köppen, it was in a very defective state of purity. The "sabadilline" of Weigelin agrees in characters with the base described under that name by Couerbe; it is remarkable, however, that neither from sabadilla seeds nor from a sample of what is sold as "sabadilline" commercially (obtained from Messrs. Burgoyne and Burbidges, agents for Kahlbaum and Co.), could we isolate any base possessing these characters, although we obtained from each source an alkaloïd agreeing with "sabadilline," in the physical property of very sparing solubility in ether, but furnishing on analysis numbers very different from those of Weigelin. As to the "sabatrine" of Weigelin, our own observations lead us to the belief that it and the "hydrate of sabadilline" of Couerbe are nondescript mixtures of alteration-products of the other bases present, which we find to be—

(*a.*) The veratrine of Couerbe (amorphous, giving crystalline salts).

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(*b.*) The veratrine of Merck (crystallisable; salts non-crystalline, saving the gold salt).

(*c.*) The third base, almost insoluble in ether just referred to (amorphous; salts amorphous).

Of these three bases the first furnishes on saponification dimethyl-protocatechuic (veratric) acid, whilst the second, and apparently also the third gives rise to an acid which is apparently the "cevadic acid" of Pelletier and Caventou (obtained by them from sabadilla seeds, by treating with ether and saponifying the oil thus obtained by potash, *vide* § 3), and also identical with the methyl-crotonic acid of Frankland and Duppa. Accordingly we propose to designate the bodies respectively—

(*a.*) Veratrine (because the prior right to that name rests with this base, and because it furnishes veratric acid).

(*b.*) Cevadine (because it forms cevadic acid).

(*c.*) Cevadilline (because it appears to form cevadic acid, and because in insolubility in ether it corresponds with the "sabadilline" of Weigelin and Dragendorff, which, however, we have been unable to find.

As regards the views of Weigelin, and of Schmidt and Köppen, that the mass of the sabadilla alkaloïd is made up of uncrystallisable bodies, isomeric with "veratria" (of Merck, our cevadine), one of which is soluble in water, our experiments show that the facts observed by them admit of a different explanation. Very small quantities of non-crystalline impurity prevent the "veratrine" of Merck from crystallising readily, whilst a mixture of a non-crystalline salt of Merck's "veratrine" with one of Couerbe's veratrine prevents the latter from crystallising; so that it is impossible to get either the one free base or the other salt to crystallise from such mixtures. On the other hand these alkaloïds readily saponify, especially in contact with alkalis; the supposed soluble modification of "veratrine" is probably simply a salt or mixture of salts formed by partial saponification during standing, &c. (*vide* § 6).

The data from which these conclusions are drawn are given in detail in the subsequent sections.

§ 2. *Isolation of Alkaloïds from Sabadilla Seeds.*

In order to avoid as far as possible saponification during extraction, we employed the process found to give satisfactory results with the aconitine alkaloïds, viz., percolation of the coarsely pulverised seeds with alcohol acidulated with tartaric acid (1 part acid to 100 parts of

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seeds), evaporation to a small bulk, precipitation of resin by water, and extraction of alkaloïds by adding sodium carbonate, and repeatedly shaking with ether, the ethereal solution being agitated with tartaric acid to remove alkaloïds, and used over again; in this way a tartaric acid solution of bases free from resin is obtained. Former experimenters have almost invariably extracted the alkaloïds by methods involving heating in contact with dilute sulphuric acid, or with alkalis, or with both successively, which must necessarily have brought about a good deal of saponification; probably, indeed, the veratric acid found by Merck in sabadilla seeds was thus formed. The acid tartrates obtained were then treated with sodium carbonate, and shaken with a moderately large bulk of ether, whereby all was dissolved; the almost colourless ethereal solution obtained utterly refused to crystallise on spontaneous evaporation, nor could any crystals be obtained by dissolving the residue in alcohol, and leaving the solution at rest. On boiling with benzoline the viscid, honey-like mass left, a portion dissolved, which appeared to crystallise indistinctly on spontaneous evaporation; the ethereal solution was therefore cautiously mixed with benzoline (previously diluted with a little ether, to avoid much precipitation), until a permanent precipitate began to form, and set aside; the ether, being more volatile than the benzoline, evaporated most quickly, so that the liquid became relatively richer and richer in benzoline; at first viscid, honey-like masses separated, but when about $\frac{5}{6}$ths of the total alkaloïd had deposited, crystals began to form, and continued to deposit until the end. The crystals, mixed with viscid matter, were stirred up with a few drops of alcohol, and well drained and slightly washed with alcohol on the filter-pump; the nearly pure crystals thus obtained were readily crystallisable from hot alcohol on cooling and standing; after two or three recrystallisations they melted at 205°, and were evidently the alkaloïd described by Merck, and by Schmidt and Köppen, as "veratrine," *i.e.*, the base which, as above stated, we propose to term *cevadine*. On saponification these crystals yielded only cevadic acid; the viscid, honey-like precipitates, however, yielded veratric acid on saponification, with a larger quantity of cevadic acid.

In order to isolate the second base thus evidently present, we endeavoured to crystallise out as much as possible of the cevadine by repeating the evaporation with ether-benzoline; on dissolving up in ether the viscid masses for this purpose, a portion refused to dissolve (the amount of ether used being very much less than in the case of the first ethereal solution). The insoluble portion was purified by solution in tartaric acid, addition of sodium carbonate, and agitation of the freshly precipitated flakes with ether, this process being repeated two or three times. The insoluble substance finally obtained was then examined, as described in § 5; that it was not the base yielding vera-

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tric acid on saponification was readily shown, no veratric acid, but instead, cevadic acid being obtained from it on saponification.

The ethereal solution, on treatment with benzoline and evaporation, yielded viscid, honey-like precipitates at first, with finally a small quantity of crystals of cevadine; the only way by which the base yielding veratric acid could be extracted was the following:—The resinoïd precipitates which first separated from the ether-benzoline fluid were dissolved in dilute sulphuric acid, precipitated with ammonia, drained on the filter-pump, and partially dried by exposure to air. On stirring up in a mortar the nearly dry base with dilute nitric acid, a sticky mass of nitrate was formed, of which part was only sparingly soluble in water, even on boiling; the portion insoluble gradually became granular; this was filtered off hot, and purified by two or three boilings with small quantities of water. On regenerating the free base by shaking with sodium carbonate and ether, it was found impossible to crystallise it from ether or alcohol; on saponification it yielded veratric acid copiously; on solution of the base in dilute sulphuric acid, fine crystals of sulphate resembling paper-pulp formed on standing. These were collected and drained on the filter-pump; on drying by spontaneous exposure to air the mass lost its crystalline texture, and became a resinoïd substance of conchoidal fracture; on solution of this in water and standing, crystals were again formed. From the purified crystals of sulphate the base, the *veratrine* of Couerbe, was obtained and examined, as described in § 4.

In the hope of obtaining the "sabadilline" and "sabatrine" of Weigelin, the original liquors from which all alkaloïds soluble in ether had been removed by repeated shaking with that solvent, were agitated with fusel oil, and the fusel oil extract thus obtained was evaporated to dryness. A small quantity of brown resinoïd alkaloïdal matter was thus obtained, which however yielded scarcely a trace to boiling water, and though soluble in ether, benzene, and alcohol, utterly refused to crystallise from any solvent. No appreciable amount of "sabadilline" could therefore have been present in these liquors, Weigelin's method of extracting the body examined by him consisting of agitation of the liquors from which precipitable bases had been thrown down by ammonia with fusel oil, separation of "sabadilline" from "sabatrine" in the fusel oil residue by ether, in which the former is almost insoluble, and purification of the former by solution in water, and crystallisation from benzene.

In this way we obtained from 20 lbs. of sabadilla seeds some 60—70 grams of rough mixture of alkaloïds, finally yielding some 8—9 grams of pure crystallised cevadine; about 5—6 grams of not quite pure veratrine, and 2—3 of rough cevadilline. The great majority of the alkaloïd would not crystallise, nor could crystallisable salts be ob-

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tained from it: on analysis and saponification it yielded numbers indicating that it was essentially a mixture of cevadine and veratrine, the former predominating. It is possible, as supposed by Weigelin, and by Schmidt and Köppen, that the substance contained an isomeric modification of cevadine; but it seems far more probable that it was simply a mixture of bases, the one preventing the other from crystallising. On treatment with water, the resinoïd masses left by the spontaneous evaporation of alcoholic or ethereal solutions of these mixtures, part dissolved, the solution drying up to a gummy mass on evaporation; the soluble portion, however, appeared to be simply a mixture of the salts of the bases with cevadic and veratric acids, formed by spontaneous saponification on standing, &c.

In order to obtain a larger quantity of cevadine, some ounces of commercial so-called "veratria" were purchased from Messrs. Hopkin and Williams. This wholly dissolved in ether, yielding no insoluble cevadilline or "sabadilline"; the ethereal solution treated with benzoline behaved just as that prepared by ourselves; at first resinoïd masses separated, and ultimately crystals of cevadine easily purified by alcohol. The resinoïd masses yielded some veratric acid on saponification; but we did not succeed in isolating any granular nitrate of veratrine from them, there being apparently a much smaller quantity of veratrine here than in the batch worked up by ourselves: probably this was due to difference in mode of preparation, the purchased product having been presumably prepared in the ordinary way, which involves heating with dilute sulphuric acid, precipitation with alkalis, and contact with alkaline fluids, &c., highly conducive to loss by saponification.

§ 3. *Composition and Derivatives of Cevadine* (the "Veratrine" of Merck, and of Schmidt and Köppen).

According to Schmidt and Köppen, the crystallised base melts, when pure, at 205°; the purest crystals we obtained by several recrystallisations melted at 206° (corrected), whilst other specimens fused at 203°, 204—205°, and 205°. In the hope of obtaining greater purity, the purest crystals were converted into gold salt, which was then recrystallised from alcohol, and the crystals, after drying in the air to remove adherent spirit, suspended in water and decomposed by sulphuretted hydrogen: the base regenerated from the resulting hydrochloride by means of sodium carbonate and ether, did not crystallise from alcohol so readily as the original substance, and the crystals, after recrystallisation from alcohol, fused at 204°. In other similar experiments in which the gold salt was suspended in alcohol instead of water, the base finally regenerated and recrystallised from

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alcohol fused at 205°. No additional purity therefore seemed to be gained by this treatment, but rather the contrary.

The following numbers were obtained on analysis:

(A.) Purest crystals several times recrystallised from alcohol, obtained from sabadilla seeds by the tartaric acid process, &c., as above described.

0·2825 gram gave 0·6680 CO_2, and 0·2160 H_2O.
0·5900 gram burnt with soda lime gave 0·0975 Pt.

(B.) Alkaloïd regenerated from crystallised gold salt.

0·2770 gram gave 0·6590 CO_2, and 0·2135 H_2O.
0·6390 gram burnt with soda lime neutralised acid equal to 0·01456 nitrogen.

(C.) Base prepared from commercial so-called "veratria" purchased from Hopkin and Williams.

0·2570 gram gave 0·6075 CO_2, and 0·1995 H_2O.

(D.) Specimen C recrystallised twice more from alcohol.

0·3085 gram gave 0·7360 CO_2, and 0·2395 H_2O.

	Calculated.		Found. A.	B.	C.	D.		Mean.
C_{32}.....	384	64·97	64·49	64·88	64·46	65·06		64·72
H_{49}.....	49	8·29	8·50	8·56	8·62	8·62		8·57
N	14	2·37	2·34	2·28	—	—		2·31
O_9	144	24·37	—	—	—	—	by diff.	24·40
$C_{32}H_{49}NO_9$..	591	100·00	—	—	—	—		100·00

The gold salts yielded the following numbers after drying at 100° till constant.

From specimen A. 0·5185 gram gave 0·1085 Au = 20·93 per cent.
B. 0·5000 ,, 0·1050 21·00 ,,
D. 0·3720 ,, 0·0790 21·13 ,,

Mean .... 21·04

Calculated for $C_{32}H_{49}NO_9$, HCl, $AuCl_3$ = 21·08

These numbers agree closely with the formula assigned, and moreover are practically identical with those found by Merck, and by Schmidt and Köppen (with the exception, as pointed out above, of Merck's single N determination).

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	Calculated for $C_{32}H_{49}NO_9$.	Merck. Mean of 4 combustions, 1 nitrogen and 4 gold determinations.	Schmidt and Köppen. Mean of 7 combustions, 3 nitrogen and 5 gold determinations.	Wright and Luff. Mean of 4 combustions, 2 nitrogen and 3 gold determinations.
Carbon in base..	64·97	64·81	64·63	64·72
Hydrogen.....	8·29	8·71	8·62	8·57
Nitrogen	2·37	5·50	2·66	2·31
Gold in gold salt	21·08	21·01	21·09	21·04

Merck also determined the percentage of carbon and hydrogen in the gold salt, and of carbon and hydrogen and SO_3 in the sulphate, finding numbers very close to those required for the formula $C_{32}H_{49}NO_9$, as is manifest from the circumstance that he deduced from these numbers the formula, $C_{32}H_{52}N_2O_8$ = molecular weight 592 instead of $C_{32}H_{49}NO_9 = 591$. Schmidt and Köppen similarly determined the carbon and hydrogen in the gold salt, the SO_3 in the sulphate, the HCl in the hydrochloride, and the mercury and chloride in the mercurochloride, in all cases finding numbers closely accordant with the formula, $C_{32}H_{49}NO_9$, they themselves deducing from these numbers the almost identical formula, $C_{32}H_{50}NO_9$ = molecular weight 592 instead of 591.

There can, therefore, be no doubt that the formula, $C_{32}H_{49}NO_9$, represents the composition of cevadine as nearly as repeated analysis can possibly fix it: whence it results that the substance examined by Weigelin and Dragendorff, and regarded by them as Merck's base, must have been very impure, for they found the melting point to be 150°, and obtained the percentages—

Carbon in base.....	64·42
Hydrogen in base	8·70
Nitrogen by soda lime	2·92, 2·95, 2·86
,, by volume	2·87
Gold in gold salt.....	23·17, 23·08

hence their formula, $C_{52}H_{86}N_2O_{15}$, *à priori* not very probable, is clearly utt rly erroneous.

Cevadine crystallises anhydrous from alcohol, but from ether it separates only as a varnish, becoming crystalline on moistening with alcohol containing a little water, and well stirring. As previously stated by Merck, and by Schmidt and Köppen, it utterly refuses to form crystallisable salts, with the exception of the aurochloride. On adding gold chloride to a solution of the pure base in hydrochloric acid, an amorphous, very sparingly soluble, yellow precipitate falls, soon becoming crystalline: when drained and boiled with alcohol con-

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taining a little water, it dissolves, crystallising in well defined small needles on cooling. The crystals thus obtained contain $C_{32}H_{49}NO_9$. $HCl.AuCl_3 + 2H_2O$, the water of crystallisation being lost at 100° only slowly.

1·4295 grams of air dry crystals lost at 100°
0·0555 gram, becoming constant in weight only after several hours ..... = 3·88 per cent.
Calculated ..... = 3·73 „

Cevadine is powerfully sternutatory; the crystals at first are transparent, becoming white and opaque by exposure to air without material loss of weight.

When cevadine is heated in sealed tubes with water, or better if saponified by cohobation with alcoholic soda, it breaks up in accordance with the reaction—

$$C_{32}H_{49}NO_9 + H_2O = C_5H_8O_2 + C_{27}H_{43}NO_8,$$

perfectly parallel with that undergone by the aconite alkaloïds, and like them forming an acid, cevadic acid, and a new base. The latter, to which we propose to apply the term *cevine*, is non-crystalline, and readily decomposed by long boiling with alkalis, forming a resinoïd non-basic or feebly basic body: wherefore the determination of the amount of acid formed by titration methods is inexact, and the yield of the basic saponification-product but small after purification. The former product (cevadic acid) also appears to be affected by continued boiling with potash, splitting up into propionic and acetic acids to some extent, in just the same way as is effected more rapidly by fusion with potash (*vide infra*): for on acidulating the product of saponification with sulphuric acid, and distilling with a large bulk of water, somewhat more than one equivalent of volatile acid is produced for one of cevadine employed. The acid, $C_5H_8O_2$, thus first produced, corresponds pretty closely with the description of cevadic acid given by Couerbe, and appears to be also identical with the methylcrotonic acid of Frankland and Duppa. To procure it in a pure state, cevadine was saponified by long continued boiling with alcoholic soda, an inverted condenser being attached; the alcoholic fluid was diluted with water, acidulated with sulphuric acid, and distilled as long as any acid came over. A portion of the distillate heated with a slight excess of pure baryta, freed from the excess by a current of carbon dioxide, boiled to a small bulk, filtered, and evaporated to dryness at 100°, yielded a gummy readily soluble residue which did not crystallise on moistening with water and allowing to stand: of this 0·4275 gram gave 0·3075 $BaSO_4$ = 42·29 per cent. Ba.

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The formula $Ba(C_5H_7O_2)_2$, requires 40·89 per cent. Ba, whilst barium propionate requires 48·41 per cent., and barium acetate 53·72 per cent., from which it would seem that the production of propionic and acetic acids by secondary action of the alkali is but slight, although quite perceptible both by the process of titration and by the examination of the barium salt.

The acid distillate was neutralised with soda and evaporated to a small bulk; on adding phosphoric or sulphuric acid and heating, a distillate was obtained partly consisting of fluid acids readily soluble in water, and partly of crystals or of an oil becoming crystalline on standing. In another experiment the soda salt was acidulated with sulphuric acid, and shaken with ether; on distillation, after the ether had passed over, an acid liquid began to distil at a little above 100°, the temperature quickly rising, so that the greater part passed over at 185—190°; the distillate at this temperature solidified on cooling to a mass of crystals wetted with an acid liquid. After pressure in blotting paper, pearly scales were obtained, the fusing points of two specimens of which were respectively 64° and 65° (corrected), somewhat lower temperatures being found with less pure specimens. (Methyl crotonic acid melts at 62° (Frankland and Duppa), its isomeride, angelic acid, at 45°.) The acid thus obtained possessed a peculiar aromatic odour somewhat recalling that of butyric acid, but more pleasant: when rendered just neutral with ammonia, silver nitrate threw down a white precipitate somewhat soluble on washing; the silver salt thus formed darkened slightly on drying in the dark; another specimen prepared by boiling the acid with freshly precipitated well washed silver carbonate, filtering hot, and leaving the filtrate to evaporate spontaneously over sulphuric acid in the dark, consisted of perfectly white granular crystals, which yielded the following numbers:

First crop of crystals, 0·4285 gram gave 0·4570 CO_2, 0·1365 H_2O, and left behind 0·2235 gram Ag.

Second crop obtained on further evaporation, 0·3005 gram gave 0·1575 Ag.

	Calculated.			Found.	
				1st crop.	2nd crop.
C_5	60	28·99		29·08	—
H_7	7	3·38		3·54	—
Ag.....	108	52·17		52·16	52·41
O_2	32	15·46	(by diff.)	15·22	—
$C_5H_7O_2.Ag$..	207	100·00		100·00	

The copper salt of this acid, prepared by precipitating the neutral barium salt with copper nitrate, was so far soluble in water as to be readily dissolved during washing—

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0·0790 gram dried over sulphuric acid gave 0·0245 CuO = 31·0 per cent.

The formula Cu $(C_5H_7O_2)_2$, requires = 30·4 per cent.

On heating to 100° the copper-salt was apparently decomposed, as it gave off a strong odour of the acid, and lost in weight nearly 4 per cent.

On fusion of a known weight of acid with caustic potash at about 280° hydrogen was evolved; on dissolving the product in water, neutralising exactly, and then adding enough standard acid to set free about 5 per cent. of the total acids present, no crystallisable substance was extracted by agitation with ether, indicating complete decomposition. Enough acid was then added to set free about 15 per cent. of the acids formed, and the whole distilled until scarcely any more acid passed over; the distillate, on agitation with pure barium carbonate, evaporation to a small bulk, filtration, and evaporation to dryness, yielded a varnish-like salt, of which

0·2520 gram gave 0·2080 $BaSO_4$ Ba = 48·52 per cent.
Calculated for Ba $(C_3H_5O_2)_2$.... = 48·41 ,,

Enough acid to liberate all acid present, save some 20 to 30 per cent., was then added, and the whole distilled; the barium-salt from this distillate contained 50·61 per cent. Ba, indicating a mixture of propionate and acetate; finally, the last portions of acid were liberated, distilled off, and made into barium-salt: of this, when dried at 100°—

0·1705 gram gave 0·1545 $BaSO_4$ Ba = 53·27 per cent.
Calculated for Ba $(C_2H_3O_2)_2$ .. = 53·72 ,,

Hence, on fusion with potash the acid saponification-product of cevadine splits up into propionic and acetic acids with evolution of hydrogen, thus: $C_5H_8O_2 + 2H_2O = C_3H_6O_2 + C_2H_4O_2 + H_2$, in this respect exactly agreeing with both angelic and methyl crotonic acids. As, however, the former melts at 45° and the latter at 62° (Frankland and Duppa), whilst our specimens melt at 64° and 65° respectively, there can be little doubt that our acid is actually methyl-crotonic acid.

The cevadic acid obtained by Pelletier and Caventou appears to have been this saponification product in an imperfectly pure state; they do not appear to have separated the crystallised acid completely from other substances (*e.g.*, the propionic and acetic acids formed by its partial decomposition), and hence found that it melted at 20°; in all other respects their description of cevadic acid exactly tallies with our product (which, when not freed from small quantities of fluid acids, melts in the hand): in particular the ammonium-salt of our product yields with ferric chloride the white, or nearly white, floccu-

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lent precipitate, described by Pelletier and Caventou as similarly formed with their cevadic acid. Moreover, it is highly probable that Pelletier and Caventou's substance was actually formed by the decomposition of cevadine, for they obtained it by treating the seeds with ether (probably containing alcohol), and saponifying the resinous matter extracted with potash; were any alkaloïd or alkaloïdal salt dissolved out along with the resinous matter, it must inevitably have given rise to our acid by this treatment.

Hence, as there remains little doubt that "cevadic acid" is really identical with the saponification-product of cevadine, and as this name is of earlier date than "methyl-crotonic acid," we propose to keep to the former term in referring to this acid.

In order to isolate the complementary alkaloïdal product *cevine*, the acid liquid left after distilling off the volatile acid was filtered from resinous matter, rendered alkaline with caustic soda, and shaken with fusel oil; the filtered fusel oil extract left on evaporation a brownish varnish, which dissolved in dilute acetic acid, leaving behind resinous flakes. The filtrate from these, on treatment with soda and fusel-oil (after fractionally precipitating to get rid of colouring matter) gave an amber-coloured varnish perfectly soluble in acids; in a capillary tube this did not frit below 140°, and fused at 145°; in alcohol and fusel-oil it dissolved readily, in chloroform but sparingly, in ether hardly perceptibly. Neither the base nor its salts were obtained crystallised. On analysis the following numbers were obtained:—

0·2650 gram gave 0·6215 CO_2 and 0·2035 H_2O.

0·7255 gram burnt with soda-lime, and titrated gave 0·02038 nitrogen; by conversion into platinum-salt gave 0·1400 Pt.

	Calculated.		Found.	
C_{27}	324	63·65	63·96	—
H_{43}	43	8·45	8·52	—
N	14	2·75	2·81	2·73
O_8	128	25·15		
$C_{27}H_{43}NO_8$..	509	100·00		

By adding potassium mercuriodide to a solution of cevine in acetic acid white flakes were precipitated insoluble in water, or nearly so; after drying over sulphuric acid, and finally at 100°—

0·4920 gram gave 0·3210 AgI Iodine = 35·24 per cent.
Calculated for $C_{27}H_{43}NO_8.HI.HgI_2$.... = 34·94 „

It results from these experiments that the formula of cevadine may be written—

$$(C_{27}H_{42}NO_7)—O—CO—C(CH_3)=C_2H_4,$$

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since on saponification it forms methyl-crotonic acid, known to have the structure, $C_2H_4{=}C(CH_3) - CO.OH$. In order to see if cevadine is analogous to the aconite alkaloïds in containing hydroxyl-groups also, the base was heated to 100° with twice its weight of benzoic anhydride (containing a trace of fluid impurity which rendered it liquid at 100°) for three hours. On dissolving the product in a little alcohol, adding ether and aqueous tartaric acid, and shaking, an aqueous acid solution of tartrates was obtained; from this, by the aid of caustic soda and ether, the alkaloïds were withdrawn. On spontaneous evaporation the ethereal solution deposited fine arborescent crystals half an inch in length on the side of the dish (cevadine does not crystallise from ether), with only a very small quantity of non-crystalline matter; by stirring up the residue with a little ether, filter-pumping, and slightly washing with ether, the new derivative was obtained snow-white. The crystals when air dry were hydrated, containing $C_{39}H_{53}NO_{10}1\frac{1}{2}H_2O$, the base itself being formed by the reaction—

$$C_{32}H_{49}NO_9 + (C_7H_5O)_2O = C_7H_6O + C_{32}H_{48}(C_7H_5O)NO_9,$$

and hence being *benzoyl-cevadine*. It fused at a temperature between 170° and 180°, the melting point not being clearly defined, and the substance beginning to frit together at 160°—

0·5425 gram dried in the air lost at 100° 0·0205 = 3·78 per cent.
0·4805 gram dried over sulphuric acid lost at 100° 0·0180 = 3·75 per cent.
Calculated = 3·74 per cent.
0·2760 gram dried at 100° gave 0·6780 CO_2 and 0·2050 H_2O.

	Calculated.		Found.
C_{39}	468	67·34	67·00
H_{53}	53	7·63	8·25
N	14	2·02	
O_{10}	160	23·02	
$C_{32}H_{48}(C_7H_5O)NO_9$..	695	100·00	

0·3005 gram of gold-salt dried at 100° gave 0·0565 Au = 18·80 per cent.
Calculated for $C_{39}H_{53}NO_{10}.HCl.AuCl_3$ = 18·95 per cent.

Hence it results that cevadine contains one and only one hydroxyl-group, so that its formula may be written—

$$(C_{27}H_{41}NO_6)\begin{matrix}OH\\O.CO.C(CH_3){=}C_2H_4.\end{matrix}$$

On comparing this formula with that deduced for pseudaconitine (this Journal, 1878, i, 151),

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$$(C_{27}H_{37}NO_5)\begin{cases}OH\\OH\\OH\\O.CO.C_6H_9(O.CH_3)_2,\end{cases}$$

it is noticeable that the carbon in the two nitrogenous radicles is the same, whilst the other elements are not very far apart; so that it is highly probable that some deeper connection exists between these two alkaloïds than mere similarity in structure, so far as saponifiability and presence of hydroxyl-groups are concerned. The results described in the next section indicate that veratrine (of Couerbe) is closely allied to cevadine, being indicated by the formula $(C_{28}H_{41}NO_7) - O.CO.C_6H_3(O.CH_3)_2$, and possibly by $(C_{28}H_{43}NO_6)<\begin{matrix}OH\\O.CO.C_6H_3(OCH_3)_2,\end{matrix}$ whilst aconitine contains a radicle with C_{26}, being indicated by the formula $(C_{26}H_{35}NO_7\begin{cases}OH\\OH\\OH\\O.CO.C_6H_5\end{cases}$; so that it is also highly probable that the sabadilla and aconite bases generally are allied together, having perhaps some common central nucleus-radicle.

§ 4. *Composition and Derivatives of Veratrine (the Veratrine of Couerbe).*

The following numbers were obtained with the base isolated as described in § 2, from the crystals of the sulphate by treatment with sodium carbonate and ether, and spontaneous evaporation; no crystals could be obtained from the varnish-like residue by the use of any solvent tried, or by any artifice—

0·2440 gram dried at 100° gave 0·5805 CO_2 and 0·1755 H_2O.
0·2455 ,, ,, 0·5755 ,, 0·1790 ,,
0·8310 gram burnt with soda-lime gave by titration 0·01681 nitrogen, and by conversion into platinum-salt 0·1320 Pt.

	Calculated.		Found.		Mean.
C_{37}	444	64·63	64·88	63·93	64·41
H_{53}	53	7·71	7·99	8·09	8·04
N	14	2·04	2·02	2·24	2·13
O_{11}	176	25·62			
$C_{37}H_{53}NO_{11}$.	687	100·00			

0·4590 gram of gold-salt gave 0·0885 Au ..... = 19·28 per cent.
0·5035 ,, ,, 0·0960 ,, ... = 19·07 ,,
Calculated for $C_{37}H_{53}NO_{11},HCl.AuCl_3$ ..... = 19·10 ,,

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The gold-salt was wholly non-crystalline; on adding gold chloride to a solution of the base in hydrochloric acid a gelatinous yellow precipitate was thrown down, drying to a semi-translucent horny mass over sulphuric acid, and not crystallisable from alcohol. On triturating the alkaloïd with dilute nitric acid a horny nitrate was produced, almost insoluble in water, even when boiling; dilute sulphuric acid readily dissolved the base, the solution crystallising in extremely fine needles on standing; on drying, these needles adhered and finally became a horny translucent mass, reproducing crystals on solution in water and standing. The hydrochloride exhibited a similar behaviour, save that the crystals were not so well marked and distinct. It was hoped that a check on the formula deduced from the above numbers might be obtained from the analysis of the crystals of sulphate prepared by dissolving the base in a slight excess of sulphuric acid, draining the crystals formed on the filter-pump, and recrystallising from water; the horny mass into which the crystals ultimately passed on exposure to air gave the following numbers:—

0·5000 gram of air-dry substance (constant in weight in the air) lost at 100° 0·0945 gram = 18·90 per cent.

0·4055 gram of the dry residue gave 0·1000 $BaSO_4$: H_2SO_4 = 10·36 per cent.

The acid sulphate, $C_{37}H_{53}NO_{11}.H_2SO_4$, requires H_2SO_4 = 12·48 per cent.

The neutral sulphate $(C_{37}H_{53}NO_{11})_2\ H_2SO_4$ requires H_2SO_4 = 6·66 per cent., whence it results that the recrystallised salt was a mixture of neutral and acid sulphates, the latter predominating; the formula,

$$C_{37}H_{53}NO_{11}.H_2SO_4.10H_2O,$$

would require 18·65 per cent. of water of crystallisation.

In a capillary tube veratrine fuses at 180° (corrected). Couerbe states that his product fused at 115°, but doubtless his substance was far from pure, not having been regenerated from a crystallised salt.

On saponification with alcoholic soda veratrine breaks up in accordance with the reaction—

$$C_{37}H_{53}NO_{11} + H_2O = C_9H_{10}O_4 + C_{28}H_{45}NO_8,$$

forming veratric acid (dimethyl protocatechuic acid), and a base so closely resembling cevine in its properties that the two might well be regarded as identical were not somewhat different numbers given on combustion. To call to mind that this new base is related to veratrine somewhat as aconine to aconitine, pseudaconine to pseudaconi-

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tine, and cevine to cevadine, we propose to term it *verine*. Like cevine, it is to a great extent decomposed by the alkali used in its production, forming a resinous product insoluble in dilute acids.

1·235 grams of veratrin yielded, by treatment with ether, an extract consisting of veratric acid with a little yellowish resinous matter. On titration by standard soda the acid corresponded to 0·344 $C_9H_{10}O_4$.

1·535 grams corresponded similarly to 0·426 $C_9H_{10}O_4$.

	Calculated.	Found.	
Veratric acid formed.....	26·5	27·8	27·7

The slight excess found is probably due, as in the case of the aconite alkaloïds, to the feeble acidity of the resinous bye-product.

The veratric acid thus obtained was purified by dissolving in ammonia, digestion with animal charcoal, and precipitation by hydrochloric acid. After crystallisation from boiling water, anhydrous crystals were obtained, melting at 176—178° (corrected), and giving the following numbers on combustion:—

0·2565 gram gave 0·5595 CO_2 and 0·1355 H_2O.

	Calculated.		Found.
C_9	108	59·34	59·49
H_{10}	10	5·49	5·86
O_4	64	35·17	
$C_9H_{10}O_4$..	182	100·00	

On fusion with caustic potash it formed protocatechuic acid in quantity, readily identified by its colour reaction.

To obtain the complementary product, verine, the liquid from which the veratric acid had been removed by ether was rendered alkaline by soda and repeatedly shaken with fusel oil. On evaporation over the water-bath a brownish-yellow amorphous base was left, which was purified by solution in acetic acid, filtration from a few resinous flakes, and regeneration by means of soda and fusel oil. After drying at 100°, an amber-coloured varnish was obtained, yielding the following numbers:—

0·2705 gram gave 0·6405 CO_2 and 0·2160 H_2O.

	Calculated.		Found.
C_{28}.....	336	64·25	64·57
H_{45}	45	8·60	8·87
N	14	2·68	
O_8	128	24·47	
$C_{28}H_{45}NO_8$..	523	100·00	

Neither verine nor any of its salts appeared to be crystallisable. In

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all its properties it resembled cevine most closely, save in melting point. In a capillary tube it fritted at 95° (as it also did in the water-bath). On raising the temperature it gradually became a thick viscid mass, exhibiting no distinct melting point, and not becoming completely fluid till heated to about 130°, whilst cevine exhibited no signs of fritting below 140°, and completely fused at 145°.

From these results it is evident that veratrine possesses a composition analogous to that of cevadine, its formula being—

$$(C_{28}H_{44}NO_7) - O.CO.C_6H_3(O.CH_3)_2.$$

The amount of material at our disposal was too small to enable us to examine the action of benzoic anhydride on veratrine, and to decide how many (if any) hydroxyl groups are present; and for this reason we were unable to multiply analyses, and especially to form and examine crystallised salts. It may, therefore, perhaps happen that further experiments may cause the formula attributed to this alkaloïd to be slightly altered, the analytical numbers above stated being not incompatible with other formulæ differing but little from $C_{37}H_{53}NO_{11}$, although this formula agrees best with the numbers found. It is noticeable that the formula $C_{36}H_{51}NO_{11}$ would represent veratrine and cevadine as possessing a common radicle when these formulæ are written—

$$(C_{27}H_{42}NO_7) - O.CO.C_6H_3(O.CH_3)_2 \text{ and } (C_{27}H_{42}NO_7) - O.CO.C_4H_7,$$

and would also indicate cevine and verine as being identical. That this is the case, however, is rendered improbable, not only by the difference in analytical numbers found with these two decomposition-products, but also by the difference in their melting points. Both of these differences, however, might possibly be due to a slight impurity in one of the specimens.

§ 5. *Composition and Derivatives of Cevadilline.*

In the hope of obtaining the substance described by Weigelin as "sabadilline," for comparison with the body isolated by us, and to which we propose to apply the term cevadilline (§ 1), a substance was purchased from Messrs. Burgoyne, Burbidges, Cyriax, and Farries, under the name of "sabadilline." On examination this proved to contain no trace of any substance possessing the properties of Weigelin's product, but instead to be almost wholly composed of a base identical with our cevadilline.

The crude cevadilline obtained as described in § 1, and the material purchased from Messrs. Burgoyne and Co., were each purified in the following way. The substance was dissolved in tartaric acid, precipitated with sodium carbonate, and shaken repeatedly with ether.

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From the purchased product scarcely anything was dissolved out, and that little appeared to be identical with the undissolved portion; from our material ether dissolved only traces after the first two or three treatments with that solvent, these traces being apparently identical with the undissolved flakes. The insoluble substances were then shaken with cold benzene, which in each case dissolved out only minute quantities, the benzene extracts yielding no crystals on spontaneous evaporation, but only small quantities of varnish, apparently identical with the undissolved portions. Water too dissolved out next to nothing from either substance; whence manifestly Weigelin's "sabadilline" was not present in either our preparation or the substance bought under the name of "sabadilline."

The substances finally obtained consisted of amorphous flakes soluble in boiling benzene, and separating out in amorphous flakes on cooling, readily soluble in fusel oil. The fusel oil solutions left, on evaporation, dark amber resins, which were purified by treating with acetic acid, filtration from a little undissolved matter, and finally regeneration by means of soda and fusel oil. The varnishes thus obtained much resembled verine and cevine; on analysis they yielded practically identical numbers, agreeing fairly with the formula $C_{34}H_{53}NO_8$.

A. Base prepared by ourselves from sabadilla seeds—
0·2445 gram gave 0·6020 CO_2 and 0·2020 H_2O.

B. Base prepared from purchased product—
0·2375 gram gave 0·5885 CO_2 and 0·2005 H_2O.

0·7405 gram with soda lime gave by titration 0·01602 nitrogen; by Pt salt, 0·1120 Pt.

	Calculated.		Found.	
C_{34}	408	67·66	67·14	67·57
H_{53}	53	8·79	9·16	9·37
N	14	2·32	—	2·17 2·14
O_8	128	21·23		
$C_{34}H_{53}NO_8$..	603	100·00		

On solution in acetic acid and addition of mercuriodide of potassium, white semigelatinous precipitates were obtained in each case, which on drying over sulphuric acid became horny and semi-transparent, after drying at 100°,

Specimen A. 0·4720 gram gave 0·2765 AgI, I = 31·65 per cent.
„ B. 0·6905 „ 0·4120 „ I = 32·24 „
Calculated for $C_{34}H_{53}NO_8$, HI, HgI_2 ..... I = 32·15 „

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Gold chloride threw down in each case semi-gelatinous non-crystallisable precipitates. That from B yielded the following numbers:—

0·3860 dried over sulphuric acid for some weeks gave 0·0810 Au, Au = 20·98 per cent.

Calculated for $C_{34}H_{53}NO_8,HCl,AuCl_3$ = 20·81 per cent.

At 100° this appeared to decompose, darkening much in colour, and losing in weight several per cents.

On saponification with alcoholic soda, each specimen gave rise to a volatile acid, apparently identical with the cevadic acid obtainable from cevadine, no trace of veratric acid being formed. As with cevadine, the acid distilled over on acidification with sulphuric acid of the saponified product slightly exceeded one equivalent for one of alkaloïd employed. The quantities of material at our disposal were too small for complete study of this reaction. Admitting, as is highly probable, that the same kind of saponification takes place with cevadilline as with cevadine and veratrine, and that cevadic acid is formed, the reaction would be—

$$C_{34}H_{53}NO_8 + H_2O = C_5H_8O_2 + C_{29}H_{47}NO_7.$$

Should this be substantiated on further examination, the alkaloïdal saponification-product might be termed *cevillin*, bearing to cevadilline exactly the same relationship as cevine to cevadine, *i.e.*, differing by $+ H_2O$ − cevadic acid.

§ 6. *Constitution of Uncrystallisable Bases from Sabadilla Seeds.*

On saponifying with alcoholic potash the viscid bases precipitated on spontaneous evaporation of the ether benzoline solutions described in § 1, similar results were obtained, both with the substances prepared by ourselves, and those similarly obtained from the alkaloïdal mixture purchased from Messrs. Hopkin and Williams. In each case both veratric and cevadic acids were formed, in such quantities as to show that these non-crystallisable substances were wholly, or almost wholly made up of saponifiable bases: for the total acid formed (which distilled off after acidulation with sulphuric acid, and that extracted by ether) neutralised somewhat more standard soda than corresponded with the alkaloïd used, the excess probably arising from decomposition of the cevadic acid into propionic and acetic acids. The veratric acid thus produced neutralised in each case much less soda than the volatile acid, indicating a considerable preponderance of the base which yielded cevadic acid, viz., cevadine. On combustion of the amorphous base prepared by the tartaric process numbers were obtained agreeing fairly with a mixture of cevadine and veratrine, the former predominating;

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precisely similar results were obtained with the alkaloïdal products of the saponification of the amorphous bases, isolated by means of soda and fusel oil, and purified, as described above in § 3—

0·2670 gram of amorphous base yielded 0·6370 CO_2 and 0·2025 H_2O.
0·4040 „ gold-salt gave 0·0820 Au.

	Calculated. For veratrine.	Calculated. For cevadine.	Found.
Carbon in base....	64·63	64·97	65·07
Hydrogen.....	7·99	8·29	8·43
Gold in gold salt..	19·10	21·08	20·29

0·1395 gram of mixed verine and cevine formed by saponification gave 0·3240 CO_2 and 0·1090 H_2O.

Calculated. For Verine.	Calculated. For Cevine.	Found.
64·41	63·65	63·34
8·04	8·45	8·67

On treating with water, after standing for some weeks, the soft non-crystalline masses which separated from the ether benzoline, as described in § 2, a portion dissolved; the solution of this dried up to a gum, and yielded precipitates with alkalis. That this was not a soluble modification of cevadine, as supposed by Weigelin, and by Schmidt and Köppen, but only a mixture of salts formed by partial saponification was shown by the fact that on distillation with water, after slight acidulation with sulphuric acid, cevadic acid passed over.

On the whole, therefore, it appears that the supposed isomeric modifications of "veratrine" (cevadine) are only either mixtures of bases, preventing each other from crystallising, or alteration-products.

§ 7. *General Conclusions.*

From the foregoing experiments, conjoined with the results detailed in the papers of former investigators, we draw the following conclusions:—

(1.) The seeds of *Veratrum Sabadilla* (sometimes designated *Veratrum officinale*, *Sabadilla officinarum*, or *Asagræa officinalis*) contain an alkaloïd, first isolated by Couerbe, and termed by him *veratrine*, which is indicated by the formula, $C_{37}H_{53}NO_{11}$, or one very close thereto; this is non-crystalline, but furnishes certain crystallisable salts: on saponification it splits up into veratric acid (dimethyl-protocatechuic acid) and a new base, *verine*, thus—

$$C_{37}H_{53}NO_{11} + H_2O = C_9H_{10}O_4 + C_{28}H_{45}NO_8.$$

(2.) In addition, a considerably larger quantity of another alkaloïd

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is present, first isolated by Merck, and described by him as "veratrine." To distinguish this from the former alkaloïd, which has the prior claim to the name veratrine, we propose to term it *cevadine*, reserving the name veratrine for Couerbe's base. This cevadine is crystallisable, melts at 205—206°, and on saponification splits up in accordance with the reaction—

$$C_{32}H_{49}NO_9 + H_2O = C_5H_8O_2 + C_{27}H_{43}NO_8,$$

forming a base *cevine*, and an acid identical with the methyl-crotonic acid of Frankland and Duppa, and with the cevadic acid of Pelletier and Caventou.

(3.) The formulæ assigned by Merck, by Weigelin, and by Schmidt and Köppen, to cevadine are all more or less erroneous, that of the latter pair of chemists being nearest to the truth, $C_{32}H_{49}NO_9$.

(4.) There is no good reason for supposing the existence of isomeric modifications of cevadine (so-called "veratrine") in the sabadilla alkaloïds, these supposed bodies being either mixtures of bases, thereby rendered highly difficult to crystallise, or products of alteration by saponification of the above-named bases.

(5.) The body described as "sabadilline" by Weigelin was not to be found in the substances examined by us; neither in the alkaloïds extracted by ourselves by the tartaric acid process; nor in the commercial so-called "veratria" obtained from Hopkin and Williams; nor in the product purchased as "sabadilline" from Burgoyne and Burbidges. On the other hand, the first and last of these substances contained an alkaloïd almost insoluble in ether, and agreeing in that respect with "sabadilline," but non-crystalline and insoluble in water, and differing therefore in these respects; this body gave numbers agreeing with $C_{34}H_{53}NO_8$, and on saponification appeared to form cevadic acid. To indicate this latter fact and to connote its partial resemblance to "sabadilline," we propose to term it *cevadilline*.

(6.) The "sabatrine" of Weigelin is doubtless simply a mixture of resinoïd alteration-products, as is also Couerbe's "hydrate of "sabadilline."

(7.) The sabadilla alkaloïds are not merely constituted like the aconite bases (*i.e.*, as regards saponification, and, in the case of cevadine, hydroxylation), but they also contain nitrogenous radicles, which appear to be closely allied to those of the aconite alkaloïds.