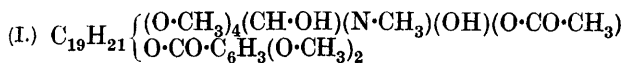


CCCCV.—*The Alkaloids of Some Indian Aconites.*
Part II. Pseudaconitine.

By THOMAS MARVEL SHARP.

Most of the species of *Aconitum* which have been examined chemically have been found to contain alkaloids, each species in general yielding a different alkaloid; pseudaconitine has, however, been obtained from two species, *Aconitum deinorrhizum* and *A. Balfourii*. The alkaloids may be subdivided into (a) poisonous alkaloids of the aconitine type and (b) relatively non-toxic alkaloids of the atisine type. With the exception of lycaconitine (Schulze and Bierling, *Arch. Pharm.*, 1913, **251**, 8) and lappaconitine (Schulze and Ulfert, *ibid.*, 1922, **260**, 230; Weidemann, *Arch. Exp. Path. Pharm.*, 1922, **95**, 166) the alkaloids of the former type (a) are similar in that they are all diacyl esters of other bases which are generically called "aconines," e.g., aconine, japaconine, pseudaconine, bikhaconine; in each of these cases one of the groups is acetyl. Aconitine, the best known of the alkaloids, is derived from a European species, *A. Napellus*, and is acetylbenzoylaconine. Two interesting reactions of this alkaloid have been described by Dunstan and collaborators (Dunstan, Tickle, and Jackson, P., 1898, **14**, 159; Dunstan and Carr, J., 1894, **65**, 176). When aconitine is heated in a sealed tube with methyl alcohol, the acetyl group is replaced by a methyl group with the formation of methylbenzoylaconine. The second reaction is also concerned with the acetyl group: when the dry base is heated slightly above its melting point, one molecule of acetic acid is split off and a new base, pyraconitine, is formed. The latter reaction has been shown to be general for those aconitine alkaloids which contain an acetyl group (Dunstan and Carr, *loc. cit.*; J., 1897, **71**, 358; Dunstan and Read, J., 1900, **77**, 60; Dunstan and Andrews, J., 1905, **87**, 1631, 1648; Majima and Suginomé, *Ber.*, 1924, **57**, 1466; Majima and Morio, *ibid.*, p. 1472) and has been studied in some detail in the cases of aconitine and japaconitine by Schulze and Liebner (*Arch. Pharm.*, 1913, **251**, 453; 1916, **254**, 567).

Formula (I) summarises what is at present known regarding the constitution of pseudaconitine.



It was thought that a careful study of the two reactions recorded by Dunstan and collaborators might throw some light on the relative positions of the groups present in pseudaconitine, and that

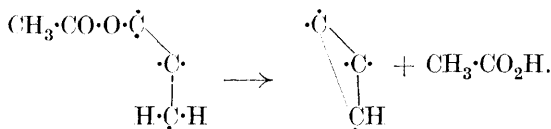
pyropseudaconitine might contain some weakened link, which would be a useful point of attack by oxidation or other degradation process, pseudaconitine having been shown in the previous paper (Henry and Sharp, this vol., p. 1105) to be very resistant to oxidation.

It is now found that when pseudaconitine is heated in a sealed tube with methyl alcohol, the acetyl group is replaced by methyl, and that the same reaction takes place—but more slowly—when the base is boiled under reflux with the alcohol. A similar reaction also takes place when tetra-acetylpsseudaconine is treated with either methyl or ethyl alcohol, one and only one of the acetyl groups being replaced by the methyl or ethyl group, the latter being introduced at a much slower rate. It is evident, therefore, that there is some group present in a particular relation to this acetyl group which facilitates the replacement. In an attempt to find such a group, a number of acetyl derivatives of comparatively simple constitution have been prepared and treated with methyl alcohol in this manner, but so far without success. The acetyl group or groups in acetylphenol, diacetylpyrocatechol, diacetylresorcinol, diacetylquinol, triacetylpyrogallol, acetylsalicylic acid, acetylpropenylguaiaicol, acetyleugenol, acetyl*isoeugenol*, acetyl*cyclohexanol*, penta-acetyl-*l*-quercitol, penta-acetylmethylinositol, and hexa-acetylmannitol are not replaced in this way.

As stated by Dunstan and Carr (*loc. cit.*), when pseudaconitine is heated above its melting point it loses acetic acid with the formation of pyropseudaconitine, which has now been crystallised. The operation is best carried out in a vacuum, but it is possible that the reaction takes place in more than one way, since a portion of the product could not be induced to crystallise.

The loss of acetic acid can take place in three ways : (*a*) by the removal of acetic acid between the acetyl group and a hydroxyl, in which case an ether linkage will be formed ; (*b*) by the removal of a hydrogen atom from a neighbouring carbon atom, in which case a double bond will be formed ; (*c*) by the removal of a hydrogen atom from a carbon atom in a remote position, with the formation of a bridged linkage. Pseudaconitine was shown in the previous paper (*loc. cit.*) by indirect means to contain two hydroxyl groups ; this is now directly proved by the formation of a diacetyl derivative. In case (*a*), therefore, only a monoacetyl derivative of pyropseudaconitine should be formed ; in cases (*b*) and (*c*) pyropseudaconitine should yield a diacetyl derivative, and (*b*) would probably be readily reduced by hydrogen in the presence of an active catalyst. If case (*a*) holds, tetra-acetylpsseudaconine, which does not contain a free hydroxyl group, should not lose acetic acid on heating, or if

it does so behave, the aconine obtained from it on hydrolysis should be different from that obtained by the hydrolysis of pyropseudaconitine. As a fact, tetra-acetylpsuedaconine on heating does lose one molecule of acetic acid with the formation of triacetylpyropseudaconine, and this on hydrolysis furnishes pyropseudaconine identical with the base obtained on hydrolysis of pyropseudaconitine. Moreover, on acetylation, pyropseudaconitine yields a compound which contains three acetyl groups but has only five methoxyl groups, whereas pyropseudaconitine has six. Analysis leaves no doubt that the substance has been formed by the acetylation of the two hydroxyl groups and the replacement of one methyl by an acetyl group. The aconine obtained on hydrolysis of this substance is quite different from that obtained from pyropseudaconitine and triacetylpyropseudaconine in that all attempts at crystallisation have failed, whereas the base from the other sources crystallises readily. It is difficult to choose between (b) and (c), but, as triacetylpyropseudaconine resists catalytic reduction by hydrogen, it is highly probable that the loss of acetic acid takes place between the acetyl group and a hydrogen atom attached to a remote carbon atom, and therefore that a bridged linkage is formed. This would cause the carbon atom in question to become asymmetric so long as it formed part of a saturated chain or ring, according to some such scheme as the following :



This view receives support from the specific rotations of pyropseudaconitine and triacetylpyropseudaconine, which are much greater than those of the bases from which they are derived.

It is interesting to compare these results with those obtained by Schulze and Liebner (1916, *loc. cit.*) with aconitine. According to these authors, aconitine, which contains three hydroxyl groups, on heating yields pyraconitine by the loss of acetic acid between the acetyl and a hydroxyl group, with the formation of an ether. The evidence for this is rather slender, being based on the analysis of the gold salt of the acetyl derivative of pyraconitine, which agrees with that of a diacetyl derivative, whereas a triacetyl derivative would be formed if all the hydroxyls were unchanged by the pyrogenous decomposition. A direct estimation of the acetyl groups in the acetyl derivative did not give a conclusive result, owing no doubt to the too drastic conditions employed. If Schulze and Liebner's conclusions are correct, they would indicate a considerable

difference in the form of combination of the groups concerned in aconitine and pseudaconitine.

The two rather unusual reactions recorded above, *viz.*, the replacement of acetyl by methyl by boiling pseudaconitine with methyl alcohol, and the replacement of a methyl by acetyl in pyropseudaconitine—a replacement which does not occur when triacetylpyropseudaconitine is treated similarly with acetic anhydride—emphasise the necessity for the determination of methoxyl groups and acetyl groups in any investigation of the aconitine alkaloids. The only similar case which has been found in the literature is the replacement of one ethyl group in diethylacetal by an acetyl group (Claisen, *Ber.*, 1898, **31**, 1018); there is no evidence, however, that an acetal group occurs in pseudaconitine.

Although diacetylpyropseudaconitine is readily formed, it has only been found possible to prepare a monobenzoyl derivative.

EXPERIMENTAL.

Pyropseudaconitine.—Dry pseudaconitine (5.1408 g.) was heated at 220° for 10 minutes in a good vacuum in a tube connected through a Volhard trap, cooled with ice and salt, to a pump. It lost 0.4286 g. (8.34%), and 0.4222 g. of acetic acid was collected in the Volhard trap (calc. for the loss of 1 mol. of acetic acid, 8.7%). The acid crystallised at once on the addition of a trace of solid acetic acid, and without purification melted at 15°. The residue in the reaction tube consisted of a brittle, light reddish-brown resin, which was powdered, dissolved in 1% hydrochloric acid, made alkaline with ammonia, and extracted with ether. After drying over sodium sulphate, the ether left on evaporation 4.65 g. of a pale yellow varnish, which was dissolved in 50% aqueous alcohol; the substance was then obtained in bundles of colourless, stout needles (3.37 g.), *m. p.* 132–135°, $[\alpha]_D^{25} + 175.2^\circ$ ($c = 1.154$ in alcohol). Pyropseudaconitine is very soluble in the usual organic solvents and could only be crystallised from 50% alcohol (Found: C, 65.0; H, 7.7; OMe, 28.5; NMe, 3.1. Calc. for $C_{34}H_{47}O_{10}N$: C, 64.8; H, 7.5; 6OMe, 29.6; NMe, 4.6%). The remainder of the reaction product was only obtained as an amorphous, colourless solid and may have been formed according to one of the alternative reactions outlined in the introduction (*p.* 3095).

Pyropseudaconitine does not react with methyl iodide.

Hydrolysis. A solution of pyropseudaconitine (4.7 g.) in alcohol (75 c.c.) was treated with potassium hydroxide (4.7 c.c. of 50% aqueous solution) and kept for 24 hours. It was then acidified with sulphuric acid, filtered from potassium sulphate, and diluted with water (50 c.c.) and the alcohol was removed by distillation

under reduced pressure on a water-bath. On cooling, a white, crystalline solid (1.25 g.) separated; extraction with ether furnished a further 0.1 g. of the same substance, m. p. 187° , which was identified as veratric acid by mixed melting-point determination. The aqueous mother-liquor was made alkaline with sodium carbonate solution and extracted with chloroform. After drying over sodium sulphate, the chloroform yielded on evaporation a light brown varnish (3.2 g.), which was dissolved in ether, filtered from a little amorphous substance, evaporated to dryness under reduced pressure, and redissolved in dry ether; it then suddenly crystallised in needles. After recrystallisation from dry ether, the substance was obtained in aggregates of prismatic, faintly brown needles, m. p. 172° , $[\alpha]_D + 227.5^{\circ}$ ($c = 1.217$ in alcohol) (Found on substance dried at 110° in a vacuum: C, 64.4; H, 8.6; OMe, 26.5; NMe, 4.25. $C_{25}H_{39}O_7N$ requires C, 64.5; H, 8.45; 4OMe, 26.7; NMe, 6.2%). *Pyropseudaconine* is very soluble in organic solvents, and in water, forming an alkaline solution; an aqueous solution acidified with sulphuric acid gave only a faint white precipitate with Mayer's reagent, and a slight, brown, sticky precipitate with iodine in potassium iodide; tannic acid, sodium perchlorate, picric acid, and platinic chloride do not produce precipitates. Gold chloride gives a slight yellow cloudiness.

Acetylation. Pyropseudaconitine (3.6 g.) was boiled under reflux for $1\frac{1}{2}$ hours with acetic anhydride (15 c.c.). The solution was evaporated to dryness, and the residue dissolved in alcohol and again evaporated to dryness, the evaporation with alcohol being repeated three times. The product was then again dissolved in hot alcohol; on cooling, the compound separated in colourless prisms, m. p. 228° , $[\alpha]_D^{25} + 28.4^{\circ}$ ($c = 0.537$ in chloroform) [Found in substance dried at 120° in a vacuum: C, 63.4, 63.3; H, 7.2, 7.05; OMe, 21.2; NMe, 2.3; acetic acid (see below), 23.4. $C_{39}H_{51}O_{13}N$ requires C, 63.1; H, 6.9; 5OMe, 20.9; NMe, 3.9; $3CH_3 \cdot CO_2H$, 24.3%]. It is evident, therefore, that the substance is *triacetyldemethylpyropseudaconitine*, formed by the replacement of a methyl by an acetyl group and the acetylation of two hydroxyl groups.

Hydrolysis of Triacetyldemethylpyropseudaconitine.—Dry, finely powdered triacetyldemethylpyropseudaconitine (1.9699 g.) was suspended in 150 c.c. of neutral alcohol, potassium hydroxide (2 c.c. of 50% aqueous solution) added, and the mixture kept at room temperature for 24 hours. The clear solution was then exactly neutralised with sulphuric acid, sufficient water added to dissolve the precipitated potassium sulphate, and the alcohol removed in a current of steam generated from freshly-boiled distilled water free from carbon dioxide. The solution was acidified with sulphuric

acid and steam-distilled, and the distillate titrated with $N/2$ -sodium hydroxide and phenolphthalein. The volatile acid required 14.7 c.c. of 0.5218*N*-sodium hydroxide, equivalent to 23.36% of acetic acid, which was identified by analysis of the silver salt (Found: Ag, 63.7. Calc.: Ag, 64.7%). The residue from the steam distillation was extracted with ether (which furnished veratric acid, identified as described above), made alkaline with sodium carbonate, and extracted with chloroform. The chloroform after drying gave a colourless varnish (1.4 g.) on evaporation. This was dissolved in hot dry ether; the filtered solution slowly deposited a white, amorphous solid. On heating, the compound effervesces at about 90°. It has only been obtained in an amorphous condition, even after the addition of a trace of crystalline pyropseudaconine. Like pyropseudaconine, it gives only faint precipitates with Mayer's reagent and iodine in potassium iodide solution and does not form crystalline salts or yield precipitates with such reagents as sodium perchlorate, picric acid, platinic chloride, and tannic acid. It is very soluble in water, forming an alkaline solution, and in most organic solvents. From hot benzene it separates in an amorphous condition. A determination of methoxyl in a specimen which had separated from benzene and had been dried first in a desiccator, then at 70°, and finally at 90° in a vacuum, supports the view that the compound is a *demethylpyropseudaconine* (Found: OMe, 18.9; NMe, 3.55. $C_{24}H_{37}O_7N$ requires 3OMe, 20.6; NMe, 6.4%). This is as near to the theoretical figure as is to be expected on amorphous material.

Triacetylpyropseudaconine.—Tetra-acetylpsudaconine (5.6332 g.) (Henry and Sharp, this vol., p. 1112) was heated at 240° for 10 minutes in the manner described for the preparation of pyropseudaconitine (p. 3097). A vigorous evolution of acetic acid took place, the loss in weight being 0.5336 g. (9.47%. Calc. for 1 mol. of acetic acid, 9.22%). The residual pale yellow resin was powdered, dissolved in 1% hydrochloric acid, and made alkaline with ammonia, and the base extracted in ether. The residue left on evaporation of the solvent was dissolved in 50% alcohol; it was then obtained in colourless, six-sided plates (4.68 g.), m. p. 155–158°, $[\alpha]_D + 156.4^\circ$ ($c = 1.202$ in alcohol), $+ 156.6^\circ$ ($c = 0.709$ in alcohol) (Found: C, 63.05, 63.0; H, 7.7, 7.7; OMe, 20.3; NMe, 3.7; acetic acid, 31.1. $C_{31}H_{45}O_{10}N$ requires C, 62.9; H, 7.7; 4OMe, 21.0; NMe, 4.9; $3CH_3 \cdot CO_2H$, 30.45%). The base is very soluble in ether when freshly precipitated from a solution of a salt, and is readily soluble in alcohol, benzene, chloroform, and ethyl acetate. It does not yield crystalline salts. The acetyl groups were estimated by hydrolysis with alcoholic potassium hydroxide as described under

triacetyldemethylpyropseudaconitine. The residue from the steam-distillation was cooled, made alkaline with sodium carbonate, and extracted with chloroform. The chloroform on evaporation yielded a pale brown varnish, which, after solution in ether, was obtained in stout, prismatic needles, m. p. 173—174°, $[\alpha]_D + 230.1^\circ$ ($c = 1.12$ in alcohol). A solution of the base acidified with sulphuric acid gave a faint white precipitate with Mayer's reagent, a slight, brown, pasty precipitate with iodine in potassium iodide solution, and no precipitate with picric acid, tannic acid, sodium perchlorate, or platinic chloride. Auric chloride caused a slight yellow cloudiness. A mixed melting-point determination with pyropseudaconine obtained by the hydrolysis of pyropseudaconitine showed no depression. The products obtained by the hydrolysis of either pyropseudaconitine or triacetylpyropseudaconine are thus identical.

In order to test whether a double bond had been introduced into the molecule in the splitting off of acetic acid, triacetylpyropseudaconine (0.5 g.) was dissolved in alcohol (20 c.c.), and shaken with hydrogen under 3 atmospheres pressure with the addition of an active palladium-barium sulphate catalyst (0.1 g.) for 2 hours; no hydrogen was absorbed. The catalyst was filtered off, the filtrate evaporated to dryness, and the residue dissolved in 50% alcohol; unchanged triacetylpyropseudaconine then crystallised in characteristic six-sided plates, m. p. 155—158° (yield, quantitative).

Action of Heat on Pseudaconine.—It was thought that pseudaconine, on being strongly heated, might lose water with the formation of pyropseudaconine. A quantity of the base crystallised from acetone was therefore placed in a weighing bottle in the apparatus described above and heated at 120—130°. The compound frothed with loss of 1 mol. of acetone, which was collected in water and identified by conversion into iodoform (Found: loss at 120—130°, 10.4. $C_{25}H_{41}O_8N, C_3H_6O$ requires loss, 10.7%). The temperature was raised to 150° and then by successive rises of 10° to 210°, at which temperature the first loss in weight was observed. At this temperature also a ring of varnish collected on the cooler part of the reaction tube and the substance began to darken; it was evidently beginning to distil (with slight decomposition), since pseudaconine was recovered from the heated substance in a yield of 90%.

Veratroylmethylpseudaconine.—Pseudaconitine (5 g.) was heated in a sealed tube at 130° for 6 hours with 35 c.c. of methyl alcohol. The alcohol was removed and the residue was dissolved in 1% hydrochloric acid, made alkaline with sodium carbonate, and extracted with ether. The ether soon began to deposit crystals; it was, however, found convenient to distil the ether and convert

the residue (5 g., not completely dried) into the *hydrobromide*, which separated from water in colourless crystals containing $1\text{H}_2\text{O}$, m. p. $237-238^\circ$ (with efferv.), $[\alpha]_D + 2.15^\circ$ ($c = 2.09$ in water) (Found: loss at 120° in a vacuum, 2.6. $\text{C}_{35}\text{H}_{51}\text{O}_{11}\text{N}, \text{HBr}, \text{H}_2\text{O}$ requires loss of $1\text{H}_2\text{O}$, 2.4%. Found on anhydrous substance: C, 56.3, 56.5; H, 7.5, 6.8; N, 1.9; OMe, 28.75; NMe, 2.55; Br, 11.1. $\text{C}_{35}\text{H}_{51}\text{O}_{11}\text{N}, \text{HBr}$ requires C, 56.6; H, 7.1; N, 1.9; 7OMe, 29.3; NMe, 3.9; Br, 10.8%). The *base*, prepared from the purified hydrobromide, crystallised from 50% alcohol in colourless prisms, m. p. $206-207^\circ$, $[\alpha]_D + 29.8^\circ$ ($c = 1.12$ in alcohol) (Found on substance dried at 120° in a vacuum: C, 63.7; H, 7.9; OMe, 33.0; NMe, 2.8. $\text{C}_{35}\text{H}_{51}\text{O}_{11}\text{N}$ requires C, 63.5; H, 7.8; 7OMe, 32.9; NMe, 4.4%). The *hydrochloride* crystallised from alcohol-ether in hard, hemispherical aggregates of colourless needles, m. p. $249-250^\circ$ (decomp.), $[\alpha]_D - 3.41^\circ$ ($c = 5.43$ in water), $+ 0.38^\circ$ ($c = 2.62$ in alcohol) (Found: Cl, 5.1. $\text{C}_{35}\text{H}_{51}\text{O}_{11}\text{N}, \text{HCl}$ requires Cl, 5.1%).

Acetylation. (a) *Acetic anhydride.* Veratroylmethylpseudaconine (2 g.) was boiled under reflux for an hour with acetic anhydride (10 c.c.). Excess of the reagent was distilled off, the residue dissolved in 1% hydrochloric acid, and sodium perchlorate solution added in excess. The white precipitate was washed well with water and dried in a desiccator (2.2 g.). After crystallisation from absolute alcohol, the *perchlorate* was obtained in stout, colourless needles, m. p. $240-242^\circ$ (Found on substance dried at 110° in a vacuum: OMe, 26.9; NMe, 2.2. $\text{C}_{37}\text{H}_{53}\text{O}_{12}\text{N}, \text{HClO}_4$ requires 7OMe, 27.0; NMe, 3.6%). Acetyl groups were estimated in the manner already described (p. 3098), but owing to the sparing solubility of the salt more alcohol was required (300 c.c. for 0.7 g.) and the mixture was kept for 40 hours (Found: acetic acid, 8.5. $\text{C}_{37}\text{H}_{53}\text{O}_{12}\text{N}, \text{HClO}_4$ requires for 1 mol. of acetic acid, 7.5%). The substance is therefore a *monoacetylveratroylmethylpseudaconine perchlorate*. The mother-liquor from the steam distillation of the acetic acid was extracted with ether, which removed veratric acid (0.17 g.), made alkaline with ammonia, and extracted with chloroform. The chloroform furnished on evaporation a light brown varnish (0.5 g.), which was not obtained crystalline but must have been methylpseudaconine. It was very soluble in water and in most organic solvents and did not give any crystalline salt.

The formation of a monoacetyl derivative was unexpected in view of the fact that pseudaconitine contains two hydroxyl groups, which should have remained intact in the replacement of an acetyl by a methyl group. A diacetyl derivative was, however, obtained by acetylation with acetyl chloride.

(b) *Acetyl chloride.* Veratroylmethylpseudaconine (2.5 g.) was

boiled under reflux for an hour with acetyl chloride (12 c.c.). Excess of the reagent was evaporated, and the residue dissolved in water and made alkaline with ammonia; the white precipitate which formed was washed well with water and dried. After crystallisation from absolute alcohol *diacetylveratroylmethylpseudaconine* was obtained in colourless needles or compact crystals (2.2 g.). Either form melts at 160°, resolidifies after a time, and then remelts at 196°; $[\alpha]_D + 18.43^\circ$ in chloroform ($c = 1.248$) (Found on substance dried at 120° in a vacuum : OMe, 28.65; NMe, 2.1; acetic acid, 16.5. $C_{39}H_{55}O_{13}N$ requires 7OMe, 29.1; NMe, 3.9; $2CH_3 \cdot CO_2H$, 16.1%). Methylpseudaconine and veratric acid were recovered from the mother-liquor from the determination of acetyl groups in the manner described under monoacetylveratroylmethylpseudaconine (see above).

Triacetylmethylpseudaconine.—Tetra-acetylpsudaconine (2 g.) was heated in a sealed tube at 130° for 5 hours with methyl alcohol (25 c.c.). The product, which crystallised on cooling, separated from alcohol in colourless needles, m. p. 280—282°. The melting point varies with the rate of heating. Yield, 1.65 g., $[\alpha]_D - 18.5^\circ$ ($c = 0.766$ in alcohol) (Found : C, 61.7; H, 7.9; OMe, 24.8; NMe, 3.7. $C_{32}H_{49}O_{11}N$ requires C, 61.6; H, 7.9; 5OMe, 24.9; NMe, 4.7%). Crystalline salts could not be obtained.

Triacetylethylpseudaconine.—In the first preparation of tetra-acetylpsudaconine (this vol., p. 1112) the compound was crystallised from ethyl alcohol and during the crystallisation to constant melting point and rotation small crops with a higher melting point and higher rotation were obtained. After a long and tedious fractionation involving more than 40 fractional crystallisations, a quantity of material was obtained whose melting point (171°) and rotation ($[\alpha]_D - 25.17^\circ$ in alcohol, $c = 1.023$) were unaltered on subsequent recrystallisations; this on analysis proved to be *triacetylethylpseudaconine*. An attempt was made to prepare this compound in a simpler manner by heating tetra-acetylpsudaconine (2 g.) in a sealed tube at 120° for 47 hours with 25 c.c. of absolute alcohol. The product crystallised on cooling. After recrystallising twice from ethyl alcohol, 0.5 g. of colourless needles, m. p. 171°, $[\alpha]_D - 26^\circ$ in alcohol ($c = 0.98$), were obtained, identical with the compound obtained in the fractional crystallisation of tetra-acetylpsudaconine. Subsequent crops of crystals consisted of mixtures of the two compounds (Found : C, 62.1; H, 8.2; N, 2.2; OMe, 24.0; NMe, 3.1. $C_{33}H_{51}O_{11}N$ requires C, 62.1; H, 8.1; N, 2.2; 4OMe + OEt calc. as 5OMe, 24.3; NMe, 4.55%). Crystalline salts could not be obtained.

Hydrolysis. Triacetylethylpseudaconine (3.0640 g.) was dissolved

in 400 c.c. of alcohol, 50% aqueous potassium hydroxide (3 c.c.) added, and after 40 hours the acetic acid was determined in the usual manner (p. 3098). The steam distillate required 28.5 c.c. of 0.5218*N*-sodium hydroxide : acetic acid, 29.1%. $C_{33}H_{51}O_{11}N$ requires for 3 mols. acetic acid, 28.3%. The residue from the steam distillation was made alkaline with sodium hydroxide and extracted with ether, which removed the *ethylpseudaconine*, obtained on evaporation of the solvent as a viscous syrup which did not crystallise. It is very soluble in water to an alkaline solution and in most organic solvents. Its salts are very soluble in water and were not obtained crystalline. An aqueous solution of a salt gives a white precipitate with Mayer's reagent, but no precipitate with picric acid, sodium perchlorate, sodium thiosulphate, or with mercuric, platinum, or auric chloride.

Action of Heat on Veratroylmethylpseudaconine.—Veratroylmethylpseudaconine was dried at 150° in a vacuum and then heated at 220–230° in the manner described for the preparation of pyropseudaconitine. The substance lost 1.3% in weight, darkened considerably, and was dissolved in 1% hydrochloric acid and fractionally precipitated by ammonia. The first precipitate carried with it all the colour. The subsequent fractions were colourless and on crystallisation from 50% alcohol were identified as unchanged veratroylmethylpseudaconine. The first fraction after purification as hydrobromide was also recognised as the same substance.

On heating the hydrochloride in a similar fashion at 260° for 10 minutes and passing the vapours through Volhard traps containing in the first water and in the second standard acid, the following results were obtained : (a) A very small amount of sublimate on the cooler part of the reaction tube. This was soluble in water to an acid solution, which gave with ferric chloride a green colour changing to red on the addition of sodium bicarbonate solution. It is probably a pyrocatechol derivative formed from the veratroyl group. (b) The water wash-tubes contained hydrochloric acid and methyl alcohol; the latter was identified in the usual manner by conversion into formaldehyde with hot copper and colour reactions with resorcinol and with gallic acid. (c) The standard acid was unchanged. The reaction tube had a strong, fishy smell, but no base could be isolated; the residue was dark brown, insoluble in water and sodium hydroxide, and partly soluble in dilute hydrochloric acid. Only tarry products were obtained from it.

Benzoylation of Pseudaconitine.—Pseudaconitine (1.0 g.) was heated on a water-bath for an hour with benzoyl chloride (2 c.c.). The product was shaken for some time with ether and water, the aqueous layer run off, and the ether extracted once with 1% hydro-

chloric acid and once with water. These two extracts were added to the first aqueous layer and the whole was extracted with ether. This extract was added to the main ethereal extract; on evaporation a mixture of benzoic acid and benzoyl chloride was obtained. The aqueous extract was warmed and agitated to remove dissolved ether, cooled, and treated with excess of sodium perchlorate solution. The precipitated perchlorate was washed well with water, dried in a desiccator, and crystallised from absolute alcohol. It formed confused colourless prisms, m. p. 236° (efferv.). Yield, 0.75 g. There remained an uncrySTALLISABLE residue (Found: OMe, 21.1, 21.0; NMe, 2.05, 1.8. $C_{43}H_{55}O_{13}N, HClO_4$ requires 6OMe, 20.8; NMe, 3.25%). The acetyl and benzoyl groups were estimated together by cold hydrolysis with alcoholic potassium hydroxide, followed by steam distillation and titration of the volatile acids [0.7434 g. of substance yielded volatile acid equivalent to 3.1 c.c. of 0.5218*N*-sodium hydroxide : volatile acid, 13.05 (calc. as acetic). $C_{43}H_{55}O_{13}N, HClO_4$ requires volatile acid (1 acetic + 1 benzoic acid calc. as acetic), 13.4%]. The acids were separated and identified by evaporation of the neutralised steam distillate to a small volume, acidification, and extraction with much light petroleum (b. p. $90-120^{\circ}$), which removed the benzoic acid and left the acetic acid in solution. The petroleum extract was shaken with sodium hydroxide solution, and the alkaline liquid acidified and extracted with ether, which furnished 0.1 g. of benzoic acid on evaporation, identified by its melting point (after sublimation), $121-122^{\circ}$, its smell, and the smell of ethyl benzoate obtained on warming it with alcohol and sulphuric acid. The acid mother-liquor from the petroleum extract was neutralised with sodium hydroxide, evaporated to dryness, and extracted with alcohol to dissolve the sodium acetate. The alcohol was evaporated, the sodium salt dissolved in water, and the silver salt precipitated by silver nitrate (Found: Ag, 63.3. Calc. for $CH_3 \cdot CO_2 Ag$: Ag, 64.7%). The residue from the steam distillate was extracted with ether (which gave veratric acid), made alkaline with sodium hydroxide, and extracted with chloroform. The latter, on evaporation, left a varnish, from which pseudaconine was obtained on crystallisation from acetone, m. p. $92-94^{\circ}$, $[\alpha]_D + 36.2^{\circ}$. The benzoylation product is therefore *mono-benzoylpseudaconitine perchlorate*. The base was prepared from the purified perchlorate by treatment in alcoholic solution with an alcoholic solution of potassium acetate, but it was not obtained crystalline, nor could any other crystalline salt be obtained.

Acetylation of Pseudaconitine.—Pseudaconitine (2 g.) was boiled under reflux for an hour with 8 c.c. of acetyl chloride, the excess of the reagent distilled off, and the residue dissolved in water,

made alkaline with ammonia, and extracted with ether. The ethereal solution, without drying, deposited crystals; it was evaporated and the crystalline residue recrystallised from alcohol; the acetyl derivative was then obtained in colourless, stout needles, m. p. 229° (decomp.), $[\alpha]_D + 24.0^{\circ}$ in chloroform ($c = 1.00$). Yield of pure substance, 1.7 g. (Found on substance dried at 120° in a vacuum: OMe, 23.6; NMe, 2.1. $C_{40}H_{55}O_{14}N$ requires 6OMe, 24.1; NMe, 3.75%). Acetic acid was determined in the usual manner (p. 3098), 50% sodium hydroxide solution, however, being used in place of potassium hydroxide and sufficient water added to dissolve the sodium hydroxide. This is preferable to using potassium hydroxide, as there is less danger of the presence of carbonate (0.7944 g. gave acetic acid equivalent to 5.95 c.c. of 0.5218N-sodium hydroxide: acetic acid, 23.5. $C_{40}H_{55}O_{14}N$ requires $3CH_3 \cdot CO_2H$, 23.3%). Veratric acid and pseudaconine were recovered from the residue from the steam distillation as described under benzoylpseudaconitine. The compound is therefore *diacetylpseudaconitine* and its formation directly proves the presence of two hydroxyl groups in pseudaconitine which was previously indirectly shown by the formation of tetra-acetylpseudaconine (this vol., p. 1112). The salts of diacetylpseudaconitine were only obtained in an amorphous condition.

A *monoacetylpseudaconitine* was obtained (as perchlorate) in small yield, together with much amorphous material, by working in pyridine solution. Pseudaconitine (1 g.), dissolved in dry pyridine (5 c.c.), was well cooled with ice and salt and acetyl chloride (0.5 c.c.) was added carefully drop by drop. Pyridine hydrochloride separated. The reaction vessel was stoppered and kept over-night, the solution slowly becoming pink. The product was then poured into water (50 c.c.), and the opalescent solution distilled with steam to remove most of the pyridine. After cooling, the solution was treated with sodium perchlorate and the precipitate was washed with water, thoroughly dried, and crystallised from absolute alcohol. The salt was then obtained in small prisms which effloresced on exposure to air, m. p. $225-228^{\circ}$ (efferv.); yield, 0.55 g. (Found on substance dried at 120° in a vacuum: acetic acid, 16.3. $C_{38}H_{53}O_{13}N \cdot HClO_4$ requires for $2CH_3 \cdot CO_2H$, 14.4%). Veratric acid and pseudaconine were recovered from the mother-liquor from the hydrolysis. The base is amorphous.

Reduction of Pseudaconitine.—Attempts were made to reduce pseudaconitine with hydrogen under pressure in the presence of an active palladium-barium sulphate catalyst, the sulphate being used in aqueous solution and the base in alcoholic solution. Neither experiment was successful, the alkaloid being recovered unchanged.

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A similar result was obtained with the base in alcohol, Adams's platinum oxide catalyst and a trace of ferric chloride being used ("Organic Syntheses," vol. 8, p. 92).

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