27. *The Veratrine Alkaloids. Parts I and II.*

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Part I. The Constitution of Veratridine.

It is more than fifty years since Wright and Luff (J., 1878, **33**, 341) described the separation of commercial veratrine into cevadine, veratridine ($C_{37}H_{53}O_{11}N$), and cevadilline. These authors ascribed to cevadine the constitution of an ester of tiglic acid with a base cevine, $C_{27}H_{43}O_8N$. This has since been fully confirmed, and cevine, originally obtained only in an amorphous condition, has since been crystallised (Freund and Schwarz, *Ber.*, 1899, **32**, 800). For veratridine, Wright and Luff proposed the constitution of an ester of veratric acid with "verine," which was supposed to have the composition $C_{28}H_{45}O_8N$; and this proposal has not since been challenged. The fact, however, that pure cevine is obtained in excellent yield by the hydrolysis of crude veratrine (containing therefore veratridine) (Macbeth and Robinson, J., 1922, **121**, 1574) must give rise to the suspicion that Wright and Luff's amorphous verine is really slightly impure cevine. This matter has now been examined.

Both veratridine and cevadine could be obtained in a pure condition by Wright and

Luff's method, but the process proved tedious and wasteful, and a better method, which gives a 21% yield of veratridine, is described in the experimental section. Veratridine is amorphous, but can be purified by crystallisation of the hydrated acid sulphate described by Wright and Luff. The base is optically active, having $[\alpha]_D^{22^\circ} + 8{\cdot}0^\circ$ in alcohol.

On hydrolysis, veratridine gave veratric acid and a crystalline base, which proved to be identical with cevine. Veratridine is therefore veratroylcevine, and must have the composition $C_{36}H_{51}O_{11}N$.

EXPERIMENTAL.

Isolation of Veratridine from Commercial Veratrine.—To a solution of commercial veratrine (10 g.) in *N*/10-sulphuric acid (150 c.c.), sodium nitrate (40 c.c. of 20%) was added drop by drop with constant stirring. A sparingly soluble nitrate separated in an amorphous but easily filtrable condition, and was collected and washed with dilute sodium nitrate solution. The base was regenerated from the nitrate, washed, and dissolved (wet) in 2*N*-sulphuric acid (10 c.c.). To this solution, saturated aqueous ammonium sulphate was added drop by drop in amount just insufficient to cause a permanent turbidity. On standing, or immediately on seeding, veratridine sulphate separated in long, thin, silky needles. After being kept for some hours at 0°, the sulphate was collected and washed with a little ammonium sulphate solution. The free base was regenerated, and dried in a vacuum (1·9 g.). The filtrate from the sulphate was again precipitated with sodium nitrate, and the purification through the sulphate repeated, whereby a further 0·2 g. of veratridine was obtained, bringing the total yield up to 2·1 g.

For further purification the crude veratridine was reconverted into the *sulphate*, which was recrystallised several times. It formed a mass of white silky needles, which on drying in the air coalesced to a hard brittle resin. For analysis the substance was drained on a porous plate in an atmosphere saturated with water vapour (Found : C, 46·5; H, 7·6. $C_{36}H_{51}O_{11}N,H_2SO_4,9H_2O$ requires C, 46·3; H, 7·6%). On drying (high vac. at 110°), the substance lost sulphuric acid as well as water, and the product was very hygroscopic (Found : C, 59·3; H, 7·7; loss, 22·6. $C_{36}H_{51}O_{11}N,\frac{1}{2}H_2SO_4$ requires C, 59·8; H, 7·2; loss, 21·9%).

The free base, regenerated from the pure sulphate, formed a colourless amorphous powder, almost completely insoluble in water (wherein it differs from amorphous cevadine, which is appreciably soluble), and having $[\alpha]_D^{22^\circ} + 8{\cdot}0^\circ$ (4% solution in 96% alcohol). When heated, it softened and melted over the range 160—180°. It retained water tenaciously. After drying for some days in an evacuated desiccator, and then for 15 hours at 0·001 mm. over phosphoric oxide, it was by no means anhydrous (Found : C, 61·7; H, 7·8; N, 2·2. $C_{36}H_{51}O_{11}N,1{\cdot}5H_2O$ requires C, 61·7; H, 7·8; N, 2·2%). On drying at 110° in a high vacuum, the substance lost its adsorbed water, but also decomposed slightly with further loss of water (Found : C, 65·5; H, 7·7; loss, 5·6. $C_{36}H_{51}O_{11}N$ requires C, 64·2; H, 7·6; loss, 3·9%. $C_{36}H_{51}O_{11}N$, having lost an additional 0·7 molecule of water, requires C, 65·5; H, 7·6; loss, 5·7%).* The colour reactions of veratridine are : (1) Concentrated hydrochloric acid; colourless, changing during a few days to pale orange-pink. (2) Concentrated sulphuric acid; orange-red, with *no* fluorescence; after 24 hours, becoming crimson and acquiring a blue fluorescence. (3) Mixed with sugar, and moistened with sulphuric acid : intense green, becoming blue, and finally dirty purple. (4) Mixed with phosphoric oxide and kept in a loosely stoppered tube : a pink colour develops after some hours. The corresponding reactions of cevadine are : (1) Colourless, remaining so (*not* violet, as is stated in the literature). (2) Bright yellow, with an intense green fluorescence. The colour rapidly changes to orange, then more slowly to crimson-red, and the fluorescence changes to greenish-blue. (3) Similar to veratridine, but not so intense. (4) Similar to veratridine.

The filtrate from the insoluble nitrate was treated with ammonia, and the precipitate collected, dried, and dissolved in alcohol (7 c.c.). Cevadine crystallised readily on seeding, and was collected after 24 hours. Yield, 0·9 g. of a white crystalline powder, m. p. 199—201°. It was pure after a single recrystallisation.

The various mother-liquors are being examined for subsidiary alkaloids.

Hydrolysis of Veratridine.—Veratridine (2 g.) in alcohol (3 c.c.) was mixed with a solution of potassium hydroxide (4 g.) in the same solvent (10 c.c.), and the mixture refluxed for ½ hour.

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* The author is not suggesting the existence of a definite hydrate. His object is simply to show that the analytical figures are in complete agreement with the formula proposed, provided that allowance is made for adsorbed water, which is lost on drying together with a little constitutional water. Such behaviour is not unusual among complex amorphous compounds.

On cooling, the characteristic potassium derivative of cevine separated; it was washed with cold saturated alcoholic caustic potash and then with ether, dissolved in water (10 c.c.), and decomposed with carbon dioxide; the white crystalline solid (1·15 g.) obtained was identified as cevine by its m. p. and mixed m. p., its crystal form and solubilities, and by the m. p. and mixed m. p. of its methiodide (Freund and Schwarz, *J. pr. Chem.*, 1917, **96**, 238).

The aqueous filtrate from the cevine was made acid with concentrated hydrochloric acid, giving a copious white precipitate, which was collected. A further small amount was obtained by diluting the alcoholic mother-liquors from the potassium cevine and making them acid, followed by extraction with ether, shaking with aqueous sodium carbonate, and precipitation with acid. The combined crops of acid were crystallised from water, giving pure veratric acid, m. p. 179°. The yield (0·49 g.) was not much below that theoretically possible (0·54 g.).

Part II. Cevine.

Cevadine (Freund and Schwarz, *Ber.*, 1899, **32**, 800) and veratridine, the two main constituents of commercial veratrine, can both be hydrolysed to give a crystalline base, cevine, $C_{27}H_{43}O_8N$, about which little is known. It is a tertiary base, and of the eight oxygen atoms two are present as hydroxyl groups, two are contained in a lactone group, and the function of the remaining four is uncertain. On distillation with soda-lime it gives a small amount of a volatile base, almost certainly *l*-coniine.

All attempts to investigate the structure of cevine by a study of its oxidation (see particularly Macbeth and Robinson, J., 1922, **121**, 1574) have been unsuccessful. The molecule either breaks down completely or gives amorphous products. It is necessary, therefore, to find a new method of attack which, while preserving the greater part of the carbon skeleton, will nevertheless give crystalline products. Dehydrogenation with selenium, which has hitherto been applied to only one other alkaloid, yohimbine (Mendlik and Wibaut, *Rec. trav. chim.*, 1931, **50**, 91; Barger and Scholz, *Helv. Chim. Acta*, 1933, **16**, 1343), has proved to be such a method.

As the result of a number of comparative experiments, conditions have been found which give a crystalline base in a yield (as crude picrate) of nearly 10%. This base, termed *cevanthridine*, appears to have the composition $C_{23}H_{25}N$, and this formula is supported by the analyses of the *hydrochloride* and *methiodide*. The properties of cevanthridine suggest that it contains a phenanthridine nucleus, and mention should be made of its similarity in many respects to the base thebenidine, obtained by the zinc-dust distillation of thebenine (Vongerichten, *Ber.*, 1901, **34**, 768). The formula of cevanthridine corresponds to that of thebenine, $C_{15}H_9N$, with the addition of C_8H_{16}, *i.e.*, saturated side chains.

At higher temperatures the yield of cevanthridine is diminished and a crystalline hydrocarbon can be isolated. As yet it has been isolated only in very small amount.

Work on the further degradation of cevanthridine is in progress.

EXPERIMENTAL.

Cevanthridine.—Hydrated cevine (5 g.) and selenium (10 g.), contained in a 25 c.c. Pyrex flask provided with a short air-condenser, were heated together by means of a metal bath. The temperature of the bath was kept at 270—280° for ½ hour, then gradually raised during the next ½ hour to 320—330°, and kept at this temperature for 15 hours. The water which was given off in the earlier stages was driven over from time to time by warming the air condenser. This was necessary to avoid splashing of the hot melt due to refluxing of drops of water. After cooling, the flask was broken and the regulus separated, powdered, and extracted continuously for 12 hours with ether. The extract was orange in colour, later deepening to brown, and had an intense green fluorescence. The ethereal extract was shaken with dilute sulphuric acid, which caused the separation of dark-coloured resinous salts, from which the ethereal solution * was decanted. The insoluble salts were washed with ether, and the bases liberated and taken up in ether. After drying over potassium carbonate, the ether was removed, the gummy residue dissolved in acetone (5 c.c.), and picric acid (2 g.) in acetone (5 c.c.) added. On scratching or seeding, an orange-brown crystalline picrate separated, which, after cooling at 0° for some hours, was collected and washed with acetone and ether. Yield, about 0·4 g.

Attempts to purify the picrate were not successful. Even after five recrystallisations from acetone, correct analytical figures were not obtained (Found : C, 65·2; H, 5·3; N, 9·5%).

The following method of purification was finally adopted. The picrate was decomposed, and the base crystallised from acetone, collected, dissolved in boiling alcohol (10 c.c.), and treated with hot 2*N*-sulphuric acid (10 c.c.). On cooling, the sparingly soluble yellow sulphate separated. The base regenerated from this was crystallised from acetone (charcoal). After two further crystallisations from the same solvent pure *cevanthridine* was obtained as colourless plates, m. p. 207° (Found : C, 87·8, 87·5, 87·7; H, 8·0, 7·7, 8·1; N, 4·4, 4·6, 4·7. $C_{23}H_{25}N$ requires C, 87·6; H, 8·0; N, 4·4%). The yield from 5 g. of cevine amounted to about 100 mg.

Cevanthridine dissolves in neutral organic solvents to give colourless solutions with a marked violet fluorescence. Its salts with hydrochloric, nitric, and sulphuric acids are very sparingly soluble in water, are yellow in colour, and in solution show an intense green fluorescence. The *hydrochloride*, prepared from the base (20 mg.) in boiling alcohol (1 c.c.) by the addition of 2*N*-hydrochloric acid (0·5 c.c.), formed long, thin, lemon-yellow needles, which sintered and darkened above 230°, and were finally molten at 245° (Found : C, 72·7; H, 7·7. $C_{23}H_{25}N,HCl,1{\cdot}5H_2O$ requires C, 72·9; H, 7·7%).

The *picrate*, prepared from the base (15 mg.) in boiling acetone (4 c.c.) and picric acid (12 mg.) in acetone (1 c.c.), crystallised on cooling in bright yellow prisms, which blackened and decomposed at 230—240°. Analysis showed that the substance, although apparently homogeneous, contained picric acid in rather less than the 1 : 1 ratio (Found : C, 65·1, 65·2; H, 5·4, 5·4; N, 8·8%. Cf. analysis of the picrate in the previous section).

When cevanthridine (20 mg.) and methyl iodide (1 c.c.) were warmed together, the base dissolved at once, the solution rapidly became yellow, and the *methiodide* soon separated in rosettes of microscopic yellow plates. After refluxing for 1½ hours, the mixture was cooled, and the product collected and washed with ether (Found : C, 62·8; H, 6·1; I, 27·8. $C_{24}H_{28}NI$ requires C, 63·0; H, 6·2; I, 27·8%). The substance melts at 254—256° (decomp.), sintering and darkening a few degrees lower, and is very sparingly soluble in most solvents. When its suspension in hot alcohol is treated with a drop of aqueous potash, an intense green colour is produced. This rapidly fades, leaving a pale purple-red solution in which black particles are suspended.

The Crystalline Hydrocarbon.—The ethereal solution (marked * above) on evaporation gave a resinous residue, which in some cases deposited traces of crystalline material. If the dehydrogenation is carried out at a higher temperature (360° for 20 hours), the yield of crude cevanthridine picrate is diminished (0·08 g.) and the amount of non-basic crystalline material increases. The non-basic fraction from such a dehydrogenation was treated in ethereal solution with charcoal, the filtrate evaporated, and the residue crystallised from methyl alcohol (2 c.c.). The crude crystallisate was dried and sublimed in a high vacuum. At 0·001 mm. sublimation was rapid at 130°. The sublimate was again crystallised from methyl alcohol (0·7 c.c.), giving rosettes of very thin, colourless needles, m. p. 139—143° with previous sintering. Though the substance was obviously still impure, the yield (2·5 mg.) did not allow of further purification (Found : C, 90·3; H, 8·0%). The *hydrocarbon* dissolves in concentrated sulphuric acid to an orange solution having a yellowish-green fluorescence. This solution slowly becomes green and then blue. The picrate forms long red needles, readily soluble in most solvents.

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