Veratramine, a New Alkaloid of White Hellebore (*Veratrum grandiflorum* Loes. fil.)*.

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In a previous communication[1] a method of isolating alkaloids from the so-called resinous matters was described. As the chief constituent jervine was obtained with a yield of 37%. Extraction of the resinous matters with ether gave a phenolic substance, melting at 262°. On treatment with dilute alkali the residue was decomposed into bases and acidic substances with angelic acid and an acid melting at 102°. The so-called resinous matters were consequently considered as a mixture of salt-like substances, consisting of alkaloids, acids, and free phenolic substances. A second alkaloid has now been isolated: some experiments on its constitution are hereunder described.

Attempts to isolate a crystalline substance from the material by formation of salts were unsuccessful because the bases are soluble in dilute acids. On the other hand the acidic substances combined with the bases are quite unstable against alkali. Fortunately it has been found that calcium acetate safely decomposes into bases and acids the salt-like compounds dissolved in alcohol, producing soluble acetates and insoluble calcium salts. From the latter substances chelidonic acid was obtained, as was proved by forming oxalic acid by the addition of an alkali. It has now been proved that an acid[1] together with phenolic substances, melting at 102° described before is oxalic acid.

The basic substances thus isolated, however, could not be obtained in crystalline state as they were chemically as well as physically quite similar, forming a solid solution. These were finally separated through sulphates, being soluble with difficulty in water. The salts consisted chiefly of jervine and a new alkaloid for which the name veratramine is proposed. Conversion of the sulphates into hydrochlorides separated jervine, because jervine hydrochloride is less soluble in alcohol than those of the accompanying alkaloids. After being regenerated from the hydrochloride, freed from jervine, the base was again converted into sulphate. After repeated recrystallisation from dilute alcohol, the sulphate was finally converted into acetate, from which veratramine was obtained by dissolving the salt in alcohol, adding ammonia and crystallising the precipitate from alcohol.

Veratramine crystallises from alcohol with one mol. of water in needles, melting at 209.5–210.5°, and having $[\alpha]_D^{19°} = -70°$, anhydrous base in methyl alcohol. Analyses of the free base, hydrated as well as anhydrous, and its derivatives, show that it has the formula $C_{26}H_{35}O_2N$.

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* On the Alkaloids of White Hellebore IV.

(1) K. Saito and H. Suginome, this Bulletin, **11** (1936), 168.

In dilute acids, such as hydrochloric, sulphuric, nitric, acetic, oxalic, etc. the base is difficultly soluble.

On treatment with hydrogen in the presence of platinum-black an acetic acid solution of veratramine absorbs the equivalent of two atoms of hydrogen, indicating the presence of one double bond in the molecule. This is consistent with the result of determination of double bond according to Wijs.

Veratramine contains no methylimido-group, methoxyl or dioxymethylene group and behaves as a secondary amine. When veratramine is treated with methyl iodide and sodium carbonate it yields, however, a quarternary ammonium compound, m. p. 268°.

Acetylation of veratramine with acetic anhydride yields a neutral acetate, m. p. 205.5°–206°. Analyses as well as acetyl determinations show that this substance is the diacetyl derivative, being acetylated at oxygen and nitrogen atom. On heating with alcoholic potassium hydroxide, the acetyl derivative undergoes a remarkable hydrolysis, producing a new compound, m. p. 179–180° and having $[\alpha]_D^{19°} = +7°$. This can be, however, converted into the original diacetylveratramine by acetic anhydride. The acetyl compound may be again hydrolysed by the same reagent to furnish a lowmelting veratramine, m. p. 179–180° and having $[\alpha]_D^{19°} = +7°$. Veratramine treated with alcoholic potassium hydroxide, however, melts at 209.5–210.5° and has $[\alpha]_D^{19°} = -70°$ in methyl alcohol, showing that the base itself undergoes no change by alcoholic potassium hydroxide. As veratramine is not only insoluble in aqueous ammonia, carbonates, and caustic alkali but also is not coloured by ferric chloride, it appears to contain neither phenolic hydroxyl nor carbonyl group. Further evidence of this is afforded by the fact that veratramine does not react with diazomethane. Veratramine is unsaponifiable by alcoholic potassium hydroxide indicating the absence of lactone or ester group. Veratramine is indifferent to carboxyl reagents.

From the above observation one of two oxygen atoms must occur as a member of an alcohol group and the other appears to be indifferent bridged oxygen.

Hence veratramine may be represented by the extended formula:

$$\left.\begin{matrix} HO \\ O \\ \lceil_1 \end{matrix}\right\} C_{26}H_{33}NH.$$

Experimental.

Decomposition of the so-called resinous matters. The material (120 g.), prepared as before,[2] was dissolved in alcohol (500 c.c.) and filtered. To the filtrate 2 N-calcium acetate (200 c.c.) was added; after a while calcium chelidonate separated in crystalline state. After being left at room temperature for two days, the chelidonate was collected, washed, and dried. Yield 19.2 g. The latter was dissolved in 2N-hydrochloric acid (400 c.c.), with boiling, to a yellow solution and was then

(2) This Bulletin, **11** (1936), 168.

treated with charcoal. On being allowed to stand overnight, chelidonic acid separated in needles, yielding 15 g. The acid, after recrystallisation from water, melted either alone or with an authentic specimen at 262° with decomposition (Found: C, 45.55; H, 2.27. Calculated for $C_7H_4O_6$: C, 45.64; H, 2.19 %). The acid was further identified by derivation of the ethyl ester by refluxing a solution of the acid (2.0 g.) thus obtained in absolute alcohol (20 c.c.) in a current of hydrochloric acid, for one hour. Ethyl chelidonate was obtained in prismatic crystals, m. p. 65.5–66.5° (Found: C, 54.73; H, 4.88. Calculated for $C_{11}H_{12}O_6$: C, 54.98; H, 5.02 %). The ester was identified by the mixed melting point method.

The mother-liquor of calcium chelidonate was acidified with acetic acid and treated with a larger amount of water, whereupon some calcium salts and acetates separated. After filtering off these, ammonium hydroxide was added, a mixture of free bases was separated. This was collected, dried, and worked up applying the following method, yielding pure jervine hydrochloride (8.8 g.), pure veratramine sulphate (4.2 g), and other free alkaloids (9.0 g.).

Isolation and purification of veratramine. The crude alkaloids (103 g.), isolated from the resinous matters by treating first with dilute acetic acid and subsequently with ether, were dissolved in 0.5 N-acetic acid (800 c.c.). To the filtrate from this was added 2 N-sodium sulphate (300 c.c.), separating sulphates of bases in gelatinous form. After being left overnight these were decanted, treated with a solution of sodium sulphate for its coagulation and was then collected. Yield 71 g. A mixture of the sulphate (71 g.), sodium carbonate (20 g.) and alcohol (700 c.c.) was refluxed. After filtering off the inorganic salts, the filtrate was treated with hydrogen chloride in alcohol, when jervine hydrochloride separated crystalline. After being allowed to stand for two days the hydrochloride was collected, obtaining 36.6 g.

The free base was recovered from the above mother-liquor and was dissolved in 0.5 N-acetic acid. On careful addition of 2 N-sodium sulphate, the sulphate of the base separated gradually as a fine powder, being left overnight. This was collected, washed first with water and next with 50% alcohol. Yield 19.4 g. The sulphate thus obtained was converted into free base and was neutralised by dilute sulphuric acid, yielding 13.8 g. of veratramine sulphate in crystalline state. A mixture of the sulphate (13.5 g.), sodium carbonate (5 g.), and alcohol (100 c.c.) was refluxed and then diluted with water. On cooling, crude veratramine crystallised in slightly brown-coloured needles. Yield 10.3 g. This was dissolved, with rapid heating, in 2 N-acetic acid (50 c.c.), and hot filtered. On being left in the ice-chest overnight veratramine acetate crystallised in prisms whilst the other alkaloids remained in the solution. This was collected, obtaining 7.7 g. From the mother-liquor some more veratramine may be obtained. It was treated with aqueous ammonia, separating free base. On treating with dilute acetic acid the acetate separated crystalline which was collected, to the amount of 1.5 g. Total yield of the acetate is 9.2 g. or 0.1% calculated on the dried roots. The acetate was purified by recrystallisation from dilute alcohol forming prisms, m. p. 201–202°.

Veratramine. The pure base can be obtained from the acetate in alcohol by basifying with aqueous ammonia and crystallising from alcohol. Veratramine forms colourless needles from alcohol and melted at 209.5–210.5° (Found: C, 76.05, 76.06; H, 9.26; N, 3.47; H_2O, 4.04, 4.05. Calculated for $C_{26}H_{35}O_2N \cdot H_2O$: C, 75.86; H, 9.07; N, 3.41; H_2O, 4.38%. Found: C, 79.25, 79.19; H, 9.14, 9.31; N, 3.65, 3.63. Calculated for $C_{26}H_{35}O_2N$: C, 79.33; H, 8.97; N, 3.56%).

Vertramine is soluble in methyl and ethyl alcohols, acetic ester, acetone, and toluene but insoluble in light petroleum, water and alkali. The base forms salts with inorganic as well as organic acid and the salts dissolve with difficulty in water. Veratramine reduces neither ammoniacal silver nitrate nor Fehling's solution and Gaebel's test for methylenedioxy-groups was negative. It gave no colour reaction with ferric chloride.

$$[\alpha]_D^{19^\circ} = \frac{-1.50^\circ \times 100}{2 \times 1.065} = -70^\circ \text{ in methyl alcohol.}$$

Hydrochloride. It crystallised from alcohol in colourless plates, m. p. 310° (Found: C, 72.73; H, 8.96; N, 3.37. Calculated for $C_{26}H_{35}O_2N \cdot HCl$: C, 72.60; H, 8.44; N, 3.26%).

Picrate. Crystallised from dilute alcohol in yellow plates, m. p. 217.5–218° (Found: N, 8.85, 8.90. Calculated for $C_{26}H_{35}O_2N \cdot C_6H_3O_7N_3$: N, 9.00%).

Dihydroveratramine. Veratramine (0.82 g.) was dissolved in glacial acetic acid (5. c.c.) and hydrogenated in the presence of Adam's platinum catalyst (0.1 g.); after one hour 45.5 c.c. or 1.02 mol. of hydrogen was taken up. The catalyst was filtered off, the acetic acid removed under reduced pressure, water added to the residue, and the solution was basified with aqueous ammonia. After collecting, the free base was washed and dried. This was crystallised from benzene and then from dilute alcohol, giving plates, m. p. 197–198° (Found: C, 78.75; H, 9.57. Calculated for $C_{26}H_{37}O_2N$: C, 78.94; H, 9.43%).

Determinatin of double bond. The double bond in the molecule was determined by the method of Wijs.

0.1081 g. Subst. absorbed 69.78 mg. iodine.

Calculated for $C_{26}H_{37}I_2O_2N$ 79.11 mg. iodine.

The base (0.5 g.) in methyl alcohol (10 c.c.) was refluxed with methyl iodide (1.5 g.) and sodium carbonate (0.6 g.) for 3 hours. After filtering off the inorganic salts, the solvent and the excess of methyl iodide were removed, when the methiodide crystallised in colourless prisms. These were collected, washed, and dried, yielding 0.65 g. Crystallisation from methyl alcohol formed a colourless mass of needles decomp. at 268° (Found: C, 61.47; H, 7.68; CH_2, 5.39. Calculated for $C_{26}H_{34}O_2N \cdot CH_3 \cdot CH_3I$: C, 61.17; H, 7.34; CH_3, 5.47%).

Methylveratramine methochloride. The above methiodide was dissolved in methyl alcohol and then treated with freshly prepared silver

chloride. On filtering off the silver halides, the solvent was removed. The methochloride crystallised from dilute methyl alcohol in colourless needles, m. p. 277° (Found: C, 73.18; H, 8.65. Calculated for $C_{26}H_{34}O_2N \cdot CH_3CH_3Cl$: C, 73.38; H, 8.80%).

Diacetylveratramine. A mixture of the base (0.5 g.) and acetic anhydride (5 g.) was refluxed for 2 hours and then cooled. After removal of most of the acetic anhydride under reduced pressure, the acetate was precipitated by water and was then treated with a solution of sodium carbonate. This was collected, washed, and dried. Yield 0.63 gr. It crystalised from dilute alcohol in colourless needles, m. p. 205–206.5°, containing 1 mol of water and 0.5 mol of alcohol (Found: $H_2O + \frac{1}{2}C_2H_6O$, 7.96, C_2H_5OH, 4.56. Calculated for $C_{26}H_{33}NO_2(C_2H_3O)_2 \cdot H_2O \cdot \frac{1}{2}C_2H_6O$: $H_2O + \frac{1}{2}C_2H_6O$, 7.92; $\frac{1}{2}C_2H_6O$, 4.44%. Found: C, 74.37, 74.32; H, 8.33, 8.06; N, 3.00, 2.97; CH_3-CO, 17.97. Calculated for $C_{26}H_{33}O_2N(CH_3CO)_2$: C, 75,42; H, 8.23; N, 2.94; CH_3CO, 18.03%).

$$[\alpha]_D^{18°} = \frac{+0.72° \times 100}{2 \times 0.9172} = +39° \text{ in methyl alcohol.}$$

Alkaline hydrolysis of diacetylveratramine. After treatment of the acetate with 2 N-ethyl-alcoholic potassium hydroxide (25 c.c.) for 4 hours on the boiling water-bath, the solvent was distilled off. The hydrolysed base was obtained as a crystalline mass, recrystallised from 70% alcohol in plates, m. p. 179–180°.

Treatment of veratramine with ethyl-alcoholic potassium hydroxide. After being refluxed for 3 hours with N-ethyl-alcohol potassium hydroxide (10 c.c.), the base (0.5 g) was recovered as a crystalline mass, on distilling off the solvent and treating with water. This was proved to be veratramine, m.p. 209.5°–210.5°, after crystallisation from alcohol.

$$[\alpha]_D^{19°} = \frac{-1.40° \times 100}{2 \times 0.9792} = -70° \text{ in methyl alcohol.}$$

The action of diazomethane on veratramine. A solution of the base (0.5 g.) in methyl alcohol (10 c.c.) was treated with diazomethane in ether, prepared from nitroso-N-methylurethane (2 c.c.) and was left overnight; two drops of dilute acetic acid were added. On removing the solvent, unchanged veratramine was recovered as needles, m.p. 209.5–210.5°.

Treatment of Veratramine with Hydroxylamime. (1) *In neutral medium.* A solution of the base (0.25 g.), hydroxylamine hydrochloride (0.5 g.), and sodium acetate (0.75 g.) in 70% ethyl alcohol was refluxed for 3 hours, and then kept for 10 days at room temperature. This was basified by sodium carbonate and diluted with water, when a solid mass was separated. After crystallisation from alcohol it was shown to be veratramine, m. p. 209.5–210.5°, by the mixed melting point method.

(2) *In alkaline medium.* A solution of the base (0.25 g.), hydroxylamine hydrochloride (0.5 g.) and potassium hydroxide (0.5 g.) in 70% alcohol was allowed to stand at room temperature for several days. This

was diluted with water and worked up as above, recovering unchanged veratramine, m. p. 209.5–210.5°.

Treatment of veratramine with semicarbazide. The base was treated under the same conditions as above and also unchanged veratramine, m. p. 200–201.5°, was recovered.

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