

ON THE ALKALOIDS OF WHITE HELLEBORE. III. EXPERIMENTS ON THE CONSTITUTION OF JERVINE.

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In Parts I⁽¹⁾ and II⁽²⁾ it has been shown that the constituent alkaloids of *Veratrum grandiflorum* Loes. fil. can be extracted in a yield of 2.6% referring to the roots and from these alkaloids jervine hydrochloride may be isolated in a pure state in a yield of 23%, or 0.6% of the material. In the present communication some experimental results concerned with the constitution of jervine are given.

Jervine reacts as a secondary base giving a *N*-methyl derivative on methylation with diazomethane or better with methyl iodide and potassium hydroxide. Treatment of the latter with an excess of methyl iodide in a sealed tube gives a crystalline methiodide, while the same derivative can be obtained directly from jervine by boiling with methyl iodide and anhydrous potassium carbonate. Further evidence of this is afforded by the formation of a nitroso-compound on treatment of the alkaloid with sodium nitrite and acetic acid.

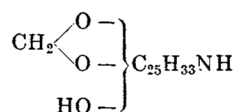
Jervine contains neither methoxyl nor carbonyl group and does not form an oxime or semicarbazone. Two oxygen atoms of the base appear to be present in the form of dioxymethylene, while the last one is in the form of an alcoholic hydroxyl group. The alkaloid dissolves in strong sulphuric acid, forming a yellow solution which becomes green on standing. It gives, however, reddish brown colouration with strong sulphuric acid together with phloroglucinol. On boiling with acetic anhydride the alkaloid yields a diacetyl derivative, melting at 176–177°, while it gives a monoacetyl compound, melting at 161–162°, with the same reagent but at room temperature. The former has been proved to be *O*, *N*-diacetyljervine and the latter to be *N*-acetyljervine. The *N*-methyl compound gives a monoacetyl derivative which melts at 186–187° at the boiling point of the reagent. On the other hand it furnishes no acetyl derivative at room temperature. At room temperature, therefore, the acetylation of jervine occurs at nitrogen but at the boiling point of acetic anhydride at both nitrogen and oxygen. The

(1) This Bulletin, **9** (1934), 15.

(2) *Ibid.*, **11** (1936), 163.

diacetyljervine is hydrolysed in steps as in the case of diacetyl-iso-yohimbine⁽³⁾. On hydrolysis with dilute and concentrated alcoholic caustic soda the acetyl compound furnishes the *N*-acetyl derivative and jervine respectively. Jervine has also been treated with acetic anhydride and anhydrous sodium acetate but the results are just the same as in the case of acetic anhydride only.

The functions of oxygen and nitrogen atoms of jervine have now been revealed as having two active hydrogen atoms, one in the hydroxyl and the other in the imino group. These were supported further by the results of determination of active hydrogen atoms after Zerewitinoff. Jervine may, therefore, be represented by the extended formula shown above.



Experiments concerned with the degradation of jervine are in progress.

Experimental.

Purification and properties of jervine. The alkaloid was stated by the earlier investigators to melt at various temperatures⁽⁴⁾ and to give different colouration, showing that the purity of the base was doubtful. Jervine is present in nature with many other alkaloids which are hardly crystallisable. Consequently the specimen purified by the usual method may accompany more or less another veratrum alkaloid. In view of the minor alkaloids mixed with jervine the purification of the base was fundamentally tried. Taking advantage of the easiness with which the minor alkaloids could be decomposed, it was warmed with alcoholic potash when the impurities passed into solution in brown colour. The solution was concentrated and water was added: the base separated was collected, washed, and dried. This was crystallised from alcohol, forming colourless needles, melting at 243.5–244.5°⁽⁵⁾. The base in this purity may also be obtained through repeated recrystallisation from alcohol or acetic ester. Jervine thus purified showed $[\alpha]_D^{21} = -150^\circ$ in absolute alcohol (see Part I).

Pure jervine gives no colouration with concentrated hydrochloric acid but a specimen melting at 240–241° furnishes a yellow colour reaction. The colour reaction of jervine of inferior quality with strong sulphuric acid was described by Wright and Luff⁽⁶⁾. Pure jervine, melting at 243.5–244.5°, dissolves in cold strong sulphuric acid to a yellow fluid which in a very short time successively becomes orange, green, and then decolourises after several hours, whilst the impure specimen leaves a red solution instead of decolourisation. On dilution of the coloured solution it becomes colourless but may be reversed by adding strong concentrated sulphuric acid. When jervine was kept in the air it

(3) G. Hahn and W. Schuch, *Ber.*, **62B** (1929), 2953.

(4) Will: 200°, *Ann.*, **35** (1840), 117. Pehkschen, *J. Chem. Soc.*, **90** (1891), 88; *J. Pharm.*, (5), **22**, 265; *Pharm. Zeit. Russ.*, **29**, 339. Wright and Luff: 237–239°, *J. Chem. Soc.*, **35** (1879), 411. Salzberger: 238–242°, *Arch. Pharm.*, **228** (1890), 462. Bredemann: 241°, *Chem. Zentr.*, **1906**, I, 607; *Apoth. Ztg.*, **21**, 41.

(5) On melting it decomposes slightly and the m.p. depends more or less upon the rate of heating. It was determined by the bath preheated to 180°.

(6) Wright and Luff, *J. Chem. Soc.*, **35** (1879), 410.

became impure, colouring pale yellow with a depression of melting point. For instance, it melted unsharply at 239–240° after 7 days and at 220–229°, sintering at 160°, after 7 months. The specimen, however, in a closed vessel could be kept stable, and was found quite pure after 2 years.

Methylation of jervine with diazomethane. To a solution of jervine (0.5 g.) in methanol (50 c.c.) was added an ethereal solution of diazomethane prepared from nitrosomethylurethane (2 c.c.). On allowing to stand overnight, the solvents were removed, leaving a crystalline mass. This was treated with ether to remove the unchanged substance. On distilling off the solvent, *N*-methyljervine was left in colourless crystals (0.3 g.); it crystallised from dilute alcohol, m.p. 201–202°. It was shown to have 1 mol of water of crystallisation. (Found for air dry crystals on dehydration at 120° and 20 mm.: H₂O, 4.22, 4.02. Calc. for C₂₆H₃₆O₃N-CH₃·H₂O: H₂O, 4.07%. Found for dehydrated substance: C, 76.56; H, 9.17; -CH₃, 3.79. Calc. for C₂₆H₃₆O₃N-CH₃: C, 76.18; H, 9.24; -CH₃, 3.53%.)

The behaviours of methyljervine toward organic solvents are similar to those of jervine but the former is more soluble than the latter.

Methylation of jervine with methyl iodide and potassium hydroxide. Jervine (0.5 g.) in alcohol (12 c.c.) was heated with methyl iodide (1.4 g.) and potassium hydroxide (0.7 g.) for two hours on the water bath. After cooling, potassium iodide separated, which was filtered off, and the solvent was then removed. The residue was collected by means of water and dried. The yield was 0.5 g. This was crystallised from dilute alcohol in colourless crystals, m.p. 201–202°. There was no depression of melting point on admixture with *N*-methyljervine prepared by methylation with diazomethane. (Found: -CH₃, 3.87. Calc. for C₂₆H₃₆O₃N-CH₃: -CH₃, 3.53%.)

***N*-Methyljervine methiodide and methochloride.** *N*-Methyljervine (0.5 g.) was heated in a sealed tube with methyl iodide (1 c.c.) at 100° for 6 hours. After cooling the excess of methyl iodide was distilled off when *N*-methyljervine methiodide separated in rosettes, melting at ca. 247°. It was dissolved in dilute alcohol and treated with moistened silver chloride. The silver iodide produced was filtered off and the filtrate evaporated, leaving a crystalline mass melting at 245° with decomposition. This is freely soluble in methanol and dilute alcohol, and sparingly soluble in ether and light petroleum. It recrystallised from absolute alcohol in needles melting at 252° with decomposition. The dried substance was analysed. (Found: Cl, 7.13. Calc. for C₂₆H₃₆O₃N-CH₃·CH₃Cl: Cl, 7.45%.)

The methiodide and methochloride are freely soluble in most organic solvents, especially in dilute alcohol, but they are insoluble in ether and light petroleum.

Treatment of jervine with methyl iodide and anhydrous potassium carbonate. A solution of jervine (0.5 g.) in methanol (10 c.c.) was heated with methyl iodide (1.4 g.) and anhydrous potassium carbonate (0.6 g.) on the water bath for 3 hours. It was cooled and the inorganic salt was filtered off. On removing the solvent a crystalline mass was separated; it was collected, washed, and dried. The yield was 0.6 g., m.p. 247° with decomposition. This was converted into the methochloride by treating with silver chloride as in the other case. The methochloride thus obtained, melting at 252° with decomposition, was proved to be identical with the chloride described above.

Nitrosojervine. Jervine (0.5 g.) in 2*N* acetic acid (5 c.c.) was treated with sodium nitrite (0.1 g.) in water (1 c.c.) when crystalline powders separated. These were collected,

washed, and dried. The yield was 0.5 g. After repeated crystallisation from alcohol it melted at 251-252° with decomposition. (Found: N, 6.44. Calc. for $C_{26}H_{36}O_3N-NO$: N, 6.36%.)

Tetrahydrojervine. A solution of jervine (2 g) in pure glacial acetic acid (10 c.c.) was shaken in hydrogen with platinum oxide (0.42 g.). Absorption of hydrogen occurred at room temperature but it was rather slow; 198 c.c. or 1.98 mols were taken up in 24 hours. For the first one mol it took ca. 80 minutes but for the second ca. 22 hours. The solution was diluted with water, and the catalyst was removed. Tetrahydrojervine was separated by making the filtrate alkaline, collected, and washed. The yield was 2.1 g. Tetrahydrojervine was freely soluble in most organic solvents with the exception of light petroleum. It was hardly crystallisable from usual organic solvents. A solution of tetrahydrojervine in benzene was treated with light petroleum until the solution was set in turbidity. On allowing the solution to stand tetrahydrojervine crystallised out in colourless needles which, after drying, melted at 208-210°. The hydrochloride in needle crystals was made by treating an alcoholic solution with hydrochloric acid in the same solvent. It did not melt at 360°. (Found: C, 69.10; H, 9.34. Calc. for $C_{26}H_{41}O_3N \cdot HCl$: C, 69.57; H, 9.37%.)

N-Acetyljervine. Jervine (5 g.) was dissolved in acetic anhydride (50 c.c.), and was allowed to stand overnight. The reaction mixture was treated with water, and a crystalline mass separated. This was collected and dried. The yield was 5.3 g. It was crystallised from dilute alcohol in stout crystals, melted at 161-162° with immediate foaming. (Found: C, 70.88, 70.63; H, 9.01, 9.15. Calc. for $C_{28}H_{33}O_4N \cdot H_2O$: C, 71.29; H, 8.77%. The air-dried substance lost 4.02% at 115° and 16 mm. Calc. for $C_{28}H_{39}O_4N \cdot H_2O$: 3.82%. Found for anhydrous substance: C, 74.23; H, 8.68%. Calc. for $C_{28}H_{39}O_4N$: C, 74.11; H, 8.67%.)

It is soluble in methyl alcohol, ethyl alcohol, acetone, chloroform, acetic ester, and benzene, but sparingly soluble in ether and light petroleum.

Diacetyljervine. A solution of jervine (5 g.) in acetic anhydride (50 c.c.) was boiled on the wire gauze 1.5 hours. The excess of the acetic anhydride was distilled off under reduced pressure and the trace of the latter was removed by treating with methyl alcohol; a syrupy substance was obtained. This was then treated with water when the acetylated compound separated in crystals. It was collected, washed, and dried. The yield was 5.95 g. It was recrystallised from dilute alcohol, rosettes, m.p. 176-177°. (Found: C, 73.14, 73.17; H, 7.75, 8.23. Calc. for $C_{30}H_{41}O_5N$: C, 72.68; H, 8.34%.)

It is soluble in methyl alcohol, ethyl alcohol, acetone, acetic ester, chloroform, and benzene, but sparingly soluble in ether and light petroleum.

Hydrolysis of diacetyljervine. A solution of diacetyljervine (0.23 g.) in alcohol (14 c.c.) was treated with 0.1 N alcoholic caustic soda and was warmed for 4 hours on the water bath. On evaporation a crystalline mass (0.15 g.) was obtained; it was collected by means of water and dried. It was recrystallised from dilute alcohol, six-sided plates, m.p. 158-159° with decomposition. The hydrolysed substance was proved in every point to be N-acetyljervine described above. This was treated once more with the same but more concentrated reagent. The mixture was heated for 6 hours. On working up the reaction mixture jervine was obtained. Moreover diacetyljervine was also treated with concentrated alcoholic caustic alkali as above, jervine being obtained in one step.

Acetylation of *N*-methyljervine. *N*-Methyljervine prepared by the method described above was treated with acetic anhydride in the cold as in the case of jervine. On working up, the starting substance was recovered unchanged.

O-Acetyl-*N*-methyljervine. *N*-Methyljervine (0.3 g.) was dissolved in acetic anhydride (10 c.c.) and was kept boiling for an hour. The excess of acetic anhydride was removed under diminished pressure and the reaction product, on treating with water, was collected, washed, and dried. After crystallisation from dilute alcohol, needle crystals in rosettes melted at 186–187°. The yield was 0.07 g. (Found: C, 74.50; H, 8.96. Calc. for $C_{29}H_{41}O_4N$: C, 74.47; H, 8.84%.)

It is soluble in most organic solvents with the exception of light petroleum.

Determination of active hydrogen. Active hydrogen in jervine was determined by the method of Zerewitinoff using pyridine⁽⁷⁾ as the solvent (Found: active hydrogen, 0.54% or 2.17 atoms. Calc. for 2H in $C_{26}H_{37}O_3N$: 0.49%).

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(7) Th. Zerewitinoff, *Ber.*, **47** (1914), 2417.