98. *The Alkaloids of Ergot. Part III. Ergine, a New Base obtained by the Degradation of Ergotoxine and Ergotinine.*

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AT the present time, little is known of the constitution of ergotoxine and ergotinine; comparatively few degradation products have been obtained and these are of but simple structure. *iso*Butyrylformamide is obtained by the thermal decomposition of the alkaloids (Barger and Ewins, J., 1910, **97**, 290) and recently Dr. A. Soltys, working in Prof. Barger's laboratory, has obtained ammonia by the action of alcoholic sodium hydroxide, benzoic acid by oxidation with permanganate, and *p*-nitrobenzoic acid by treatment with nitric acid (Barger, " Ergot and Ergotism," 1931).

On treating the alkaloids with alcoholic potassium hydroxide we have ourselves observed the evolution of ammonia and in addition we have been able to isolate from the products of reaction a new base which we have named *ergine*. This base is crystalline and gives crystalline salts. The analytical data for the base and its salts indicate that ergine has the empirical formula $C_{17}H_{21}ON_3$, so that it constitutes roughly one half of the ergotoxine molecule. Ergine retains to a remarkable degree many of the properties of the parent alkaloids. Solutions of the base show a beautiful bluish-violet fluorescence, which is particularly marked when acetone is the solvent. The base has a high specific optical rotation and a dispersion coefficient similar to that of the alkaloids. The absorption spectrum is identical with that of the alkaloids between $\mu\mu$ 245 and $\mu\mu$ 345, showing a maximum at $\mu\mu$ 318 and a minimum at $\mu\mu$ 270. There is no indication of the inflexion at $\mu\mu$ 242 recently recorded for ergotinine (J., 1931, 1889). Ergine contains no methoxyl group, but one methylimino-group is present. It gives an alkaline reaction with moist litmus paper. The colour reactions are, in the main, those usually given by indole or its derivatives. In addition a reddish-amber colour is given by sodium diazobenzenesulphonate in alkaline solution (Pauly's glyoxaline reagent).

Dr. J. W. Trevan of the Wellcome Physiological Research Laboratories has kindly examined the pharmacological action of ergine with the following results: Tested for paralysis of the adrenaline effect on the uterus of the rabbit, it has a very slight action, but 4 mg. is weaker than 0·01 mg. of ergotoxine ethanesulphonate. It raises the blood pressure of the pithed cat slightly.

EXPERIMENTAL.

Ergotinine or ergotoxine (5 g.) was boiled under reflux for 1 hour with *N*-methyl-alcoholic potassium hydroxide (125 c.c.). A slow current of nitrogen was passed through the apparatus throughout the experiment and the issuing gases were washed with *N*-hydrochloric acid. The alcoholic solution after dilution with water was concentrated under reduced pressure and extracted thoroughly with ether. The ethereal extracts were united and washed first with 1% potassium hydroxide solution and then with water. After being dried with magnesium sulphate, the ether was removed by distillation. The residue was crystallised from methyl alcohol. Yield, 0·5 g. The hydrochloric acid in the gas absorption apparatus was evaporated and the residue dried in a vacuum at 100° (Found: Cl, 63·6. Calc. for NH_4Cl: Cl, 66·3%. Calc. for $CH_3{\cdot}NH_2,HCl$: Cl, 52·5%). A part of the residue was converted into the chloroplatinate [Found: Pt, 43·9. Calc. for $(NH_4)_2PtCl_6$: Pt, 43·9%].

Ergine is sparingly soluble in methyl alcohol and is conveniently separated from more soluble impurities by this solvent. It crystallises in colourless prisms which decompose with frothing at about 135°; blackening with evolution of gas occurs at about 230° The crystals contain one molecular proportion of methyl alcohol, which is retained with remarkable tenacity and is not completely removed by many hours' heating at 90° in a vacuum. Ergine is readily soluble in acetone, soluble in chloroform and ethyl acetate, sparingly soluble in methyl and ethyl alcohols, ether, benzene, and almost insoluble in light petroleum and water. It crystallises very readily from aqueous acetone in long colourless plates which decompose with frothing at 115° and on further heating blacken and undergo further decomposition at about 230°. This form is a dihydrate which is stable in air but completely loses its water when kept over sulphuric acid in a vacuum desiccator [Found (a) in material crystallised from methyl alcohol and air-dried: C, 68·4, 68·6; H, 7·8, 7·5; N, 13·5; OMe, 8·0; NMe, 9·3. $C_{17}H_{21}ON_3,MeOH$ requires C, 68·5; H, 8·0; N, 13·3; OMe, 9·8; NMe, 9·2%. (b) In material crystallised from aqueous acetone, (1) air-dried: C, 63·5; H, 7·4; loss on drying, 11·6. $C_{17}H_{21}ON_3,2H_2O$ requires C, 63·9; H, 7·9, H_2O, 11·3%; (2) dried over sulphuric acid in a vacuum: C, 72·1, 72·0; H, 7·3, 7·3; N, 14·9, 15·0; OMe, nil; NMe, 10·4; *M*, 315 (Menzies–Wright ebullioscopic method with acetone as solvent). $C_{17}H_{21}ON_3$ requires C, 72·0; H, 7·5; N, 14·8; NMe, 10·2%; *M*, 283. (c) In base precipitated from the hydrochloride (*vide infra*) and dried over sulphuric acid in a vacuum: C, 72·1; H, 7·3; N, 15·4%].

Ergine has a high specific optical rotation. In acetone solution $[\alpha]_{5461}^{20^\circ}$ + 514°; $[\alpha]_{\text{Hg yellow}}^{20^\circ}$ + 432° ($c = 1·0$). Dispersion coefficient 1·19. In chloroform solution $[\alpha]_{5461}^{20^\circ}$ + 598°; $[\alpha]_{\text{Hg yellow}}^{20^\circ}$ + 503° ($c = 1·5$). A solution in dilute hydrochloric acid gives precipitates with potassium mercuric iodide solution, potassium bismuth iodide solution, and picric acid solution. Ergine resembles the ergot alkaloids in giving a blue colour with *p*-dimethylaminobenzaldehyde under the conditions described by M. I. Smith (*U.S. Public Health Reports*, 1930, **45**, 1466). Colorimetric comparisons of solutions of ergine and ergotoxine by means of this test show that equimolecular solutions give colours of equal intensity. Ergine gives a number of colour reactions usually associated with indole or indole derivatives. A solution of the base (0·1%) in aqueous tartaric acid (1%) was used for the following tests. Benzaldehyde in sulphuric acid gives a deep blue colour. Formaldehyde and sulphuric acid give a blue ring. Glyoxylic acid and sulphuric acid give a deep blue colour. Dilute nitric acid and a trace of sodium nitrite give a yellow colour. Sodium nitroprusside and sodium hydroxide in aqueous solution give a yellow colour which becomes reddish-violet on addition of acetic acid and boiling. Alcoholic *p*-dimethylaminobenzaldehyde and hydrochloric acid give a violet-red colour on keeping. In addition ergine gives with sodium *p*-diazobenzenesulphonate in alkaline solution (Pauly's reagent) a reddish-amber colour, which is only slightly changed on addition of acids. When ergine is heated it decomposes with evolution of vapours which give a reddish-purple colour to pinewood moistened with hydrochloric acid.

Ergine hydrochloride was prepared by treating a solution of the base in alcohol with dilute hydrochloric acid and adding ether. The salt separated in colourless plates, which may be crystallised from methyl alcohol by addition of ether or from water. On heating, it gradually becomes grey at about 200° and decomposes with frothing and formation of a black tar at 255—260° (Found : C, 63·8; H, 6·7; N, 13·3; Cl, 11·0. $C_{17}H_{21}ON_3,HCl$ requires C, 63·8; H, 6·9; N, 13·1; Cl, 11·1%).

Ergine hydrobromide was prepared by treating a solution of the base in acetone with hydrobromic acid, and crystallised by the addition of ether. It crystallised in colourless prisms, which contract at about 200°, gradually darken and at 260° decompose with evolution of gas and formation of a black tar. It has $[\alpha]^{20^\circ}_{5461} + 349^\circ$, $[\alpha]^{20^\circ}_{\mathrm{Hg\ yellow}} + 291{\cdot}5^\circ$ (c in water, 0·66) (Found : C, 55·7; H, 6·0; N, 11·7; Br, 22·0; OMe, nil; NMe 8·8. $C_{17}H_{21}ON_3,HBr$ requires C, 56·0; H, 6·1; N, 11·5; Br, 22·0; NMe, 8·0%).

Ergine nitrate was prepared by treating a solution of the base in acetone and alcohol with dilute nitric acid and adding ether. It crystallised in long colourless plates, which become grey at about 200° and decompose with evolution of gas and blackening at 225—230° (Found : C, 59·1; H, 6·4; N, 16·3; OMe, nil; NMe, 8·6. $C_{17}H_{21}ON_3,HNO_3$ requires C, 58·9; H, 6·4; N, 16·2; NMe, 8·4%).

Ergine picrolonate was prepared in acetone solution, from which it separated in pale yellow plates, which darkened at 210° and decomposed at 215°, giving a black tar (Found : N, 17·5.

$$C_{17}H_{21}ON_3,C_{10}H_8O_5N_4$$

requires N, 17·9%).

Ergine perchlorate was prepared by adding a solution of sodium perchlorate in water to a solution of the base in water containing a little acetic acid. The precipitate was recrystallised from alcohol in which it was somewhat sparingly soluble. It formed fine needles, which gradually darkened at about 200° and decomposed at 225°, giving a black tar (Found : C, 53·1; H, 6·1; N, 11·1.

$$C_{17}H_{21}ON_3,HClO_4$$

requires C, 53·2; H, 5·8; N, 11·0%).

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