141. *The Alkaloids of Ergot. Part V. The Nature of Ergine.*

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IT has been shown (J., 1932, 763, 1543) that the ergot alkaloids when treated with alcoholic potassium hydroxide give rise to a crystalline base, ergine, which constitutes about one half of the parent molecule. In the course of an investigation of the conditions most favourable for the formation of ergine it was found that the base is itself decomposed by alkalis, though at a much slower rate than the alkaloids. One molecular proportion of ammonia is evolved in the course of the reaction and a crystalline substance having both basic and acidic properties can be obtained in good yield. This substance dissolves readily in solutions of the alkalis and alkaline earths and is precipitated by acids. The basic properties are indicated by the formation of a crystalline *sulphate*. When heated, the substance undergoes decomposition with evolution of carbon dioxide. It can also be methylated and the product no longer dissolves in dilute alkali, whilst the basic properties become more pronounced. Analyses of the acid, the sulphate, and the methyl ester indicate the formula $C_{16}H_{16}O_2N_2$, so, on the assumption that the substance is formed by the simple elimination of ammonia from an amide, the formula of ergine must be $C_{16}H_{17}ON_3$ instead of $C_{17}H_{21}ON_3$ as previously suggested. Further analyses of ergine and its salts, of which the hydrochloride seems to be the most suitable, are also in favour of the formula $C_{16}H_{17}ON_3$. After the completion of this work a paper by Jacobs and Craig (*J. Biol. Chem.*, 1934, **104**, 547) described the formation of an acid by the action of aqueous alkali upon the alkaloid ergotinine. This acid, which they named lysergic acid, has properties similar to those of the acid which we have prepared from ergine and there is no doubt that the two substances are identical and that ergine is the amide of lysergic acid. Robinson (*Ann. Rev. Biochem.*, 1933, II, 442) has suggested a structural formula for ergine composed of a methylindole linked through two methylene groups with a substituted glyoxaline ring, but since the present work shows that one of the nitrogen atoms is present in a carbamide group a formula of this type must now be regarded as untenable.

EXPERIMENTAL.

Ergine (1·22 g.) was boiled with *N*-methyl-alcoholic sodium hydroxide (36 c.c.) under reflux for 8 hours in a current of nitrogen and the issuing gas was washed with *N*-hydrochloric acid. The alcoholic solution was diluted with water and extracted with ether. The ethereal extract was washed with sodium hydroxide solution and dried over potassium carbonate, and the ether removed by distillation. The slight residue was crystallised from methyl alcohol, a little ergine (0·06 g.) being recovered. After extraction with ether the alkaline solution was concentrated under reduced pressure to remove alcohol and ether and then, whilst still hot, rendered just acid to litmus by the addition of acetic acid. Clusters of plates soon separated (0·75 g.) and were purified by solution in warm dilute aqueous ammonia and precipitation with acetic acid. Yield, 0·67 g.

The acid solution in the gas absorption apparatus was evaporated to dryness, and the residue converted into the chloroplatinate [Found : Pt, 43·7. Calc. for $(NH_4)_2PtCl_6$: Pt, 43·9%].

Estimation of ammonia. Ergine (7·9 mg.) was washed into a micro-Kjeldahl apparatus with 2 c.c. of acetone and distilled for 10 minutes with 15 c.c. of 30% sodium hydroxide solution. The ammonia was collected in *N*/100-hydrochloric acid, and the excess of acid titrated as usual. Found : N, 5·1, 5·1. Calc. for one molecule of ammonia : N, 5·2%.

Lysergic acid is sparingly soluble in water, alcohol, acetone, ethyl acetate, chloroform, light petroleum, and benzene. A hot aqueous solution is slightly acid to litmus. It dissolves readily in solutions of sodium hydroxide and sodium carbonate and is precipitated by the addition of acetic acid. It is soluble in warm dilute acetic acid and, on cooling, the acid separates in hexagonal plates. It is crystallised by dissolving it in warm dilute aqueous ammonia and acidifying the solution with acetic acid. It can also be purified by the evaporation of a solution in aqueous ammonia. Lysergic acid decomposes with frothing and blackening at about 240°. The colour reactions are similar to those obtained with ergine (Found for material dried at 100° : C, 71·8, 71·7, 71·7; H, 6·3, 6·2, 6·2; N, 10·2, 10·4; NMe, 10·4, 10·5. Calc. for $C_{16}H_{16}O_2N_2$: C, 71·6; H, 6·0; N, 10·5; NMe, 10·3%).

Action of heat on lysergic acid. The acid (0·5 g.) was heated in a stream of pure nitrogen, which was passed into lime water. Carbon dioxide began to come off freely at 200° and heating was continued to 280°. The residue was black and charred, but contained traces of a basic substance.

Lysergic acid sulphate was prepared by dissolving the acid in 0·2*N*-sulphuric acid by heating on a water-bath; on cooling, the sulphate separated in clusters of thin plates, which blackened and frothed at 245° (Found : C, 60·6, 60·4; H, 5·4, 5·3; N, 8·8, 8·8; S, 5·2. $C_{16}H_{16}O_2N_2,\frac{1}{2}H_2SO_4$ requires C, 60·5; H, 5·4; N, 8·8; S, 5·1%).

Methyl lysergate. The acid was triturated with a little methyl alcohol, suspended in ether, and shaken with an excess of an ethereal solution of diazomethane until it had nearly all dissolved. After several hours the ethereal solution was washed with dilute sodium hydroxide solution and dried over potassium carbonate, and the ether removed by distillation. The residue soon crystallised and was rapidly recrystallised from a little methyl alcohol, the methyl ester forming thin needles which blackened and frothed at 170° with previous softening (Found : C, 72·6; H, 6·4; N, 9·6; OMe, 11·3; NMe, 8·5. Calc. for $C_{17}H_{18}O_2N_2$: C, 72·3; H, 6·4; N, 9·9; OMe, 11·0; NMe, 10·3%).

Analyses of ergine. (a) The base was crystallised from dilute acetone and dried at 90° in a vacuum. Found : C, 71·9, 71·9, 71·5, 71·8, 71·7; H, 6·5, 5·6, 6·4, 6·4, 6·5; N, 15·5, 15·7, 15·7. Calc. for $C_{16}H_{17}ON_3$: C, 71·9; H, 6·4; N, 15·7%. (b) The base was crystallised from methyl alcohol and air-dried. Found : C, 68·5, 68·3, 68·2; H, 7·1, 7·1, 7·0; N, 13·7, 14·0; OMe, 10·3; NMe, 8·9. Calc. for $C_{16}H_{17}ON_3,MeOH$: C, 68·2; H, 7·1; N, 14·0; OMe, 10·4; NMe, 9·7%.

Analyses of ergine hydrochloride (crystallised from aqueous alcohol by the addition of ether, and dried at 100°). Found : C, 63·4, 63·3; H, 6·1, 6·1; N, 13·7; NMe, 9·6; Cl, 11·7, 11·9. Calc. for $C_{16}H_{17}ON_3,HCl$: C, 63·3; H, 6·0; N, 13·8; NMe, 9·6; Cl, 11·7%.

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