83. *The Alkaloids of Ergot. Part VIII. New Alkaloids of Ergot: Ergosine and Ergosinine.*

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To the list of those alkaloids of ergot regarded as definite and well-characterised substances which was given in Part VII (J., 1936, 1440) must now be added two new alkaloids, *ergosine* and *ergosinine*, the isolation of which we have briefly reported elsewhere (*Nature*, 1936, **137**, 111, 1075).

Ergosinine probably owes its escape from earlier recognition to the resemblance which it bears to ergotinine and ψ-ergotinine. Like these alkaloids, it is sparingly soluble in methyl alcohol and the specific rotations of ergotinine and ergosinine are almost identical in acetone solution, though they differ in chloroform solution. In the case of ergosinine and ψ-ergotinine the specific rotations are similar in chloroform solution, but differ in acetone solution:

$[\alpha]_{5461}^{20°}$.	Ergotinine.	Ergosinine.	ψ-Ergotinine.
In acetone	+ 478°	+ 475°	+ 509°
In chloroform	+ 464°	+ 522°	+ 512°

Ergosinine is readily isolated by boiling the total water-insoluble alkaloids of ergot with benzene and extracting the benzene-soluble portion with dilute sodium hydroxide

solution. The alkaline extract contains the alkaloids ergotoxine and ergosine and on acidification with sulphuric acid gives a precipitate of ergotoxine sulphate, ergosinine sulphate remaining mainly in solution, a separation which, though not sharp, is adequate for preparative purposes. The solution of the water-soluble sulphates on basification gives a precipitate, from which ergosinine is readily separated by treatment with methyl alcohol. The nearly pure ergosinine so obtained is easily purified by recrystallisation.

Like the other ergot alkaloids of high dextrorotation, ergosinine is partly and easily transformed into a corresponding lævorotatory alkaloid by treatment with acid or alkali. The new alkaloid, ergosine, obtained in this way has $[\alpha]_{5461}^{20°}$ — 193° in chloroform solution and crystallises readily. It is easily reconverted by similar means into ergosinine and the two alkaloids thus constitute a pair with a relationship to each other similar to that existing between the earlier known pairs of ergot alkaloids. The close similarity, in this respect, to the amides and substituted amides of the isomeric lysergic acids (see Parts VI and VII) makes it highly probable that ergosine differs from ergosinine only in the configuration of the lysergic acid portion of the molecule. Ergosinine and ergosine give the colour reactions typical of the ergot alkaloids. With dimethylaminobenzaldehyde the blue colour given by both alkaloids is approximately equal in intensity and slightly greater than that given by ergotinine. This suggests that the two alkaloids are isomeric and that the molecular weight is slightly less than that of ergotinine. Like the other ergot alkaloids, solutions of ergosine and ergosinine fluoresce strongly in daylight and on exposure to ultra-violet light the fluorescence is intense. The absorption spectra of the two alkaloids are similar to those of the other ergot alkaloids. In addition to the characteristic peak at A. 3180 they show the inflexion at A. 2420 which we previously observed in the case of ergotinine (J., 1931, 1889). Ergosinine gives a stronger inflexion than ergosine and in this resembles ergotinine rather than ergotoxine.

In a preliminary announcement (*Nature, loc. cit.*) the formula $C_{30}H_{35}O_5N_5$ was tentatively suggested as the result of analyses of the crystalline bases, but the results of degradative experiments (*vide infra*) indicate clearly that the formula $C_{30}H_{37}O_5N_5$ containing two more atoms of hydrogen is correct. Ergosinine has given no crystalline salts, but an amorphous hydrochloride has been obtained. Ergosine forms salts which crystallise with one molecular proportion of acetone. Ergosinine contains no methoxyl group, but one methylimino-group is present, which must be derived from the ergine nucleus (*vide infra*), which is known to contain this group. The ergine group is also probably responsible for the evolution of ammonia which occurs on alkaline hydrolysis, a process which converts ergine into lysergic acid and ammonia. Ergine, $C_{16}H_{17}ON_3$, which has previously been shown to be a nucleus common to the ergot alkaloids (J., 1932, 763, 1543), has also been obtained from ergosinine by alkaline hydrolysis. The latter has also been degraded to lysergic acid, $C_{16}H_{16}O_2N_2$ (Jacobs and Craig, *J. Biol. Chem.*, 1934, **104**, 547; Smith and Timmis, J., 1934, 674), of which ergine is the amide. Alkaline hydrolysis also liberates pyruvic acid, the presence of which in the ergotamine molecule has been reported by Jacobs and Craig (*Science*, 1935, **81**, 256). Another degradation product, leucine, has been obtained from ergosinine by the process of acid hydrolysis first used by Jacobs and Craig (*J. Biol. Chem.*, 1935, **110**, 521) for the cleavage of ergotinine. The only ergot alkaloid which has hitherto given leucine on hydrolysis is ergoclavine (Jacobs and Craig, *J. Amer. Chem. Soc.*, 1935, **57**, 960). The properties of ergoclavine described by Küssner (*Jahresber.*, 1933, **47**, 5; *Arch. Pharm.*, 1934, **272**, 503) are widely different from those of ergosine and ergosinine and according to E.P. specification 7972/1935 it is a mixture of unidentified alkaloids. We have observed that ergosinine and ergosine readily crystallise together from chloroform or ethyl acetate as a molecular *compound*, which is less soluble than either of its components. The pure compound from ethyl acetate melts with decomposition at about 200°, and has $[\alpha]_D^{20°}$ + 128° in chloroform solution. An equimolecular mixture of the two alkaloids would have (by calculation) $[\alpha]_D^{20°}$ + 129°, which is close to the value + 124° given by Küssner (*loc. cit.*) for ergoclavine. The latter, however, melts at 177° and the reported elementary composition differs significantly from that of ergosine and ergosinine. When ergosinine is heated under reduced pressure, it gives rise to several crystalline products, of which the least volatile after purification melts at 148° and according to the

analyses and molecular weight determination must have the formula $C_{11}H_{18}O_2N_2$. On acid hydrolysis it yields only two products, *l*-leucine and *d*-proline, the latter being identified by formation of the aurichloride of the betaine. The substance must therefore be l-*leucyl*-d-*proline lactam* (3 : 6-*diketo*-5-iso*butyl*-1-2-*trimethylenepiperazine*).

In the course of purifying the lactam two other crystalline substances were obtained in quantities too small for complete identification, but neither of these is the amide of pyruvic acid. A crystalline sublimate, highly volatile under reduced pressure, was also produced from ergosinine, but in a very small yield. This proved to be a mixture, but it possibly contained pyruvamide, because it sublimed and melted similarly to this substance and gave evidence of hydrolysis to pyruvic acid and ammonia when it was treated with alkali. The degradation products derived from ergosinine are therefore ergine (or lysergic acid), leucine, proline, and pyruvic acid. The condensation of these four substances with elimination of three molecules of water requires the formula $C_{30}H_{37}O_5N_5$ as suggested above.

Ergosinine has the high specific dextrorotation typical of the physiologically weak ergot alkaloids, whereas ergosine has a specific rotation comparable with that of the physiologically active ergot alkaloids. The pharmacological action of ergosine and ergosinine is at present under investigation by Dr. White (at the Wellcome Physiological Research Laboratories) and the results will be published elsewhere. Briefly, he reports that examination of the actions of ergosine and ergosinine so far shows that they form a pair of alkaloids which show differences analogous to those found with other similar ergot alkaloid pairs, *e.g.*, ergotoxine and ergotinine, and ergotamine and ergotaminine. Ergosine is the more active and in its toxic symptoms closely resembles ergotoxine and ergotamine. The action of ergosine in paralysing the adrenaline response of the rabbit uterus is more powerful than that of ergotoxine.

Experimental.

Isolation of Ergosinine.—The total alkaloids of ergot were extracted with boiling benzene. The solution, after being cooled, was separated from sparingly soluble substances and extracted with 1% sodium hydroxide solution. The extract was made just acid to Congo-red by the addition of dilute sulphuric acid. The precipitate of sparingly soluble sulphates was removed by filtration, and the filtrate basified with sodium bicarbonate. The precipitate so formed, after being dried over sulphuric acid in a vacuum desiccator, was treated with a little methyl alcohol. The resulting crystalline precipitate of crude ergosinine was purified by recrystallisation from hot aqueous acetone. A further quantity was obtained by extracting the precipitate of sparingly soluble sulphates with water, basifying the solution with sodium bicarbonate, and treating the resulting precipitate with methyl alcohol as above.

Ergosinine is very readily soluble in chloroform, readily soluble in acetone, less soluble in ethyl acetate, sparingly soluble in benzene, very sparingly soluble in methyl alcohol, and almost insoluble in water. It crystallises very readily. From 90% alcohol, aqueous acetone, benzene, and ethyl acetate it separates in solvent-free prisms which decompose with blackening and frothing at 228°. From methyl alcohol it separates in needles, m. p. 220° (decomp.), which contain methyl alcohol (Found in air-dried material: MeO, 2·9; loss at 100°, 3·0. $C_{30}H_{37}O_5N_5,\frac{1}{2}MeOH$ requires MeO, 2·8; MeOH, 2·9%). The specific rotations are: $[\alpha]_{5461}^{20°}$ + 522° and $[\alpha]_D^{20°}$ + 420° (in chloroform, $c = 1$), $[\alpha]_{5461}^{20°}$ + 475° and $[\alpha]_D^{20°}$ + 380° (in acetone, $c = 1$); c refers to the solvent-free substance in each case (Found in material crystallised from aqueous acetone: C, 65·8; H, 6·6; N, 12·8; NMe, 6·6; in material crystallised from benzene: C, 65·9; H, 6·6; N, 12·7; in material crystallised from ethyl acetate: C, 66·0; H, 6·7; N, 13·1. $C_{30}H_{37}O_5N_5$ requires C, 65·8; H, 6·8; N, 12·8; NMe, 5·3%). Ergosinine in dilute solution acidified with hydrochloric acid gives precipitates with potassium mercuric iodide, potassium bismuth iodide and mercuric acid sulphate. It gives a blue colour with the dimethylaminobenzaldehyde reagent as modified by Allport and Cocking (*Quart. J. Pharm.*, 1932, **5**, 341) and compared with ergotinine the relative intensities are 102 : 100 and approximately inversely proportional to the molecular weights. Ergosinine gives the other colour reactions typical of the ergot alkaloids: a blue colour with glyoxylic acid, a yellow colour with dilute nitric acid and a trace of sodium nitrite, and in acetic acid a blue colour with sulphuric acid and a trace of ferric chloride.

The absorption spectrum of ergosinine measured between A. 2500 and A. 3500 shows the maximum at A. 3180 and the minimum at A. 2700 typical of the ergot alkaloids. It also shows the less well-defined inflection at A. 2420 which we have recorded in the case of ergotinine and

ψ-ergotinine (J., 1931, 1889). The measurements were made with $M/10{,}000$ and $M/30{,}000$ solutions in absolute alcohol.

Ergosinine Hydrochloride.—The base, dissolved in acetone, was treated with excess of 10% hydrochloric acid. The precipitate which first formed soon redissolved and the solution was poured into ether. The salt is amorphous, and readily soluble in water, giving an acid solution from which the *hydrochloride* is precipitated by the addition of hydrochloric acid. It darkens at 200° and decomposes at about 206° (Found: C, 61·8; H, 6·6; N, 12·0; HCl, 6·2. $C_{30}H_{37}O_5N_5$,HCl requires C, 61·8; H, 6·5; N, 12·0; HCl, 6·3%).

The salt prepared by adding 10% sulphuric acid to a solution of the base in acetone and pouring the solution into ether is amorphous, begins to darken at 190°, and decomposes at about 200°. It is a mixture of the normal and the acid sulphate. The nitrate, prepared by precipitating a solution of the base in dilute lactic acid with dilute nitric acid, is also amorphous; it begins to go grey at 190° and decomposes at about 200°.

Alkaline Hydrolysis of Ergosinine.—The base (1 g.) was heated with aqueous potassium hydroxide (8%, 25 c.c.) on a water-bath for 1 hour. The solution, which had a strong odour of ammonia, was acidified (litmus) with acetic acid. The granular precipitate was rapidly crystallised from hot water. Yield, 0·2 g. It darkened at 200°, decomposed at 235°, and had $[\alpha]_{5461}^{20°}$ + 55° (in pyridine, $c = 0{\cdot}4$) (Found: C, 71·8; H, 6·2; N, 10·4; NMe, 9·0. Calc. for lysergic acid, $C_{16}H_{16}O_2N_2$: C, 71·6; H, 6·0; N, 10·4; NMe, 10·8%). When treated with alcoholic potassium hydroxide and worked up as described in Part III (J., 1932, 763), ergosinine gave the characteristic needles of ergine, which frothed at 135°.

A portion of the filtrate from the lysergic acid, treated with sodium nitroprusside and potassium hydroxide, gave the red colour, changing to blue on addition of solid ammonium chloride, which is typical of pyruvic acid. The bulk of the filtrate was extracted with ether, the ethereal extract evaporated, and the residue, which had an odour of pyruvic acid, heated with water. The aqueous solution was separated from a little sticky material and treated with phenylhydrazine, potassium acetate and acetic acid. The resulting precipitate crystallised readily from methyl alcohol in needles, m. p. 188°, which did not depress the m. p. of pyruvic acid phenylhydrazone.

Acid Hydrolysis of Ergosinine.—The base (1 g.) was dissolved in concentrated hydrochloric acid (15 c.c.) and heated on a steam-bath for 16 hours. The black solution was diluted with water and extracted with ether. The ethereal extract gave a slight residue on evaporation, but nothing was isolated from it. The aqueous solution was evaporated to dryness. The residue was extracted with water, the solution treated with charcoal and filtered, and the hydrochloric acid removed with silver sulphate. The silver was removed with hydrogen sulphide, and the sulphuric acid with barium carbonate. The filtrate on concentration gave 0·12 g. of irregular plates, which after crystallisation from hot water formed the plates characteristic of leucine (Found: C, 54·8; H, 9·8; N, 10·5. Calc. for $C_6H_{13}O_2N$: C, 55·0; H, 10·0; N, 10·7%). It had $[\alpha]_D^{20°}$ — 6° (in water, $c = 0{\cdot}13$). The sign of rotation was reversed in 10% hydrochloric acid. It gave the typical red colour with benzoquinone. On oxidation with chloramine-T it gave *iso*valeraldehyde, which was isolated as the *p*-nitrophenylhydrazone, m. p. 115° (after crystallisation from dilute alcohol). Leucine, similarly treated, gave the *p*-nitrophenylhydrazone, m. p. 115°. The mixed m. p. was the same. Wooley and Peterson (*J. Biol. Chem.*, 1936, **114**, 88) give m. p. 108°.

Action of Heat.—Ergotoxine and ergotinine give crystalline sublimates of *iso*butyrylformamide on pyrolysis at atmospheric pressure (Barger and Ewins, J., 1910, **97**, 284). Ergosinine, heated in precisely the same way, gave no crystalline sublimate.

Ergosinine (1 g.) was heated at 210—230°/3—4 mm. in a small flask with a long neck. Immediately above the bulb 4 inches of the neck were surrounded by a steam jacket, leaving a length of about 6 inches, which was kept cool by surrounding it with filter-paper moistened with alcohol, to condense a sublimate (B). A partly crystallised gum (A) condensed inside the steam jacket and the ergosinine was heated for 25 minutes to give the best yield. The product was dissolved in chloroform, treated with charcoal, filtered, and evaporated to dryness, giving a hard, light brown gum (0·37 g.). This was redistilled at 3—4 mm. (oil-bath at 200—220°). The light yellow, semi-crystalline solid was triturated with ether and yielded a white semi-crystalline solid, which was recrystallised from ethyl acetate until it gave well-formed rods of constant m. p., 148°. The mother-liquors yielded two crystalline white substances, (a) m. p. 125° and (b) m. p. 170°, which were not further purified. The pure compound (m. p. 148°) is very sparingly soluble in ether, easily soluble in alcohol, and less soluble in water, giving a neutral (litmus) solution; $[\alpha]_{5461}^{20}$ + 105° (approx., water, $c = 1$) (Found for material

dried at 80° in a vacuum : C, 63·1; H, 8·6; N, 13·2; *M*, Rast, 230. *Leucylproline lactam*, $C_{11}H_{18}O_2N_2$, requires C, 62·9; H, 8·6; N, 13·3%; *M*, 210).

Hydrolysis of l-*Leucyl*-d-*proline Lactam*.—The pure substance (70 mg.) was digested with concentrated hydrochloric acid (10 c.c.) for 19 hours in a steam-bath. The solution was evaporated to dryness, the residue freed from hydrochloric acid with silver sulphate, the free sulphuric acid removed with barium carbonate, and the solution evaporated to dryness. By trituration with alcohol the crystalline material (0·031 g.) remained out of solution. After recrystallisation it melted at about 290°, gave the benzoquinone colour reaction for leucine, and had $[\alpha]_D^{20°}$ − 11° (water, c = 2). The 3 : 5-dinitrobenzoyl derivative had m. p. 185°, not depressed by dinitrobenzoyl-leucine (Found for the substance dried at 100° in a vacuum : C, 48·1; H, 4·7; N, 12·8. Calc. for $C_{13}H_{15}O_7N_3$: C, 48·0; H, 4·6; N, 12·9%).

The alcohol-soluble fraction gave on evaporation a soft gum (0·036 g.), which had $[\alpha]_{5461}^{20°}$ + 62° (water, c = 1). This material gave the pine-wood reaction for proline and was very easily soluble in water. It was dissolved in water (2 or 3 c.c.), made just alkaline with dilute caustic soda solution, and shaken with methyl sulphate (0·2 c.c.) until the latter had passed into solution. Caustic soda solution was added when required to keep the solution alkaline. The solution was acidified with concentrated hydrochloric acid, and a slight excess of 10% solution of gold chloride added. The precipitate was recrystallised from 10% hydrochloric acid containing a trace of gold chloride. The crystals melted sharply at 245° (after sintering) when heated from 220° and gave $[\alpha]_{5461}^{20°}$ + 5° (approx. 2% HCl, c = 2) (Found for the substance dried at 80° in a vacuum : C, 17·5; H, 3·0; Au, 40·6; Cl, 29·2. Calc. for $C_7H_{13}O_2N,HAuCl_4$: C, 17·4; H, 2·9; Au, 40·8; Cl, 29·4%). A sample of the betaine aurichloride prepared from *l*-proline ($[\alpha]_{5461}^{20°}$ − 101°, water, c = 1) by the same technique melted similarly at 245° and had $[\alpha]_{5461}^{20°}$ − 14° (approx.). Evidently the *d*-proline from the lactam had partly racemised during the hydrolysis.

The sublimate (B), resublimed at 30—50°/3 mm., gave hard white needles, m. p. 115° to 125° according to the rate of heating. Pyruvamide could only be obtained in soft leaflets, though they showed a similar m. p. The analytical figures indicated a mixture. On warming with 10% sodium hydroxide solution, a strong ammoniacal smell was observed and the cooled solution after acidification with hydrochloric acid, followed by addition of ammonia and sodium nitroprusside, gave the typical blue colour for pyruvic acid.

Conversion of Ergosinine into Ergosine with Acid.—The base (10 g.) was boiled with acetone (90 c.c.), phosphoric acid (*d* 1·75, 2·5 c.c.), water (5 c.c.), and alcohol (10 c.c.) for 9 hours in an atmosphere of nitrogen. The mixture was diluted with water, concentrated under reduced pressure to remove the organic solvents, basified with sodium bicarbonate, and extracted with chloroform. The extract, after being dried over magnesium sulphate, was evaporated to dryness, and the residue crystallised twice from ethyl acetate. Yield, 1·0 g. (direct). Fractionation gave further quantities of ergosine and unchanged ergosinine.

Ergosine is readily soluble in chloroform, fairly readily soluble in methyl alcohol and acetone, sparingly soluble in ethyl acetate and benzene. It is less soluble in chloroform and much more soluble in methyl alcohol than ergosinine. It crystallised readily from ethyl acetate in prisms, m. p. 228° with blackening and frothing. It crystallises from methyl alcohol free from solvent. The specific rotations are : $[\alpha]_{5461}^{20°}$ − 193°, $[\alpha]_D^{20°}$ − 161° (in chloroform, c = 1); $[\alpha]_{5461}^{20°}$ + 24°, $[\alpha]_D^{20°}$ + 16° (in acetone, c = 1) (Found : C, 65·8; H, 6·8; N, 12·9%). Ergosine gives the typical blue colour with the dimethylaminobenzaldehyde reagent (*loc. cit.*) and, compared quantitatively with ergosinine, the colour intensities are approximately equal. It also gives the colour reactions mentioned under ergosinine.

The absorption spectrum measured in *M*/10,000 and *M*/30,000 solution in absolute alcohol is identical with that of ergosinine except that the inflexion at A. 2420 is less marked.

Conversion of Ergosinine into Ergosine with Alkali.—Ergosinine (1 g.) was dissolved in a mixture of *N*-alcoholic potash (50 c.c.) and water (50 c.c.) in an atmosphere of nitrogen, and the solution kept at the ordinary temperature for 45 minutes. It was then diluted with water, acidified with hydrochloric acid, and made alkaline with sodium bicarbonate, and the alkaloids exhaustively extracted with ether. After drying over sodium sulphate, the ethereal solution was evaporated to dryness. The solid gave a blue colour with dimethylaminobenzaldehyde approximately equal to that given by ergosinine. The solid was triturated with methyl alcohol to yield semi-crystalline ergosinine and the methyl-alcoholic filtrate was evaporated to dryness to give a residue which yielded crude ergosine by trituration with ethyl acetate. The ethyl acetate filtrate was evaporated; the residue again yielded crude ergosinine and ergosine by treatment with methyl alcohol and ethyl acetate. The total crude ergosinine

(0·41 g.) and ergosine (0·42 g.) had $[\alpha]_{5461}^{20°}$ + 480° and $[\alpha]_{5461}^{20°}$ − 40°, respectively (chloroform, $c = 1$). These rotations correspond to ergosinine–ergosine mixtures containing respectively 94% of ergosinine and 78% of ergosine, by calculation. They were purified by recrystallisation from 90% acetone and ethyl acetate, respectively, and then gave $[\alpha]_{5461}^{20°}$ + 520° and $[\alpha]_{5461}^{20°}$ − 194° (chloroform, $c = 1$) respectively (Found for the respective materials dried at 100° in a vacuum: C, 66·1; H, 6·9; N, 12·7; C, 66·0; H, 6·8; N, 13·0. Calc. for $C_{30}H_{37}O_5N_5$: C, 65·8; H, 6·8; N, 12·8%).

Ergosine Hydrochloride.—The base (0·1 g.), dissolved in acetone (5 c.c.), was treated with hydrogen chloride until the solution became acid. Diamond-shaped plates, m. p. 235° (decomp.), separated in a few minutes. The *hydrochloride* is moderately easily soluble in water, the solution is slightly acid, and the salt is precipitated in the amorphous state by the addition of hydrochloric acid. It crystallises in combination with acetone (Found: C, 62·2; H, 7·0; N, 10·7; HCl, 5·9. $C_{30}H_{37}O_5N_5$,HCl,$COMe_2$ requires C, 61·8; H, 6·9; N, 10·9; HCl, 5·7%).

Ergosine hydrobromide was prepared by the addition of 40% hydrobromic acid to a solution of the base in acetone. It crystallised in needles, which began to darken at 200° and decompose with blackening and frothing at 230°. It is moderately easily soluble in water, giving an acid solution from which it is precipitated in the amorphous condition by the addition of hydrobromic acid (Found for the crystals: C, 57·7; H, 6·3; N, 10·4; HBr, 12·0. $C_{30}H_{37}O_5N_5$,HBr,$COMe_2$ requires C, 57·7; H, 6·4; N, 10·2; HBr, 11·8%).

Ergosine nitrate was prepared by the addition of concentrated nitric acid, diluted with acetone, to a solution of the base in acetone. It crystallised in needles which began to darken at 185° and decompose at 215°. It is moderately easily soluble in water, giving an acid solution, from which the amorphous salt is precipitated on the adddition of nitric acid (Found for the crystals: C, 59·2; H, 6·4; N, 12·9; HNO_3, 9·6. $C_{30}H_{37}O_5N_5$,HNO_3,$COMe_2$ requires C, 59·3; H, 6·6; N, 12·6; HNO_3, 9·5%).

Ergosine methiodide was prepared by the addition of methyl iodide to a solution of the base in a little chloroform. It separated as an amorphous powder, which decomposed at 215° with previous darkening and could not be crystallised (Found: C, 53·7; H, 5·7; N, 10·2. $C_{30}H_{37}O_5N_5$,MeI requires C, 53·9; H, 5·8; N, 10·2%).

Ergosinine–Ergosine Molecular Compound.—Mixtures of ergosinine and ergosine in the proportions, respectively, of 2 to 3 and 3 to 2 were repeatedly crystallised from ethyl acetate. In each case a compound of constant optical rotation was obtained in small fine needles. The same substance was similarly obtained from chloroform, but less conveniently, owing to the easier solubility of the crystals. The crystals are less soluble in chloroform or ethyl acetate than either alkaloid. The crystals melted (decomp.) at about 200°. The material, dried at 100° in a vacuum, had $[\alpha]_{5461}^{20°}$ + 164°; $[\alpha]_{D}^{20°}$ + 128° (chloroform, $c = 0·5$) (Found: C, 66·0; H, 6·9; N, 12·8. $C_{30}H_{37}O_5N_5$ requires C, 65·8; H, 6·8; N, 12·8%). The constituents are separable by treating the crystals with methyl alcohol, ergosinine remaining undissolved.

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(*Addendum, March 5th*) Through the kindness of Prof. Barger we have been able to examine a specimen of ergoclavine supplied by Merck. It melted at 175° and had $[\alpha]_{D}^{20°}$ + 130° (chloroform, $c = 1$) (Found: C, 65·8; H, 6·9; N, 12·5%). After three crystallisations from ethyl acetate the crystals closely resembled those of the ergosine–ergosinine complex, melted at the same temperature, and had the same elementary composition (Found: C, 65·8; H, 6·9; N, 12·6%). Treatment with methyl alcohol effected a separation into a sparingly soluble and a readily soluble fraction. These after crystallisation from aqueous acetone and ethyl acetate respectively gave ergosinine, m. p. 228°, $[\alpha]_{5461}^{20°}$ + 520° (chloroform, $c = 1$) (Found: C, 65·9; H, 6·9; N, 12·8%), and ergosine, m. p. 228°, $[\alpha]_{5461}^{20°}$ − 194° (chloroform, $c = 1$) (Found: C, 66·1; H, 6·8; N, 13·0%). These results leave no doubt that ergoclavine is a complex of ergosine and ergosinine, and the value for the optical rotation is that of an equimolecular mixture of the two.

Küssner (*Z. angew. Chem.*, 1937, **50**, 34) also has recognised that his ergoclavine is a mixture of two alkaloids and has separated it into an alkaloid having $[\alpha]_{D}$ + 410°, m. p. 196°, and another, $[\alpha]_{D}$ − 149°, m. p. not given (both rotations in chloroform). These are no doubt ergosinine and ergosine incompletely purified.