247. *The Alkaloids of Ergot. Part VI. Ergometrinine.*

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SOME years ago Moir (*Brit. Med. J.*, 1932, I, 1119) was able to demonstrate by clinical experiments that aqueous extracts of ergot, which at that time were considered by pharmacologists to be inert, actually contain a principle capable of causing rapid and vigorous contractions of the human puerperal uterus. This principle was subsequently isolated by Dudley and Moir (*ibid.*, 1935, I, 520) and found to be a crystalline water-soluble alkaloid to which they gave the name ergometrine. Its chemical and physical properties have since been precisely described by Dudley (*Proc. Roy. Soc.*, 1935, **118**, *B*, 478) and a detailed account of its pharmacological action has been given by Brown and Dale (*ibid.*, p. **446**). Its clinical action has been described by Moir (*Proc. Roy. Soc. Med.*, 1935, **28**, 1654). The same alkaloid has been described by other workers under the names ergostetrine (Thompson), ergotocin (Davis, Adair, Rogers, Kharasch, and Legault), and ergobasine (Stoll and Burckhart), but there is now agreement concerning the identity of the substance (*Nature*, 1936, **137**, 403).

Examination of the mother-liquors from the crystallisation of ergometrine led us to the discovery of an isomeric alkaloid which we have briefly described elsewhere (*ibid.*, 1935, **136**, 254). Its high dextrototation $[\alpha]_{5461}^{20^\circ} + 520^\circ$ (in chloroform, $c = 0{\cdot}45$) suggested analogies with the pharmacologically inactive alkaloids ergotinine and ergotaminine, both of which have a high dextrorotation, and it was accordingly named *ergometrinine*. It has since been examined at the Wellcome Physiological Research Laboratories by White and found to have little oxytocic or adrenaline paralysing action. Reports of comparative inactivity have been made by Raymond-Hamet (*Compt. rend. Soc. Biol.*, 1935, **120**, 1208), Zunz and Vesselovsky (*ibid.*, 1936, **121**, 1343), and Chen, Swanson, and Hargreaves (*Proc. Exp. Biol. Med.*, 1936, **34**, 183). Clinical experiments (Moir; see Dale, *Schweiz. Med. Woch.*, 1935, **65**, 1077) in comparison with ergometrine indicate that it has but little clinical action. These results support the opinion that all the ergot alkaloids occur in pairs, one member of which in each case has but little pharmacological action, while the other has an intense activity. In each of the previously known cases, the inert analogue is convertible into the active modification by appropriate treatment and the change is reversible. Similarly, ergometrinine is convertible into ergometrine, and the reverse change has also been effected, in both cases by methods applicable to the other alkaloidal pairs.

Jacobs and Craig (*Science*, 1935, **82**, 16; *J. Biol. Chem.*, 1935, **110**, 521) have shown that since ergometrine on hydrolysis yields lysergic acid and *d*-β-aminopropyl alcohol it is to be regarded as the hydroxy*iso*propylamide of lysergic acid. When ergometrinine is hydrolysed in the same way it gives precisely the same hydrolytic products. It is assumed, therefore, that a change in the configuration of the lysergic acid group in one or both alkaloids occurs during the process of hydrolysis, so that both ergometrine and ergometrinine give products with the configurations stable under the conditions of hydrolysis. Since both alkaloids give the same hydrolytic products, an explanation of the differences in physiological action between ergometrine and ergometrinine may ultimately be found in differences in configuration of the respective molecules and probably, in particular, of the ergine portion of the molecule, although other forms of isomerism susceptible to facile reversibilty cannot be excluded from consideration.

Experimental.

Isolation of Ergometrinine.—The water-soluble fraction of the total alkaloids of ergot as produced, *e.g.*, by Dudley's method (*Pharm. J.*, 1935, I, 709; II, 63) was extracted with chloroform, and the chloroform solution was concentrated, until the sparingly soluble ergometrine–chloroform compound separated. The ergometrinine in the mother-liquor was separated from other alkaloids by virtue of its different solubilities in water, chloroform, and benzene, and of its stronger basicity, as follows: The mother-liquor was evaporated to dryness. The resulting hard gum (A) was extracted with 100 parts of boiling benzene, leaving a residue (B). The hot benzene solution on cooling deposited a soft gum which was converted, by stirring, into a powder, consisting mainly of ergometrinine (C). The mother-liquor was extracted fractionally with 1% sulphuric acid, yielding respectively two extracts, D and E, of which D was the richer in ergometrinine. Extract D was diluted with sufficient water so that on making alkaline with ammonia the water-soluble alkaloids remained dissolved. This solution was filtered, and extracted with chloroform. The first chloroform extract yielded crude ergometrinine (F) on evaporation. Fractions C and F were triturated with ethyl acetate and yielded nearly pure ergometrinine. The residue B was dissolved in dilute sulphuric acid, basified, extracted with chloroform, and the extract treated like the mother-liquor from the precipitation of ergometrine. Extract E was basified and extracted with chloroform and this, together with the remaining chloroform extractions from extract D, was evaporated to a gum which was then worked up as for A. The yield of ergometrinine was about one-half of the weight of ergometrine filtered off from the original concentrated chloroform liquors. An additional quantity of ergometrinine was obtained from the water-insoluble fraction of the total alkaloids where its presence was due to its sparing solubility in water and to its adsorption by the other alkaloids. This fraction was extracted with dilute hydrochloric acid and the extract on being made alkaline gave a solution of water-soluble alkaloids which were worked up by the methods described above. The semi-crystalline ergometrinine was purified either by recrystallisation from acetone or by conversion into the nitrate, which is particularly suitable for this purpose.

Ergometrinine crystallises from acetone in short stout prisms, which decompose at 195—197°. It has $[\alpha]_{5461}^{20°}$ + 520°, $[\alpha]_{D}^{20°}$ + 414° (in chloroform, c = 0·45); $[\alpha]_{5461}^{20°}$ + 413°, $[\alpha]_{D}^{20°}$ + 328° (in methyl alcohol, c = 0·7) (Found: C, 70·0; H, 7·1; N, 12·8. $C_{19}H_{23}O_2N_3$ requires C, 70·1; H, 7·1; N, 12·9%). It is very sparingly soluble in water, giving an alkaline solution; sparingly soluble in ethyl acetate; more soluble in acetone, chloroform, and methyl and ethyl alcohols. It is sparingly soluble in cold benzene and more readily in boiling benzene. It crystallises from acetone, benzene, and chloroform, being much more soluble than ergometrine in the last solvent. Unlike ergometrine, it crystallises without solvent of crystallisation, and thus resembles the other physiologically inactive alkaloids ergotinine and ergotaminine rather than ergotoxine and ergotamine which crystallise associated with solvent. A solution acidified with hydrochloric acid gives precipitates with potassium mercuric iodide, potassium bismuth iodide, and acid mercuric sulphate. It gives the same blue colour with dimethylaminobenzaldehyde reagent (Allport and Cocking modification) as ergine, but the respective intensities are as 267 : 340 and are therefore nearly inversely proportional to the molecular weights of $C_{19}H_{23}O_2N_3$ and $C_{16}H_{17}ON_3$. Ergometrinine also resembles the other ergot alkaloids in giving a blue colour with the glyoxylic acid reagent, a yellow colour with dilute nitric acid and a trace of sodium nitrite, and a reddish-amber colour with Pauly's reagent. The absorption spectrum of ergometrinine in absolute alcohol (c = 0·006%) measured between 2450 and 3400 A. has a peak at 3130 A. and a minimum at 2700 A. like that of the other ergot alkaloids and ergine.

Ergometrinine hydrochloride was prepared by treating a solution of the base in warm acetone with *N*-hydrochloric acid. It crystallised in small needles which decomposed with effervescence at 175—180°. It is very soluble in water. The air-dried material lost 4·8% when dried at 100° in a vacuum ($C_{19}H_{23}O_2N_3$,HCl,H_2O requires H_2O, 4·7%) (Found, for the anhydrous material: C, 62·9; H, 6·6; N, 11·4; Cl, 9·8. $C_{19}H_{23}O_2N_3$,HCl requires C, 63·0; H, 6·7; N, 11·6; Cl, 9·8%). The *hydrobromide* was prepared by addition of aqueous hydrobromic acid to a suspension of the base in acetone. A little water was added to form a clear solution, and the salt was precipitated with ether. It recrystallised in needles on addition of ether to a solution in aqueous acetone. The crystals were not dehydrated at all when heated at 75° in a vacuum, and at higher temperatures slight decomposition occurred; they melted and decomposed indefinitely between 130° and 190° [Found (dried at 75° in a vacuum): C, 53·6; H, 6·3; N, 9·8; Br, 18·7. $C_{19}H_{23}O_2N_3$,HBr,H_2O requires C, 53·7; H, 6·2; N, 9·9; Br, 18·8%].

The *perchlorate* was prepared by the addition of aqueous sodium perchlorate to a solution of

the base in dilute acetic acid. The salt crystallises in needles which on heating become grey at 210° and decompose with effervescence at 225°. It is sparingly soluble in water [Found (dried at 100° in a vacuum) : C, 53·3; H, 5·6; N, 9·9. $C_{19}H_{23}O_2N_3,HClO_4$ requires C, 53·6; H, 5·7; N, 9·9%].

The *nitrate* was prepared by addition of dilute nitric acid to a suspension of the base in methyl alcohol, followed by addition of ether, which precipitated the salt in stout prismatic crystals. It was recrystallised by adding ether to a solution in aqueous methyl alcohol. On heating, it became grey at 200° and decomposed with effervescence at 235°. It is less soluble in water than the hydrochloride and hydrobromide. It has $[\alpha]_{5461}^{20°}$ + 361°; $[\alpha]_{D}^{20°}$ + 282° (in water, c = 0·98) [Found (dried at 100° in a vacuum) : C, 58·9; H, 6·4; N, 14·4. $C_{19}H_{23}O_2N_3,HNO_3$ requires C, 58·8; H, 6·2; N, 14·4%].

The *hydrogen sulphate* was prepared by addition of dilute sulphuric acid to a suspension of the base in water. On addition of ether to a solution in aqueous methyl alcohol, it crystallised in short stout prisms, which began to go grey at 230° and decomposed with effervescence at 250°. It is less soluble in water than the hydrobromide and hydrochloride [Found (dried at 100° in a vacuum) : C 54·0; H, 6·0; N, 9·8; S, 7·7. $C_{19}H_{23}O_2N_3,H_2SO_4$ requ ires C, 53·9; H, 6·0; N, 9·9; S, 7·6%].

Acid Hydrolysis of Ergometrinine and Ergometrine. Isolation of d-β-*Aminopropyl Alcohol.*—Ergometrinine (0·5 g.) was heated in a steam-bath with 20 c.c. of concentrated hydrochloric acid for 20 hours. The liquor was then evaporated to dryness, and the residue taken up in about 5 c.c. of water, treated with charcoal, and filtered. The filtrate was freed from hydrochloric acid by the addition of silver sulphate, the silver chloride was filtered off, and the filtrate successively treated with hydrogen sulphide to remove silver and with barium hydroxide to remove sulphate, and incidentally an intense dark blue colouring matter. After removal of barium with carbon dioxide the solution was evaporated to dryness and the residue extracted with absolute alcohol, the extract on evaporation leaving 0·12 g. of light brown residue. This was dissolved in pyridine (5 c.c.) and warmed with *p*-bromobenzoyl chloride (1·0 g.) until the initial precipitate was dissolved. The solution was cooled and filtered from a crystalline pyridine–bromobenzoyl chloride addition compound. The filtrate was mixed with an excess of 10% sulphuric acid, and the precipitate was separated and triturated with 5% aqueous caustic soda to remove free *p*-bromobenzoic acid. The remaining semicrystalline *d*-β-aminopropyl dibromobenzoate weighed 0·38 g. (yield 56%). Recrystallised by dissolution in pyridine and addition of water, it gave white anhydrous needles which softened at 155° and melted at 160°, $[\alpha]_{5461}^{20°}$ + 62°, $[\alpha]_{D}^{20°}$ + 57° (in pyridine, c = 2) (Found : C, 46·4; H, 3·3; N, 3·0; Br, 36·1. Calc. for $C_{17}H_{15}O_3NBr_2$: C, 46·3; H, 3·4; N, 3·2; Br, 36·2%). Jacobs and Craig found for the substance from ergometrine, m. p. 155° and $[\alpha]_{D}^{28°}$ + 48° (in pyridine, c = 0·125).

Alkaline Hydrolysis of Ergometrinine. Isolation of Lysergic Acid.—Ergometrinine (0·5 g.) was boiled in methyl-alcoholic *N*-potassium hydroxide (15 c.c.) for 5 hours in an atmosphere of nitrogen. Water (10 c.c.) was added, and the solution was concentrated under reduced pressure to remove alcohol. After removal of the base with ether, the aqueous liquor was acidified with sulphuric acid. The semicrystalline precipitate of crude lysergic acid (0·25 g.) was purified as described by Jacobs and Craig (*J. Biol. Chem.*, **1934**, **104**, 547) and gave crystals of a dihydrate, which had $[\alpha]_{5461}^{20°}$ + 50° (in pyridine, c = 0·5), m. p. 238°.

The Interconversion of Ergometrine and Ergometrinine.—Either of these alkaloids is transformed into the other by the action of either acids or alkalis. Hydrolysis of the base, presumably at the hydroxy*iso*propylamide group, always occurs, but it is evidently a slower reaction than the transformation of one base into another.

In acid solution. Ergometrine (0·25 g.) was dissolved in glacial acetic acid (3 c.c.), water (30 c.c.) added, and the solution heated on the steam-bath, at about 90°, for 1 hour. The solution was made alkaline with ammonia, and the alkaloids were exhaustively extracted with ether. After being dried over potassium carbonate, the ethereal solution was evaporated and gave a mixture (0·13 g.) which had $[\alpha]_{5461}^{20°}$ + 190° (in methyl alcohol, c = 0·5). Assuming that only ergometrine and ergometrinine were present, calculation from the known specific rotations of these bases indicates that the mixture contains 0·045 g. of ergometrinine and 0·085 g. of ergometrine. By trituration with ice-cooled chloroform, 0·080 g. of ergometrine–chloroform was obtained. The filtrate was evaporated, and the residue by trituration with ethyl acetate yielded 0·040 g. of semicrystalline ergometrinine. The filtrate from this was evaporated, and the residue on trituration with chloroform gave 0·010 g. of ergometrine–chloroform. The total yield of ergometrine–chloroform (0·090 g.) corresponds to 0·065 g. of ergometrine. The ergometrinine isolated had $[\alpha]_{5461}^{20°}$ + 398° (in methyl alcohol, c = 0·5) and gave an almost quantitative yield of

the well-crystallised nitrate, which had $[\alpha]_{5461}^{20°}$ + 358° (in water, c = 1). The ergometrine–chloroform had $[\alpha]_{5461}^{20°}$ + 55° (in methyl alcohol, c = 0·5) equivalent to about + 75° for the chloroform-free base.

In alkaline solution. A solution of ergometrinine (0·1 g.) in *N*-alcoholic potassium hydroxide (5 c.c.) was boiled in a current of nitrogen for 30 minutes. The brown solution was diluted with water (15 c.c.), acidified with hydrochloric acid, and then made alkaline with sodium carbonate. The liquor was freed from alkaloid by extraction with ether. The ethereal solution, after being dried (potassium carbonate), was evaporated, and gave a residue which weighed 0·082 g. (solvent-free) and had $[\alpha]_{5461}^{20°}$ + 180° (in methyl alcohol, c = 0·5). This figure corresponds to a mixture of 0·056 g. of ergometrine and 0·026 g. of ergometrinine. By following the procedure described above, 0·045 g. of ergometrine ($[\alpha]_{5461}^{20°}$ + 80°) and 0·022 g. of ergometrinine ($[\alpha]_{5461}^{20°}$ + 395°) were isolated.

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