## 311. *The Alkaloids of Ergot. Part VII.* iso*Ergine and* iso*Lysergic Acids.*

By Sydney Smith and Geoffrey Millward Timmis.

In the group of ergot alkaloids the property of physiological activity is accompanied by that of lævorotation and usually by the ability to crystallise in association with solvents. It is also characteristic that the lævorotatory, physiologically active alkaloids can be transformed readily into alkaloids of high dextrorotation with only a weak physiological action and that the change is readily reversible. The ergot alkaloids thus fall into two groups :

| Physiologically active. | $[\alpha]_{5461}$. | Physiologically weak. | $[\alpha]_{5461}$. |
|---|---|---|---|
| | | $\psi$-Ergotinine ..... | +513° |
| Ergotoxine ..... | −226° | Ergotinine ..... | +466 |
| Ergotamine ..... | −181 | Ergotaminine ..... | +450 |
| Ergometrine ..... | — | Ergometrinine ..... | +520 |

All rotations are for solutions in chloroform : the value for ergometrine is omitted, as it cannot be determined in this solvent owing to the sparing solubility of the alkaloid. For solutions in pyridine the values (not previously published) are : ergometrine $[\alpha]^{20°}_{5461}$ − 16° ($c$ = 1), ergometrinine $[\alpha]^{20°}_{5461}$ + 596° ($c$ = 0·5). Sensibamine and ergoclavine are not included in this table, since according to Stoll (*Schweiz. Med. Woch.*, 1935, **65**, 885, 1077) and E.P. Specification 7972/1935, Chem. Works, formerly Sandoz, they are not definite substances, but mixtures.

It has already been shown that all the ergot alkaloids on alkaline hydrolysis yield the same dextrorotatory base ergine, $C_{16}H_{17}ON_3$ (Smith and Timmis, J., 1932, 763, 1543; this vol., p. 1166) or, on more drastic treatment, the carboxylic acid, lysergic acid (Jacobs and Craig, *J. Biol. Chem.*, 1934, **104**, 547), of which ergine is the amide. Since ergine has a high dextrorotation, $[\alpha]^{20°}_{5461}$ + 598° (in chloroform, $c$ = 1·5), and only a weak physiological activity, properties typical of the ergotinine rather than of the ergotoxine group, it seemed probable that the methods used for the conversion of ergotinine into ergotoxine could be successfully employed for the conversion of ergine into a new lævorotatory isomeride which might have a more powerful physiological action. Ergine has now been converted by these methods into an isomeric base, iso*ergine*, the specific rotation of which cannot be determined in chloroform solution owing to sparing solubility, but which in pyridine solution has $[\alpha]^{20°}_{5461}$ + 25°, the corresponding value for ergine in pyridine solution being + 635°. The difference between the two values is practically identical with that between ergometrine and ergometrinine, also in pyridine solution. The reverse change of *iso*ergine into ergine can be effected readily, thus showing a close similarity to the interconversion of the above alkaloidal pairs. There can thus be little doubt that the isomerism of the ergot alkaloids is associated with the ergine nucleus which is common to them all. The physiological activity of *iso*ergine is under examination at the Wellcome Physiological

Research Laboratories, but the results so far obtained indicate but little difference in activity between ergine and *iso*ergine (Dr. White, private communication). Nevertheless it seems probable that the physiologically active alkaloids have the *iso*ergine configuration and that a high degree of physiological activity only occurs when the *iso*ergine nucleus is attached to a side chain which may be as short as $-CHMe\cdot CH_2\cdot OH$ in the case of ergometrine or longer and more complex as in the alkaloids of higher molecular weight.

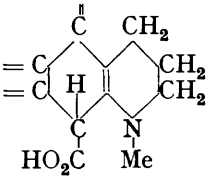
Since ergine on alkaline hydrolysis gives lysergic acid, it might at first be expected that *iso*ergine would give a corresponding *iso*lysergic acid. Investigation showed that alkalis rapidly isomerise ergine and *iso*ergine to an equilibrium mixture of the two bases and that iso*lysergic acid* (obtained by another method; *vide infra*) is partly isomerised by alkalis to lysergic acid. Actually only the latter acid could be obtained by the alkaline hydrolysis of either ergine or *iso*ergine, though with larger quantities of material it might be possible to separate the *iso*-acid which is presumably present in equilibrium with lysergic acid. *iso*Lysergic acid can be prepared from lysergic acid by the methods employed for the conversion of ergotoxine into ergotinine or better by the action of hot water. It has the high dextrorotation typical of the ergotinine group:

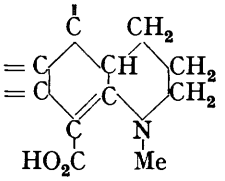
| | $[\alpha]_{5461}$. | | $[\alpha]_{5461}$. |
|---|---|---|---|
| Ergometrine | −16° | Ergometrinine | +596° |
| *iso*Ergine | +25 | Ergine | +635 |
| Lysergic acid | +49 | *iso*Lysergic acid | +365 |

All the rotations are for solutions in pyridine.

With diazomethane, *iso*lysergic acid is more slowly esterified than lysergic acid. This may be due to the effects of steric hindrance caused by geometrical isomerism or alternatively by isomerism due to the shifting of a double bond. A formula provisionally suggested for lysergic acid by Jacobs and Craig (*J. Biol. Chem.*, 1936, **113**, 771) contains the structure (I), which can be constructed in two forms in which the NMe group occupies different

(I.)





(II.)

positions relative to the carboxyl group. It also permits the shift of a double bond (II) which could powerfully affect the esterification rate (cf. the difference in esterification rate of β-ethylacrylic acid, $CH_2Me\cdot CH{:}CH\cdot CO_2H$, and β-ethylidenepropionic acid, $CHMe{:}CH\cdot CH_2\cdot CO_2H$; Sudborough and Thomas, J., 1912, **101**, 320; Sudborough and Gittins, J., 1909, **95**, 315). When steric hindrance to the esterification of a carboxylic acid occurs, it is usually also observed in the formation and hydrolysis of its amide. If differences could be observed in the rates of hydrolysis of the isomeric ergines, each of these bases might be linked up with the corresponding isomer of lysergic acid and thus confirm the relationships deduced by comparing the specific rotations of the acids and bases. Attempts to ascertain the comparative rates of hydrolysis of ergine and *iso*ergine and their substitution products, ergometrine and ergometrinine, failed owing to the rapid production of an equilibrium mixture of the respective bases and acids referred to above.

In addition to the optically active lysergic acids an *optically inactive lysergic acid* can be obtained by the action of barium hydroxide solution at a high temperature on either lysergic or *iso*lysergic acid. It could not be converted back into lysergic or *iso*lysergic acid by the action of alkalis.

## Experimental.

*Alkaline Hydrolysis of Ergometrine and Ergometrinine.*—The experiment (this vol., p. 1168) in alkaline solution was repeated except that ergometrine (0·1 g.) was used instead of ergometrinine. The resulting mixed alkaloids weighed 0·079 g. and had $[\alpha]^{20°}_{5461}$ + 176° (in methyl

alcohol, $c = 0{\cdot}5$), which corresponds to a mixture of 0·054 g. of ergometrine and 0·025 g. of ergometrinine, of which 0·045 g. of ergometrine and 0·021 g. of ergometrinine were isolated.

Ergometrine (1·0 g.), dissolved in a mixture of *N*-alcoholic potassium hydroxide (50 c.c.) and water (50 c.c.), was kept boiling under reflux in a current of nitrogen. Samples were withdrawn at intervals and the total alkaloids were isolated from each sample. The composition of the alkaloidal mixture was ascertained from the rotation in each case and checked by separation of the constituents as previously described.

| | | | | |
|---|---|---|---|---|
| Time, mins. | 15 | 45 | 75 | 135 |
| Base hydrolysed, % | 29 | 40 | 53 | 72 |
| $[\alpha]^{20°}_{5461}$ (in methyl alcohol, $c = 0{\cdot}5$) of unhydrolysed base | +260° | +268° | +266° | +259° |

The above experiment was repeated except that ergometrinine was used instead of ergometrine. After 15, 30 and 45 minutes' boiling, 28, 33 and 37% respectively of the base was hydrolysed. The residual bases had $[\alpha]^{20°}_{5461}$ + 267°, + 270° and + 269° respectively (in methyl alcohol, $c = 0{\cdot}5$).

*The Conversion of Ergine into* iso*Ergine*.—Ergine (1·0 g.), dissolved in a mixture of 90% alcohol (33 c.c.) and 90% phosphoric acid (1·75 g.), was boiled for 10 hours in an atmosphere of nitrogen. Most of the alcohol was then removed by evaporation and the residual liquor, after being made alkaline with sodium carbonate, was extracted with chloroform. The extract, after being dried with potassium carbonate and treated with charcoal, was concentrated. Crude iso*ergine* was deposited. It was washed with cold acetone, and then crystallised from hot methyl alcohol in stout solvent-free prisms, m. p. 242° (decomp.). The base is very sparingly soluble in chloroform and is much less soluble than ergine in acetone and pyridine. It has $[\alpha]^{20°}_{5461}$ + 25°; $[\alpha]^{20°}_{D}$ + 10° (in pyridine, $c = 0{\cdot}5$). A suspension of the base in water gives with Pauly's reagent an amber colour similar to that given by ergine, but developing more slowly, probably owing to the lesser solubility of *iso*ergine in water. The blue colour given with *p*-dimethylaminobenzaldehyde (Allport and Cocking, *Quart. J. Pharm.*, 1932, **5**, 341) is quantitatively the same as that given by ergine (Found: C, 72·1; H, 6·4; N, 15·6. $C_{16}H_{17}ON_3$ requires C, 71·9; H, 6·4; N, 15·7%).

iso*Ergine hydrochloride* was prepared by acidifying a suspension of *iso*ergine in alcohol with hydrochloric acid and adding about 10% of water. On the addition of ether the salt crystallised slowly in needles containing one molecule of water of crystallisation. It is easily soluble in water, but less so than ergine hydrochloride. The anhydrous salt melts with decomposition at 269° after turning grey (Found: C, 63·0; H, 6·0; N, 13·9; Cl, 11·7. $C_{16}H_{17}ON_3$,HCl requires C, 63·2; H, 6·0; N, 13·8; Cl, 11·7%. Found: Loss at 100° in a vacuum, 5·4. $C_{16}H_{17}ON_3$,HCl,$H_2O$ requires $H_2O$, 5·6%).

*Alkaline Hydrolysis*.—Alkaline hydrolysis was tried with the object of relating ergine and *iso*ergine to the two lysergic acids by means of the methods described in the experiments on ergometrine and ergometrinine. The results were similar in demonstrating the rapid interconversion of ergine and *iso*ergine and the consequent impossibility of discovering any differences that might exist in the rates of hydrolysis of the two amides. When the hydrolysis was prolonged beyond 1½ hours, some decomposition of the lysergic acid nucleus was observed whereby non-basic material was produced. Ergine (1·0 g.) was hydrolysed in boiling solution with 50 c.c. of *N*-potassium hydroxide in alcohol and 50 c.c. of water.

| | | | | |
|---|---|---|---|---|
| Time, mins. | 15 | 30 | 50 | 75 |
| Base hydrolysed, % | 45 | 50 | 60 | 80 |
| $[\alpha]^{20°}_{5461}$ (in pyridine, $c = 0{\cdot}5$) of unhydrolysed bases | +277° | +265° | +265° | +250° |

*The Interconversion of Ergine and* iso*Ergine in Alkaline Solution*.—Ergine (0·1 g.) was boiled for 15 minutes in *N*-alcoholic potassium hydroxide (10 c.c.) in an atmosphere of nitrogen. The red solution was diluted to 50 c.c. with water, acidified with hydrochloric acid, made alkaline with sodium carbonate, and exhaustively extracted with ether. The extract, after being dried over potassium carbonate, was evaporated and gave a residue (0·078 g.) which had $[\alpha]^{20°}_{5461}$ + 280° (pyridine, $c = 0{\cdot}5$). This was triturated with acetone and the precipitate (*iso*ergine) was removed. The filtrate was evaporated and the residue was treated with methyl alcohol, which precipitated ergine methyl alcoholate; $[\alpha]^{20°}_{5461}$ + 530° (pyridine, $c = 0{\cdot}5$), m. p. 131°. The filtrate was evaporated and triturated with chloroform, which yielded a small precipitate of *iso*ergine. The yields of crude *iso*ergine ($[\alpha]^{20°}_{5461}$ + 50°; pyridine, $c = 0{\cdot}5$) and ergine were respectively 0·039 g. and 0·028 g. By calculation from the rotation value the mixture contained 0·045 g. and 0·033 g. respectively. The identities of the *iso*ergine and ergine were confirmed by elementary analysis.

*iso*Ergine (0·1 g.) was treated with alkali in an exactly similar way. The basic residue weighed 0·079 g. and had $[\alpha]_{5461}^{20°}$ + 260° (pyridine, $c$ = 0·5). This yielded 0·040 g. and 0·027 g. of *iso*ergine and ergine respectively. The calculated values were 0·048 g. and 0·031 g. respectively.

*Hydrolysis of* iso*Ergine to Lysergic Acid.*—*iso*Ergine was hydrolysed by the method previously described for the hydrolysis of ergine (J., 1934, 674) and gave lysergic acid in about the same yield. Crystals of the dihydrate were obtained which were identified by the rotation ($[\alpha]_{5461}^{20°}$ + 55°; pyridine, $c$ = 0·5, for anhydrous material) and elementary analyses.

Lysergic acid, prepared from ergine as previously described (*loc. cit.*) or by following substantially the process of Jacobs and Craig (*J. Biol. Chem.*, 1934, **104**, 547), separated as a dihydrate, which lost its water at 100° in a vacuum, though Jacobs and Craig describe only a monohydrate which was difficult to dehydrate. It melted at 240° (decomp.) and had $[\alpha]_{5461}^{20°}$ + 49°; $[\alpha]_{D}^{20°}$ + 32° (in pyridine, $c$ = 0·5) [Jacobs and Craig, *loc. cit.*, record $[\alpha]_{D}^{20°}$ + 40° (in pyridine, $c$ = 0·5)]. The variation in the specific rotation is probably due to contamination with the highly dextrorotatory *isolysergic acid* (see below) formed by the isomerising action of hot water.

Methyl lysergate is more rapidly formed in benzene than in ether (J., 1934, 674) or acetone (*J. Biol. Chem.*, 1934, **104**, 550). A suspension of the acid in benzene containing a trace of methyl alcohol was treated with a solution of diazomethane in benzene, the reaction being complete within a few minutes. The ester crystallised from benzene in leaflets containing one molecule of benzene. The specific rotation, not previously recorded, is $[\alpha]_{5461}^{20°}$ + 115°; $[\alpha]_{D}^{20°}$ + 82° (in chloroform, $c$ = 0·5).

*Conversion of Lysergic Acid into* iso*Lysergic Acid.*—Lysergic acid is partly converted into the isomeric acid by the action of pyridine, hot methyl or ethyl alcohol or sodium hydroxide solution, but the best method was found to be the action of boiling water. A solution of lysergic acid (2 g.) in boiling water (500 c.c.) was boiled in an atmosphere of nitrogen for 6 hours. The solution was evaporated under reduced pressure to a volume of 100 c.c., treated with charcoal, and cooled. A semicrystalline solid (1·4 g.) separated, with $[\alpha]_{5461}^{20°}$ + 230° (pyridine, $c$ = 0·5). It was dissolved in dilute aqueous ammonia and fractionally precipitated with acetic acid. The first crop, $[\alpha]_{5461}^{20°}$ + 290° (pyridine, $c$ = 1), was refractionated from solution in aqueous ammonia as before, and the first crop recrystallised from hot water to give pure *iso*lysergic acid. It crystallises with two molecules of water and is more soluble in water and in pyridine than lysergic acid. It melts with decomposition and effervescence at 218°, and has for the anhydrous substance $[\alpha]_{5461}^{20°}$ + 368°, $[\alpha]_{D}^{20°}$ + 281° (in pyridine, $c$ = 1). *iso*Lysergic acid is a stronger base than lysergic acid. Aqueous solutions (0·2%) of the two acids treated with methyl-red showed a redder colour for lysergic acid, thus confirming the evidence for the stronger basicity of *iso*lysergic acid which was afforded by the fractional precipitation method of separating the two acids (Found: C, 71·8; H, 5·8; N, 10·5. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 5·9; N, 10·4%).

iso*Lysergic acid nitrate* was deposited in well-formed needles when 10% aqueous nitric acid was added to an aqueous solution of *iso*lysergic acid. It melted and decomposed at about 185° (Found for material dried at 80° in a vacuum: C, 55·0; H, 5·3; N, 11·7. $C_{16}H_{16}O_2N_2,HNO_3,H_2O$ requires C, 55·0; H, 5·5; N, 12·0%).

*Methylation of* iso*Lysergic Acid.*—Repeated trials showed that, under the same conditions, *iso*lysergic acid takes at least six to seven times as long to esterify with diazomethane as lysergic acid, though both acids are practically insoluble in cold benzene. For example, lysergic acid (0·04 g.) and *iso*lysergic acid (0·04 g.), both anhydrous, were each suspended in benzene (4 c.c.) containing 5% of methyl alcohol and to each was added a benzene solution (3·5 c.c.) of diazomethane prepared from nitrosomethylurea (0·35 g.), a large excess of diazomethane thus being provided. Both solutions were then shaken under identical conditions. The lysergic acid was dissolved in 10 minutes, but the *iso*lysergic acid required 70 minutes. In a separate test the material remaining undissolved after the methylation of *iso*lysergic acid had started was separated and recrystallised quickly from boiling water. The crystals were proved to be *iso*lysergic acid by their melting point, optical rotation ($[\alpha]_{5461}^{20°}$ + 365°, pyridine, $c$ = 1, for the substance dried at 100°), elementary analysis, and qualitative properties.

*Methyl* iso*lysergate*, purified by crystallisation from benzene, formed slender rods containing no solvent of crystallisation. It melted with decomposition at 174° after sintering at 170°. It had $[\alpha]_{5461}^{20°}$ + 236°, $[\alpha]_{D}^{20°}$ + 179° (in chloroform, $c$ = 0·5) (Found: C, 72·6; H, 6·5; N, 10·0; NMe, 10·5; OMe, 8·8. $C_{17}H_{18}O_2N_2$ requires C, 72·3; H, 6·4; N, 9·9; NMe, 10·4; OMe, 9·4%).

*Conversion of* iso*Lysergic Acid into Lysergic Acid.*—*iso*Lysergic acid (0·1 g.), dissolved in

3 c.c. of 10% aqueous potassium hydroxide, was heated on the steam-bath for 1 hour in an atmosphere of nitrogen. On acidification of the brown solution with acetic acid crude lysergic acid was precipitated. On purification this yielded semicrystalline lysergic acid (0·06 g.), which crystallised from hot water in the characteristic leaflets of lysergic acid; m. p. 240°, $[\alpha]_{5461}^{20°}$ + 60° (in pyridine, $c = 1$) for the anhydrous substance.

*Inactive Lysergic Acid.*—Lysergic acid (2 g.), dissolved in 1·5% barium hydroxide solution (50 c.c.), was heated at 150° in an atmosphere of nitrogen for 4 hours. The solution after cooling was filtered from a small black precipitate and made just acid to litmus with hydrochloric acid. The grey semicrystalline precipitate was filtered off and dissolved in boiling water (300 c.c.), and the solution treated with charcoal, filtered, and cooled; the practically pure crystalline acid was then deposited. Further quantities were obtained by extracting the charcoal with boiling water and by concentration of the mother-liquor. Yield, 1·15 g. The *acid* crystallises from water in leaflets. It melts with decomposition at 250° and is less soluble than lysergic acid in water (Found for the dried substance: C, 71·6; H, 6·2; N, 10·4. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 5·9; N, 10·4%. Found: Loss at 100° in a vacuum, 12·0. $C_{16}H_{16}O_2N_2,2H_2O$ requires $H_2O$, 11·8%).

The *methyl* ester was prepared in the same way as the esters of lysergic and *iso*lysergic acids. The reaction with diazomethane was slower than in the case of lysergic acid. The ester crystallised from benzene in rods, which melted indefinitely with decomposition at about 160° (Found for material dried at 80° in a vacuum: C, 72·2; H, 6·3; N, 9·9; NMe, 10·5; OMe, 8·8. $C_{17}H_{18}O_2N_2$ requires C, 72·3; H, 6·4; N, 9·9; NMe, 10·4; OMe, 9·4%).

*Action of Alkali on Inactive Lysergic Acid.*—The acid (0·1 g.), dissolved in a mixture of *N*-alcoholic potassium hydroxide (5 c.c.) and water (5 c.c.), was boiled in an atmosphere of nitrogen for 1 hour. Crystalline inactive lysergic acid (0·082 g.) was recovered from the solution and neither of the other lysergic acids could be detected in the mother-liquor.

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(ADDENDUM: October 3rd.)—Following the submission of the above paper, Jacobs and Craig (*J. Biol. Chem.*, 1936, **115**, 227) have reported the isolation of the isomeric α- and γ-dihydrolysergic acids, from, *e.g.*, ergotamine and ergotaminine, by hydrogenation and then hydrolysis. This confirms the view (see above and Part VI) that the presence of lysergic acid in the alkaloids of this series is probably responsible for their characteristic isomerisation. Jacobs and Craig also show that reduction of the double bond in methyl α-dihydrolysergate suppresses its ability to isomerise. This result supports our suggestion (see above) that the isomerisation may be due to shifting of the double bond.