THE TOTAL SYNTHESIS OF LYSERGIC ACID
AND ERGONOVINE

Sir:

The striking physiological effects attributable to ergot have been known since pre-Christian times, and were familiar to medieval Europe, where the ingestion of grain infected by the fungus Claviceps purpurea not infrequently caused outbreaks of the dread malady known as St. Anthony’s Fire. More recently, the active principles have been shown to be amides of lysergic acid (I, R = –OH), of which the simplest is ergonovine (I, R = –NH(CH₂CH₂)CH₂OH), whose oxytocic effect has led to its widespread use in obstetrical medicine. We now wish to record the first total synthesis of lysergic acid.

The reaction of N-benzoyl-3-(β-carboxyethyl)dihydronindole, followed by aluminum chloride, gave 1-benzoyl-5-keto-1,2,2a.-3,4,5-hexahydrobenz[d]indole (II, R = –CO–C₆H₅, R’ = H) (m.p. 143–146°C (uncor.); calcd. for C₁₉H₁₄N₂O₅: C, 70.95; H, 4.64; N, 6.89. Found: C, 70.95; H, 4.69; N, 6.95). Acid hydrolysis of the latter yielded the diketone (II, R = H, R’ = –N(CH₃)CH₂CO₂H) (m.p. 109–110°C; calcd. for C₁₉H₁₄N₂O₅: C, 70.95; H, 6.43; N, 10.55. Found: C, 70.60; H, 6.43; N, 10.55. Found: C, 70.60; H, 6.43; N, 10.55). The diketone (II, R = H, R’ = –N(CH₃)CH₂CO₂H) was converted to the tetracyclic ketone (III, R = –OH) (m.p. 155–156°C; calcd. for C₁₉H₁₄N₂O₅: C, 74.97; H, 6.71; N, 11.65. Found: C, 75.08; H, 6.93; N, 11.78). Acetylation of the ketone afforded (III, R = –CO₂CH₃) (m.p. 169–170°C; calcd. for C₂₁H₁₆N₂O₅: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.61; H, 6.53; N, 9.75), which on reduction with sodium borohydride gave the alcohol (IV, R = –CO₂H, R’ = OH) (m.p. 187–188°C). The hydrochloride (m.p. 245–246°C (dec.); calcd. for C₂₁H₁₆N₂O₅Cl: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.47; H, 6.81; N, 8.96) of the latter, when treated with thionyl chloride in liquid sulfur dioxide, furnished an amorphous chloride hydrochloride, which was converted by sodium cyanide in liquid hydrogen cyanide to the nitrile (IV, R = –CO₂H, R’ = –CN) (m.p. 181–182°C; calcd. for C₂₁H₁₆N₂O₅: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.41; H, 6.53; N, 14.17). Methanalysis of the nitrile gave the ester (IV, R = H, R’ = –CO₂CH₃) (m.p. 160–161°C; calcd. for C₂₁H₁₆N₂O₅: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.88; H, 7.19; N, 10.05). Alkaline hydrolysis of the latter, followed by catalytic dehydrogenation in water using a deactivated Raney nickel catalyst gave dl-lysergic acid (I, R = –OH) (m.p. 241–242°C (dec.); calcd. for C₂₁H₁₆N₂O₅: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.51; H, 6.10; N, 10.32). The synthetic dl-lysergic acid was converted to the corresponding ester by means of diazomethane and thence with hydrazine to dl-erysogine acid hydrazide (I, R = –NHNH₂) (m.p. 224–227°C (dec.); calcd. for C₂₁H₁₆N₂O₅: C, 68.06; H, 6.43; N, 19.83. Found: C, 68.06; H, 6.44; N, 19.76). Both the acid and hydrazide were identical with the corresponding samples derived from natural ergot alkaloids in melting point, mixture melting point, ultraviolet spectrum, infrared spectrum, paper chromatographic behavior and X-ray diffraction pattern.

Since dl-erysogine acid hydrazide (I, R = –NHNH₂) has already been resolved and reconverted to ergonovine (I, R = –NH.CH₂CH₂OH), the present work constitutes also a total synthesis of this ergot alkaloid.

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