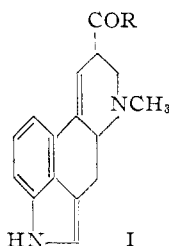


COMMUNICATIONS TO THE EDITOR

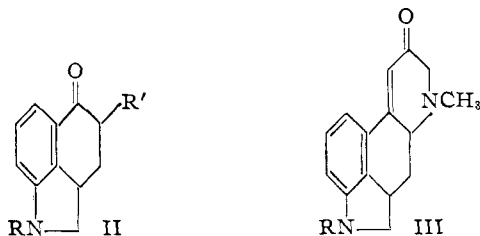
THE TOTAL SYNTHESIS OF LYSERGIC ACID AND ERGONOVINE

Sir:

The striking physiological effects attributable to ergot have been known since pre-Christian times, and were familiar to mediaeval 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-CH(CH₃)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.



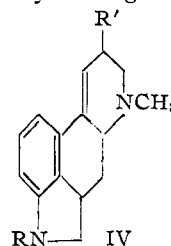
The reaction of N-benzoyl-3-(β-carboxyethyl)-dihydroindole¹ with thionyl chloride, followed by aluminum chloride, gave 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole (II, R = -CO-C₆H₅, R' = H) (m.p. 148-150° (uncor.); calcd. for C₁₈H₁₅NO₂: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.81; H, 5.29; N, 5.15). Bromination of the tricyclic ketone gave the 4-bromo derivative (II, R = -COC₆H₅, R' = Br) (m.p. 181-182°; calcd. for C₁₈H₁₄BrNO₂: N, 3.94; Br, 22.44. Found: N, 3.94; Br, 22.14), which was converted by reaction with methylaminoacetone ethylene ketal to the ketal-ketone (II, R = -COC₆H₅; R' =



-N(CH₃)CH₂C(CH₃)OCH₂CH₂O) (m.p. 135-136°; calcd. for C₂₄H₂₆N₂O₄: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.49; N, 6.95). Acid hydrolysis of the latter yielded the diketone (II, R = H, R' = -N(CH₃)CH₂COCH₃) (m.p. 109-110°; calcd. for C₁₅H₁₃N₂O₂: C, 69.74; H, 7.02; N, 10.85. Found: C, 70.00; H, 7.41; N, 10.91), which on treatment with sodium methoxide was converted to the tetracyclic ketone (III, R = H) (m.p. 155-157°; calcd. for C₁₅H₁₆N₂O: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.08; H, 6.95;

(1) B. K. Blount and R. Robinson, *J. Chem. Soc.*, 3158 (1931).(2) E. C. Kleiderer and E. C. Kornfeld, *J. Org. Chem.*, **18**, 455 (1948).(3) S. Smith and G. M. Timmis, *J. Chem. Soc.*, 1440 (1936).

N, 11.78). Acetylation of the ketone afforded (III, R = -COCH₃) (m.p. 169-170°; calcd. for C₁₇H₁₈N₂O₂: 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 = -COCH₃, R' = OH) (m.p. 187-188°). The hydrochloride (m.p. 245-246° (dec.); calcd. for C₁₇H₂₁N₂O₂Cl: 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 = -COCH₃; R' = -CN) (m.p. 181-182°; calcd. for C₁₈H₁₉N₃O: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.41; H, 6.53; N, 14.17). Methanolysis of the nitrile gave the ester (IV, R = -COOCH₃) (m.p. 160-161°; calcd. for C₁₇H₂₀N₂O₂: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.86; H, 7.19; N, 10.05). Alkaline hydrolysis of the latter, followed by catalytic dehydrogenation in water using a deactivated Raney nickel catalyst² gave *dl*-lysergic acid (I, R = -OH) (m.p. 241-242° (dec.); calcd. for C₁₆H₁₆N₂O₂: 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*-isolysergic acid hydrazide (I, R = -NHNH₂) (m.p. 224-227° (dec.); calcd. for C₁₆H₁₈N₄O: C, 68.06; H, 6.43; N, 19.85. Found: C, 68.00; H, 6.44; N, 19.76). Both the acid and hydrazide were identical with the corresponding samples derived from natural ergot alkaloids^{3,4} in melting point, mixture melting point, ultraviolet spectrum, infrared spectrum, paper chromatographic behavior and X-ray diffraction pattern.

Since *dl*-isolysergic acid hydrazide (I, R = -NHNH₂) has already been resolved and reconverted to ergonovine (I, R = -NHCH(CH₃)CH₂OH),⁵ the present work constitutes also a total synthesis of this ergot alkaloid.

THE LILLY RESEARCH LABORATORIES
INDIANAPOLIS 6, INDIANA

EDMUND C. KORNFIELD
E. J. FORNEFELD
G. BRUCE KLINE
MARJORIE J. MANN
REUBEN G. JONES
R. B. WOODWARD

(4) A. Stoll and A. Hofmann, *Z. physiol. Chem.*, **250**, 7 (1937).(5) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 922, 944 (1943).