

SYNTHESIS IN THE SERIES OF LYCOPODIUM ALKALOIDS V.

THE SYNTHESIS OF ANNOTININE LACTAM

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The Lycopodium alkaloid annotinine I (1) was converted by MacLean and Prime (2) in a simple three-step sequence to the lactam II. We now wish to report the total synthesis of this compound.

Our starting material was the keto lactam III, the synthesis of which we have described recently (3). The synthetic racemic compound III (82 mg.) was heated with potassium cyanide and ammonium chloride (4) in 5 ml. dimethyl formamide for 60 hours to 140-150°C. The crude nitrile IV was obtained in a 90% yield and it was homogeneous in T.L.C. [I.R. (CHCl₃): 2230 (CN), 1720 (ketone), 1650 cm⁻¹ (lactam).]

The conversion of IV into the keto ester V was accomplished as follows. The crude compound IV was refluxed with 4 ml. of methanol and 1 ml. of conc. sulphuric acid for 80 hours. The mixture was poured on ice and extracted with chloroform. Evaporation of the organic solvent yielded 36 mg. of the ester V.* Another 23 mg. of the same compound was obtained by extracting the aqueous layer continuously with ether and esterifying the extract with diazomethane. Compound V was purified by preparative T.L.C. on silica gel and recrystallized from methanol to a m.p. 189-190°C. [I.R. (CCl₄): 1740 (ester), 1730 (ketone), 1650 cm⁻¹ (lactam). M.V.: (mass spectroscopy) 305.]

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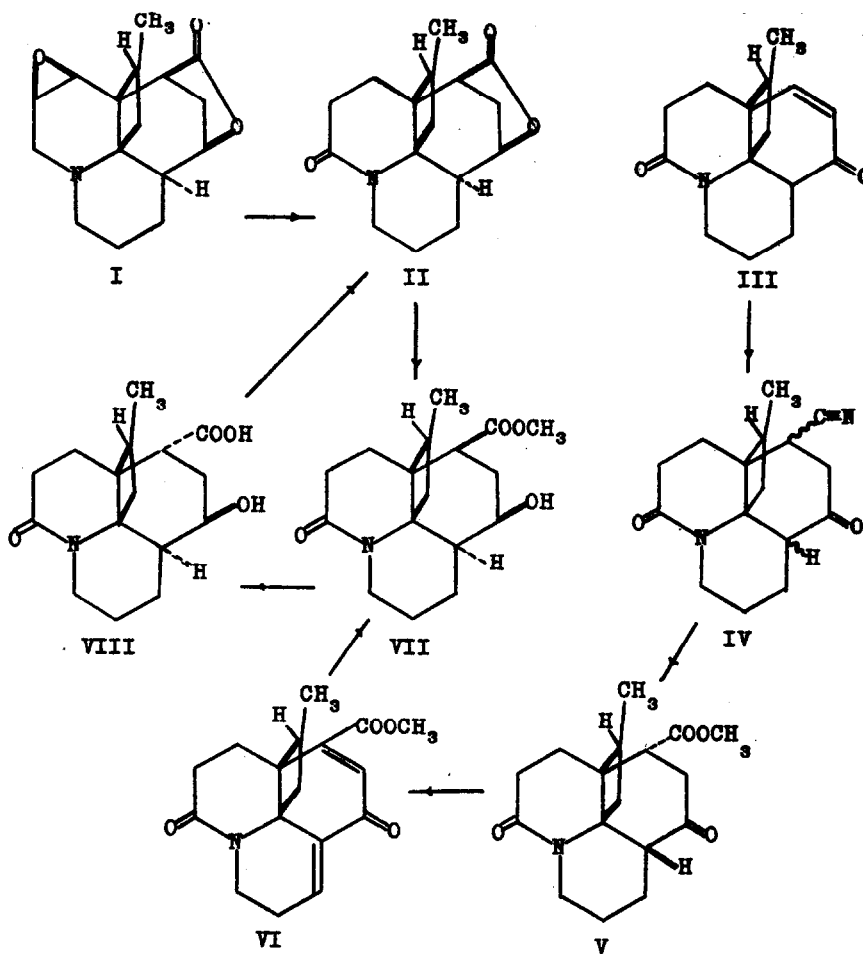
* The configuration of V follows from studies performed on the optically active enantiomer of this compound derived from annotinine (1).

The synthetic racemate V was identical with the optically active product of the same structure (1) (obtained from annotinin), when compared by T.L.C., I.R. in CCl_4 and a KBr pellet and mass spectrum.

We have described already 10 years ago (1) the conversion of V to VI by selenium dioxide oxidation and the hydrogenation of VI to VII. Compound VII is also obtainable directly from II (5) and it may be converted to the acid VIII by epimerization of the ester group and hydrolysis (5).

The hydroxy acid VIII was finally converted into the annotinine lactam II as follows. Compound VIII (162 mg.) and 220 mg. of *p*-toluenesulphonic acid were dissolved in 3 ml. DMF and 50 ml. benzene. The benzene was gradually distilled off and new absolute benzene added from a dropping funnel. After 24 hours of reflux, the yield was 67 mg. of pure lactone II. The remainder of the material was the unchanged acid VIII. The product II melted at 179-180°C. [I.R. (CHCl_3): 1770 (lactone), 1620 cm^{-1} (lactam). M.V.: (mass spectroscopy) 275.] Identity with authentic compound II (2) was established by mixed melting point, T.L.C., infrared spectrum (KBr) and mass spectrum.

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