

SYNTHESIS IN THE SERIES OF LYCOPODIUM ALKALOIDS. VII.

THE SYNTHESIS OF 12-*epi*-LYCOPODINE

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(Received in USA 10 August 1967)

12-*epi*-Lycopodine (I) is a diastereoisomer of the naturally occurring alkaloid, lycopodine. It has been described by Ayer and Iverach (1) who obtained it together with lycopodine by a catalytic hydrogenation of anhydrolycodoline. Thus compound I and lycopodine are rigorously interrelated. We wish to describe now the total synthesis of I.

We have applied for this end the synthetic strategy which we have developed (2) some time ago with the important modification that we have substituted our photochemical reaction (3) for the Grignard reaction used previously (2).

The starting material was the cyanoethylation product of dihydro-oreinol (II) (4). This compound was allowed to stand for five days at room temperature in a mixture of T.H.F./20% aqueous HCl (1:1). The product III was obtained in a yield of 55%, and crystallized from chloroform-pet. ether.\*  
[ C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub>; m.p. 198-9°C.; I.R.: 3400, 1705, 1640 cm<sup>-1</sup>; U.V.: λ<sub>max</sub>. = 289 mμ, ε = 18,000. ] Benzoylation of III with benzyl chloride in absolute D.M.F. and one mole of sodium hydride at 115°C. for 18 hours gave compound IV in a yield of 60%. It was crystallized from pet. ether and ether.

[ C<sub>17</sub>H<sub>19</sub>NO<sub>2</sub>; m.p. 98-100°C.; I.R.: 1705, 1645, 1620, 1490 cm<sup>-1</sup>. ] Compound IV  
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\* All crystalline compounds gave checking elemental analyses. N.M.R. spectra have been recorded for all compounds and found in agreement with the structures assigned. Only especially diagnostic N.M.R. data are reported.

was irradiated as described before (3) with allene at  $-70^{\circ}\text{C}$ . for 15 hours. After chromatography on Florisil and crystallization from benzene the adduct V was obtained in a yield of 30%.<sup>\*</sup> [ $\text{C}_{20}\text{H}_{23}\text{NO}_2$ ; m.p.  $147-9^{\circ}\text{C}$ .; I.R.: 1710, 1660, 1490, 897  $\text{cm}^{-1}$ ; M.w. (mass spec.): 309.] Compound V yielded the ketal (VI) with ethylene glycol and *p*-toluenesulphonic acid in refluxing benzene. It was crystallized from acetone. [ $\text{C}_{22}\text{H}_{27}\text{NO}_3$ ; m.p.  $109-111^{\circ}\text{C}$ .; I.R.: 1640, 900  $\text{cm}^{-1}$ .] The ketal (VI) was epoxidized with 1.5 moles of perbenzoic acid and 1.5 moles of solid sodium bicarbonate in chloroform. The yield of the oily epoxide (VII) was quantitative. [I.R.: 1640  $\text{cm}^{-1}$ ; N.M.R.: no vinylic hydrogen.] The compound was homogeneous in T.L.C. The epoxide (VII) was reduced with lithium borohydride in refluxing T.H.F. The oily but T.L.C. homogeneous product (VIII) was obtained in a yield of 95%. [ $\text{C}_{22}\text{H}_{29}\text{NO}_4$ ; I.R.: 3580, 3330, 1640  $\text{cm}^{-1}$ ; N.M.R.: singlet (3H)  $\tau = 8.51$  p.p.m., methyl unshielded by the tertiary hydroxyl.]

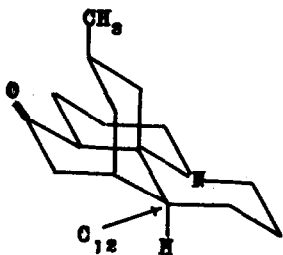
Compound VIII was allowed to stand at room temperature in T.H.F. with 2% aqueous HCl (1:1). The diketone (IX) was obtained in a yield of 70% and recrystallized from acetone-hexane. [ $\text{C}_{20}\text{H}_{25}\text{NO}_3$ ; m.p.  $172-5^{\circ}\text{C}$ .; I.R.: 1730, 1640  $\text{cm}^{-1}$ ; N.M.R.: singlet (3H)  $\tau = 7.9$  p.p.m., methyl ketone.] The diketone (IX) was allowed to stand at room temperature in ethanol with 0.2% aqueous sodium hydroxide (1:1) for 3 days. The aldolization product (X) was isolated by crystallization from acetone in a yield of 45%. [ $\text{C}_{20}\text{H}_{25}\text{NO}_3$ ; m.p.  $192-3^{\circ}\text{C}$ .; I.R.: 3640, 3450, 1720, 1660  $\text{cm}^{-1}$ ; N.M.R.: only one C-methyl as unresolved doublet (3H)  $\tau = 9.1$  p.p.m.] Compound X was treated with an excess of phosphorus pentachloride in methylene chloride for 2 minutes at  $0^{\circ}\text{C}$ . The product XI was obtained by chromatography on Florisil as a foam [ $\text{C}_{20}\text{H}_{24}\text{NO}_2\text{Cl}$ ; I.R.: 1725, 1650  $\text{cm}^{-1}$ .] The compound XI was ketalized in refluxing benzene with ethylene glycol and *p*-toluenesulphonic acid and the .....

\* The low yield is due to the formation of an oily reverse addition product. Experiments to suppress this undesirable reaction by using other blocking groups instead of the benzyl group are in progress.

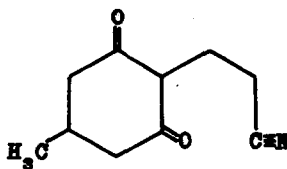
crude ketal immediately reduced with sodium in a mixture of ether and liquid ammonia. The product XII was obtained in a yield of 75% by chromatography on Florisil. It was oily but homogeneous in T.L.C. [  $C_{15}H_{23}NO_3$ ; I.R.: 3420, 1660, 1100  $cm^{-1}$ ; M.w. (mass spec.) = 265. ] Deketalization of XII in T.H.F. with 2% aq. HCl (1:1) gave the crystalline product (XIII) in a yield of 70%. It was recrystallized from acetone-hexane. [  $C_{13}H_{19}NO_2$ ; m.p. 258-61°C.; I.R.: 3390, 1715, 1660  $cm^{-1}$ . ]

The ketal (XII) was reduced in refluxing dioxane with lithium aluminum hydride and the resulting base deketalized in a solution of T.H.F.-2% aqueous HCl (1:1) overnight at room temperature. The amino ketone (XIV) was obtained in a yield of 60%. It was homogeneous on T.L.C. [  $C_{13}H_{21}NO$ ; I.R.: 1715  $cm^{-1}$  ]. Treatment of XIV with 1.2 moles of acrylyl chloride and an excess of triethylamine in benzene gave the amide (XV). This compound was obtained after chromatography on Florisil in a yield of 60%. It was homogeneous in T.L.C. [  $C_{16}H_{23}NO_2$ ; I.R.: 1720, 1650, 1615  $cm^{-1}$ . ] Compound XV was cyclized by refluxing in absolute toluene with *p*-toluenesulphonic acid. The product (XVI) is a lactam with the epi-lycopodine skeleton (see formula I). After preparative T.L.C. on silica gel it was homogeneous in several T.L.C. systems and crystallized. It was however not recrystallized from solvent.

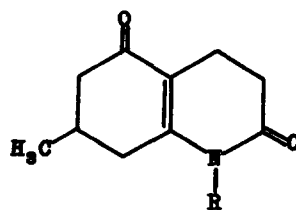
[  $C_{16}H_{23}NO_2$ ; I.R.: 1725, 1640  $cm^{-1}$ ; M.w. (mass spec.) = 261. ] The lactam (XVI) was finally converted into racemic epi-lycopodine (I) by reduction with lithium aluminum hydride in T.H.F. at reflux, followed by Jones oxidation. epi-Lycopodine was obtained in a yield of 90% and a total amount of 20 mg. It was purified by preparative T.L.C. and sublimation at 70°C. in high vacuo. The product was homogeneous in several T.L.C. systems and indistinguishable from authentic epi-lycopodine supplied by Professor W. A. Ayer. The I.R. spectrum in carbon tetrachloride and mass spectrum of the synthetic material were superimposable with the corresponding spectra of the authentic sample.



I

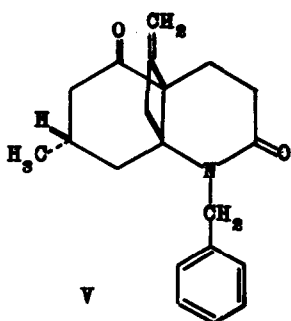


II

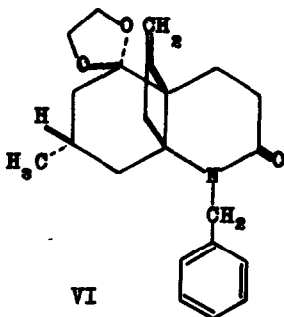


III (R = H)

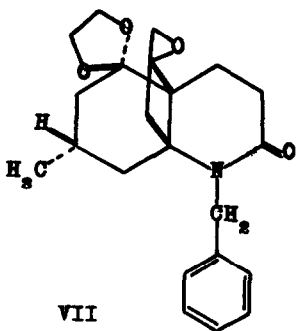
IV (R = )



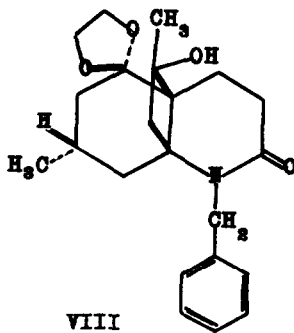
V



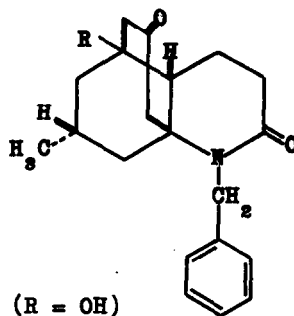
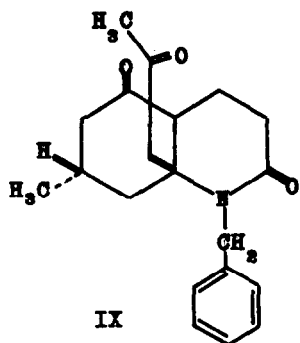
VI



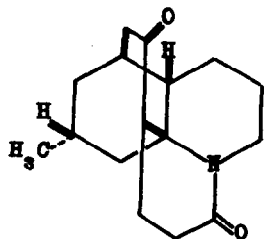
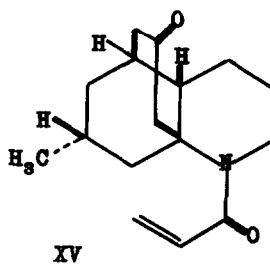
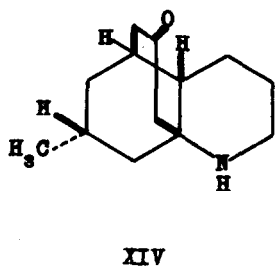
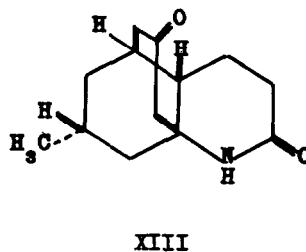
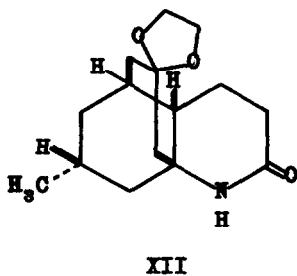
VII



VIII



XI (R = Cl)



[ $C_{16}H_{25}NO$ ; I.R.: 2850, 2800, 2745, 2650 (Bohlmann bands),  $1704\text{ cm}^{-1}$ ; M.w. (mass spec.) = 247.] After a second sublimation the synthetic racemate crystallized and melted at  $56-8^{\circ}\text{C}$ . It was further converted into a perchlorate which after two crystallizations melted at  $231-3^{\circ}\text{C}$ . (with decomposition).

We wish to thank the National Research Council, Ottawa, for studentships to H.D. and M.H. and to the National Research Council and the Ciba Company for the support of these studies.

#### R E F E R E N C E S

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