Tetrahedron Letters No.54, pp. 5643-5646, 1968. Pergamon Press. Printed in Great Britain.

# SYNTHESES IN THE SERIES OF LYCOPODIUM ALKALOIDS. IX.
# TWO SIMPLE STEREOSPECIFIC SYNTHESES OF 12-epi-LYCOPODINE

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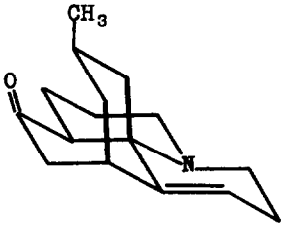
(Received in USA 20 August 1968; received in UK for publication 4 October 1968)

Some time ago we reported the synthesis (1) of 12-epi-lycopodine II. This compound is a hydrogenation product of anhydrolycodoline I (2) and has not yet been found in nature. However, alkaloids derived from II are known (3) and consequently we were interested in designing a stereospecific synthesis of II which would be simple and efficient enough to make the material freely available for transformations into natural products.

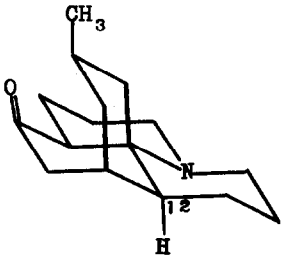
The previously described (1) bicyclic compound III was alkylated in dry DMF with sodium hydride and 6-bromo-1,2-hexadiene (4) at 80°C. The product IV was obtained in a 68% yield. Compound IV was an oil homogeneous in T.L.C. [I.R. ($CCl_4$): 1950, 1700, 1655, 1620 $cm^{-1}$; N.M.R.: multiplets (1 H) $\tau$ = 4.90 p.p.m., (2 H) $\tau$ = 5.26 p.p.m.; M.W. (mass spec.) = 259.] Compound IV was irradiated (1) in dry THF at -70°C. The product V was an oil homogeneous in T.L.C. and it was obtained in a yield of 70%. [I.R. ($CCl_4$): 1710, 1660 $cm^{-1}$; N.M.R.: doublet (2 H) centered at $\tau$ = 5.0 p.p.m.; M.W. (mass spec.) = 259.] Ketalization of V as described before (1) yielded the ketal VI (5) [m.p. 145-146°C.; M.W. (mass spec.) = 303]. Epoxidation of the exocyclic double bond in VI with perbenzoic acid in chloroform gave a quantitative yield of the corresponding epoxide VII [m.p. 158-160°C.; M.W. (mass spec.) = 319]. Reduction of VII with lithium borohydride in THF yielded the tertiary alcohol VIII in a 96% yield

[m.p. 123-126°C.; I.R. ($CCl_4$): 3560, 1655 $cm^{-1}$; N.M.R.: singlet (3 H) $\tau$ = 8.65 p.p.m.; M.W. (mass spec.) = 321]. The alcohol VIII was converted to the diketone IX by treatment with 1% hydrochloric acid in THF-water (1:1) at room temperature for 45 minutes. Compound IX was obtained in a yield of 47% [m.p. 163-166°C.; I.R. ($CCl_4$): 1720, 1650 $cm^{-1}$; N.M.R.: singlet (3 H) $\tau$ = 7.70 p.p.m.; M.W. (mass spec.) = 277]. The diketone IX was stirred with a mixture of methanol and 0.6% aqueous sodium hydroxide (1:1) for 36 hours. The bridgehead alcohol X was obtained in a yield of 80% [m.p. 257-258°C.; I.R. ($CHCl_3$): 3400, 1700, 1615 $cm^{-1}$; M.W. (mass spec.) = 277]. The alcohol X was stirred with an equal weight of phosphorus pentachloride in methylene chloride at -5°C. for 4.5 minutes. The chloride XI was obtained in a yield of 83% [m.p. 201-203°C.; I.R. ($CCl_4$): 1715, 1650 $cm^{-1}$; M.W. (mass spec.) = 295 ($Cl^{35}$) and 297 ($Cl^{37}$)]. Reduction of XI with zinc dust in glacial acetic acid yielded the 12-epi-lycopodine lactam XII in a 93% yield [m.p. 140°C.; I.R. ($CCl_4$): 1710, 1640 $cm^{-1}$; M.W. (mass spec.) = 261]. Finally $LiAlH_4$ reduction of XII, followed by Jones oxidation of the resulting amino alcohol gave 12-epi-lycopodine II (m.p. 56°C.) in a yield of 60%. The synthetic material was identical in T.L.C. in several systems, infrared in carbon tetrachloride, and mass spectrum with authentic 12-epi-lycopodine (2) and the previously synthesized (1) racemate of the same compound. Also the melting points of the two synthetic products were the same.

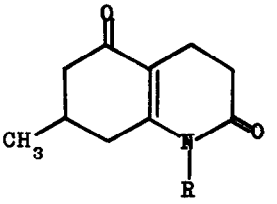
A further great improvement in simplicity and overall yield was achieved as follows. The bicyclic compound III was alkylated as described above with the bromoketal XIII (6). The product XIV was isolated as an oil homogeneous in T.L.C. in a yield of 63%. It was immediately deketalized by treatment with 2% hydrochloric acid in THF-water (1:1) at room temperature. The oily ketone XV which resulted was homogeneous in T.L.C. [I.R. ($CHCl_3$): 1710, 1690, 1650, 1620 $cm^{-1}$; N.M.R.: singlet (3 H) $\tau$ = 7.89 p.p.m.; M.W. (mass spec.) = 277]. The ketone XV (780 mg.) was dissolved



I



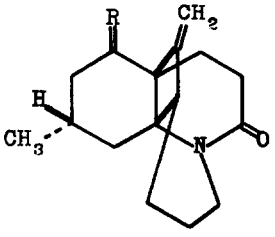
II



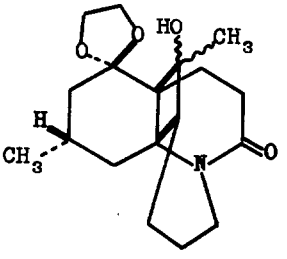
III (R = H)

IV (R = $-(CH_2)_3-C(H)=C=CH$)

XIV (R = $-(CH_2)_4-$  $-CH_3$)



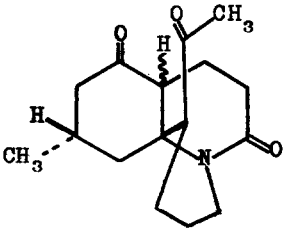
V (R = =O)



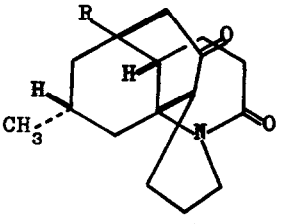
VIII

XV (R = $-(CH_2)_4-C(=O)-CH_3$)

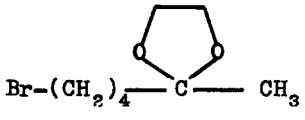
VI (R =  )



IX



X (R = OH)
XI (R = Cl)
XII (R = H)



XIII

in 60 ml. of 0.4% methanolic sodium methoxide. After 36 hours the methanol was distilled off in vacuo, water added and the product isolated by extraction and chromatography. A 30% yield of the alcohol X identical in all respects with the product obtained by the photochemical route resulted. The diketone IX formed by a stereospecific Michael reaction must clearly be an intermediate in this process.

## REFERENCES

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3. W. A. Ayer, T. E. Habgood, V. Deulofeu and H. R. Juliani, Tetrahedron 21, 2169 (1965).
4. This compound was synthesized by well known methods and will be described in the full paper, cf. A. Meisters and J. M. Swan, Australian J. Chem. 18, 163 (1965).
5. All crystalline compounds yielded correct elemental analyses. All the spectra of all compounds were recorded, but only specially relevant spectroscopic data are given.
6. Compound XIII will be described in a full paper; it was prepared by ketalization of the corresponding bromoketone, cf. E. P. Anderson, J. V. Crawford and M. L. Sherrill, J. Am. Chem. Soc. 68, 1294 (1946).