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SYNTHESES IN THE SERIES OF LYCOPODIUM ALKALOIDS IV.
A SIMPLE PHOTOCHEMICAL SYNTHESIS OF AN ANNOTININE DERIVATIVE

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At the outset of our studies directed towards the synthesis of various Lycopodium alkaloids, one of us (K.W.) proposed to approach the annotinine problem by a sequence which contained as a key step the novel photochemical addition I → II. It was not possible to utilize immediately this route because of difficulties which we experienced in the synthesis of the key compound I. Thus, the proposed photo addition was only studied on a cyclic model compound (1).

The difficulties in the preparation of I have now been overcome and we wish to report a stereospecific synthesis of the annotinine degradation product III by our photochemical method.

The starting material for the preparation of I was the known and readily available vinylogous amide IV (2). Compound IV was heated for ninety minutes with a 15% excess of acrylic acid to 135°C. Under these conditions compound I was formed quantitatively and it was purified by chromatography on silica gel.* (3) [($C_{12}H_{15}NO_2$), m.p. 81-83°C.; m.v. (mass spec.) 205; I.R. ($CHCl_3$) 1695, 1645, 1610 cm^{-1}; U.V. $\lambda_{max.}$ 298 mμ (log ε = 4.1).]

* All crystalline compounds gave satisfactory elemental analyses. An alternative synthesis of I worked out by C.A.J. Williams will be described in the full paper.

Compound I was dissolved in tetrahydrofuran and irradiated at -70°C. with an excess of allene in the already described manner (1). The adduct II was formed quantitatively.* It was purified by chromatography on alumina and a small amount of a persistent impurity was removed by aeration of an alkaline solution for 10 minutes. Finally, the product crystallized from ethyl acetate. It melted at 154-157°C. and was homogeneous in T.L.C. [($C_{15}H_{19}NO_2$); m.v. (mass spec.) 245; I.R. ($CHCl_3$) 1700 (ketone), 1640 (lactam), 908 cm^{-1} (exocyclic methylene); N.M.R. narrow doublet (2H) τ = 5 p.p.m. (vinylic hydrogen).]

The adduct II was ketalized in a refluxing benzene solution with ethylene glycol and p-toluenesulphonic acid. The crude ketal was hydrogenated over platinum oxide in ethanol and the hydrogenation product deketalized with p-toluenesulphonic acid in a refluxing acetone solution as described in the model series (1). The reduction product V obtained stereospecifically** in this manner was homogeneous in T.L.C. and was recrystallized to a m.p. 165-167°C. from ethyl acetate. [($C_{15}H_{21}NO_2$); m.v. (mass spec.) 247; I.R. (CCl_4) 1700 (ketone), 1660 cm^{-1} (lactam); N.M.R. clean doublet (3H) τ = 8.94, 9.05 p.p.m. (methyl).]

Compound V was reduced with sodium borohydride in aqueous tetrahydrofuran to the alcohol VI in quantitative yield. [($C_{15}H_{23}NO_2$); m.p. 182-183°C. (benzene); m.v. (mass spec.) 249; I.R. ($CHCl_3$) 3600 (OH), 1620 cm^{-1} (lactam).] The alcohol VI was converted into the mesylate VII with mesyl chloride in pyridine. The yield was quantitative and the product was purified by crystallization from benzene to a constant melting point of 162-164°C. [($C_{16}H_{25}NO_4S$); I.R. ($CHCl_3$) 1620 (lactam), no

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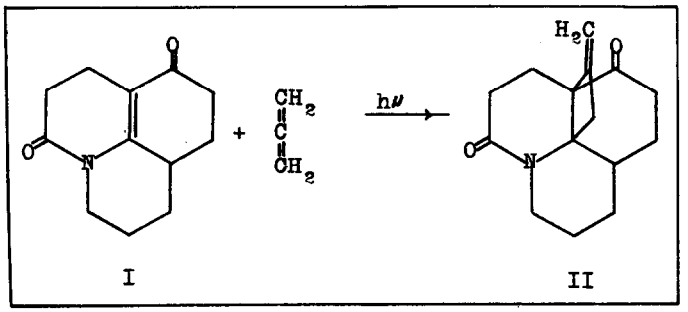
* The structure proof of II by an opening of the cyclobutane ring was performed by H. Dugas in connection with the utilization of II for the synthesis of various other Lycopodium alkaloids to be reported at a later date.

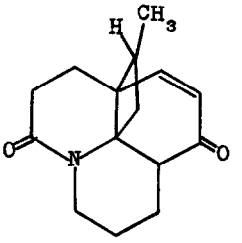
** The stereospecificity of the hydrogenation is clearly due to the one-sided shielding of the exocyclic double bond by the dioxolane grouping.

OH, 1375, 1175 cm^{-1} (OSO_2).] It was now our intention to eliminate the mesyl group from VII and obtain the olefin VIII. It turned out that this cannot be accomplished without some rearrangement. Remarkably, we obtained the best result by refluxing the mesylate VII with 3 - 4 moles of potassium cyanide in dimethylformamide. Under these conditions, the olefins VIII and IX were obtained in a 70% yield and equal quantities. Without separation, they were converted into the compounds III and XII and these were then separated by chromatography and crystallization. The mixture of VIII and IX was first oxidized with 1.5 moles of selenium dioxide in 97% acetic acid for 18 hours at reflux. The resulting acetates were hydrolysed with an excess of 1% methanolic potassium hydroxide to the alcohols X and XI and these finally oxidized to the ketones III and XII with chromium trioxide in pyridine. These products were separated by chromatography on silica gel and crystallized from ether-hexane. Compound III: [($C_{15}H_{19}NO_2$); m.p. 150-152°C.; m.v. (mass spec.) 245; I.R. ($CHCl_3$) 1690 (ketone), 1660 (double bond), 1620 cm^{-1} (lactam); U.V. $\lambda_{max.}$ 230 mμ (log ε = 4).] The infrared spectrum of III was superimposable with the spectrum of the corresponding optically active product obtained by us previously from annotinine (4). Compound XII: [($C_{15}H_{19}NO_2$); m.p. 164-165°C.; m.v. (mass spec.) 245; I.R. ($CHCl_3$) 1690 (ketone), 1660 cm^{-1} (lactam); N.M.R. singlet (1 H) τ = 3.6 p.p.m. (vinylic hydrogen); U.V. $\lambda_{max.}$ 250 mμ (log ε = 4.1).] The synthesis of III, besides corroborating the annotinine structure in general, constitutes the first chemical proof for the configuration of the annotinine methyl group.

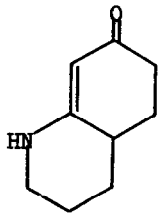
We wish to thank the National Research Council, Ottawa, the Ciba Company, Dorval, and the Research Corporation, New York, for supporting this work.



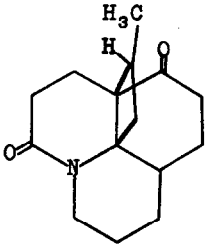
I II



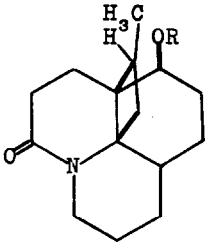
III



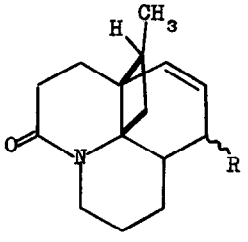
IV



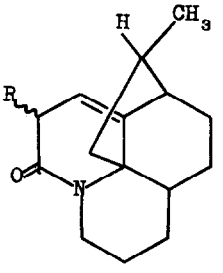
V



VI (R = H)
VII (R = Mesyl)



VIII (R = H)
X (R = OH)



IX (R = H)
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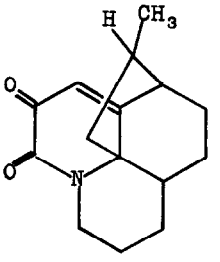

XII

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