Tetrahedron Letters No.49, pp. 4937-4940, 1967. Pergamon Press Ltd. Printed in Great Britain.

# SYNTHESIS IN THE SERIES OF LYCOPODIUM ALKALOIDS VIII.[1]
# THE TOTAL SYNTHESIS OF ANNOTININE

K. Wiesner and Lizzie Poon
Department of Chemistry, University of New Brunswick
Fredericton, New Brunswick, Canada

(Received in USA 10 August 1967)

More than ten years ago we have reported the structure determination of the first Lycopodium alkaloid annotinine (1) V. We now wish to announce the total synthesis of this compound. The synthesis of the annotinine lactam I has been described by us recently (2) and the present communication deals with the conversion of this compound to annotinine.

Compound I (250 mg.) prepared from annotinine (3) was dissolved in 150 ml. of carbon tetrachloride and 270 mg. of N-bromosuccinimide was added to the solution. The solution was irradiated at reflux with a strong visible light source for 30 minutes. Six identical runs were combined and the products separated by chromatography on silica. Elution with 30% chloroform-benzene and crystallization gave 300 mg. of the main product II* [ $C_{16}H_{18}O_3NBr$; m.p. 212°C.; I.R. (KBr): 1785, 1655, 1630 $cm^{-1}$. ] The infrared spectrum of compound II was superimposable on the spectrum of the previously known (3) chlorine containing analog prepared from annotinine (oxoanhydroannotinine-chlorohydrin). Also the mass spectra of both derivatives were identical except for the shift due to the difference in the atomic weight of chlorine and bromine.

.....

* Brominations of this type were first studied in our laboratory by Dr. J. A. Findlay and Dr. J. McCluskey. Compound II was however not obtained under the conditions employed by these workers.

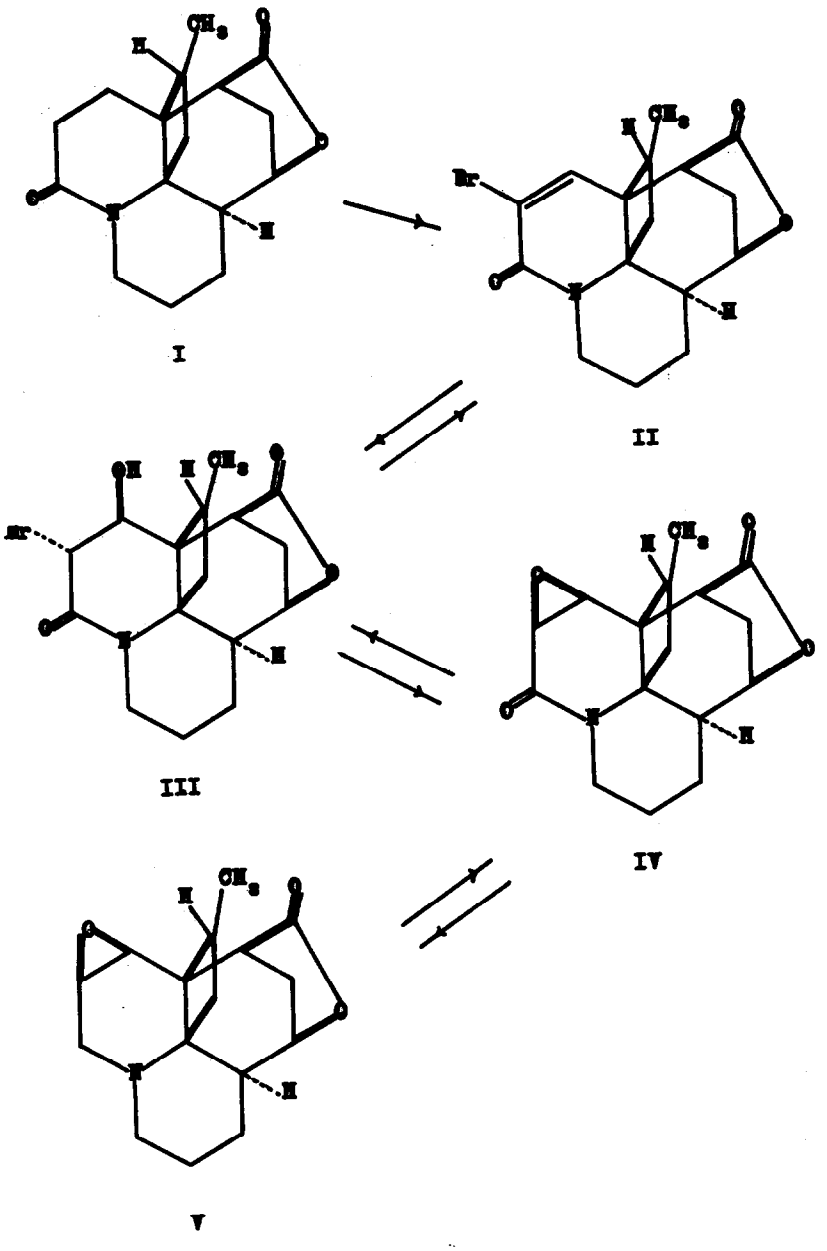
Compound II was identical by T.L.C. in several systems, mixed melting point and infrared spectrum in chloroform and KBr with the material prepared from oxoannotinine IV (vide infra). The bromo derivative II (120 mg. of the material prepared by bromination of I was used in this experiment) was heated with 80 ml. of 10% hydrobromic acid at 100°C. overnight. The bromohydrin III crystallized directly from the reaction mixture and was recrystallized from methanol [ $C_{16}H_{20}O_4NBr$; m.p. 260-2°C.; I.R. (KBr): 1765, 1630 $cm^{-1}$.] The product was identical by mixed melting point, infrared spectrum in KBr, mass spectrum, and T.L.C. with the material prepared from IV (vide infra).

Compound III (200 mg.) was dissolved in 25 ml. of acetone and 75 mg. of sodium bicarbonate in 2 ml. of water were added. The mixture was refluxed for four hours. Evaporation of the acetone and addition of water caused crystallization of the product IV. It was recrystallized from methanol. [ $C_{16}H_{19}O_4N$; m.p. 234°C.; I.R. (KBr): 1780, 1635 $cm^{-1}$.] The product was identical by infrared spectrum in KBr, mixed melting point, mass spectrum and T.L.C. with the previously known compound oxoannotinine (3).

The conversion of oxoannotinine IV to annotinine V has been already described (4) by Betts and MacLean and thus the first synthesis of a naturally occurring Lycopodium alkaloid is complete.

Oxoannotinine IV (2 g.) was heated for 2 hours with 260 ml. of 19% hydrobromic acid to 100°C. The product III was filtered off and crystallized from methanol. The yield was 1.8 g. and the data for this material are identical with those reported above.

The bromohydrin III (500 mg.) obtained from IV was refluxed for two hours with 30 ml. of $POCl_3$. The product was chromatographed on alumina and crystallized from methanol. The yield was 122 mg. of compound II. The data for this material were identical with those reported above.


I
II
III
IV
V

We wish to thank the National Research Council, Ottawa, The Research Corporation, New York, and the Hoffmann - La Roche Company, Nutley, New Jersey, for the financial support of our synthetic studies on annotinine.

## REFERENCES

1. K. Wiesner, Z. Valenta, W. A. Ayer and C. Bankiewicz, Chemistry and Industry, 1019 (1956); K. Wiesner, W. A. Ayer, L. R. Fowler and Z. Valenta, Chemistry and Industry, 564 (1957).
2. K. Wiesner and I. Jirkovsky, Tetrahedron Letters No. 22, 2077 (1967).
3. D. B. MacLean and H. C. Prime, Can. J. Chem. 31, 543 (1953).
4. E. E. Betts and D. B. MacLean, Can. J. Chem. 35, 211 (1957).