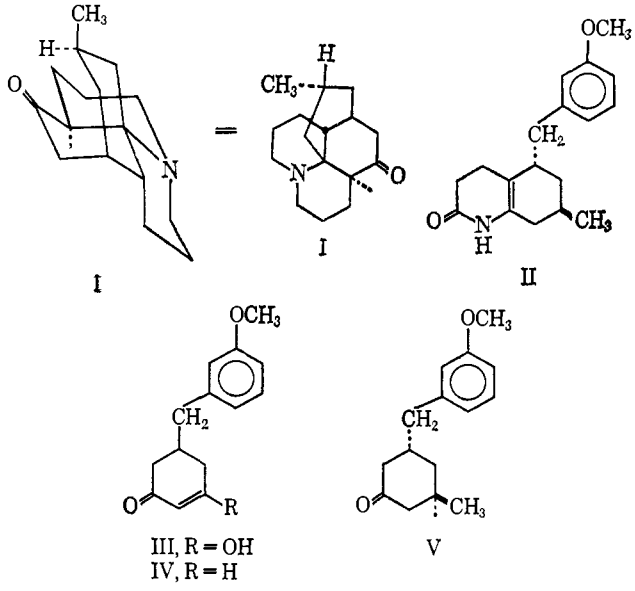
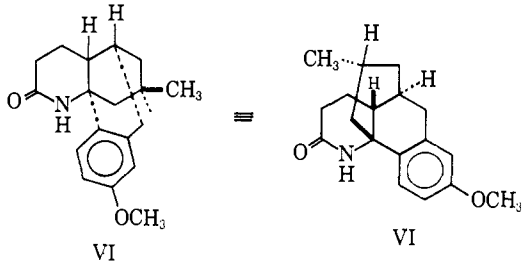
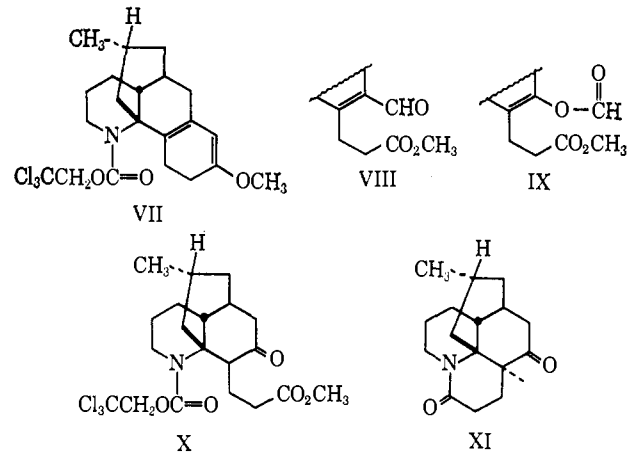


It was anticipated that only one of the two (reversibly) protonated species derivable from II would cyclize readily to the stereochemistry required of VI. This proved to be the case: treatment of II with 1:1 80% phosphoric acid–formic acid at room temperature for 20 hr gave, in addition to some *ortho* cyclization isomer, mp 201–202°, easily recognized by its nmr spectrum, a 55% yield of VI, mp 213.5–215.5° (δ ($CDCl_3$) 0.83 (broad, 3 H)), as the sole product of cyclization *para* to the methoxy group. The following sequence of steps



served to convert VI into the N-protected keto ester X. Removal of the amide carbonyl (lithium aluminum hydride–tetrahydrofuran) was followed by reduction of the anisole ring (lithium–ammonia, *t*-butyl alcohol, ether), conjugation (potassium *t*-butoxide in dimethyl sulfoxide, 4 hr, room temperature) to the homoannular diene (λ^{EtOH} 275 mμ (ε ~3800), λ^{film} 6.02 and 6.22 μ), the amino group of which was then protected as the trichloroethyl carbamate[5] VII, and ozonolysis (methanol, −80°) led to the aldehydo methyl ester VIII (λ^{EtOH} 249 mμ, λ^{film} 5.80, 5.85, and 6.01 μ, δ 3.67 (3 H, s), 10.2 (s)). Cleavage of the unsaturated aldehyde proceeded (selenium dioxide–anhydrous hydrogen peroxide in *t*-amyl alcohol, 3 hr at 70°) to the enol formate IX (δ 8.14 (s, 1 H)) which gave (1% sodium methoxide, 30 min, room temperature) the keto ester X, mp 141–141.5°, thus obtained in ~30% over-all yield starting from VI.

Heating with zinc dust in methanol (150°, 20 hr) removed the protecting group and formed the tetracyclic



keto lactam XI, mp 143–144° (λ^{CHCl_3} 5.88 and 6.18 μ; *m/e* 261 and 204 (base; loss of bridge)) from which lithium aluminum hydride reduction[6] (40-hr reflux in tetrahydrofuran) gave *dl*-dihydrolycopodine (*dl*-complanatine), mp 182–184°. The infrared spectrum in $CHCl_3$ of this substance was identical in every detail with that of a sample of authentic dihydrolycopodine,[7] mp 169°, prepared from natural lycopodine.[8] Oxidation[9] with chromic acid–acetone–sulfuric acid then gave *dl*-lycopodine, mp 130–131°, the mass spectrum of which was essentially identical with that of the natural alkaloid.[10]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

(5) *Cf.* T. B. Windholz and D. B. R. Johnston, *Tetrahedron Letters*, 2555 (1967).

(6) *Cf.* W. A. Ayer, J. A. Berezowsky, and G. G. Iverach, *Tetrahedron*, 18, 567 (1962); W. A. Harrison, M. Curcumelli-Rodostamo, D. F. Carson, L. R. C. Barclay, and D. B. MacLean, *Can. J. Chem.*, **39**, 2086 (1961).

(7) R. H. F. Manske, D. G. Lewis, and L. Marion, *ibid.*, **B20**, 87 (1942).

(8) We thank Professor L. Marion for a sample of natural lycopodine.

(9) *Cf.* B. Douglas, D. G. Lewis, and L. Marion, *Can. J. Chem.*, **31**, 272 (1953).

(10) W. A. Ayer, W. R. Bowman, T. C. Joseph, and P. Smith have also succeeded in synthesizing lycopodine (*cf. J. Am. Chem. Soc.*, **90**, 1648 (1968)), while a synthesis of an epimer has been described by H. Dugas, M. E. Hazenberg, Z. Valenta, and K. Wiesner (*Tetrahedron Letters*, 4937 (1967)).

Gilbert Stork, R. A. Kretchmer, R. H. Schlessinger

Department of Chemistry
Columbia University, New York, New York 10027

Received December 22, 1967

The Synthesis of *dl*-Lycopodine

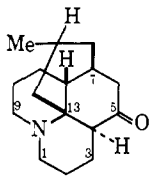
Sir:

Lycopodine, the most widely occurring of the *Lycopodium* alkaloids, has been shown[1] to possess structure **1**. We report herein a synthesis of lycopodine *via* the natural relay **2**.

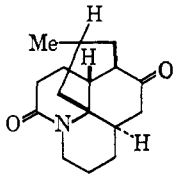
The immonium salt **3**, the synthesis of which has been reported,[2] was treated in tetrahydrofuran with the

(1) W. A. Harrison and D. B. MacLean, *Chem. Ind.* (London), 261 (1960); F. A. L. Anet, *Tetrahedron Letters*, **No. 20**, 13 (1960); W. A. Harrison, M. Curcumelli-Rodostamo, D. F. Carson, L. R. C. Barclay, and D. B. MacLean, *Can. J. Chem.*, **39**, 2086 (1961).

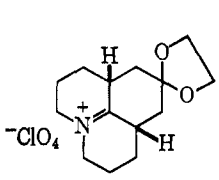
(2) W. A. Ayer, W. R. Bowman, G. A. Cooke, and A. C. Soper, *Tetrahedron Letters*, 2021 (1966).



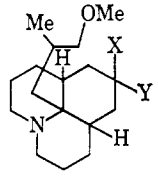
1



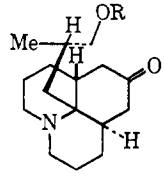
2



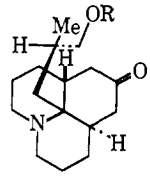
3



4, X = Y = ethylene ketal
5, X = Y = carbonyl

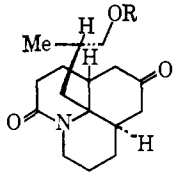


6, R = CH_3
8, R = H

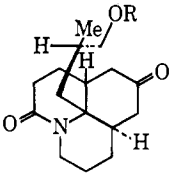


7, R = CH_3
9, R = H

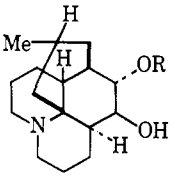
Grignard reagent prepared from 1-chloro-2-methyl-3-methoxypropane[3] to give in 90% yield the *cis,cis*-hexahydrojulolidine **4**: mp 49–51°; $\gamma_{max}^{CCl_4}$ 2805 and 2760 (Bohlmann bands) cm^{-1}. Hydrolysis of the ketal grouping in **4** gave ketone **5**: mp 48–53° (hydroperchlorate mp 128–131°); $\gamma_{max}^{CCl_4}$ 2820, 2775, 2700, and 1720 cm^{-1}. Treatment of **5** with boron tribromide in methylene chloride[4] gave the corresponding alcohol (**5**, OH in place of OCH_3), the stereochemistry of which has been established.[2] Isomerization of **5** by the method previously reported,[2] *i.e.*, bromination, dehydrobromination, and lithium–ammonia reduction, gave a mixture of the racemic diastereoisomeric ketones **6** and **7**. The over-all yield in this sequence was 15%. Although we have been unable to separate **6** and **7**, the corresponding alcohols **8** and **9**, prepared by treatment of the mixture of **6** and **7** with boron tribromide in methylene chloride,[4] are easily separable on an alumina column. Alcohol **8** was obtained,[5] in 20% yield, as an amorphous solid ($\gamma_{max}^{CCl_4}$ 3100 and 1700 cm^{-1}; τ 9.05 (3 H, d, $J \sim 5.5$ cps)), shown to be homogeneous by thin-layer chromatography (tlc) in several solvent systems. Alcohol **9**, which had a lower R_f value than **8** (tlc on alumina), was obtained in 30% yield and showed $\gamma_{max}^{CHCl_3}$ 3100 and 1720 cm^{-1}; τ 8.96 (3 H, d, $J \sim 5.5$ cps). Tosylation of **8** and **9** led to the formation of quaternary salts *via* internal ring closure on nitrogen. The alcohols **8** and **9** were therefore acetylated (acetic anhydride–pyridine) and oxidized (potassium permanganate in acetone) to the lactams **10** and **11**, respectively. Hydrolysis of **10** with 2% potassium hydroxide in methanol gave the lactam alcohol **12** as a chromatographically homogeneous oil: mol wt 279 (mass spectroscopy); $\gamma_{max}^{CHCl_3}$ 3600, 1720, and 1620 cm^{-1}. Treatment of **12** with methanesulfonyl chloride in pyridine gave the mesylate **13** (single spot on tlc) which, without further purification, was treated with potassium *t*-butoxide (2 equiv) in refluxing *t*-butyl alcohol for 15 min. The product consisted mainly of two components (tlc) which were separated by preparative tlc. The major component, isolated in 36% yield, was racemic lactam **2**: mp 157–158°; mol wt 261.1730 (mass spectrum), identical (ir spectrum, mass spectrum, and tlc behavior in several solvent systems) with the optically active lactam **2** described below. The minor component from this reaction has not as yet been identified.



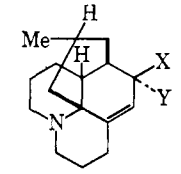
10, R = Ac
12, R = H
13, R = Ms



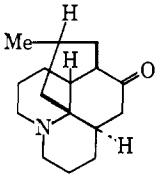
11, R = Ac
14, R = Ms



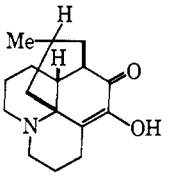
15, R = H
16, R = Ac



17, X = H; Y = OAc
18, X = H; Y = OH
19, X = Y; carbonyl
22, X = Y = H



20



21

Cyclization of the mesylate **14** derived from the acetate **11** gave a compound, $C_{16}H_{23}O_2N$ (mp 151–152°, $\gamma_{max}^{CHCl_3}$ 1708 and 1615 cm^{-1}), which had a mass spectrum very similar to that of the lactam **2** but which differed distinctly in infrared and nmr spectra. This compound is believed to be epimeric with **2** at C-15.

Lycopodine (**1**) was transformed into the diol **15** as previously described.[6] Acetylation of the diol **15** with acetic anhydride–pyridine at room temperature for 7 hr gave, in 71% yield, the monoacetate **16**: mp 57–59°; $[\alpha]^{27}D$ −53° (*c* 0.45, $CHCl_3$); $\gamma_{max}^{CCl_4}$ 3600, 3450, 1732, and 1235 cm^{-1}. Dehydration of **16** with thionyl chloride–pyridine gave the unsaturated acetate **17** which was immediately hydrolyzed with sodium hydroxide in aqueous methanol to the unsaturated alcohol **18**: mp 220–221°; $[\alpha]^{27}D$ −171° (*c* 0.2, EtOH); $\gamma_{max}^{CHCl_3}$ 3595 cm^{-1}; τ 4.42 (1 H, d, $J \sim 4$ cps), 6.25 (CHOH), and 9.17 (3 H, d, $J \sim 5$ cps). Oxidation of **18** with manganese dioxide in chloroform gave the unsaturated ketone **19**: mp 58–59° (hydroperchlorate mp 250–252°); uv λ_{max} (95% EtOH) 245 mμ (ϵ 10,400); $\gamma_{max}^{CCl_4}$ 1680 and 1630 cm^{-1}. Reduction of **19** with lithium–ammonia gave ketone **20**: mp 94–96°; methiodide mp 282–286°; ORD in ethanol (*c* 0.22): $[\alpha]_{579}$ −103°, $[\alpha]_{315}$ −1890° (trough), $[\alpha]_{274}$ +1550° (peak); $\gamma_{max}^{CHCl_3}$ 1708 cm^{-1}. The over-all yield of **20** from **16** was 60%. Oxidation of **20** with potassium permanganate in acetone at room temperature gave, in 22% yield, the lactam **2**: mp 142–143°; $[\alpha]^{27}D$ −32°; $\gamma_{max}^{CHCl_3}$ 1700 and 1613 cm^{-1}; τ 8.93 (3 H, d, J = 6 cps); mol wt 261.1732 (mass spectroscopy).

In order to complete the synthesis of lycopodine, lactam **2** was reduced with lithium aluminum hydride to the mixture of C-6 epimeric alcohols which, without further purification, was oxidized with Jones' reagent[7] to the ketone **20** (over-all yield from **2**, 88%). Oxida-

(3) E. E. Glover and G. Jones, *J. Chem. Soc.*, 3021 (1958).
(4) R. D. Youssefyeh and Y. Mazur, *Chem. Ind.* (London), 609 (1963).
(5) At this stage it was not possible to distinguish between **8** and **9**. The assignment of structures follows from the transformation of **8** into the keto lactam **2** of established stereochemistry.
(6) (a) W. A. Ayer and D. A. Law, *Can. J. Chem.*, **40**, 2088 (1962); (b) W. A. Ayer, J. A. Berezowsky, and D. A. Law, *ibid.*, **41**, 649 (1963).
(7) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

tion of **20** with selenium dioxide in aqueous dioxane provided the known[6a] diosphenol **21** in 30% yield. The diosphenol **21** was heated to 155° for 1 hr with hydrazine hydrate in diethylene glycol. The product, separated on alumina, consisted of lycopodine (**1**, 26%), anhydrodihydrolycopodine (**22**, 40%), which is also a naturally occurring *Lycopodium* alkaloid,[8] and dihydrodeoxylycopodine[6a] (**1**, C=O replaced by CH_2, ~10%). Since lycopodine has been transformed into annofoline[9] and into alkaloid L.20[6b] this synthesis also represents, in a formal sense, a synthesis of these alkaloids.[10]

Acknowledgment. We wish to express our thanks to the National Research Council of Canada for supporting this study. We also thank J. F. McCutcheon and A. C. Soper for their help in various phases of this work.

(8) B. Douglas, D. G. Lewis, and L. Marion, *Can. J. Chem.*, 31, 272 (1953).

(9) W. A. Ayer, D. A. Law, and K. Piers, *Tetrahedron Letters*, 2959 (1964).

(10) G. Stork, R. A. Kretchmer, and R. H. Schlessinger, *J. Am. Chem. Soc.*, 90, 1647 (1968), have also completed a synthesis of *dl*-lycopodine. Simultaneous publication has been arranged.

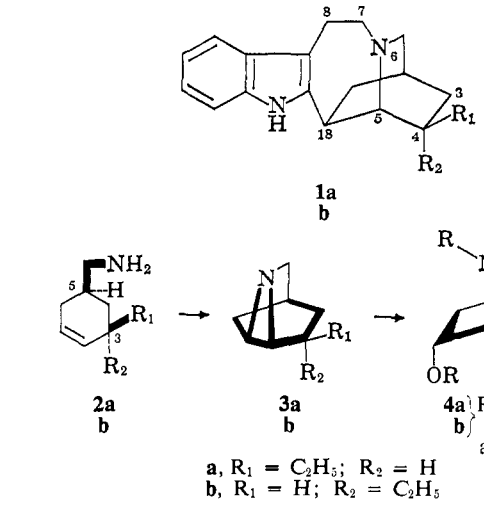
William A. Ayer, W. Russell Bowman, T. C. Joseph, Peter Smith
Department of Chemistry, University of Alberta
Edmonton, Alberta, Canada
Received December 22, 1967

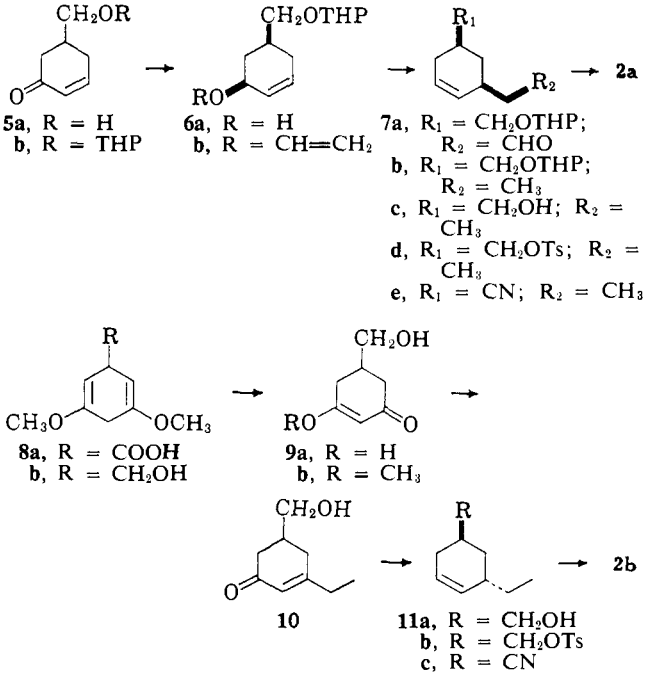
A Stereochemically Controlled Total Synthesis of *dl*-Ibogamine and *dl*-Epiibogamine

Sir:

A recent communication[1] on the stereocontrolled total synthesis of *dl*-ibogamine prompted us to disclose our own total synthesis of *dl*-ibogamine (**1a**) and *dl*-epiibogamine (**1b**).[2,3] Our synthesis is also stereochemically controlled, proving the assigned configurations of the ethyl side chains as depicted in **1a** and **1b**.

As was the case in our previous synthesis[4] of the alkaloid skeleton (desethylibogamine), the key reaction steps of the present synthesis comprise one-step conversion of *cis*- and *trans*-3-ethyl-5-aminomethylcyclohexenes (**2a,b**) into the bridged aziridines **3a,b** and cleavage of them to the isoquinuclidines **4a,b**.[4,5] For stereoselective synthesis of **2a**, the known compound **5a**,[6] after conversion into the tetrahydropyranyl ether **5b**[7] (83%), bp 123–129° (0.8–0.9 mm), was reduced with $LiAlH_4$ to **6a** (91%), bp 130–134° (0.5 mm), which on vinylation [**6b** (80% based upon the consumed **6a**), bp 110–115 (0.1 mm)] followed by pyrolysis[8] gave the aldehyde **7a**. The crude **7a** underwent the Huang-Minlon reduction giving **7b** (69% over-all yield from **6b**), bp 123–130° (6 mm), which on hydrolysis [**7c**, bp 97–100° (6 mm)] followed by tosylation (**7d**) and the Gabriel amination was transformed into pure **2a** in 67% over-all yield [**2a**, bp 104–106° (34 mm); picrate mp 153–154.5°]. The *cis* configuration in **2a** was based on the following evidence. On careful oxidation[9] followed by oximination and dehydration, **7c** was converted into the olefinic *cis*-nitrile **7e**,[10] bp 115–118° (32 mm), which was hydrogenated to *cis*-3-ethylcyclohexane-1-carbonitrile, bp 130° (bath temperature, 38 mm), identical with an authentic sample,[11] and reduced with $LiAlH_4$ to the amine **2a** identical with that prepared as described earlier. For the preparation of **2b**, the known compound **8a**[12] was reduced ($LiAlH_4$) giving **8b** (84%, *p*-





(1) S. I. Sallay, *J. Am. Chem. Soc.*, 89, 6762 (1967).

(2) The work was presented at the 11th National Symposium on the Chemistry of Natural Products, Oct 9, 1967, Kyoto, Japan. See the Abstracts, p 41.

(3) For previously reported total syntheses, see (a) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Am. Chem. Soc.*, 87, 2073 (1965); 88, 3099 (1966); (b) J. P. Kutney, W. J. Cretney, P. Le Quesne, B. McKague, and E. Piers, *ibid.*, 88, 4756 (1966). The formulas are shown in their absolute configuration. *Cf.* J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, 44, 637 (1966), and ref 3a.

(4) W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *J. Am. Chem. Soc.*, 89, 5046 (1967).

(5) W. Nagata, S. Hirai, K. Kawata, and T. Aoki, *ibid.*, 89, 5045 (1967).

(6) E. E. Van Tamelen and G. T. Hildahl, *ibid.*, 78, 4405 (1956).

(7) Satisfactory elemental analyses were obtained for all the compounds for which melting point or boiling point values are given. All the compounds cited showed reasonable spectral data.

(8) A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, 83, 198 (1961).

(9) K. E. Pfitzner and J. G. Moffat, *ibid.*, 85, 3027 (1963); 87, 5661, 5670 (1965).

(10) Separation of the *cis* and *trans* isomers by glpc was effective only for the olefinic nitriles 7e and 11c. This is the reason for this transformation.

(11) Preparation of the authentic sample will be described in a full paper.

(12) A. J. Birch, P. Hextall, and S. Sternkell, *Australian J. Chem.*, 7, 256 (1954).