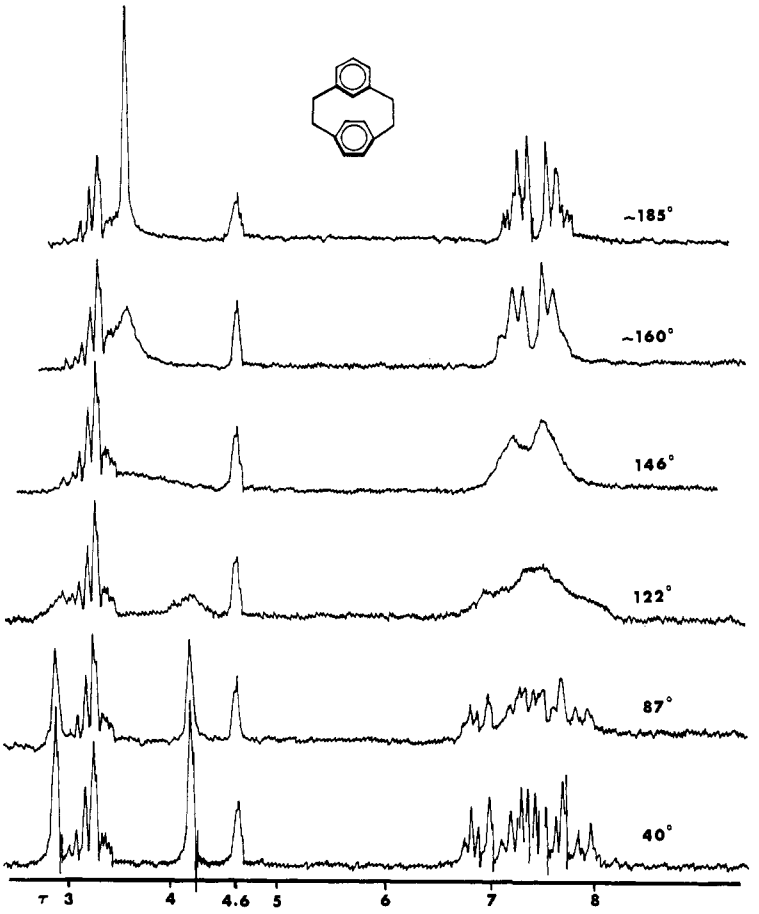

Figure 2. Nmr spectra of [2.2]metaparacyclophane (I) in hexachlorobutadiene (60 MHz).

ture (T_c = 140°) of the protons: k_1 = 85 sec^{-1}, k_{-1} = 175 sec^{-1} ($K_{140°}$ = 0.48). The activation parameters are listed. From these the half-life at 25° of IIe, with regard to reaching equilibrium with IIIe, was 14 sec.

Rate constant	$\Delta H^{\ddagger}$, kcal mol^{-1}, at −14–140°	$\Delta G_{140°}{}^{\ddagger}$, kcal mol^{-1}	$\Delta S_{140°}{}^{\ddagger}$, eu
k_1	17.7 ± 0.3	20.8 ± 0.4	−7.8 ± 2.2
k_{-1}	17.6 ± 0.3	20.2 ± 0.4	−6.1 ± 2.4

Hydrocarbon I also exhibited ring rotation[4] in its nmr spectrum in hexachlorobutadiene (Figure 2). Protons H_{12} and H_{13} (τ 2.87) and H_{15} and H_{16} (τ 4.12, $J \approx 1.5$ Hz) were observed to coalesce at 146°.[7] By *ca.* 185° these protons formed a sharp singlet and the methylene protons a symmetrical multiplet (AA'BB'). With $\Delta\nu$ = 75 Hz and the equation, $k = \pi\Delta\nu/\sqrt{2}$,[8] k = 167 sec^{-1} at 146°, and $\Delta G_{146°}{}^{\ddagger}$ = 20.6 ± 0.3 kcal mol^{-1}. This energy barrier indicates a half-life for ring inversion at 25° also on the order of seconds.

Carboxylic acid IIb was resolved through its brucine salt (recrystallized to constant rotation five times from methanol) to give material (23%), mp 168–169° (unchanged by recrystallization), $[\alpha]_{546}{}^{25}$ 34.2° (*c* 1.07, $CHCl_3$). At 25° the rotation was time independent, a fact that demonstrates that only *one of the two rings* is flipping. Should both turn over with respect to one another, (+)-IIb would racemize as well as pseudoepimerize (go to optically active IIIb). A sample of (+)-IIc when heated at 200° for 25 hr neat gave back (+)-IIc of unchanged rotation. Examination of molecular models of IIe indicates that the steric barrier to passing H_a of the *meta* past the *para* ring should be vastly less than that to passing the H_c's of the *para* past the *meta* ring.[9]

(7) Our chemical shifts and coalescence temperatures are more in agreement with those of ref 4a than those of ref 4b.

(8) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance," Vol. 1, Pergammon Press, Oxford, 1965, p 481.

(9) The authors wish to thank Professor F. A. L. Anet and his coworkers for their assistance and fruitful discussions, and Dr. H. J. Reich for carrying out and interpreting the C-13 nmr on IV.

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Biosynthesis of Lycopodine. The Incorporation of Pelletierine[1]

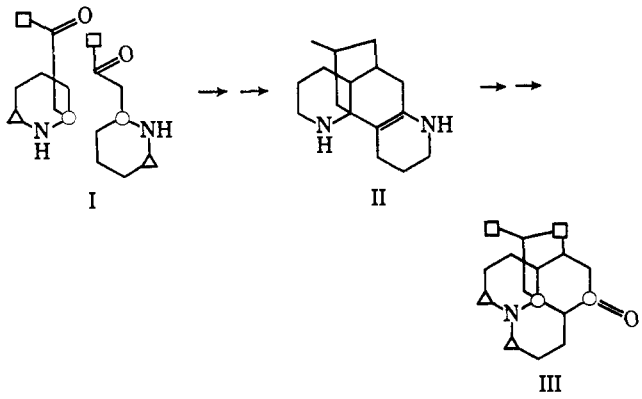
Sir:

Based on our observation[2] of nonrandom incorporation of radioactivity from [2-^{14}C]- and [6-^{14}C]lysine into lycopodine (III), we made the suggestion that the Lycopodium alkaloids originate from two pelletierine (I) units, whose piperidine nucleus is derived from lysine. The structural correspondence of pelletierine (I) to the obscurine skeleton (II), and hence to lycopodine (III),

(1) This investigation was supported by a grant from the National Research Council of Canada.

(2) R. N. Gupta, M. Castillo, D. B. MacLean, I. D. Spenser, and J. T. Wrobel, *J. Am. Chem. Soc.*, 90, 1360 (1968).

Scheme I



I II III

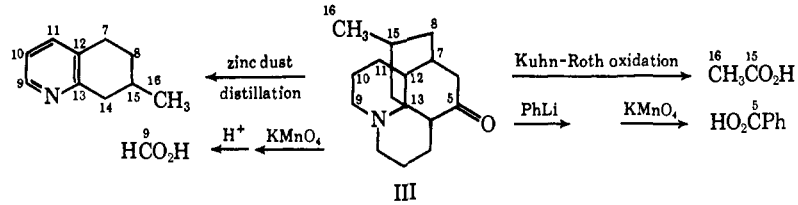
is shown in Scheme I. We now report the results of an experimental examination of the biosynthetic relationship of pelletierine and lycopodine.

The lycopodine samples were partially degraded to locate the sites of ^{14}C labeling. The degradation products which were isolated are shown in Scheme II.[5]

The relative specific activities of these products, obtained from the active samples of lycopodine, are presented in Table I.

The recovery, from the experiment with [^{3}H,^{14}C]-pelletierine, of lycopodine whose ^{3}H:^{14}C ratio matched that of the precursor was consistent with the hypothesis that lycopodine is a modified dimer of pelletierine. The absence of activity derived from [2-^{14}C]pelletierine at C-5 of lycopodine (benzoic acid) was not, however. The hypothesis demands 50% of activity at this site. It is evident that the C_8 unit of the lycopodine molecule which includes C-5 (*i.e.*, C-1 to -8) is not derived from pelletierine in the predicted manner. Since all activity derived from [2-^{14}C]pelletierine was confined to the portion of the molecule represented by 7-methyl-5,6,7,8-tetrahydroquinoline (C-7 to -16), it seemed likely that,

Scheme II



III

Labeled pelletierine was synthesized[3] by the reaction of acetoacetate with Δ^1-piperideine, which in turn was prepared by the oxidation of lysine. The following radiomers of pelletierine, prepared by this method, were administered to *Lycopodium tristachyum*:[4] [4,5-$^{3}H_2$,2-^{14}C]pelletierine (^{3}H:^{14}C 9.5 ± 0.1), [6-^{14}C]-pelletierine, and [2,3′-$^{14}C_2$]pelletierine, which was shown to contain 18 ± 0.3% of its label in the C-methyl group (C-3′) and 79 ± 2% of its label at C-2 of the piperidine ring.

Table I. Incorporation of Pelletierine into Lycopodine

Product	Precursor: [2-^{14}C]-Pelletierine[a]	[2,3′-$^{14}C_2$]-Pelletierine	[6-^{14}C]-Pelletierine
	Relative specific activity, %		
Lycopodine	100 ± 2	100 ± 2	100 ± 2
7-Methyl-5,6,7,8-tetrahydroquinoline (C-7 to -16)	94 ± 4	96 ± 3	
Acetic acid[b] (C-15,16)		18 ± 1	
Formic acid[b] (C-9)			104 ± 3
Benzoic acid (C-5)	1 ± 0.1		

[a] The data in this column refer to the ^{14}C activity of the sample of lycopodine derived from [4,5-$^{3}H_2$,2-^{14}C]pelletierine. [b] Isolated as the α-naphthylamide.

Radioactive lycopodine was isolated from each of the three feeding experiments. The sample from the experiment with [4,5-$^{3}H_2$,2-^{14}C]pelletierine showed a ^{3}H:^{14}C ratio (^{3}H:^{14}C 9.6 ± 0.1) identical with that of the precursor.

(3) R. N. Gupta and I. D. Spenser, *Can. J. Chem.*, 47, 445 (1969).

(4) A voucher specimen of the plant used in our experiments is now deposited in the herbarium of Algonquin Provincial Park, Ontario. It is unfortunate that an erroneous designation of the species used in our work was reported[2] in our earlier communication.

whereas the C_8 unit, C-1 to -8, was not derived from pelletierine at all, a pelletierine unit did indeed serve as the precursor of the other C_8 unit of the lycopodine molecule, C-9 to -16. This conclusion is supported by the recovery from C-9 (formic acid) of all activity derived from [6-^{14}C]pelletierine. Intact incorporation of a pelletierine moiety into the C_8 unit, C-9 to -16, is clearly established by the results of the experiment with [2,3′-$^{14}C_2$]pelletierine. Not only was all activity from this precursor present in the quinoline derivative (C-7 to -16), but the fraction of this activity, recovered in the Kuhn–Roth acetate (C-15,16), was identical with the fraction of activity at the C-methyl group of the precursor.

It is thus demonstrated that an intact pelletierine unit serves as a specific precursor of C-9 to -16 of lycopodine, as predicted. Contrary to prediction, however, lycopodine is not a modified dimer of pelletierine, since C-1 to -8 are not derived from this precursor. The origin of the latter C_8 unit is under investigation.

(5) We are greatly indebted to Dr. W. A. Ayer for informing us, prior to publication, of the results of D. A. Law (Ph.D. Thesis, University of Alberta) bearing on the oxidative cleavage of the C-9,10 bond of lycopodine and the isolation and identification of the resulting N-formylamino acid from which formic acid (representing C-9 of lycopodine) was obtained by hydrolysis.

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An "Artificial Enzyme" Combining a Metal Catalytic Group and a Hydrophobic Binding Cavity

Sir:

Although rate increases of up to 10^9 have been attained in some metal ion promoted reactions,[1] such