REACTIONS OF α-CYANOBROMOLYCOPODINE

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By

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SCOPE AND CONTENTS:

The reaction of α-cyanobromolycopodine with alkali proceeds with elimination of hydrogen bromide and a new ring is formed in the process. The properties of the compound, α-cyclocyanolycopodine, resulting from this cyclization reaction have been studied and a mechanism for its formation has been postulated. The olefin corresponding to that expected from the elimination of hydrogen bromide from α-cyanobromolycopodine has been prepared indirectly and the oxidative degradation of the olefin has been investigated.

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The author wishes to express his deep appreciation to Professor D. B. MacLean for his kind advice and encouragement during the course of this research.

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GENERAL INTRODUCTION

Lycopodine $C_{16}H_{25}ON$ is the most widely distributed of the Lycopodium alkaloids and has been found in all but two of the ten species (3) (4) (14-19) so far examined. The structural investigation of this alkaloid was begun by Manske and Marion who reported its dehydrogenation to quinoline derivatives. MacLean, Manske and Marion were able to demonstrate the existence of a carbonyl group in the molecule and reported that the reaction of lycopodine with cyanogen bromide yielded two isomeric cleavage products α - and β -cyanobromolycopodine, $C_{17}H_{25}ON_2Br$. The study of these cleavage products has been pursued in these laboratories during the past few years to yield further information on the structure of the molecule.

In this thesis, a study is reported of the reaction of α-cyanobromolycopodine with alkali. This reaction was first discovered by MacLean, Manske and Marion who reported that an elimination of hydrogen bromide had occurred through a cyclization process. Our findings support this explanation and indicate rather conclusively that the cyclization took place at a position α- to the carbonyl group in lycopodine. In our work, we were able to prepare indirectly the olefinic compound $C_{17}H_{24}ON_2$ which would have been expected to form by elimination of hydrogen bromide from α -cyanobromolycopodine.

This olefinic material is an important intermediate in that a study of its oxidation products would indicate whether lycopodine and annotinine have different skeletal structures (Annotinine is the only Lycopodium alkaloid whose structure is known,) The oxidation did

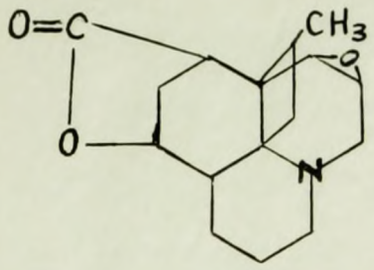
indeed occur, but with difficulty, and formaldehyde was isolated as expected as one of the oxidation products. The second product of the oxidation varied with the oxidising agent but in no case has it been adequately characterized. It can be stated, however, that an acid was not isolated as primary oxidation product and this fact strongly suggested that annotinine and lycopodine have different skeletal structures.

HISTORICAL INTRODUCTION

Lycopodine was first isolated by Boedeker (1) in 1881 from Lycopodium complanatum L. and was assigned the formula $C_{32}H_{52}O_3N_2$. In 1938 Ackmatowicz and Uzieblo (2) isolated this alkaloid along with two other alkaloids from Lycopodium clavatum L. They changed Boedeker's formula and assinged the formula $C_{16}H_{25}ON$ to lycopodine and found that the base did not contain any methoxyl, N-methyl or active hydrogen groups.

In 1942, Manske and Marion (3) reported the isolation of lycopodine and seven other alkaloids from Lycopodium flabelliforme Fernald, and confirmed the formula $C_{16}H_{25}ON$ for lycopodine which had been assigned by Achmatowicz and Uzieblo. Manske and Marion have also investigated other species of Lycopodium and reported the isolation of over thirty alkaloids (4) from ten plant species of the Lycopodium family.

The investigation of the detailed structure of the Lycopodium alkaloids has so far been limited to only a few alkaloids and the structure of only one of these, annotinine $C_{16}H_{21}O_3N$ has been determined (5) (6), as shown below.



Douglass, Lewis and Marion (7) found that lycopodine was related to two of the minor Lycopodium alkaloids. Anhydrodihydrolycopodine, which was prepared by dehydration of dihydrolycopodine with phosphorus

pentachloride, was shown to be identical with alkaloid L.14 isolated from L. tristachyum. The O-acetate of dihydrolycopodine was found to be identical with alkaloid L.2 which has been isolated from L. flabelliforme. It was found in this laboratory that the alkaloid L.1 assigned the formula $C_{18}H_{31}ON$ by Manske and Marion (3) was actually dihydrolycopodine.

Manske and Marion, in their second paper (8), reported the results of degradation studies with lycopodine. From the products of selenium dehydrogenation, they isolated five bases of which two were identified as 7-methylquinoline and 5, 7-dimethylquinoline. 7-methylquinoline was also obtained by treating lycopodine with palladium-barium sulphate or with phthalic anhydride. Lycopodine failed to react with phenyl magnesium bromide and could not be hydrogenated at 200° C., over Raney nickel at 2000 p.s.i. They concluded therefore that the alkaloid contained a completely reduced quinoline nucleus and no ketonic group in the molecule and considered the oxygen to be probably present in a cyclic ether linkage.

A more extensive investigation by MacLean, Manske and Marion (9) showed that the oxygen atom in lycopodine was present in a carbonyl group and not in an ether linkage. This was first indicated by the infrared spectrum which showed a strong absorption at 1693 cm^{-1} in the carbonyl region. This was also confirmed by the formation of a hydrazone, by hydride reduction to an alcohol (dihydrolycopodine) and by the formation of a tertiary carbinol with phenyl lithium.

MacLean, Manske and Marion attempted to degrade lycopodine through the N-oxide and by the Emde and Hofmann degradation but were unsuccessful.

However they found that the Von Braun reaction of lycopodine with cyanogen bromide (9) proceeded to yield two isomeric bromocyanamides ($C_{16}H_{25}ON_2Br$), designated α- and β-cyanobromolycopodine of which the former was formed in greater yield. α-Cyanobromolycopodine was converted to α-cyanoacetoxylycopodine ($C_{19}H_{28}O_3N_2$) by treatment with potassium acetate in ethanol and hydrolysis of the latter yielded an alcohol, α-cyanohydroxylycopodine ($C_{17}H_{26}O_2N_2$). Oxidation of the alcohol yielded an acid which contained the same number of carbon atoms. It was thus established that α-cyanobromolycopodine was a primary bromide. When β-cyanobromolycopodine was treated with ethanolic potassium acetate, a non-alcoholic, halogen-free neutral compound $C_{17}H_{24}ON_2$ was obtained, which was resistant to oxidation and catalytic hydrogenation. The same compound was obtained from β-cyanobromolycopodine by treatment with methanolic potassium hydroxide. It was postulated by MacLean et.al. that the β-product $C_{17}H_{24}ON_2$ was a cyclized compound formed by the removal of hydrogen bromide. An isomeric cyclized compound, α-cyclocyanolycopodine, $C_{17}H_{24}ON_2$, was also obtained by them from α-cyanobromolycopodine by treatment with methanolic potassium hydroxide.

A study of the reactions of β-cyanobromolycopodine has been made by Harrison (10) with a view toward carrying out a series of reactions similar to those reported for the α-compound. However, in all cases, the main product was the β-cyclocyanolycopodine $C_{17}H_{24}ON_2$. A comprehensive study by Harrison of the reactions of this compound has failed to reveal its structure. Harrison has suggested two alternative structures which could account for the properties of this unusual compound (a) an enol ether structure and (b) a cyclopropyl ketone structure,

but neither structure satisfactorily explains all of the experimental results.

In a recent paper (11) published by Barclay and MacLean of this laboratory, the reactions of α-cyanobromolycopodine and its derivatives were reported. In their investigation a study of the reactions of α-cyanobromolycopodine was undertaken in the expectation that more information concerning the ring structure of the alkaloid would be obtained but their work was only moderately successful. They converted α-cyanobromolycopodine to α-cyanolycopodine by the method of MacLean, Manske and Marion (9) and this compound was hydrolysed to the secondary base, α-des-dihydrolycopodine ($C_{16}H_{27}ON$). It was methylated by formaldehyde and formic acid to a tertiary base which analysed for a single N-methyl group. Conversion of the tertiary base to a quaternary salt by methyl iodide proceeded in very poor yield making it of little use for degradation studies. An attempt to carry out a reductive fission of the quaternary salt was unsuccessful. There is no satisfactory explanation offered for the failure of tertiary N-methyl base to form a methiodide readily. Lycopodine, on the other hand, formed a methiodide rapidly and quantitatively when an acetone solution of the base was mixed with methyl iodide.

Barclay and MacLean reported an investigation of the hydride reduction of α-cyanobromolycopodine and its derivatives. From their work, convenient methods were developed for the formation of the following intermediates used in their studies and in subsequent investigations. The secondary keto base $C_{16}H_{27}ON$ was converted to the carbinol $C_{16}H_{29}ON$ by lithium aluminium hydride. This carbinol was also obtained directly from α-cyanobromolycopodine by reduction with lithium aluminium

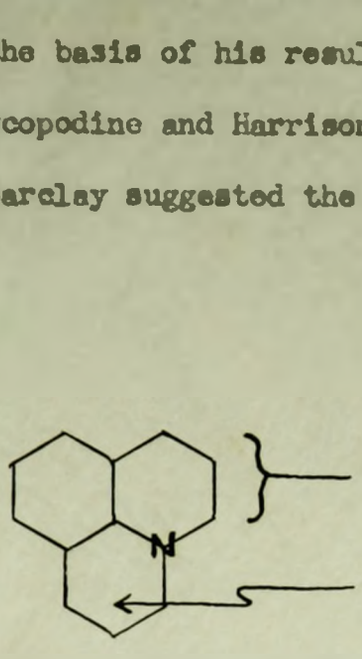
hydride. The reaction of α-cyanobromolycopodine with sodium borohydride yielded the compound $C_{17}H_{28}ON_2$ in which the carbonyl group was reduced and the bromine was replaced by hydrogen. However the borohydride failed to affect the cyanamide group.

Barclay also investigated the dehydrogenation of α-des-tetrahydrolycopodine $C_{16}H_{29}ON$ (12). Dehydrogenation of the compound with palladium-charcoal produced a small amount of a dehydrogenation product which from spectroscopic evidence appeared to be an alkylated quinoline containing at least one methyl group and possibly other alkyl groups or an attached saturated ring. It was suggested that a saturated quinoline ring system was still present in α-cyanobromolycopodine and its derivatives.

Harrison (10), of this laboratory, converted the α-cyanobromolycopodine to the α-cyanolycopodine carboxylic acid and the acid was hydrolysed to the amino acid hydrochloride, which upon esterification with diazomethane was partially converted to a lactam, $C_{16}H_{23}O_2N$. The lactam carbonyl absorbed at 1635 cm.$^{-1}$ in the infrared, which indicated a lactam ring of six atoms or larger. Reduction of the lactam with lithium aluminium hydride yielded dihydrolycopodine. He also converted α-cyanolycopodine carboxylic acid to a mixture of the hydroxy acid and a lactone $C_{17}H_{24}O_2N_2$ by reduction with sodium borohydride. The infrared spectrum of the lactone showed a strong peak at 1743 cm.$^{-1}$ (nujol mull) or 1760 cm.$^{-1}$ (CCl_4 solution). Since the $>C=O$ stretching absorption of five- and six-membered lactones

are 1760 - 1780 cm.$^{-1}$ and 1735 - 1750 cm.$^{-1}$ respectively, it is not clear whether the lactone was five-membered or six-membered.

On the basis of his results on the dehydrogenation of α-des-tetrahydrolycopodine and Harrison's work on the formation of the lactam, $C_{16}H_{23}O_2N$, Barclay suggested the following partial structure for lycopodine



potential quinoline ring system in the α-compounds

ring opened in the formation of α-cyanobromolycopodine

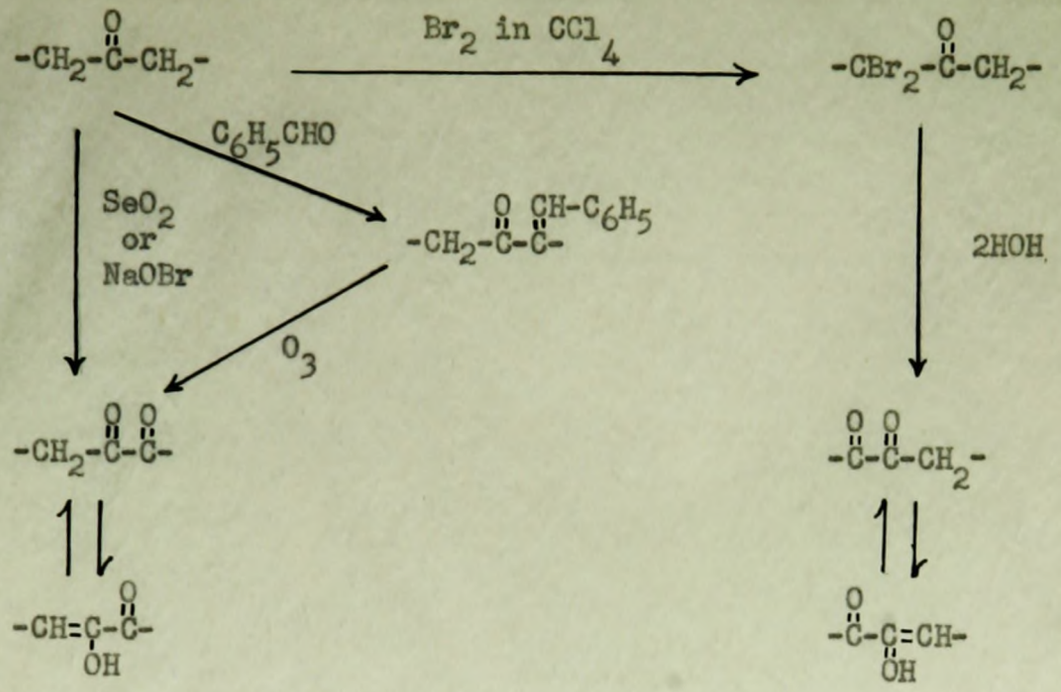
Barclay and MacLean also reported their studies of the bromination of lycopodine, α-des-dihydrolycopodine and α-cyanolycopodine. Lycopodine and α-des-dihydrolycopodine readily formed monobromo derivatives isolated as their hydrobromides. Unfortunately they could not investigate these derivatives (12) further because they underwent decomposition on conversion to their corresponding bases. α-Cyanolycopodine reacted readily with bromine in carbon tetrachloride to form an amorphous precipitate, from which a small amount of monobromo derivative was isolated. The carbonyl absorption in the infrared of this brominated derivative was displaced by 10 cm.$^{-1}$ to 1710 cm.$^{-1}$ from its position at 1700 cm.$^{-1}$ in the starting material, a displacement consistent with the formation of an α-bromoketone. Treatment of the amorphous residue with alkaline aqueous dioxane yielded a product from which a crystalline compound was obtained. This crystalline compound $C_{17}H_{24}O_2N_2$ had enolic properties and infrared and ultraviolet absorption spectra

indicated a structure of the type $-C(OH)=C-C(=O)-$. Such a structure would arise from an α , α -dibrominated ketone, $-CH-CBr_2-C=O$. This result thus established the presence of an active methylene group in lycopodine adjacent to the carbonyl group. This was confirmed by the formation of a benzal derivative of α -cyanolycopodine.

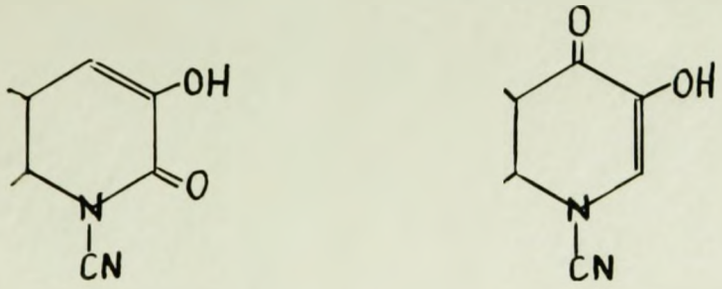
The position of the carbonyl group was also considered to be close to the nitrogen in lycopodine from the evidence that monobromination of lycopodine and α -des-dihydrolycopodine greatly reduced the basicity of these bases.

Like Douglass et.al., Barclay and MacLean were not able to prepare a benzal derivative of lycopodine which suggests that the position adjacent to the carbonyl group was hindered in lycopodine and that the opening of the ring in the formation of the α-compound made it more accessible.

Barclay also investigated the reactions of the benzal derivative of α-cyanolycopodine, which proved to be a convenient starting point for further degradation studies. Ozonolysis of the benzal compound in methanol yielded an enol isomeric with that obtained from α-cyanolycopodine by bromination and hydrolysis. The isomeric enol was also obtained by oxidation of α-cyanolycopodine with selenium dioxide and sodium hypobromide. These results suggest that two such enols could arise from two active methylene groups in α-cyanolycopodine as shown below.



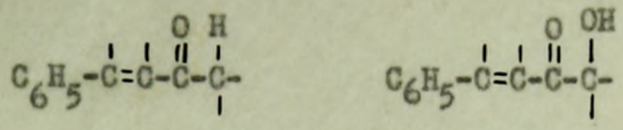
On the basis of these results, Harrison (10) proposed a β-piperidone structure for lycopodine. He suggested that a β-piperidone relationship of the carbonyl and nitrogen could explain the different enols obtained from α-cyanolycopodine under different conditions as well as the basicity determinations carried out by Barclay (11) on lycopodine and some of its derivatives. The two enols were thus formulated as follows.



Barclay presented evidence, based on spectroscopic studies of these compounds, which preclude these structures. Instead he suggested that the carbonyl and nitrogen were present in adjoining rings.

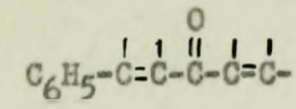
Oxidation of the benzal tertiary base $C_{24}H_{33}ON$ with selenium

dioxide yielded a hydroxy base $C_{24}H_{33}O_2N$. From spectroscopic evidence, Barclay postulated that the new hydroxyl function entered alpha and axial to the carbonyl group as shown.

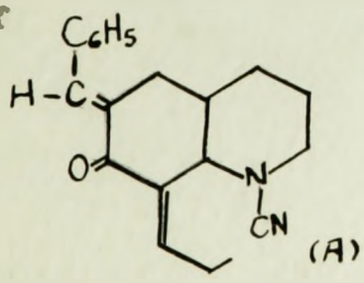


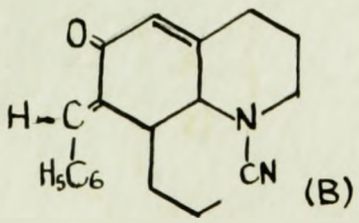
The hydroxy base failed to oxidize both under the usual Oppenhauer oxidations and under the conditions of the modified Oppenhauer reaction with potassium tertiary butoxide and benzophenone. Thus he suggested the hydroxyl function might be tertiary.

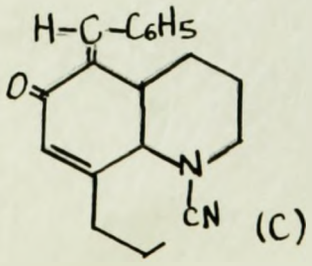
Benzal α-cyanolycopodine $C_{24}H_{30}ON_2$ also reacted with selenium dioxide to yield two oxidation products. One of these products was found to be a hydroxylated compound $C_{24}H_{30}O_2N_2$, with the hydroxyl group apparently alpha to the carbonyl group. A second neutral oxidation product was a brilliant yellow crystalline solid which analysed for $C_{24}H_{28}ON_2$. Infrared and ultraviolet spectrum studies of this compound indicated a chromophore of the following type;



Thus, Barclay suggested the following partial structures for the second neutral oxidation product $C_{24}H_{28}ON_2$ and considered partial structure (A) to be the most likely since it has the closer relationship of

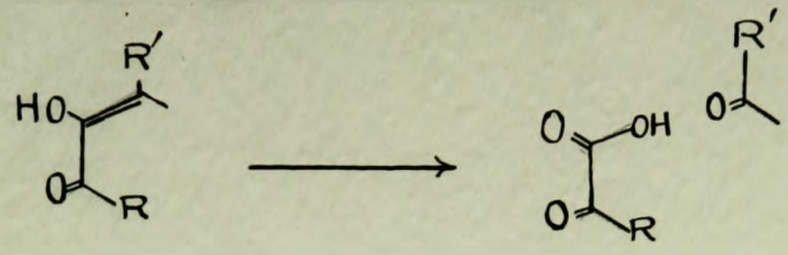

(A)


(B)

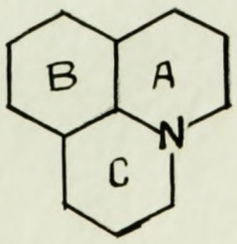

(C)

the carbonyl to the nitrogen.

Harrison (13) has recently subjected the enol obtained by Barclay from ozonolysis of the benzal compound to permanganate oxidation. The product was apparently a diketo carboxylic acid with one carbonyl group α- to the carboxyl group as shown:



From this review of the chemistry of lycopodine, it is obvious that only a few structural features can be definitely assigned. These are (a) the presence of a methylene group adjacent to the nitrogen atom which is contained in a ring of six atoms or more, (b) a carbonyl group which forms part of a six-membered or larger ring and which is flanked by one methylene group. There is however a large body of evidence, which, although not unequivocal, allows one to postulate a partial structure for the molecule. As evidence in this category one may cite (a) the dehydrogenation data of Manske and Marion and of Barclay, (b) the oxidation studies of the benzal derivative of α -cyanolycopodine by Barclay and by Harrison and (c) the lactonization and lactamization of α -cyanolycopodine carboxylic acid by Harrison. A skeletal structure consistent with these observations is shown below in which the carbonyl group would be situated in ring B.



In this structure no attempt is made to assign a position to the fourth ring of lycopodine.

The work which is presented in this thesis is concerned mainly with the mode of formation of α-cyclocyanolycopodine. An attempt has also been made to determine whether or not lycopodine has a different skeletal structure than annotinine.

DISCUSSION OF RESULTS

The reaction of lycopodine with cyanogen bromide was first reported by MacLean, Manske and Marion (9). In this reaction two isomeric products were formed which were designated α - and β -cyanobromolycopodine. It was observed by the above workers that α-cyanobromolycopodine was converted into a compound $C_{17}H_{24}ON_2$ by the action of methanolic potassium hydroxide. This compound had none of the properties of an olefin which they had expected to obtain. It was proposed by them that the elimination of hydrogen bromide was accompanied by a cyclization reaction probably α- to the carbonyl group. In a second attempt to obtain an olefinic compound they converted α-cyanobromolycopodine into α'-cyanotrimethyl ammonium lycopodine bromide. Conversion of the quaternary salt to the quaternary base followed by pyrolysis yielded two products, a neutral product similar to that obtained by the action of alkali on the α-cyanobromolycopodine, and a basic product which proved to be α-cyanodimethylaminolycopodine. These reactions are summarized in Figure 1.

This investigation was undertaken to study this cyclization reaction in more detail and to test the postulate of MacLean, Manske and Marion concerning the mode of formation of the cyclic compound. In the course of this work, the olefin which had eluded the previous workers was prepared and a study of its preparation and degradation was undertaken.

(1) α-Cyclocyanolycopodine

The presence of a carbonyl group in this compound was demonstrated by an examination of its infrared absorption spectrum which showed a strong absorption in the carbonyl region at 1700 cm.$^{-1}$. The nitrile group absorption occurred at 2200 cm.$^{-1}$ but no absorption characteristic of a double bond was noted. The ultraviolet spectrum failed to show any significant absorption. The presence of the carbonyl group was confirmed by conversion to α-cyclo(cyano)dihydrolycopodine $C_{17}H_{26}ON_2$ by reduction with sodium borohydride. In one experiment an isomeric dihydro compound was obtained. Both isomers analysed for $C_{17}H_{26}ON_2$ and their infrared absorption spectra were found to be nearly identical. They melted at 219° and 141° C. respectively. These compounds must be epimeric. Later attempts to prepare the isomer (M.P. 141° C.) under various modified conditions were unsuccessful. Oxidation of both isomers with chromic acid gave the same compound, α-cyclocyanolycopodine.

The properties of the α-cyclized compound contrast with those of β-cyclocyanolycopodine formed by the action of bases on β-cyanobromolycopodine. The β-cyclized compound has been investigated quite extensively by Harrison (10). He found that the infrared spectrum of the β-cyclized compound had a band at 1675 cm.$^{-1}$ replacing the carbonyl band found at 1700 cm.$^{-1}$ in β-cyanobromolycopodine, and that the compound was inert to the action of hydrides and other carbonyl reagents.

α-Cyclocyanolycopodine was obtained by MacLean et.al. from the quaternary salt of α-cyanodimethylaminolycopodine $C_{20}H_{34}ON_3Br$ by Hofmann decomposition. The same sequence of reactions has been

carried out with the reduced compound, ∝-cyanodihydrodimethylaminolycopodine in order to determine the role of the carbonyl function in the cyclization reaction. The reaction of ∝-cyanobromolycopodine with dimethylamine yielded ∝-cyanodimethylaminolycopodine $C_{19}H_{31}ON_3$, which was reduced with sodium borohydride to ∝-cyanodihydrodimethylaminolycopodine $C_{19}H_{33}ON_3$ and the latter was converted to the quaternary salt by treatment with methyl iodide. Treatment of the quaternary salt with potassium tertiary butoxide yielded two fractions, a neutral, which was found to be a mixture of two olefins ($C_{17}H_{24}ON_2$ and $C_{17}H_{26}ON_2$) and a basic product, which proved to be a mixture of ∝-cyanodimethylaminolycopodine and its dihydro derivative. (These reactions are summarized in Figure 2 and will be discussed later in detail.) Since cyclization did not occur in the dihydro compound, it suggested that the carbonyl group was a necessary structural feature for cyclization to occur. It can be argued therefore that the cyclization reaction very likely took place at a position ∝- to the carbonyl group.

(2) Attempted Formation of a Benzal Derivative

The presence of a methylene group adjacent to the carbonyl group in the ∝-cyanolycopodine has been shown by Barclay and MacLean who were able to prepare a benzal derivative of this compound in good yield.

An attempt was therefore made to prepare a benzal derivative of ∝-cyclocyanolycopodine but no reaction occurred. The failure to form a benzal compound might be attributed to the absence of a methylene group in this compound but could also be the result of steric

hindrance. (Lycopodine fails to form a benzal derivative although α-cyanolycopodine does.) Although this evidence is not conclusive, it indicates that the cyclization took place at the methylene group adjacent to the carbonyl function.

(3) Attempted Dehydration of α-Cyclodihydrolycopodine

The dehydration of the α-cyclized compound was attempted in order to prepare an olefinic compound for further degradation study. It was hoped that information concerning the carbon centre at which cyclization took place could be obtained.

Dehydration of α-cyclocyanodihydrolycopodine was attempted first in toluene using p-toluene sulfonic acid as a dehydrating agent. The infrared spectrum of the reaction product still showed a strong absorption in the hydroxyl region at 3500 $cm.^{-1}$ as well as -C≡N absorption at 2200 $cm.^{-1}$. There were also absorption bands at 1700, 1680 and 1630 $cm.^{-1}$. The band at 1630 $cm.^{-1}$ indicated that the dehydration of the compound took place to some extent but the bands at 1700 and 1680 $cm.^{-1}$ have not been assigned. The mixture obtained in this reaction could not be separated by chromatography on alumina as by other methods. Dehydration with other agents (p-toluene sulfonyl chloride, iodine, phosphorus oxytrichloride) in various solvents were also unsuccessful.

The Chugaev reaction was also considered as a possible reaction to the preparation of an olefin. Despite repeated attempts, it was not possible to prepare the intermediate xanthate derivative.

The reaction of phenyl lithium with α-cyclocyanolycopodine was attempted in the expectation that a phenyl carbinol derivative of

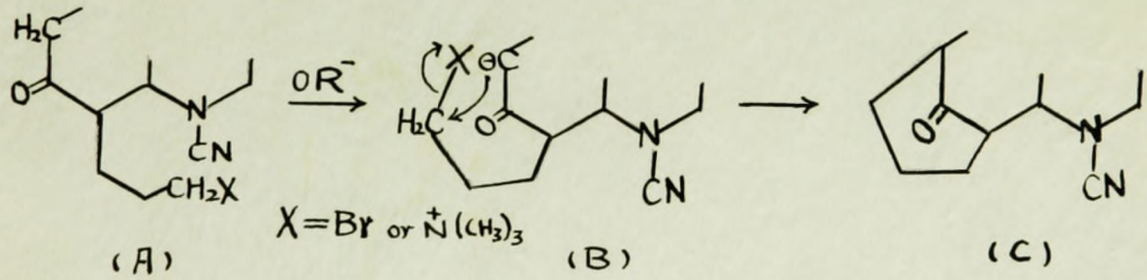
the compound would form which could dehydrate easily to give an olefin. α-Cyclocyanolycopodine was treated with phenyl lithium in a manner which gave a successful reaction with lycopodine. The infrared absorption spectrum of the crude reaction product had no -C≡N absorption band at 2200 cm.$^{-1}$ but still showed a strong band at 1700 cm.$^{-1}$ in the carbonyl region as well as the characteristic phenyl absorption bands at 1600 and 1580 cm.$^{-1}$. There was also a broad band in the region 3200 - 3500 cm.$^{-1}$, possibly an -NH absorption, and a band at 1660 cm.$^{-1}$. The crude product was chromatographed on alumina with chloroform as eluant and several fractions were separated, none of which were obtained crystalline. The band at 1700 cm.$^{-1}$ was present in all the compounds separated which indicated that phenyl lithium did not react with the carbonyl group, although it apparently reacted with the cyanamide group.

It was considered possible that the reaction of phenyl lithium with the cyanamide group could have interfered with its reaction with the carbonyl group. α-Cyclocyanolycopodine was therefore converted to the secondary amine $C_{16}H_{25}ON$ and this compound was methylated with formaldehyde and formic acid to the tertiary base $C_{17}H_{27}ON$. The α-cyclized tertiary base was treated with phenyl lithium in the same manner as before. From the reaction product, 65% of the starting material was recovered. The remaining reaction product, which was also basic, had an infrared spectrum with absorption bands at 1690 cm.$^{-1}$ in the carbonyl region, a weak band at 1600 cm.$^{-1}$ and fairly strong absorption in the hydroxyl region. It was obviously a mixture and probably contained a small amount of phenyl carbinol mixed with starting material.

The results of the phenyl lithium reaction of the α-cyclized compound suggested that the failure of the reaction was due mainly to a steric effect. The same explanation can be used to account for the fact that a xanthate derivative could not be obtained from α-cyclocyanodihydrolycopodine. It is however difficult to understand why the attempted dehydration reactions were not successful.

Attempts were made to prepare the quaternary salts of N-methyl α-cyclolycopodine and its dihydro derivative. Neither of these compounds would react with methyl iodide. This behaviour is similar to that of α-des-dihydrolycopodine reported by Barclay. A satisfactory explanation of these results is not forthcoming but it is interesting to note the similar behaviour in the two series of compounds.

The evidence now before us allows one to formulate a mechanism for the cyclization reaction which is depicted in the partial structure below.

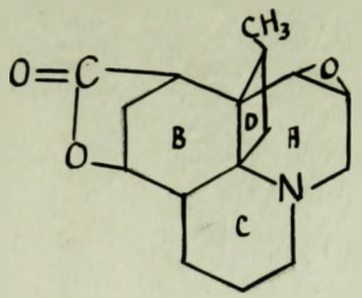


In the presence of basic catalyst, a proton is abstracted from the methylene group in A α- to the carbonyl function to yield the intermediate B. The anion so formed now displaced the group X (either Br or $\overset{+}{N}(CH_3)_3$) to form the cyclic compound C, α-cyclocyanolycopodine. This scheme is supported by (a) the failure of α-cyanotrimethylammonium dihydrolycopodine to form cyclic derivative, (b) the failure of α-cyclocyanolycopodine to form a benzal derivative and (c) the failure of α-cyclo-

N-methyl lycopodine to react readily with phenyl lithium indicating a more hindered carbonyl group than that found in lycopodine itself.

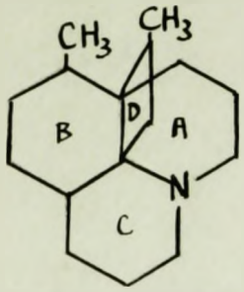
(4) Preparation and Reactions of the Olefin

One of the major alkaloids in the Lycopodium family, annotinine, is also a sixteen carbon alkaloid like lycopodine. It is the only alkaloid in this family whose structure has been determined as shown below.



Annotinine

It is expected that these alkaloids are related at least biogenetically, and may have the same skeletal structure. In the latter event, lycopodine could be represented according to the formula below,



in which a carbonyl group is situated in one of the three six-membered rings but most likely in ring B. (The evidence for this assignment is discussed in the Introduction.) Harrison has shown that α-cyano-bromolycopodine is formed by fission of a six-membered or larger ring; in this case it would involve either ring A or ring C. Oxidative degradation of the olefin $C_{17}H_{24}ON_2$ formed by the action of potassium

tertiary butoxide on the quaternary salt of α-cyanodihydrodimethylaminolycopodine would indicate whether lycopodine had a different ring structure than annotinine. Formation of a ketone, for example, would preclude the same skeletal structure, although formation of an acid on oxidation would not give a definite answer to this question. The olefin therefore is an important intermediate in the degradation study and it is for this reason that considerable effort was devoted to a study of its formation and oxidation.

(i) Preparation of the Olefin

α-Cyanodimethylaminolycopodine was prepared quantitatively from α-cyanobromolycopodine by treatment with methanolic dimethylamine. It was found that β-cyanobromolycopodine was converted to the β-cyclized compound by the same treatment. Since the α-product was basic whereas the β-cyclized compound was neutral, this treatment was found to be one of a number of convenient methods for the separation of α- and β-compounds from a mixture of α- and β-cyanobromolycopodine.

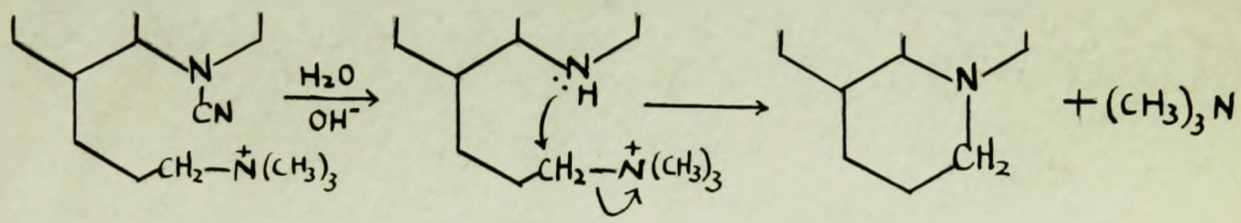
The α-dimethylamino compound was converted to its dihydro derivative by reduction with sodium borohydride but not without complication. In the borohydride reduction, there formed a large amount of a complex which was broken down with methanolic potassium hydroxide. The complex did not dissolve in dilute acid and thus the complex could be separated easily from the uncomplexed crude reaction product by extraction of the latter with dilute acid solution. Since the complex

would not dissolve in acid and a complex of this kind was never observed in borohydride reduction of α-cyclocyanolycopodine, the nitrogen atom of the tertiary amino group is apparently involved in its formation. An analysis of the complex was made but its composition could not be determined.

α-Cyanodimethylaminodihydrolycopodine was easily converted to the quaternary salt by treatment with methyl iodide. Decomposition of the quaternary salt was undertaken under various conditions in order to establish satisfactory conditions for the conversion. In the course of this study, decomposition with potassium tertiary butoxide using tertiary butanol as a solvent was found to be the most satisfactory. The decomposition product was a mixture of dimethylamino compounds and olefins. The yield of olefin was not consistent and the maximum yield was about 50%. The other portion of the reaction product was recovered as a mixture of α-cyanodihydrodimethylaminolycopodine and a small amount of α-cyanodimethylaminolycopodine. There still remained a considerable portion of material which could not be accounted for and which probably remained in the aqueous portion as quaternary salt or quaternary base. The olefinic material proved to be a mixture of keto-olefin, $C_{17}H_{24}ON_2$, and hydroxy-olefin, $C_{17}H_{26}ON_2$. There was no definite relationship between the ampunt of hydroxy- and keto-olefin formed. The formation of keto-olefin was unexpected but its formation can be explained readily since it is known that butoxide acts as an oxidation catalyst in the presence of a hydride ion acceptor.

Results, which were essentially the same as those described above, were obtained when the decomposition of the quaternary salt was

carried out with sodium methoxide and when the quaternary base was pyrolytically decomposed. The reaction followed a different course when the quaternary salt was heated under reflux with thirty per cent aqueous alkali. Under these conditions the major product was dihydrolycopodine, $C_{16}H_{27}ON$, identified by comparison with a sample prepared by the hydride reduction of lycopodine. The formation of dihydrolycopodine can be explained by assuming (a) hydrolysis of the cyanamide to the secondary amine followed by (b) nucleophilic displacement of trimethyl amine by the secondary amino group.



(ii) Reactions of the Olefin

The neutral compound obtained from the decomposition of the quaternary salt had in its infrared absorption spectrum peaks characteristic of an olefin at 3050, 1640 and 910 cm.$^{-1}$ as well as a strong $>C=O$ absorption at 1700 cm.$^{-1}$, a nitrile absorption at 2200 cm.$^{-1}$ and absorption in the hydroxyl region. It was apparently a mixture of hydroxy- and keto-compounds. They were separated easily by chromotography on alumina with chloroform as eluant. The olefins analysed for $C_{17}H_{26}ON_2$ and $C_{17}H_{24}ON_2$ for the hydroxy- and keto-olefin respectively.

Sodium borohydride reduction of the keto-olefin, $C_{17}H_{24}ON_2$, yielded the same hydroxy-olefin, $C_{17}H_{26}ON_2$, which was obtained from the decomposition of the quaternary salt. Catalytic reduction of the keto-

olefin yielded a compound which was found to be identical with α-cyano-lycopodine, $C_{17}H_{26}ON_2$, obtained by MacLean et.al.

Attempts were made to rearrange the double bond in the keto-olefin to a position conjugated with the carbonyl group by treatment of the keto-olefin with alkali. The compound, after being refluxed in alkali solution for six hours, showed a new additional infrared absorption band in the double bond region at 1625 cm.$^{-1}$ but there was no significant absorption in the ultraviolet spectrum. Treatment with alkali for another thirteen hours brought a change in the absorption spectrum in which the peak at 1625 cm.$^{-1}$ disappeared completely and a new absorption peak showed up at 1670 cm.$^{-1}$. An ultraviolet spectrum of this compound also did not show any conjugation. The absorption band at 1640 cm.$^{-1}$ consistently showed up in the infrared spectrum in all the reaction products. The reaction product was apparently a mixture of the starting material and the compound with the new absorption peak in the double bond region. The mixture was chromotographed on alumina and most of it was found to be the starting material. There was no satisfactory explanation for the absorption peaks at 1625 and 1670 cm.$^{-1}$ which were formed during the reaction.

(iii) Oxidation of the Hydroxyl- and Keto-Olefins

The importance of the oxidative degradation of this olefin was pointed out in the introductory remarks to this section of the discussion. The reaction has been investigated extensively but unfortunately the products of the oxidation reactions have not been fully characterized. The oxidizing reagents which were studied were ozone and alkaline per-

manganate. The oxidation of the keto-olefin and the hydroxy-olefin have both been studied with these two oxidizing agents. The results have not been conclusive but are recorded and discussed for the guidance of future workers.

Treatment of the hydroxy- and the keto-olefin with ozone followed by hydrogenolysis yielded formaldehyde which was isolated as its dimedone derivative. The double bond must therefore be situated at the end of the carbon chain as expected. The second product from the ozonolysis would be expected to differ in the two cases and these will be discussed separately.

The crude non-volatile product from the ozonolysis of the hydroxy-olefin was neutral and had an infrared absorption spectrum with bands at 1705, 1675 $cm.^{-1}$, weak absorption at 1600 $cm.^{-1}$, the usual nitrile band at 2200 $cm.^{-1}$ and strong absorption in the hydroxyl region. The crude material would not crystallize and was separated by chromatography into several fractions, none of which could be induced to crystallize. One of the fractions from the chromatographic separation had only weak hydroxyl absorption but had absorption at 1670 $cm.^{-1}$ and 2200 $cm.^{-1}$ and was similar in many respects to fractions isolated in other work described below. None of these fractions oxidized readily with permanganate which would make the presence of an aldehyde function unlikely.

The crude non-volatile fraction from the ozonolysis of the keto-olefin was also chromatographed to yield several fractions. In this case the main fraction solidified. Examination of its infrared absorption spectrum showed bands at 1670 and 2200 $cm.^{-1}$(-C≡N). This

compound proved to be identical (mixed melting point and infrared spectrum) with a compound obtained by oxidation of the keto-olefin with permanganate.

It was rather surprising that both the hydroxy- and keto-olefins were quite resistant to permanganate oxidation. Treatment of both compounds with permanganate in acetone for a prolonged time yielded a neutral compound and a trace of acidic compound. The neutral product obtained from permanganate oxidation of the keto-olefin using acetone as a solvent was separated into three different fractions by chromatography. The major fraction was a compound which crystallized when it was taken to dryness and melted at 134 - 135° C. The infrared spectrum of the compound showed absorption bands at 2200 $cm.^{-1}$ ($-C\equiv N$) and 1670 $cm.^{-1}$. No significant absorption was observed in the ultraviolet spectrum of the compound. Analysis of this compound corresponded to a formula $C_{16}H_{25}ON_2$. The other two compounds had infrared spectra which were similar to each other with absorption bands at 2200, 1700, 1665 $cm.^{-1}$, a weak absorption in the 1600 $cm.^{-1}$ region and fairly strong absorption in the hydroxyl region. The difference in the spectra of these two compounds was that the one had a strong peak at 1665 $cm.^{-1}$ and a weak peak at 1700 $cm.^{-1}$ whereas the other one had the intensities of these two peaks in reverse order.

The infrared absorption spectrum of the product obtained from permanganate oxidation of the hydroxy-olefin showed bands at 1705, 2200 $cm.^{-1}$, a weak absorption at 1610 $cm.^{-1}$ and a broad band in the hydroxyl region. Since this product was never characterized, it is not possible to state whether the carbonyl absorption at 1705 $cm.^{-1}$ resulted

from double bond oxidation or from oxidation of the secondary hydroxyl group.

An absorption in the infrared at 1660 - 1675 cm.$^{-1}$ region was characteristic of all the oxidation products of the keto- and hydroxy-olefins when permanganate or ozone was employed as oxidizing agent. In the one crystalline compound which was isolated from the oxidation of the keto-olefin, the original ketone absorption at 1700 cm.$^{-1}$ had disappeared and was replaced by the new absorption at 1670 cm.$^{-1}$. This peak is not due to a conjugated carbonyl for these compounds failed to absorb in the ultraviolet. An assignment could not be made but it does seem likely that some interaction must have occurred between the original keto or hydroxyl function and the new function formed in cleavage of the double bond. It is interesting to note that vinyl ethers and furans absorb in the region 1660 1675 cm.$^{-1}$ and it is possible that such an arrangement may be present in these compounds.

In summary, these oxidation results have shown the terminal character of the double bond. The virtual absence of acids or of lactones in the oxidation products suggests that the second carbon of the double bond was dialkylated and that on oxidation an interaction of unknown character took place between the new function introduced and the function already present in the molecule.

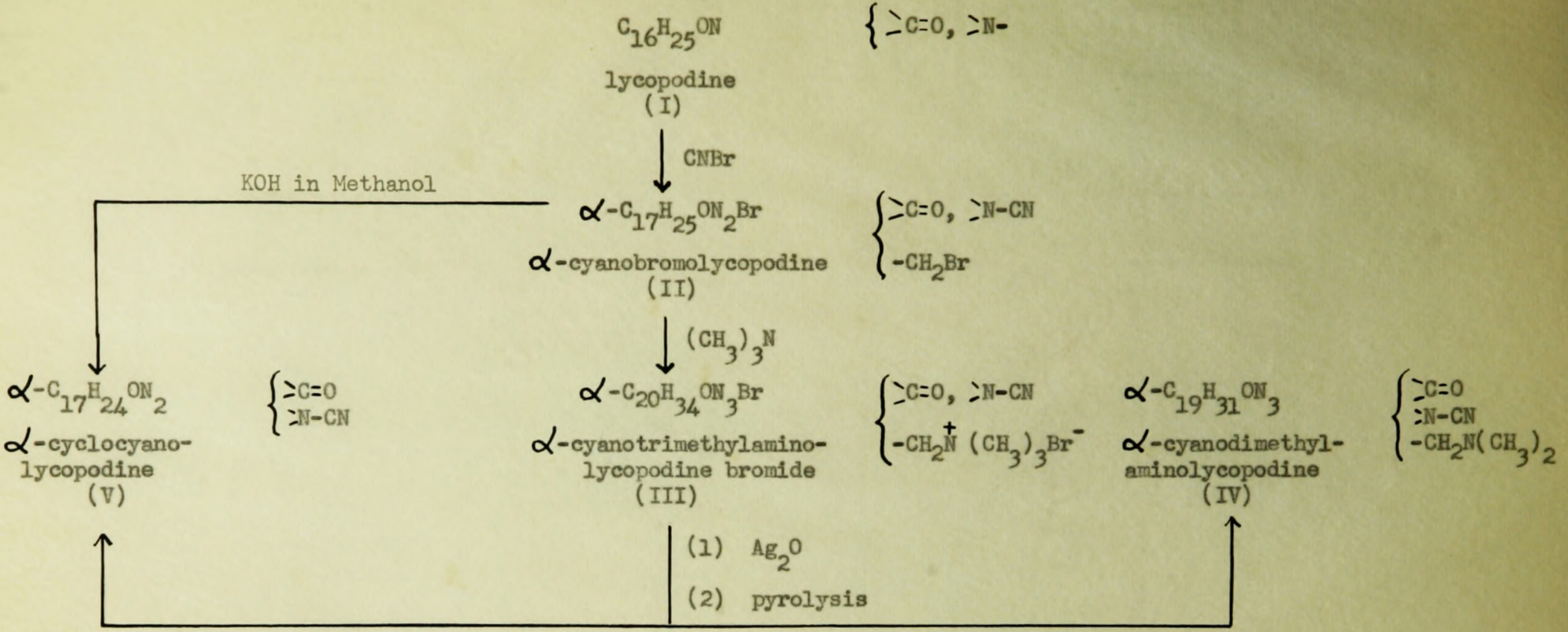

$C_{16}H_{25}ON$
lycopodine
(I)
$\{\geq C=O, \geq N-$
CNBr
KOH in Methanol
α-$C_{17}H_{25}ON_2Br$
α-cyanobromolycopodine
(II)
$\{\geq C=O, \geq N-CN$
$-CH_2Br$
$(CH_3)_3N$
α-$C_{17}H_{24}ON_2$
α-cyclocyano-
lycopodine
(V)
$\{\geq C=O$
$\geq N-CN$
α-$C_{20}H_{34}ON_3Br$
α-cyanotrimethylamino-
lycopodine bromide
(III)
$\{\geq C=O, \geq N-CN$
$-CH_2\overset{+}{N}(CH_3)_3Br^-$
α-$C_{19}H_{31}ON_3$
α-cyanodimethyl-
aminolycopodine
(IV)
$\{\geq C=O$
$\geq N-CN$
$-CH_2N(CH_3)_2$
(1) Ag_2O
(2) pyrolysis

Figure 1

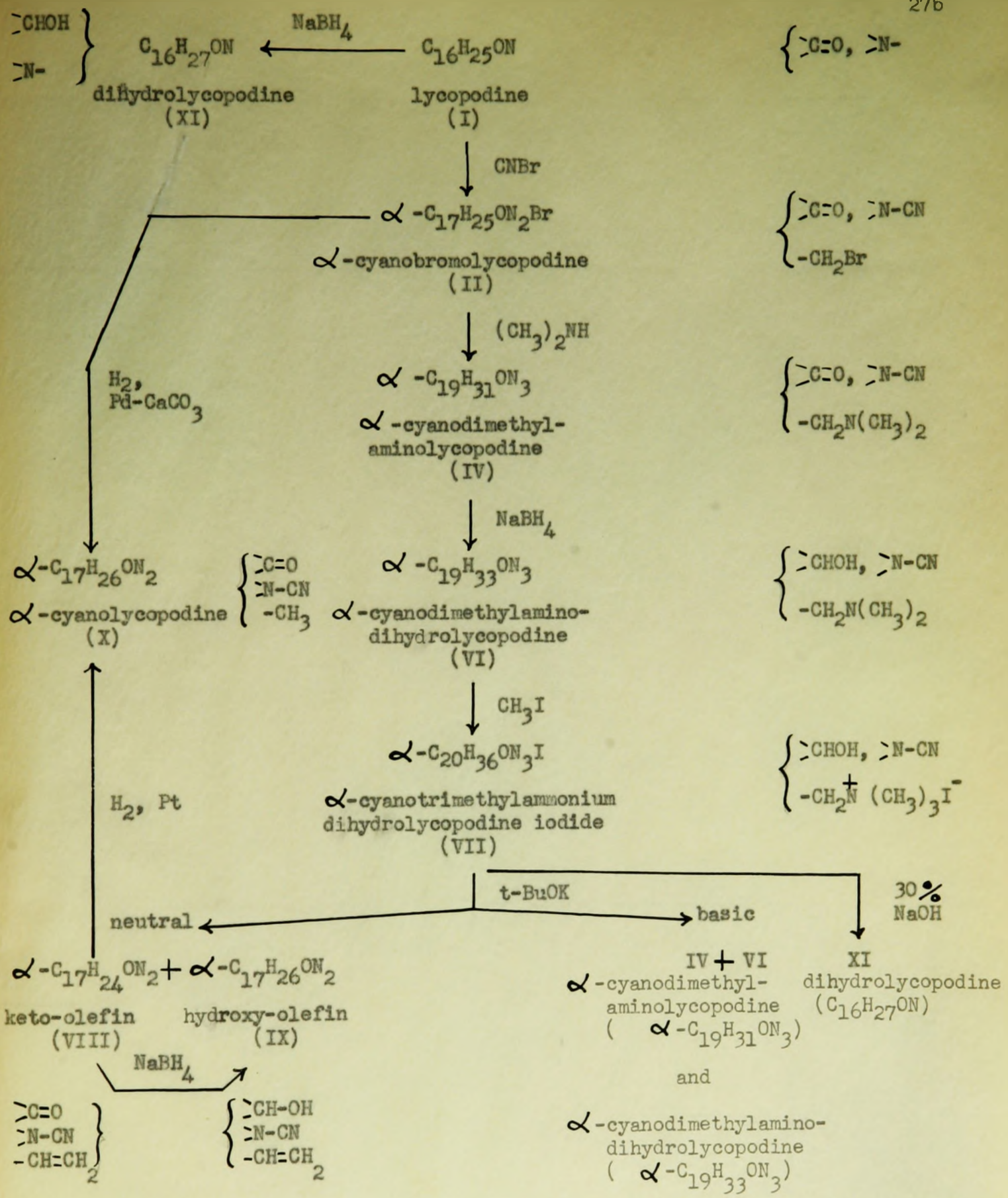

>CHOH
>N-
C16H27ON
dihydrolycopodine (XI)
NaBH4
C16H25ON
lycopodine (I)
>C=O, >N-
CNBr
α-C17H25ON2Br
α-cyanobromolycopodine (II)
>C=O, >N-CN
-CH2Br
(CH3)2NH
α-C19H31ON3
α-cyanodimethylaminolycopodine (IV)
>C=O, >N-CN
-CH2N(CH3)2
H2, Pd-CaCO3
NaBH4
α-C17H26ON2
α-cyanolycopodine (X)
>C=O
>N-CN
-CH3
α-C19H33ON3
α-cyanodimethylaminodihydrolycopodine (VI)
>CHOH, >N-CN
-CH2N(CH3)2
CH3I
α-C20H36ON3I
α-cyanotrimethylammonium dihydrolycopodine iodide (VII)
>CHOH, >N-CN
-CH2N+(CH3)3I-
H2, Pt
t-BuOK
neutral
basic
30% NaOH
α-C17H24ON2 + α-C17H26ON2
keto-olefin (VIII)
hydroxy-olefin (IX)
IV + VI
α-cyanodimethylaminolycopodine (α-C19H31ON3)
and
α-cyanodimethylaminodihydrolycopodine (α-C19H33ON3)
XI
dihydrolycopodine (C16H27ON)
NaBH4
>C=O
>N-CN
-CH=CH2
>CH-OH
>N-CN
-CH=CH2

Figure 2

EXPERIMENTAL

Infrared spectra were determined using a Perkin-Elmer Model 21 B double beam infrared recording spectrophotometer. Samples were mounted in nujol except where otherwise stated. Ultraviolet spectra were determined using a Beckmann Model DU spectrophotometer.

Analysis of samples were carried out in the Microanalytical Laboratory of Drs. G. Weiler and F. B. Strauss of Oxford, England. All melting points were corrected.

Alumina used for chromatography was Fisher chromatographic grade alumina.

Isolation of Lycopodine

The plant species Lycopodium flabelliforme was used as a source of lycopodine. The dried and ground plant material was extracted by the method of Manske and Marion (3).

Lycopodine was derived from the crude alkaloids extracted from the plant material by chromatography on alumina using benzene as an eluant. Lycopodine passed through the alumina column rapidly and was thus separated from other alkaloid constituents.

The amount of lycopodine was found to be approximately one-half of the crude alkaloid and the yield of lycopodine from this plant species was generally 0.15 %.

Lycopodine was crystallized from ether and melted at 114 - 114.5° C.

Reaction of Lycopodine with Cyanogen Bromide (9)

Lycopodine (6.45 g.), dissolved in 60 ml. of dry benzene, was added dropwise over a period of five hours at room temperature with stirring to a solution of 25 ml. of cyanogen bromide in 60 ml. of dry benzene. Stirring was continued for about ten hours after addition was completed and the reaction mixture was allowed to stand overnight at room temperature. The benzene and excess cyanogen bromide were distilled off in vacuo on a water bath, keeping the temperature in the mixture below 60° C. The residue was dissolved in chloroform and washed with water, dilute hydrochloric acid and dilute bicarbonate solution. From the solution of water washings and acid washings, 1.2 g. of unreacted lycopodine was recovered (18.6%). The chloroform solution was dried over "Drierite" and was taken to dryness. The residue was chromatographed on an alumina column with chloroform as eluant. The first portion of eluant from the column was a mixture of α- and β-cyanobromolycopodine which was followed by an intense pink band in which α-cyanohydroxylycopodine (10) was the major compound.

The mixture of α- and β-cyanobromolycopodine was crystallized from ether, the first crop yielded 4.5 g. of α-cyanobromolycopodine (m.p. 140 - 141.5° C.) followed by a second crop of 0.5 g. of a mixture of α- and β-cyanobromolycopodine.

Preparation of α-cyclocyanolycopodine

α-cyanobromolycopodine (4.5 g.) was dissolved in methanol

(150 ml.), 13 g. of potassium hydroxide added and the solution was refluxed for three hours. The methanol was evaporated off, water was added and the residue was extracted with chloroform. The chloroform extracts were taken to dryness to yield a crude residue 3.15 g. (91% yield). This residue was recrystallized from methanol to yield a compound which melted at 143 - 144.5° C. It was found to be identical (mixed melting point) to the compound reported by MacLean et.al. (9).

The infrared absorption spectrum of the cyclized compound had the carbonyl absorption similar to the α-cyanobromolycopodine. The ultraviolet absorption spectra of α-cyclocyanolycopodine and α-cyanobromolycopodine showed $\lambda_{max.} = 276$, log. $\varepsilon = 2.4$ and $\lambda_{max.} = 274$, log. $\varepsilon = 2.1$ respectively.

Attempted Formation of a Benzal Derivative of α-Cyclocyanolycopodine

α-Cyclocyanolycopodine (0.6 g.) and newly distilled benzaldehyde (0.45 g.) were dissolved in absolute methanol in a flask equipped with a dropping funnel and reflux condenser. Sodium methoxide solution (2.5 ml.) (prepared with 0.6 g. of metallic sodium and 7.5 ml. CH_3OH) in absolute methanol was added dropwise to the refluxing solution over a period of fifteen minutes. After addition was complete, the reaction mixture was condensed to one-half of its volume and kept in the refrigerator. A crystalline compound separated, which was found to be the starting material. The remaining reaction mixture was evaporated, water was added and the residue was extracted with chloroform. The chloroform extracts were distilled to yield a residue which had an infrared absorption spectrum identical with the starting

material. The residue was crystallized from ether and the crystalline compound melted at 143 - 144° C. A mixed melting point with starting material was not depressed.

Reduction of ∝-Cyclocyanolycopodine with Sodium Borohydride

∝-Cyclocyanolycopodine (1.7 g.) was dissolved in 95 % ethanol (80 ml.), sodium borohydride (3.5 g.) was added and the solution was stirred at room temperature for three hours. After the reaction mixture was allowed to stand overnight, excess borohydride was destroyed with formaldehyde (15 % solution) at ice bath temperature and the solution was made nearly neutral with acid. The solvent was distilled off, water was added to the residue and the resulting mixture was extracted with chloroform. The chloroform extracts were taken to dryness and the reaction product was purified by chromatography. The compound was crystallized from ether (85 % yield) M.P. 219° C.

Anal. Calc. for $C_{17}H_{26}ON_2$: C, 74.40; H, 9.38; N, 10.20.

Found: C, 74.49, 74.30; H, 9.48, 9.60; N, 10.02, 9.85.

It should be noted that an isomeric ∝-cyclocyanodihydroxylycopodine was once obtained during this reaction, which melted at 141° C.

Anal. Calc. for $C_{17}H_{26}ON_2$: C, 74.40; H, 9.38; N, 10.20.

Found: C, 74.37, 74.50; H, 9.50, 9.70; N, 10.2, 10.0.

Oxidation of ∝-Cyclocyanodihydrolycopodine with Chromium Trioxide Pyridine Complex

Chromium trioxide-pyridine complex (20) was prepared with 0.1 g.

of chromium trioxide and 1.5 ml. of pyridine, 0.1 g. of ∝-cyclocyanodihydrolycopodine (M.P. 219° C.) was added and the reaction flask was stoppered and mixed thoroughly. After the reaction mixture was allowed to stand overnight at room temperature, water was added and the mixture was extracted with ether. The ether extracts were taken to dryness and the residue was crystallized from methanol and found to be identical with ∝-cyclocyanolycopodine.

∝-Cyclocyanodihydrolycopodine (M.P. 141° C.) (0.1 g.) was oxidized in exactly the same way and the reaction product was also found to be identical with ∝-cyclocyanolycopodine.

Attempted Dehydration of ∝-Cyclocyanodihydrolycopodine

∝-Cyclocyanodihydrolycopodine (3.3 g.) was dissolved in toluene, p-toluenesulfonic acid (0.16 g.) was added and the solution was refluxed in a flask equipped with a water collector. During refluxing the toluene in the water collector was once replaced with fresh toluene. After the solution was refluxed for about forty hours, the toluene was distilled off, water was added and the residue was extracted with chloroform. The chloroform extracts were evaporated to yield a crude product (3.1 g.). The reaction product showed infrared absorption bands at 3500, 1700, 1680 and 1630 $cm.^{-1}$ as well as a strong -CN band at 2200 $cm.^{-1}$. It was not possible to purify the compound either by crystallization or chromatography.

Several attempted dehydrations were made with p-toluenesulfonic acid in benzene, p-toluenesulfonic acid in xylene, p-toluenesulfonyl chloride in toluene and in pyridine, iodine in toluene and phosphorous oxytrichloride in pyridine but they were all unsuccessful.

Attempts to Prepare a Xanthate Derivative of ∝-Cyclocyanodihydrolycopodine

Metallic sodium (0.1 g.) was added in pieces to a solution of ∝-cyclocyanodihydrolycopodine (0.25 g.) in 10 ml. dry ether (21). The mixture was stirred for thirty hours at room temperature and then carbon disulfide (2 ml.) was added in portions. Excess sodium metal was removed mechanically and stirring was continued for one and one-half hours longer and then methyl iodide (5 ml.) was added dropwise while the reaction mixture was kept stirring. After addition of methyl iodide was complete, the reaction mixture was stirred for three hours longer. The solvent was distilled off and the residue was worked up.

The reaction product was found to be mostly the starting material contaminated with a small amount of unidentifiable material which had fairly strong absorption at 1670 and 1690 $cm.^{-1}$ as well as -CN band at 2200 $cm.^{-1}$ in the infrared.

Several other attempts to prepare a xanthate were also made under modified conditions but all were unsuccessful.

Reaction of ∝-Cyclocyanolycopodine with Phenyl Lithium

Phenyl lithium was prepared by adding freshly distilled bromobenzene (6.8 ml.) dropwise to lithium metal (1 g.) in anhydrous ether. The mixture was vigourously stirred throughout the reaction. After the addition of bromobenzene was complete, the reaction mixture was refluxed for one hour. To this solution 1.3 g. of ∝-cyclocyanolycopodine in ether (20 ml.) was added and the mixture was refluxed and stirred for two hours longer. During the reaction, the mixture

turned brown. It was decomposed in an ice-water mixture, and the solution was made acidic to destroy complexes and then made basic again and extracted with ether. The ether extracts were dried over sodium sulfate, taken to dryness and yielded about 3 g. of crude product.

The infrared absorption spectrum of the crude product showed no -CN band but still strong absorption at 1700 cm.$^{-1}$. Apparently the carbonyl group was not affected. The reaction product was chromatographed on alumina with chloroform as eluant. The first portion of eluant contained biphenyl. The second portion of eluant from an intense brown band yielded a residue (1.1 g.) which had an infrared absorption spectrum with bands in the hydroxyl region and at 1700, 1660 cm.$^{-1}$ as well as phenyl absorption at 1600 and 1570 cm.$^{-1}$. The third portion from the slightly coloured portion of the column (1.0 g.) had an infrared absorption spectrum with bands at 3380 (weak broad band), 3660, 3640 (both weak) and 1700 cm.$^{-1}$ which had two inflections on the higher wave number side and one inflection on the lower side and also had a characteristic phenyl absorption band at 1600 and 1580 cm.$^{-1}$. The last portion of the eluant from the column yielded a residue (0.37 g.) which showed a fairly strong absorption at 3250 cm.$^{-1}$ and at 1695 cm.$^{-1}$, which had three inflections on the higher wave number side, and also bands at 1600 and 1570 cm.$^{-1}$.

An attempt to purify and characterize these products was unsuccessful.

Hydrolysis of α -Cyclocyanolycopodine

α-Cyclocyanolycopodine (3.3 g.) was dissolved in 95% ethanol

(100 ml.) and 12M-HCl (15 ml.) was added. The solution was refluxed on the steam cone for thirty hours and the solvent was distilled off. The residue was dissolved in water and filtered. The filtrate was made basic with ammonium hydroxide and extracted with chloroform. The crude reaction product (2.3 g.) was dissolved in acetone and acidified with perchloric acid and yielded a crystalline solid which was recrystallized from acetone and melted at 300 - 300.5° C.

Anal. Calc. for $C_{16}H_{26}O_5NCl$: C, 55.22; H, 7.53; N, 4.02.

Found: C, 55.27, 55.47; H, 7.39, 7.61; N, 3.93, 4.13.

The free base was liberated from the perchlorate and was recrystallized from petroleum-ether. It melted at 105.5 - 106° C.

Anal. Calc. for $C_{16}H_{25}ON$: C, 77.70; H, 10.12; N, 5.66.

Found: C, 77.39, 77.31; H, 9.74, 9.97; N, 5.56, 5.78.

The infrared absorption spectrum of the base showed a fairly sharp medium peak at 3330 $cm.^{-1}$ and a carbonyl peak at 1695 $cm.^{-1}$.

Alkylation of the α-Cyclolycopodine

α-Cyclolycopodine (2.0 g.) was dissolved in a mixture of 40% formaldehyde (7.0 ml.) and 90% formic acid (11 ml.) (11). After the reaction mixture was refluxed for thirty-three hours, it was poured into water, made basic with ammonium hydroxide and extracted with ether. The ether extract was taken to dryness to yield a residue. The residue was chromatographed on alumina with chloroform as eluant and 1.6 g. of the tertiary base was separated from the starting material. The tertiary base was dissolved in acetone and made acidic with perchloric acid

and yielded a crystalline perchlorate which melted at 249 - 250° C.

Anal. Calc. for $C_{17}H_{28}O_5NCl$: C, 56.50; H, 7.75; N, 3.8.

Found: C, 56.44, 56.57; H, 7.58, 7.77; N, 3.77, 3.91.

The free base regenerated from the perchlorate also crystallized in the absence of solvent and melted at 86.5 - 88.0° C.

Anal. Calc. for $C_{17}H_{27}ON$: C, 78.16; H, 10.33; N, 5.36.

Found: C, 77.80, 77.96: H, 10.29, 10.26; N, 5.38, 5.48.

Several attempts to form a methiodide of the base are recorded below. The N-methyl α-cyclized compound (0.55 g.) was dissolved in acetone and an excess of methyl iodide was added. The solution was kept in the refrigerator overnight but no crystalline solid separated. The solution was then refluxed on the steam cone for two hours with the same result. The starting material (0.5 g.) was recovered by a removal of the solvent.

Treatment of α-Cyclo N-methyl Lycopodine with Phenyl Lithium

Phenyl lithium was prepared as before from 7.8 ml. of bromobenzene and 1 g. of lithium metal. To the phenyl lithium solution, 1 g. of α-cyclo N-methyl lycopodine in 10 ml. of dry ether was added dropwise. The reaction mixture was stirred and refluxed for two hours and then poured into an ice-water mixture and worked up as before. The reaction product was chromatographed on alumina with chloroform as eluant and 0.65 g. of the starting material was recovered. The rest of the compound (0.3 g.) separated from the column had a strong broad absorption in the hydroxyl region and a band at 1690 $cm.^{-1}$ as well as a weak

absorption at 1600 cm.$^{-1}$. An attempt to characterize this basic reaction product was unsuccessful.

Borohydride Reduction of α -Cyclo-N-methyl Lycopodine

α -Cyclo-N-methyl lycopodine (0.45 g.) was dissolved in 50 ml. of 95 % ethanol and 0.9 g. of sodium borohydride was added. The solution was stirred for 3-4 hours and allowed to stand overnight. The excess sodium borohydride was destroyed with formaldehyde solution. The solvent was distilled and 0.46 g. of a crude product was obtained upon extraction of the residue with chloroform. The infrared absorption spectra showed the crude product to be a mixture of reduced and starting material. The mixture was chromatographed on alumina with chloroform as eluant and a fraction (0.28 g.) was collected, which had no carbonyl absorption in the infrared spectrum. It failed to crystallize from ether, but when the ether solution was acidified with perchloric acid, a crystalline solid formed. The crystalline solid was recrystallized from a mixed solvent of ether and acetone (M.P. 240 -242° C.).

Anal. Calc. for $C_{17}H_{28}O_5NCl$: C, 56.12; H, 8.25; N, 3.85.

Found: C, 56.16; H, 8.10; N, 3.83.

The reduced product (0.2 g.) was dissolved in acetone and excess methyl iodide was added. The reaction mixture was allowed to stand in the refrigerator overnight but it failed to crystallize out. The starting material was quantitatively recovered by removing acetone and methyliodide.

Preparation of Dimethylamino Derivative of α-Cyanolycopodine from the Mixture of α- and β-Cyanobromolycopodine

A mixture of α- and β-cyanobromolycopodine (mostly α-compound) (9.5 g.) was dissolved in methanol (200 ml.) saturated with dimethylamine. The reaction flask was swirled by hand for thirty minutes and allowed to stand overnight at room temperature. The methanol was distilled off and a dense syrupy residue was obtained. The crude reaction product was dissolved in dilute hydrochloric acid and a non-basic material (0.1 g.) was filtered off, which was identified as the β-cyclized compound (10). The acid extract was made basic with ammonium hydroxide and extracted with chloroform. The chloroform extract was taken to dryness and the residue was dissolved in acetone and treated with perchloric acid. A crystalline perchlorate (7.9 g.) separated which melted at 228 - 229° C. with decomposition. About 2.5 g. of impure perchlorate separated from the mother liquid.

Borohydride Reduction of α-Cyanodimethylaminolycopodine

α-Cyanodimethylaminolycopodine (4.8 g.) was dissolved in 95% ethanol (970 ml.), 10 g. of sodium borohydride in 95 % ethanol (150 ml.) was added and the mixture was stirred for three hours. The reaction mixture was allowed to stand overnight at room temperature and excess sodium borohydride was destroyed by adding 20 % formaldehyde solution at the temperature of the ice-bath. The solvent was distilled *in vacuo* and water was added to the residue, which was then extracted with chloroform. The chloroform extracts were taken to dryness and 4.35 g.

of the reduced product was obtained, which melted at 189 - 190.5° C.

Anal. Calc. for $C_{19}H_{33}ON_3$: C, 71.47; H, 10.34; N, 13.16.

Found: C, 71.16; H, 9.85; N, 12.97.

It should be noted that the reduction product was often contaminated with a large amount of acid-insoluble material which had strong infrared absorption peaks at 2270, 2320, 2370 $cm.^{-1}$. This material crystallized from ethanol and started melting at 172° C. with evolution of gas. This acid-insoluble material is probably a borate ester and was destroyed by refluxing on the steam cone for 2-3 hours in methanolic potassium hydroxide solution. From the fact that the complex would not dissolve in acid and since a complex of this kind was never observed in borohydride reduction of α-cyclocyanolycopodine, the nitrogen atom of the tertiary group is apparently involved in its formation.

Anal. Found: C, 68.0; 68.0; H, 10.07, 10.07; N, 11.9, 12.0.

Methylation of α-Cyanodimethylaminodihydrolycopodine

α-Cyanodimethylaminodihydrolycopodine (0.43 g.) was dissolved in acetone (10 ml.), treated with excess methyliodide and set aside in the refrigerator. A fine crystalline precipitate formed in the reaction mixture in a couple of hours. The crystalline precipitate was filtered (0.48 g.) and recrystallized from acetone-methanol mixture (M.P. 231 - 232° C.)

Anal. Calc. for $C_{20}H_{36}ON_3I\ H_2O$: C, 50.10; H, 7.52; N, 8.98.

Found: C, 50.63, 50.68; H, 7.77, 7.67; N, 9.05, 9.06.

Pyrolysis of the Quaternary Base

α-Cyanotrimethylammonium dihydrolycopodine iodide (0.3 g.) was dissolved in water and shaken with an excess of freshly prepared silver oxide. The solution was then filtered and the filtrate was taken to dryness. The residue was placed in a spath tube and pyrolysed under vacuum (at 1 mm. Hg). The temperature of the pyrolysis chamber was kept at 205° C. for one and one-half hours. The pyrolysed material was extracted with chloroform. The chloroform extracts were separated into a basic and a neutral fraction. The basic product (0.02 g.) was not identified. The neutral compound (0.09 g.) showed infrared absorption at 3400 $cm.^{-1}$ in the hydroxyl region, bands at 2200 (-C≡N), 1700 and 1640 $cm.^{-1}$ which were all fairly strong peaks. The neutral compound was chromatographed on alumina using chloroform as eluant and two fractions were obtained. The second fraction showed infrared absorption peaks at 3400 (broad), 3070 (weak), 2200 (-C≡N), 1640, and 910 $cm.^{-1}$ and was found to be identical with α-hydroxy-olefin which was obtained from the quaternary salt by decomposition with sodium methoxide and with potassium tertiary butoxide. The first fraction showed the same infrared spectrum except that this compound had another strong absorption peak at 1700 $cm.^{-1}$. There was not sufficient material to purify but from the results of the decomposition of the quaternary salt with sodium methoxide and with potassium tertiary butoxide this compound was regarded as the keto-olefin contaminated with a small amount of the α-hydroxy-olefin.

Decomposition of the Quaternary Base with Sodium Hydroxide

The quaternary ammonium hydroxide of α-cyanodihydrolycopodine (0.84 g.) was taken up in 30 % aqueous sodium hydroxide solution (25 ml.) and heated in an oil-bath at a temperature of 105 - 110° C. for four hours. Dry nitrogen gas was bubbled through the reaction mixture during the reaction, and a volatile gas was expelled which was captured in about 0.01 N hydrochloric acid (90 ml.) From the reaction mixture, an oily material on the liquid surface was extracted with ether. The ether extract was taken to dryness and the residue (0.14 g.) was crystallized from ether, and melted at 163 - 165° C. The crystalline compound was found to be identical (mixed melting point and infrared spectrum) to dihydrolycopodine. From the reaction mixture, a small amount of an unidentifiable compound which seemed to be a hydrolysed compound was also obtained. The infrared absorption spectrum showed a very weak -C≡N absorption and complicated peaks in the 1600 - 1700 $cm.^{-1}$ region. The 0.01 N-acid solution was evaporated under vacuum to yield a white crystalline solid. The crystalline solid was dissolved in water, the solution was made alkaline and ether was added. The mixture was warmed to drive off the ether. The distillate was collected in a flask containing an ether solution of picric acid. A yellow crystalline solid formed (M.P. 216 - 218° C.). This compound was identical, by mixed melting point, with trimethylamine picrate.

Decomposition of the Quaternary Salt with Sodium Methoxide

About 4 g. of metallic sodium was dissolved in 50 ml. of

anhydrous methanol. 1.05 g. of α-cyanotrimethylammonium dihydrolycopodine iodide was added to the sodium methoxide solution and the mixture was refluxed for nine hours. The methanol was distilled *in vacuo*, water was added to the residue and the aqueous mixture was extracted with ether. From the ether extract, 0.06 g. of a neutral product and 0.13 g. of a basic product were obtained. The basic compound was crystallized from acetone and found to be α-cyanodimethylaminodihydrolycopodine (mixed melting point). The neutral compound had an infrared absorption spectrum similar to the crude neutral product from the quaternary base by pyrolysis. The neutral product was purified by chromatography on alumina with chloroform as eluant and 0.04 g, of a compound was obtained which was crystallized from ether and melted at 200.5 - 201.5° C. The infrared spectrum of this compound showed a double bond absorption at 3070 and 1640 $cm.^{-1}$ as well as a band in the hydroxyl region at 3400 $cm.^{-1}$. and a -C≡N band at 2200 $cm.^{-1}$.

Anal. Calc. for $C_{17}H_{26}ON_2$: C, 74.48; H, 9.48; N, 10.22.

Found: C, 74.61; H, 9.25; N, 10.50.

From the column a small amount of material, which showed infrared absorptions in CCl_4 at 1680 and 1640 $cm.^{-1}$ as well as -C≡N and -OH absorption at 2200 and 3400 $cm.^{-1}$ respectively, was separated.

Decomposition of the Quaternary Salt with Potassium Tertiary Butoxide

Metallic potassium (7.4 g.) was added in pieces over a period of one hour to 160 ml. of tertiary butanol which had been dried over "Drierite" and distilled. α-Cyanotrimethylammonium dihydrolycopodine

iodide (6.7 g.) was added to the potassium tertiary butoxide solution and the mixture was refluxed about forty-two hours. The reaction mixture was taken to dryness under vacuum, water was added to the residue and the mixture was extracted with ether. From the ether extract, about 2 g. of a basic compound was obtained by extracting with dilute acid. The basic compound was found to be α-cyanodimethylaminodihydrolycopodine contaminated with a small amount of α-cyanodimethylaminolycopodine.

The neutral product (2.18 g.) from the ether extract was chromatographed on alumina with chloroform as eluant and there was obtained 1.45 g. of an olefin which contained a ketone group and 0.58 g. of an olefin which contained an hydroxyl group. The latter was found to be identical with the hydroxy-olefin obtained from the sodium methoxide decomposition reaction of the quaternary salt. The α-keto-olefin was crystallized from ether and the crystalline compound melted at 112.5 - 113° C.

Anal. Calc. for $C_{17}H_{24}ON_2$: C, 75.0; H, 8.82; N, 10.29.

Found: C, 75.3, 74.9; H, 8.96, 8.84; N, 10.3, 10.45.

The infrared spectrum of the keto-olefin showed absorption bands at 3070, 1640 and 910 $cm.^{-1}$ as well as a -CN absorption at 2200 $cm.^{-1}$ and a $>C=O$ absorption at 1700 $cm.^{-1}$.

Reduction of the Keto-Olefin with Sodium Borohydride

The keto-olefin (0.02 g.) was dissolved in 95 % ethanol (20 ml.) and 0.035 g. of sodium borohydride was added. The solution was stirred

for two hours and then allowed to stand overnight at room temperature. The excess sodium borohydride was destroyed with 36% formaldehyde. The solvent was distilled off under vacuum and 0.02 g. of a crude product was obtained by extraction of the residue with chloroform. The crude product was crystallized from ether to yield a compound which was identical with the hydroxy-olefin described above (mixed melting point and infrared spectrum).

Hydrogenation of the Keto-Olefin

The keto-olefin (0.025 g.) was dissolved in 5 ml. of freshly distilled acetic acid and hydrogenated in a microhydrogenation apparatus in the presence of 0.018 g. of platinum oxide catalyst. The catalyst was filtered off and the solvent was evaporated. The infrared spectrum of the residue showed $\geq$C=O and -CN but no double bond absorption. The residue was crystallized from ether and petroleum-ether mixture and melted at 128 - 130° C. A mixed melting point with an authentic sample of α-cyanolycopodine was not depressed and their infrared absorption spectra were identical.

Attempted Rearrangement of the Keto-Olefin

(A) A solution of potassium tertiary butoxide was prepared from 2 g. of metallic potassium and 50 ml. of tertiary butanol. 0.7 g. of the keto-olefin was added to the above solution and the mixture was refluxed for six hours. The solvent was distilled, water was added and the mixture was extracted with chloroform. The residue obtained

from the chloroform extracts had the same infrared absorption spectrum as the starting material except in the double bond region. The double bond absorption peak in the spectrum of the starting material was split into a double peak at 1640 and 1625 cm.$^{-1}$.

The crude product was dissolved in 10 ml. of benzene and the solution was added to a potassium tertiary butoxide solution which was prepared with 55 ml. of tertiary butanol and 3 g. of metallic potassium. The mixture was refluxed again for thirteen hours. The reaction mixture was worked up in the same manner as before. The infrared spectrum of the crude product showed a change only in the double bond region again. The peak at 1625 cm.$^{-1}$ had disappeared and a new peak formed at 1670 cm.$^{-1}$ which was as strong as the peak at 1640 cm.$^{-1}$. The compound (0.06 g.) with the peak at 1670 cm.$^{-1}$ was separated from the rest of the starting material by chromatography on alumina with chloroform as eluant.

(B) Potassium tertiary butoxide (12.6 g.) was dissolved in 120 ml. of dry toluene and 0.66 g. of the keto-olefin was added. The solution was heated under refluxing for forty-six hours. The reaction mixture was worked up in the usual manner and a neutral crude product and a trace of an acidic compound were obtained. The acidic compound had a very weak -CN absorption in its infrared spectrum but strong broad absorption bands both in the hydroxyl region as well as in the 1600 - 1700 cm.$^{-1}$ region. The neutral compound was chromatographed on alumina with chloroform as eluant and two fractions were obtained. The infrared spectrum of the main reaction product showed only -CN

absorption at 2200 cm.$^{-1}$. There was no >C=O or double bond absorption. This compound was crystallized from ether (M.P. 141 - 142° C.)

Anal. Found: C, 73.86; H, 9.47; N, 10.4.

(Calc. for $C_{17}H_{26}ON_2$: C, 74.48; H, 9.48; N, 10.22)

Ozonolysis of the Hydroxy-Olefin

(A) The hydroxy-olefin (0.46 g.) was ozonized (22) in methanol for thirty minutes at -35° C. During the ozonolysis one and a half litres of oxygen containing 5-6 % ozone had passed through the solution. The ozonized solution was then hydrogenated for two hours at a hydrogen gas pressure of 35 p.s.i. in the presence of platinum oxide catalyst. The catalyst was filtered, the solvent was evaporated, and the crude product was washed with dilute aqueous sodium carbonate and a neutral compound was obtained. The neutral compound was chromatographed on alumina with chloroform as eluant. The first fraction of the eluant from the column yielded a residue (0.05 g.) which showed infrared absorption bands at 1780, 1715 and 2200 cm.$^{-1}$ (-CN) as well as in the hydroxyl region. The second fraction from the column yielded a compound (0.16 g.) which had infrared absorption bands at 1710, double peaks at 1660 and 1640 cm.$^{-1}$ and peaks in the hydroxyl region. This fraction was probably contaminated with some olefin. All these compounds failed to crystallize.

(B) The hydroxy-olefin (0.3 g.) was dissolved in 10 ml. of anhydrous ethyl acetate and 1 ml. of glacial acetic acid. The solution was ozonized for thirteen minutes when an intense iodine colour

showed up in the potassium iodide solution. The ozonized solution was transferred to a 50 ml. flask and 10 ml. of glacial acetic acid and 0.4 g. of zinc dust were added to the solution. The mixture was refluxed for five minutes and then distilled until the vapour temperature reached 97° C. The distillate was collected in an ethanolic solution of 0.28 g. of dimedone containing a drop of piperidine. The mixture was swirled and then allowed to stand for one hour. The solvent was evaporated and the residue was crystallized from aqueous ethanol. A first drop of 0.13 g. was collected which melted at 189° C. A mixed melting point with the dimedone derivative of formaldehyde did not show any depression in the melting point.

The residue from the distillation was filtered and the filtrate was taken to dryness, water was added and the mixture was extracted with ether. The ether extract was evaporated to yield 0.1 g. of a crude product. The crude product was extracted with dilute aqueous sodium carbonate and a trace of acidic compound was separated from the neutral compound. The infrared spectrum of the acidic compound showed a strong absorption at 1705, 2200 $cm.^{-1}$ and a broad absorption in the hydroxyl region. The neutral compound showed infrared absorption bands at 1705, 1675, 2200 $cm.^{-1}$ (-CN) and weak absorption at 1770 and 1620 $cm.^{-1}$ as well as absorption in the hydroxyl region.

(C) The hydroxy-olefin (0.42 g.) was dissolved in 12 ml. of ethylene dichloride and the solution was ozonized at -20° C. To the ozonized solution 0.4 g. of zinc dust and 10 ml. of glacial acetic acid were added. The mixture was stirred for thirty minutes. The

zinc dust was filtered off and the filtrate was distilled until the vapour temperature reached 90° C. The distillate was collected into 10 ml. of the ethanolic dimedone (0.35 g.) solution containing a drop of piperidine. The mixture so obtained was worked up in the same manner as in part B and a crystalline dimedone derivative of formaldehyde (0.14 g.) was obtained.

The residue from the distillation was filtered and the filtrate was taken to dryness, water was added and the residue was extracted with chloroform. From the chloroform extracts, 0.2 g. of a neutral compound was obtained. The product was chromatographed on alumina with chloroform as eluant and two compounds were separated. One compound showed infrared absorption at 2200 $cm.^{-1}$ (-CN) and two blunt peaks at 1700 and 1600 $cm.^{-1}$ as well as a strong absorption in the hydroxyl region. The other compound had absorption peaks at 2200 (-CN) and 1670 $cm.^{-1}$ as well as a very weak absorption in the hydroxyl region. The reaction products failed to crystallize.

Blank solutions similar to those used in parts B and C were subjected to the same treatment and no formaldehyde was detected.

Oxidation of the Hydroxy-Olefin

The hydroxy-olefin (0.15 g.) was dissolved in 30 ml. of acetone basified with aqueous sodium carbonate and 0.35 g. of potassium permanganate in aqueous solution was added. Oxidation proceeded very slowly and therefore the reaction mixture was stirred overnight at room temperature. The excess potassium permanganate and the precipitate of manganese dioxide were destroyed with sulfur dioxide gas. The acetone was evapora-

ted and the remaining aqueous solution was extracted with chloroform. The chloroform extract was distilled and 0.12 g. of a crude product was obtained. The crude product was extracted again with 5 % sodium bicarbonate solution and 0.02 g. of an acidic compound was separated. The remaining neutral compound failed to crystallize. The infrared spectrum of the neutral compound showed strong absorption at 1705, 2200 cm.$^{-1}$ and in the hydroxyl region and weak absorption at 1610 cm.$^{-1}$.

Ozonolysis of the Keto-Olefin

The keto-olefin (0.25 g.) was dissolved in 10 ml. of glacial acetic acid. The solution was ozonized at room temperature for five minutes after iodine began to form in the potassium iodide solution. The solution was then hydrogenated for two and a half hours at an hydrogen gas pressure of 32 p.s.i. in the presence of a platinum oxide catalyst. The catalyst was filtered off and the solvent was evaporated. The reaction product was chromatographed on alumina with chloroform. The first fraction of the eluant was evaporated and yielded a solid compound which melted at 128 - 134° C. The infrared absorption spectrum of the solid compound showed peaks at 2200 (-CN) and at 1670 cm.$^{-1}$ (See "Oxidation of the Keto-Olefin"). The other compound separated from the column showed infrared absorption in chloroform at 2200, 1670 cm.$^{-1}$ and a strong blunt peak at 1700 cm.$^{-1}$ and a weak absorption at 1610 cm.$^{-1}$.

Oxidation of the Keto-Olefin with Potassium Permanganate

(A) The keto-olefin (0.17 g.) was dissolved in a mixed solvent of 10 ml. pyridine and 5 ml. of water. 0.23 g. of potassium permanganate was added to the solution and the mixture was stirred for two hours. The oxidation was apparently very slow and the reaction mixture was kept standing overnight at room temperature. The excess potassium permanganate was destroyed with sulfur dioxide gas and dilute sulfuric acid was added until the odour of pyridine was absent. The solution was extracted with chloroform. The chloroform extract was distilled off and the residue was extracted again with 5 % sodium bicarbonate. Thus a neutral compound and an acidic compound were separated from the crude product. The infrared spectrum of the acidic compound showed absorption at 2200, 1700 $cm.^{-1}$ and in the hydroxyl region. The neutral compound had infrared absorption peaks at 2200, 1715, 1670 $cm.^{-1}$ and a weak blunt peak at 1785 $cm.^{-1}$. These compounds failed to crystallize.

(B) The keto-olefin (0.3 g.) was dissolved in acetone (30 ml.) and made basic with aqueous sodium carbonate. 0.13 g. of potassium permanganate dissolved in 6 ml. of water was added to the solution. The potassium permanganate was nearly consumed during six hours stirring at room temperature. The reaction mixture was worked up in the same manner as in part A and 0.26 g. of a crude solid product was obtained. The solid product was dissolved in chloroform and extracted with dilute sodium carbonate sooution and 0.01 g. of an acidic compound was separated

from the residue of neutral compound. The neutral compound was chromatographed on alumina with chloroform as eluant. The first fraction from the column yielded 0.19 g. of a compound which crystallized when it was dried (M.P. 134 - 135° C.). The infrared spectrum of the compound showed absorption bands at 2200 and 1670 cm.$^{-1}$ and was very similar to that of the ozonolysis product of the keto-olefin. The identity of the two compounds was confirmed by mixed melting points.

Anal. Found: C, 74.21, 74.19; H, 9.67, 9.44; N, 9.93, 10.12.

The analytical results are consistent with the formula $C_{16}H_{25}ON_2$ (calc. C, 74.20; H, 9.56; N, 10.02). However, a compound with this molecular formula would not be expected to form under the conditions of the experiment.

From a narrow band on the column, a few mg. of material was obtained, which had strong absorption bands at 2200, 1700, 1665 and 1590 cm.$^{-1}$ in the infrared spectrum. The peak at 1665 cm.$^{-1}$ was stronger than that at 1700 cm.$^{-1}$. Another fraction was obtained from a strongly absorbed band eluted from the column with methanol. This fraction showed infrared absorption bands at 2200, 1700, 1665 cm.$^{-1}$ and a weak absorption at 1600 cm.$^{-1}$ as well as a strong absorption in the hydroxyl region. The 1700 cm.$^{-1}$ peak was stronger than that at 1665 cm.$^{-1}$ in this compound.

SUMMARY

The reaction of α-cyanobromolycopodine with alkali yields α-cyclocyanolycopodine in which a new ring has been formed. A series of reactions is reported which indicates that the cyclization occurred at a position alpha to the carbonyl function.

The olefinic compound which would have been expected to form by elimination of hydrogen bromide from α-cyanobromolycopodine has been prepared by an indirect route.

The oxidative degradation of the olefinic compound has been studied and has shown the terminal character of the olefin. The oxidative degradation results have also suggested that the second carbon of the double bond was dialkylated and thus lycopodine probably has a different skeletal structure than annotinine.

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