THE CHEMISTRY OF LYCOPODINE

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SCOPE AND CONTENTS:

Hydride reductions of α-cyanobromolycopodine and simple derivatives provided a number of derivatives of these compounds useful for oxidation and dehydrogenation studies. Dehydrogenation of α-des-tetrahydrolycopodine yielded a quinoline derivative. This result together with other evidence indicated that three of the four rings of lycopodine are six-membered. Two conjugated enols were isolated from oxidation experiments on α-cyanolycopodine. This indicated the presence of an active methylene group and from examination of these enols it appears unlikely that the carbonyl and nitrogen can be in the same ring. A benzal derivative was prepared from α-cyanolycopodine. This derivative was converted into a tertiary base which underwent a bond scission reaction with methyl sulfate. A selenium dioxide oxidation product of benzal-α-cyanolycopodine gave some indication of the relationship of the carbonyl to the nitrogen in lycopodine.

ACKNOWLEDGEMENT

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GENERAL INTRODUCTION

The presence of alkaloids in the cryptogamic family Lycopodiaceae was first reported in 1881 by Boedeker (1) but it was not until well into the present century that a detailed study of these alkaloids was undertaken. In 1938, Achmatowicz and Uzieblo (2) isolated three alkaloids from the species Lycopodium clavatum L. and in 1942 Manske and Marion (3) reported the first of their extensive investigations. Since that time, they have examined ten plant species and have isolated and characterized some thirty alkaloids.

Structural investigations of these alkaloids have been largely confined to the two most readily available, annotinine and lycopodine. Annotinine has been studied more intensively and complete structures have recently been postulated for it. Lycopodine has been subjected to comparatively few structural studies despite the fact that it is the most widely distributed Lycopodium alkaloid. Therefore, it has been selected here for a more extensive chemical investigation.

A von Braun ring opening was selected as the starting point in this structural study of lycopodine. The major product, α-cyanobromolycopodine, was reduced to α-cyanolycopodine and the latter is the starting material for a variety of reactions and degradations.

By means of hydride reductions, α-cyanolycopodine and

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α-cyanobromolycopodine were converted into several deriva-
tives useful for oxidation and dehydrogenation studies. A
dehydrogenation experiment indicated the presence of a satu-
rated quinoline ring system in the α-compounds.

Other experiments were carried out with a view towards
establishing the structure near the carbonyl group and at the
same time revealing information concerning the relationship of
the functional groups, the nitrogen and the carbonyl, in lyco-
podine.

α-Cyanolycopodine was found to have an active methy-
lene group through the preparation of a benzal derivative and
by oxidation to two α-diketones, isolated in the enol forms.
Examination of the ultraviolet and infrared spectra of these
enols, isolated from different reactions, indicated that the
nitrogen and carbonyl groups are not in the same ring.

The benzal derivative of α-cyanolycopodine was con-
verted into a tertiary base which failed to form a methiodide
or react with cyanogen bromide but which underwent an unusual
carbon-nitrogen bond scission reaction with methyl sulfate.
Oxidation studies with selenium dioxide on the benzal compounds
provided more information concerning the structure in the vi-
cinity of the carbonyl group and placed limitations on the
possible positions of the carbonyl group in a ring adjoining
the heterocyclic ring.

HISTORICAL INTRODUCTION

Lycopodine was first isolated by Boedeker (1) from
Lycopodium complanatum L. in 1881. He assigned the formula
$C_{32}H_{52}O_3N_2$ to the alkaloid which melted at 114-115°C. In
more recent years, Achmatowicz and Uzieblo (2) isolated this
alkaloid from the same plant. They assigned the formula
$C_{16}H_{25}ON$ and found that the base contains no active hydrogen,
N-methyl nor methoxyl groups.

Over the past fifteen years, Manske and Marion and
co-workers have carried out extensive research into the iso-
lation, characterization and chemistry of Lycopodium alka-
loids. In their first paper (3), they confirmed the formula
$C_{16}H_{25}ON$ for lycopodine proposed by Achmatowicz and Uzieblo.
In a series of papers (3 - 12), these workers described the
isolation of some thirty alkaloids from ten plants belonging
to the Lycopodium family. Lycopodine was by far the most
widely distributed alkaloid, having been isolated from all
but two of the species examined. A few simple derivatives of
lycopodine have also been isolated. Douglas, Lewis and
Marion (13) found that alkaloid L14 isolated from L. trista-
chyum was identical with anhydrodihydrolycopodine prepared
by dehydration of dihydrolycopodine. They also found that
alkaloid L2 from L. flabelliforme was the O-acetate of di-
hydrolycopodine. It was found in this laboratory that the

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alkaloid L1 assigned the formula $C_{18}H_{31}ON$ by Manske and Marion
(3) was actually dihydrolycopodine, $C_{16}H_{27}ON$. Achmatowicz and
Rodewald (14) described an alkaloid $C_{16}H_{25}ON$, m.p. $136^{\circ}C$., from
L. annotinum L. to which they gave the name isolycopodine.
They suggested that it might be identical with L13 isolated
from five plant species by Manske and Marion.

The investigation of the detailed structure of the
Lycopodium alkaloids has so far been limited to only a few
examples - annotinine, obscurine and lycopodine. Annotinine,
the major alkaloid of L. annotinum, has been studied the most
thoroughly. Wiesner et al. (15) and Marion et al. (16) have
each proposed quite different complete structures for the
alkaloid which are represented in I and II respectively. The
latest publication by Wiesner invalidates structure II as does
recent unpublished work in these laboratories (17).
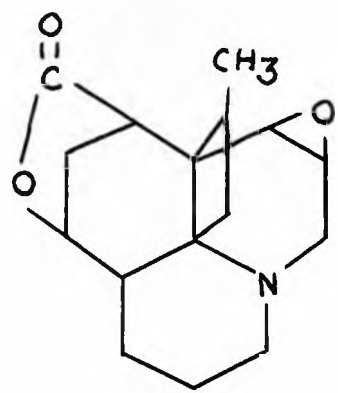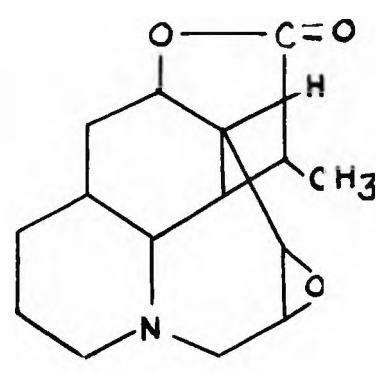
I   II

The relationship between lycopodine and annotinine is not yet apparent. They may have the same skeletal structure. They are expected to be related biogenetically at least.

Obscurine has been subjected to limited structural studies. Moore and Marion (18) found obscurine to be a mixture of two similar alkaloids which they called α-obscurine ($C_{17}H_{26}ON_2$) and β-obscurine ($C_{17}H_{24}ON_2$). Spectral studies of α-obscurine indicated a secondary amino group, and a cyclic lactam containing α,β-unsaturation. The ultraviolet spectrum of β-obscurine was almost identical to that of 6-methyl-α-pyridone. The infrared spectrum of β-obscurine also indicated an α-pyridone ring. These workers dehydrogenated α-obscurine and isolated 7-methylquinoline and 6-methyl-α-pyridone. These two fragments accounted for sixteen carbon atoms. It was suggested that the missing carbon is in a methylene group. Further work on the obscurines was apparently hampered by the small amount of alkaloid available for study. The obscurines do not appear to fit into any of the structures proposed for annotinine. Likewise there is no apparent relationship with lycopodine.

Manske and Marion (19) carried out the first degradation studies on lycopodine. Selenium dehydrogenation yielded a mixture of bases from which they were able to isolate 7-methylquinoline and 5,7-dimethylquinoline. 7-Methylquinoline was also isolated by dehydrogenation with palladium and with phthalic anhydride. It was concluded that a completely reduced

quinoline ring system is present in lycopodine. Lycopodine failed to react with phenyl magnesium bromide and would not reduce at 200°C. over Raney nickel at 2000 p.s.i.g. They concluded that there was no ketonic group in lycopodine and that the oxygen was probably present in a cyclic ether linkage.

A more thorough investigation by MacLean, Manske and Marion (20) showed that the oxygen atom in lycopodine was in a carbonyl group and not an ether linkage. The carbonyl group was detected by examination of the infrared spectrum which showed a strong absorption at 1693 cm.$^{-1}$ characteristic of a carbonyl function. This was confirmed by formation of a hydrazone, by hydride reduction to an alcohol and by conversion to a tertiary carbinol with phenyllithium. With this knowledge of the functional groups of lycopodine and its molecular formula, it can be calculated that it contains a tetracyclic ring system.

Attempts by these workers to degrade lycopodine through its N-oxide, or by the Emde or the Hofmann degradations were fruitless. However, the von Braun reaction of lycopodine with cyanogen bromide proceeded to yield two isomeric products, α - and β -cyanobromolycopodine ($C_{17}H_{25}ON_2Br$). The bromine in α-cyanobromolycopodine was replaced by an acetoxyl function and hydrolysis of the latter produced α- cyanohydroxylycopodine. Oxidation of the latter to an acid containing the same number of carbon atoms established that α -cyanobromolycopodine was a primary bromide. In a mixture

of glacial acetic acid and potassium acetate, both the cyano-
gen group and the bromine were eliminated from α-cyanobromo-
lycopodine with formation of some lycopodine. This result
established that no unusual rearrangement occurred during the
von Braun reaction to produce the α-compound. Treatment of
β-cyanobromolycopodine with ethanolic potassium acetate pro-
duced a neutral halogen-free product, $C_{17}H_{24}ON_2$, resistant to
permanganate oxidation, ozone or catalytic hydrogenation.
α-Cyanobromolycopodine was converted into an analogous iso-
meric substance with methanolic potassium hydroxide. The
apparent absence of unsaturation in these isomers was at-
tributed to a cyclization. Hydrogenation of both α- and β-
cyanobromolycopodine produced what appeared to be two isomeric
hydrogenolysis products ($C_{17}H_{26}ON_2$).

MacLean et al. converted α-cyanobromolycopodine to
α-cyanotrimethylaminolycopodium bromide. Hofmann degra-
dation of the corresponding quaternary base produced only
the α-cyclocyanolycopodine and α-cyanodimethylaminolyco-
podine but no olefin. More recent work in this laboratory
(21) along this line has indicated that a more promising ap-
proach is to prepare α-cyanodimethylaminolycopodine and re-
duce the carbonyl to an alcohol with sodium borohydride before
proceeding with the Hofmann degradation sequence. In this way,
the usual cyclization reaction was avoided. This suggests
that the cyclization reactions most probably occurred alpha
to the carbonyl. Reduction of the carbonyl group to an

alcohol apparently removed the activation necessary for the cyclization reaction. It is of interest to notice that some dihydrolycopodine was produced along with an olefin which is presently to be investigated.

Harrison (22) extended the sequence of reactions at the halogen in α-cyanobromolycopodine. He converted the latter to the α-cyanolycopodine carboxylic acid reported by MacLean et al. The acid was then hydrolyzed to the amino acid hydrochloride, which upon esterification with diazo-methane was partially converted to a lactam, $C_{16}H_{23}O_2N$. The lactam carbonyl absorbed at 1635 cm.$^{-1}$ in the infrared indicating a lactam ring of six or more members. This indicated that the ring opened in the formation of α-cyanobromolyco-podine is six-membered or larger.

Attempts were made by Harrison to replace the bromine in β-cyanobromolycopodine with a view toward carrying out a similar series of reactions as described above for the α-compound. However, in all cases, the main product was the β-cyclocyanolycopodine ($C_{17}H_{24}ON_2$) first isolated by MacLean et al. In fact, catalytic reduction of β-cyanobromolyco-podine also was found to produce this cyclized compound and not a compound isomeric with α-cyanolycopodine ($C_{17}H_{26}ON_2$) as reported earlier (20). Other reagents such as potassium hydroxide, potassium acetate, silver acetate or sodium boro-hydride resulted in this cyclization. In some cases advantage was taken of the difference in the ease of cyclization of the

two bromocyanamides to obtain easily separable compounds of the α and β series from the crude von Braun product. For example, the mixture of α - and β -cyanobromolycopodine was treated with potassium acetate followed by potassium hydroxide, to yield α-cyanohydroxyllycopodine and the β -cyclocyanolyco-podine. Sodium borohydride converted the mixture to dihydro-α -cyanolycopodine and the β -cyclocyanolycopodine. The pro-ducts from each reaction were readily separated by chroma-tography.

Because of the ready formation of the β -cyclocyano-lycopodine, Harrison made a detailed investigation of this compound. He found that this compound had a peculiarly characteristic infrared spectrum with a band at 1675 cm.[-1] replacing the carbonyl band found at 1700 cm.[-1] in the bromo-cyanamide. The lack of olefinic absorption near 1600 cm.[-1] in the infrared spectrum and the nature of the ultraviolet spectrum ruled out the possibility of an α , β -unsaturated ketone. He considered two possible structures to account for the band at 1675 cm.[-1]. One was a cyclopropane ring formed alpha to the carbonyl group. It was noted that cyclopropyl ketones show displacement of the carbonyl band somewhat like α , β -unsaturated ketones and, in addition, bands in the 850-1000 cm.[-1] region corresponded to bands observed in many cyclopropane derivatives. However, the β -cyclized compounds (both the neutral cyano-compound and the corresponding base) were found to be inert to carbonyl reagents. In particular,

these compounds would not reduce with lithium aluminum hydride even under vigorous conditions. This led Harrison to suggest a non-ketonic structure for the β-cyclocyanolycopodine such as an enol ether which would explain its inertness to carbonyl reagents and also account for the infrared spectrum. Such a structure, however, would not explain the unusual inertness of this compound nor the ultraviolet absorption at 270 $m\mu$ which is characteristic of ketones. Bromination of the β-cyclo-cyanolycopodine with bromine in carbon tetrachloride gave a complex mixture. A small amount of material with infrared absorption at 1645 cm.$^{-1}$ was isolated. Hypobromination yielded a compound, $C_{17}H_{24}O_2N_2$, which exhibited hydroxyl absorption and a band at 1680 cm.$^{-1}$. However, further experiments with this hydroxylated compound did not meet with much success. It failed to react with periodic acid and lead tetraacetate appeared to introduce an acetoxyl group rather than cleave the compound. Dehydration experiments were likewise unsuccessful. These experiments did not ascertain whether the β-cyclocyanolycopodine has a ketone or an enol-ether structure.

Harrison suggested a β-piperidone structure for lycopodine. The von Braun reaction on lycopodine was formulated as follows:
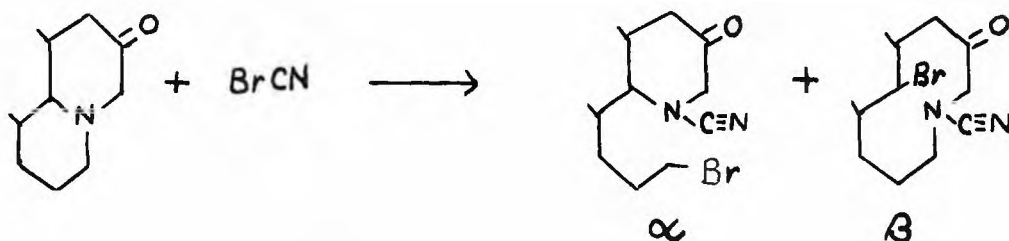
He pointed out that the above formulation for β-cyanobromo-
lycopodine provided for either a cyclopropyl ketone or an enol
ether on loss of hydrogen bromide -
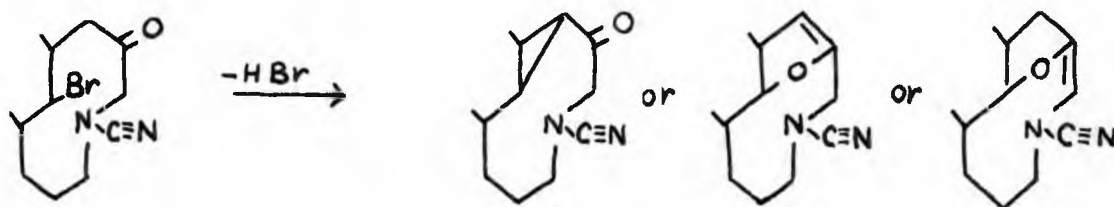
It is desirable at this point to summarize briefly
the limited information which is available concerning the
structure of lycopodine. The formula $C_{16}H_{25}ON$ has been well
established for this alkaloid. Since the oxygen was found
to be in a carbonyl group and the nitrogen is tertiary, this
formula indicates that lycopodine is a tetracyclic base with
a nitrogen which is common to two rings. Dehydrogenation
studies indicated the presence of a reduced quinoline ring
system in the alkaloid. The von Braun ring opening with
cyanogen bromide has been the most successful mild degradation.
The major product of this reaction, α-cyanobromolycopodine,
was found to be a primary bromide. The ring which opened to
form α-cyanobromolycopodine was found to be six-membered or
possibly larger. Experiments on β-cyanobromolycopodine, the
other product of the von Braun reaction, were hampered because
this compound underwent a facile cyclization reaction with
elimination of the elements of hydrogen bromide to form β-

cyclocyanolycopodine. Structures such as an enol-ether and a cyclopropyl ketone have been suggested for the latter compound but neither of these satisfactorily explained its properties.

RESULTS AND DISCUSSION

The von Braun ring scission with cyanogen bromide was
the starting point for this structural study of lycopodine.
The experiments have been limited to the reactions of the
major product of the von Braun reaction, α-cyanobromolyco-
podine, and its derivatives. The experiments in this investi-
gation can be divided into three sections - (A) preparation
of simple derivatives of α-cyanolycopodine and their re-
actions, (B) certain bromination experiments and oxidations
of α-cyanolycopodine, and (C) reactions and degradations
through the benzal derivative of α-cyanolycopodine. The re-
sults will be discussed below in this order.

A. Preparation of Simple Derivatives of α-Cyanolycopodine
   and Their Reactions

The experiments described and discussed in this section
were undertaken with several objectives in mind. First, α-
cyanolycopodine was converted through a series of reactions
to a methiodide in the hope that this would prove to be a
useful starting material for further degradation at the nitro-
gen atom. Second, the reduction of α-cyanolycopodine and α-
cyanobromolycopodine with hydride reducing agents was thoroughly
investigated. From this work, convenient methods were found
for the preparation of several useful derivatives for de-

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hydrogenation and oxidation studies and a satisfactory method
was developed for the separation of mixtures of α- and β-
cyanobromolycopodine as useful derivatives.

1. Conversion of α-Cyanolycopodine to a Methiodide

The von Braun reaction of lycopodine with cyanogen
bromide by an improved procedure yielded the isomeric α- and
β-cyanobromides (II and III) reported previously (20). Cata-
lytic reduction converted II into α-cyanolycopodine, IV.
Acid hydrolysis of IV yielded the secondary base α-des-di-
hydrolycopodine, $C_{16}H_{27}ON$, V. Treatment with acetic an-
hydride converted V into a neutral amorphous compound which
no longer showed =NH absorption but had a band at 1640 cm.$^{-1}$
in the amide region of the infrared. Methylation of V by
formaldehyde and formic acid or by methyl sulfate yielded a
tertiary base, VI, which analyzed for a single N-CH$_3$ group.
Conversion of VI into a methiodide, $C_{18}H_{32}ONI$, VII, proceeded
in very poor yield. An attempt to carry out a reductive
fission of this quaternary salt was not successful. No
satisfactory explanation can be offered for the failure of
the tertiary base, VI, to form a methiodide in reasonable
yield. Steric effects are known to influence methiodide for-
mation from tertiary amines. For example, in simpler systems,
Brown and Nelson (23) observed that bulky ortho substituents
hindered methiodide formation of N, N-dimethylaniline. The
reaction of ortho-substituted tertiary bases with methyl
iodide was sometimes slow and incomplete. They found that

the highly hindered o-t-butyl-N,N-dimethylaniline failed to form any methiodide. If steric effects hinder methiodide formation from the tertiary base, VI, one would perhaps expect such hindrance would prevent methiodide formation from lycopodine. However, lycopodine itself formed a methiodide rapidly and quantitatively when an acetone solution of the base was mixed with methyl iodide.

2. Hydride Reductions of α-Cyanolycopodine and α-Cyanobromolycopodine.

Dehydration of Dihydro-α-cyanolycopodine

A number of hydride reductions was carried out on α-cyanobromolycopodine and its derivatives to prepare compounds for dehydrogenation and other degradation studies. The secondary base, α-des-dihydrolycopodine, was converted to the corresponding carbinol, α-des-tetrahydrolycopodine, $C_{16}H_{29}ON$, VIII, by lithium aluminum hydride. An alternative and more convenient preparation of this carbinol resulted from the direct reduction of α-cyanobromolycopodine with lithium aluminum hydride. In this conversion, the bromine underwent hydrogenolysis, the carbonyl group was reduced, and the =N-CN linkage was converted to =NH. Some neutral material was also derived as a by-product of this reduction in which the =N-CN group was still present. This material proved to be the corresponding cyanamide, dihydro-α-cyanolycopodine, IX, which was also derived by two alternative procedures. The Meerwein-Ponndorf reduction of α-cyanolyco-

podine was slow and inefficient, but reduction of α-cyano-bromolycopodine with sodium borohydride proceeded readily to a good yield of IX.

The displacement of bromine by hydrogen in the sodium borohydride reduction is somewhat unusual since this reagent does not ordinarily affect carbon-halogen linkages under these conditions. Since the reaction has been carried out several times with the same result, it would appear that this is an authentic case of a sodium borohydride reduction of an aliphatic halogen.

The von Braun reaction on lycopodine produced a mixture of α- and β-cyanobromolycopodine from which most of the α-isomer was recovered from the first crop of crystals deposited from an ether solution. The residual mother liquor contained a mixture of α- and β-cyanobromolycopodine (II and III) which was very difficult to separate into its components either by fractional crystallization or chromatography. However, when an intimate mixture of II and III was reduced with sodium borohydride, II was converted as before into IX, and III was converted into β-cyclocyanolycopodine, $C_{17}H_{24}ON_2$, formed by elimination of hydrogen bromide and accompanying cyclization. These two reduction products were readily separated by chromatography on alumina by virtue of the stronger adsorption of the carbinol, IX.

Dihydro-α-cyanolycopodine, IX, was dehydrated to an amorphous neutral anhydro compound, $C_{17}H_{26}N_2$, X, by boiling

in xylene solution containing catalytic amounts of p-toluene
sulfonic acid. Ozonolysis of X followed by permanganate oxi-
dation and esterification yielded a product with infrared ab-
sorption bands in the carbonyl region at 1708 and 1733 cm.$^{-1}$
indicative of a keto ester. This result suggests that one of
the carbons adjacent to the carbonyl group is tertiary as
shown below.

$$- \overset{\overset{O}{\|}}{C} - \overset{\overset{H}{|}}{\underset{|}{C}} - \quad \xrightarrow{\text{NaBH}_4} \quad - \overset{\overset{OH}{|}}{\underset{|}{\underset{H}{C}}} - \overset{\overset{H}{|}}{\underset{|}{C}} - \quad \xrightarrow{-\text{H}_2\text{O}} \quad - \overset{\overset{H}{|}}{C} = \overset{|}{C} -$$

IX   X

$$\Big\downarrow \begin{array}{l} O_3, \\ \text{KMnO}_4 \end{array}$$

$$- \overset{\overset{O}{\|}}{C} - OH \quad O = \overset{|}{C} -$$
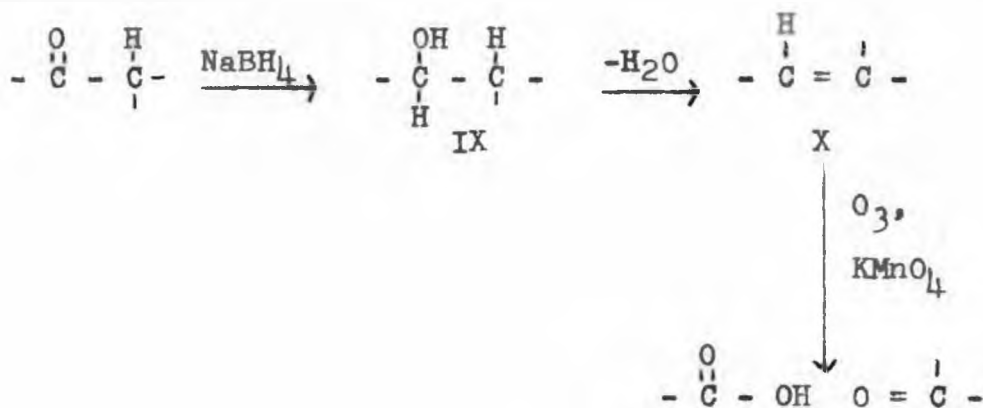
However, it is possible that rearrangement may have
occurred during the vigorous dehydration and this evidence
cannot be taken as unequivocal, especially since the anhydro
compound, X, was amorphous and possibly a mixture. Although
the anhydro compound, X, failed to crystallize, lithium
aluminum hydride reduction converted it to an amorphous
secondary base, $C_{16}H_{27}N$, XI, which yielded a crystalline hydro-
chloride.

The various hydride reduction experiments discussed
in this section are summarized in chart form in Figure 1 on
page 18.

Hydride Reductions

$C_{16}H_{25}ON$ lycopodine $\xrightarrow[\quad \bigg\rangle C = 0 \longrightarrow CHOH \quad]{LiAlH_4}$ $C_{16}H_{27}ON$ dihydrolycopodine

$C_{16}H_{27}ON$ V $\xrightarrow[\quad \bigg\rangle C = 0 \longrightarrow \bigg\rangle CHOH \quad]{LiAlH_4}$ $C_{16}H_{29}ON$ VIII

$\begin{array}{l} LiAlH_4 \\ (1) \ -CH_2Br \longrightarrow -CH_3 \\ (2) \ \bigg\rangle C = 0 \longrightarrow \bigg\rangle CHOH \\ (3) \ \bigg\rangle N-C\equiv N \longrightarrow \bigg\rangle N-H \end{array}$ $\longleftarrow$ $C_{17}H_{25}ON_2Br$ II

Figure 1

$C_{17}H_{25}ON_2Br$

II + III

$\bigg| \quad NaBH_4$

$C_{17}H_{24}ON_2$ $\longleftarrow$ $-HBr$ $\longrightarrow$

β-cyclocyanolycopodine

NaBH₄

(1) $-CH_2Br \longrightarrow -CH_3$

(2) $\bigg\rangle C = 0 \longrightarrow \bigg\rangle CHOH$

$C_{17}H_{28}ON_2$ IX

$C_{17}H_{26}N_2$ X $\xrightarrow[\quad \bigg\rangle N-C\equiv N \longrightarrow \bigg\rangle N-H \quad]{LiAlH_4}$ $C_{16}H_{27}N$ XI
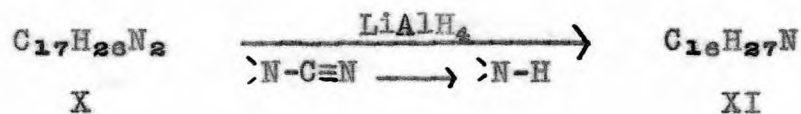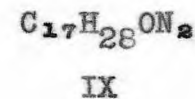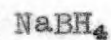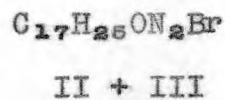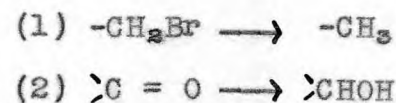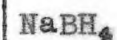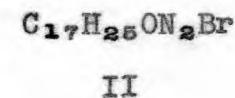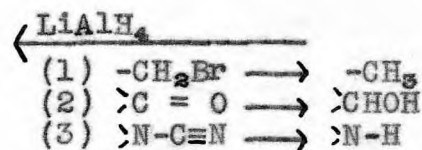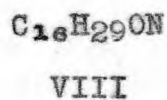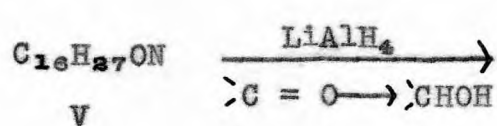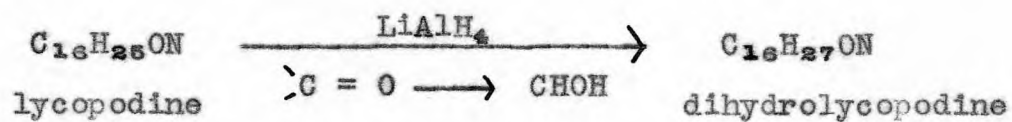
3.   Dehydrogenation of α-Des-tetrahydrolycopodine

Dehydrogenation of α-des-tetrahydrolycopodine, VIII,
with palladium-charcoal produced a small yield of a dehydroge-
nation product with a characteristic ultraviolet spectrum
shown in Figure I of the Appendix. The fine structure ab-
sorption in the 310 to 327 $m\mu$ region and the strong band at
242 $m\mu$ resembles in general the spectra of quinoline and
derivatives. Actually this spectrum shows a considerable
bathochromic shift compared to quinoline and its simple alkyl
derivatives. The strong K band at 242 $m\mu$ in this product
appears at 231 $m\mu$ in quinoline. Likewise the fine structure
absorption in the 320 $m\mu$ region has been shifted by about
10 $m\mu$ to longer wavelengths. The dehydrogenation product
also has C-CH$_3$ absorption in the infrared at 1460 cm.$^{-1}$. It
is therefore undoubtedly an alkylated quinoline containing
at least one methyl group and possibly other alkyl groups
or an attached saturated ring. This result suggests that a
saturated quinoline ring system is present in the α -com-
pounds, although the possibility of rearrangement during de-
hydrogenation is not precluded.

Reference has been made to Harrison's work (page 8)
on α -cyanobromolycopodine which indicated that the ring
opened in its formation is six-membered or possibly larger.
Taken together with these dehydrogenation results, this would
indicate that three of the four rings of lycopodine are six-
membered. The following partial structure is therefore a

convenient working model for lycopodine for the discussion of results obtained in this investigation.

→ potential quinoline ring system in the α-compounds

→ ring opened in the formation of α-cyanobromolycopodine
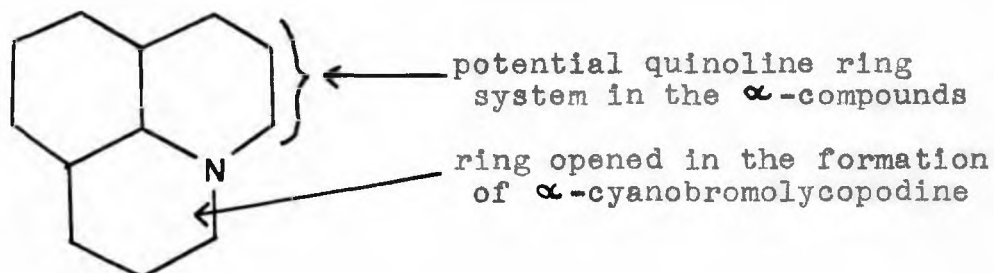
In the above partial formula for lycopodine, no attempt has been made to place the fourth ring nor to indicate the position of the carbonyl group. The remaining work in this investigation is concerned with the structure of the molecule about the carbonyl group and the attempts to relate the position of the carbonyl group to the nitrogen.

B. Bromination Experiments.

Oxidations of α-Cyanolycopodine

The bromination of lycopodine, α-des-dihydrolycopodine and α-cyanolycopodine was studied in an attempt to prepare derivatives of these compounds suitable for oxidative degradation. Bromination is expected to take place alpha to the carbonyl group, and it was expected that these experiments might provide information on the structure near this group and on its relationship to the nitrogen. Lycopodine and α-des-dihydrolycopodine readily formed monobromo derivatives isolated as their hydrobromides. Unfortunately, further in-

vestigation of these compounds was hampered by the fact that they underwent decomposition on conversion to their corresponding bases. A comparison of the pK_a values for the desbases and the brominated bases with the values for lycopodine and dihydrolycopodine leads one to believe that the relationship of the nitrogen to the carbonyl group has not been altered in the formation of α-cyanobromolycopodine during the von Braun reaction. The major portion of the bromination product from α-cyanolycopodine was an amorphous residue. However, alkali treatment of this residue yielded a conjugated enol, XII, which indicates the presence of an active methylene group alpha to the carbonyl group in α-cyanolycopodine. Oxidations of α-cyanolycopodine with sodium hypobromite and selenium dioxide were carried out in an attempt to provide more of this enol for further study. These oxidations yielded a second enol, XIII, isomeric but not identical with XII. From an examination of the infrared and ultraviolet spectra of these two enols, it appears unlikely that the nitrogen and carbonyl functions are in the same ring in α-cyanolycopodine.

1. Bromination of Lycopodine and α-Des-dihydrolycopodine. Basicity Constants of Lycopodine, the Des-bases and Their Derivatives

Both lycopodine and α-des-dihydrolycopodine readily brominated to yield monobromoderivatives isolated as their hydrobromides. These brominated hydrobromides underwent decomposition on conversion to the free bases and no identifi-

able products could be isolated from either substance. Both
of these compounds are undoubtedly α-bromoketones since the
infrared absorption of the carbonyl group is displaced by
about 10 cm.$^{-1}$ to longer wave numbers in each case (24) and
both compounds gave a Fehling's test.

The pK_a values of lycopodine, the various des-bases
and the bromo compounds are summarized below:

Lycopodine	9.1
Dihydrolycopodine	10.2
α-Des-dihydrolycopodine	9.1
α-Des-tetrahydrolycopodine	9.8
Bromolycopodine	7.3
Bromo-α-des-dihydrolycopodine	7.2

The similarity in pK_a of lycopodine and α-des-dihydrolyco-
podine suggests that in the ring fission reaction to produce
α-cyanobromolycopodine, the relationship of the nitrogen
and carbonyl groups has not been altered. This is consistent
with the fact that both bases show a comparable rise in
basicity on reduction to the carbinols. The large decrease
in basicity of both brominated bases confirms that the car-
bonyl nitrogen sequence has not been altered in the von Braun
fission. Furthermore, because the α-substituted halogens in
these bromo derivatives are not expected to exert their electron-
withdrawing effect through any distance along a chain, this
greatly decreased basicity implies a rather close proximity
of the carbonyl and nitrogen atoms in the molecule. Since the

bromine can only exert its electron-withdrawing effect in-
ductively, this decrease in pK_a would not be expected to be
large unless the bromine entered alpha to the nitrogen. How-
ever, the reliability of the pK_a measurements on the brominated
bases may well be questioned in view of their facile decom-
position in alkali. It was noticed that during the pK_a
measurements on the bromo-hydrobromides, the faintly alkaline
solutions of the titrated bases soon became strongly acid
again on standing.

2. Bromination and Oxidation of α-Cyanolycopodine.

The Two Enols Derived from α-Cyanolycopodine

In a solution of carbon tetrachloride, α-cyanolyco-
podine readily consumed bromine with deposition of a solid
amorphous precipitate. From this precipitate it was possible
to isolate, although in low yield, a monobromo derivative.
The carbonyl absorption in the infrared of this brominated
derivative was displaced by 10 cm.$^{-1}$ to 1710 cm.$^{-1}$ in com-
parison to the starting material at 1700 cm.$^{-1}$. Such a
shift is consistent with an α-bromoketone structure (24).
In contact with water or aqueous alkali, this product readily
lost bromine to produce a mixture of compounds, probably
alcoholic and olefinic in nature, which were not definitely
characterized.

The main product of this bromination was amorphous.
In common with the crystalline monobrominated product, it
readily lost its bromine in contact with aqueous alkali.

Treatment of these amorphous residues with alkaline aqueous
dioxane yielded a product from which a crystalline compound
was obtained. This compound, which analyzed for $C_{17}H_{24}O_2N_2$,
XII, had the properties of an enol. The infrared spectrum
indicated the presence of a conjugated carbonyl group, an
olefinic double bond, and a hydroxyl group. The ultraviolet
absorption spectrum (Figure II of the Appendix) shows strong
absorption at 2800 $\overset{o}{A}$ which is indicative of a hydroxylated
α, β -unsaturated carbonyl chromophore. In general, hydroxyl-
substituted α, β -unsaturated six-atom-ring ketones show an
intense absorption maximum at 2700 $\pm$ 50 $\overset{o}{A}$ (25). The analyti-
cal and spectral results suggested a structure of the follow-
ing type $-\overset{\quad OH}{C}=\overset{}{C}-\overset{}{C}=O$. Such a structure would arise from an α,
α, dibrominated ketone, $-\overset{|}{C}H-\overset{}{C}Br_2-\overset{|}{C}=O$. This result established
the presence of an active methylene group in lycopodine ad-
jacent to the carbonyl group. The bromination reaction thus
proceeded to give a mixture of mono- and di-brominated ketone.

Bromination of α -cyanolycopodine in the presence of
sodium hydroxide yielded some of the monobromo-derivative
described above. Treatment of the residue with alkali on
the steam cone yielded a small amount of an alkali soluble
compound, XIII, with the properties of an enol but with infra-
red absorption bands at 1675 and 1648 cm.$^{-1}$ compared to 1660
and 1640 cm.$^{-1}$ for the enol, XII.

Selenium dioxide oxidation of α -cyanolycopodine
yielded enol XIII in crystalline form although in small yield.

These two enols have similar ultraviolet spectra (Figure II
of the Appendix) and the only apparent difference in the
infrared spectra was in the carbonyl and unsaturation bands.
Two such enols could arise from two active methylene groups
in α-cyanolycopodine as shown below:

$$- CH_2 - \overset{\overset{O}{\|}}{C} - CH_2 - \quad \xrightarrow{\text{Br}_2 \text{ in } \text{CCl}_4} \quad - CBr_2 - \overset{\overset{O}{\|}}{C} - CH_2$$

$$\Big\downarrow \begin{array}{c} \text{SeO}_2 \\ \text{or} \\ \text{NaOBr} \end{array} \qquad\qquad \Big\downarrow \text{2HOH}$$

$$- CH_2 - \overset{\overset{O}{\|}}{C} - \overset{\overset{O}{\|}}{C} - \qquad\qquad - \overset{\overset{O}{\|}}{C} - \overset{\overset{O}{\|}}{C} - CH_2 -$$

$$\downarrow \uparrow \qquad\qquad \uparrow \downarrow$$

$$- \overset{\overset{H}{|}}{C} = \overset{\overset{OH}{|}}{C} - \overset{\overset{O}{\|}}{C} - \qquad\qquad - \overset{\overset{O}{\|}}{C} - \overset{\overset{OH}{|}}{C} = \overset{\overset{H}{|}}{C} -$$
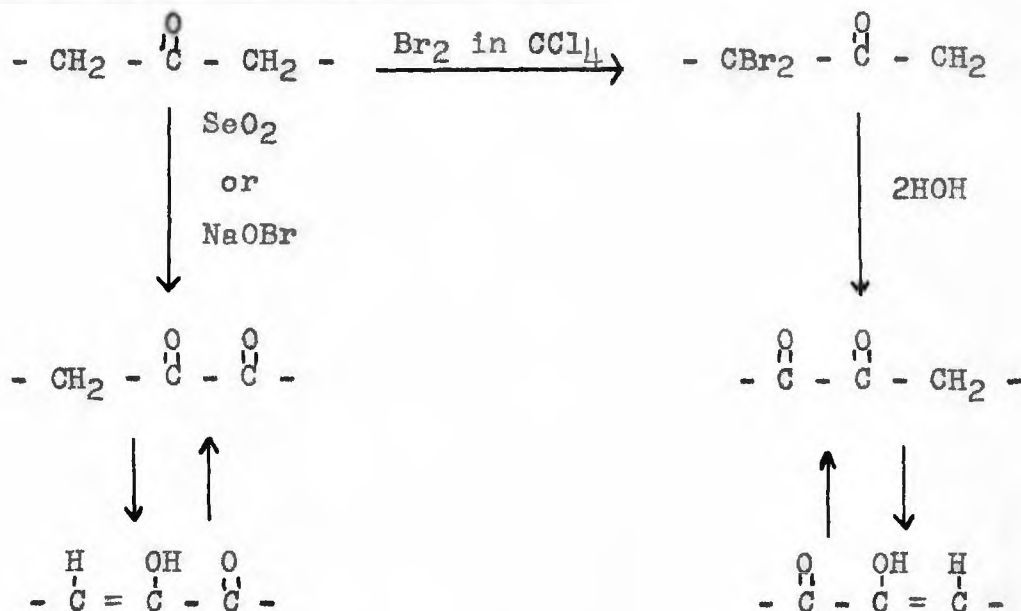
Results discussed in the preceding section suggested
that the carbonyl group is relatively close to the nitrogen
in lycopodine and the α-compounds. Harrison (22) suggested
a β-piperidone relationship of carbonyl and nitrogen to ex-
plain the different enols obtained from α-cyanolycopodine
under different conditions. The two enols were thus formu-
lated as follows:
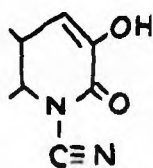
XII
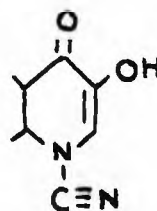
XIII

However, it should be pointed out here that Harrison's formulation for XII is really a conjugated six-membered or δ-lactam. (It would have to be at least a six-membered ring because the carbonyl stretching frequency in lycopodine appears at 1700 cm.$^{-1}$ which is characteristic of a carbonyl group in six-membered or larger rings.) Infrared spectra for conjugated six-membered lactams have been reported in the annotinine series. Wiesner and co-workers (26) found that compounds possessing such a grouping showed two similar bands. In one compound, these bands were at 1645 and 1617 cm.$^{-1}$, and in another compound at 1657 and 1616 cm.$^{-1}$. Betts and MacLean (27) also measured the infrared spectrum of conjugated lactams derived from annotinine and found two bands at 1665 and 1610 cm.$^{-1}$ in one compound, and 1655 and 1620 cm.$^{-1}$ in another. From analogy with these cases, it might be expected that a hydroxylated conjugated lactam such as XII would show the double absorption at lower frequencies than the found values of 1660 and 1640 cm.$^{-1}$, especially since the vicinal enolic hydroxyl function is expected to undergo hydrogen-bonding with the carbonyl group. If a hydrogen bond is formed to a C=O group, the carbonyl stretching frequency is lowered by 10-30 cm.$^{-1}$ (28).

The above formulation for enol XIII is an amino-substituted α, β-unsaturated ketone with the nitrogen at the β-carbon. Cromwell and co-workers (29) have made a detailed study of the infrared spectra of similar systems of the type:

$$R - \overset{\overset{O}{\|}}{C} - \overset{|}{C} = \overset{\overset{\diagdown N \diagup}{|}}{C} - R$$
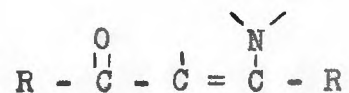
They found that the presence of an amino group on the beta
carbon atom of an α, β-unsaturated ketone lowered the car-
bonyl band by 20-80 cm.$^{-1}$ so that compounds of this general
type exhibited carbonyl absorption near the 1600 cm.$^{-1}$
region. (Compare the found value of 1675 cm.$^{-1}$ for enol
XIII.) These arguments suggest that the above γ-piperidone
structure for enol XIII is most unlikely and therefore the
carbonyl function is probably not in the same ring as the
nitrogen. In the present case, XIII is not exactly analogous
with the series studies by Cromwell and co-workers because
XIII is a neutral cyanamide. In the -N-CN grouping the un-
shared pair on the nitrogen would not likely be as readily
available for conjugation as in a free base because of the
inductive effect of the -C≡N group. However, in work to be
discussed in later chapters, XIII was converted to the corre-
sponding enol base and the latter exhibited carbonyl absorption
at 1662 cm.$^{-1}$. While this is a low frequency shift, it is not
at all comparable to that expected of a β-amino-α,β-unsatu-
rated ketone.

Further evidence against the β-amino-α,β-unsatu-
rated ketone structure for enol XIII comes from its ultraviolet
spectrum. The effect of electron-repelling groups, especially
a nitrogen at the end of a conjugated system, is well known
to cause a bathochromic displacement. Thus, 4-amino-3-penten-

2-one (β-aminoethylideneacetone) (30):

$$CH_3 - \overset{\overset{\displaystyle O}{\|}}{C} - \overset{\overset{\displaystyle H}{|}}{C} = \overset{\overset{\displaystyle NH_2}{|}}{C} - CH_3$$
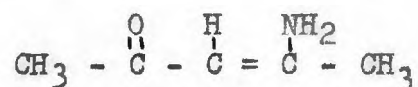
has $\lambda_{max.}$ 285 $m\mu$, $\epsilon = 6120$ compared to $\lambda_{max.}$ 224 $m\mu$, $\epsilon = 9730$ for 3-penten-2-one (31). Consequently, one would expect that enol XIII, as formulated, would absorb at longer wavelengths than XII where the nitrogen is not at the end of the conjugated system. Such was not the case. In fact, the spectra of these two compounds (Figure II of the Appendix) are practically identical. Since the bathochromic shift of the nitrogen auxochrome in a nitrogen substituted $-\alpha, \beta$- unsaturated ketone is expected to depend on the electron release of the nitrogen, it is now desirable to measure the ultraviolet spectrum of the enol base, XVI, for comparison. Experiments are at present underway to do so.

The β-piperidone structure for lycopodine cannot be ruled out by this spectral evidence alone; nevertheless, this structure should be re-examined in the light of the above objections to the formulations for the two enols. The carbonyl group is more likely in an adjoining six-membered ring:
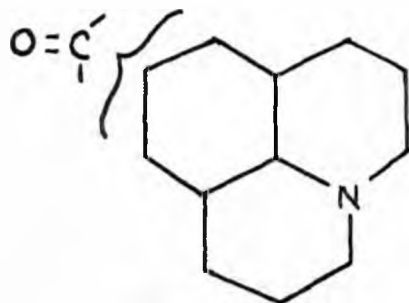
In the following section, experiments are discussed which apply limitations on the possible positions for the carbonyl group.

C.   The Reaction of α-Cyanolycopodine with Benzaldehyde. Reactions and Degradations of the Benzal Compounds

In order to confirm the presence of an active methylene group, α-cyanolycopodine was converted to a benzal derivative. Ozonolysis of the benzal compound in methanol provided more of the enol, XIII, which was described earlier. The benzal compound also proved to be a convenient starting point for further degradations. It was converted to the corresponding secondary base and thence to a N-CH_3 tertiary base. Unfortunately, the tertiary base would not react with methyl iodide or cyanogen bromide. It did react slowly with methyl sulfate. This reaction apparently resulted in a bond scission since a base was isolated which readily formed a methiodide and the latter was degraded to yield trimethyl-amine. The nature of these changes is not yet clear. Finally, the benzal compounds were oxidized with selenium dioxide. The oxidation products provide more information concerning the structure about the carbonyl group and its relationship with the nitrogen.

1.   The Preparation and Ozonolysis of Benzal-α-cyano-lycopodine

α-Cyanolycopodine formed a benzal derivative,

$C_{24}H_{30}ON_2$, XIV, in good yield which confirmed the presence of an active methylene group in lycopodine. Under similar conditions, lycopodine failed to react with benzaldehyde in agreement with the work of Douglas et al. (13). This suggests that this methylene group occupied a hindered position in lycopodine and that the hindrance was relieved on ring fission in the formation of α-cyanobromolycopodine.

Ozonolysis of XIV in ethylacetate solution and decomposition of the ozonide with hydrogen over a palladium catalyst yielded a compound, $C_{17}H_{24}O_3N_2$, XV, which had strong infrared absorption bands at 1780, 1742 cm.$^{-1}$ and in the 1050-1120 cm.$^{-1}$ region. Such absorption is attributed to a cyclic acid anhydride, $-\overset{O}{\overset{||}{C}}-O-\overset{O}{\overset{||}{C}}-$. Bellamy (32) gives the ranges 1850-1800 and 1790-1740 cm.$^{-1}$ for open and cyclic anhydrides with no ring strain. This unusual product most probably resulted from oxidation of the α-diketone, the expected product of the ozonolysis. In the decomposition of the ozonide, the uptake of hydrogen by the palladium catalyst was very slow and peroxides undoubtedly acted as the oxidizing agent to convert the diketone to the acid anhydride:

$$- \overset{O}{\overset{||}{C}} - \overset{O}{\overset{||}{C}} - \quad \xrightarrow{\text{H}_2\text{O}_2} \quad - \overset{O}{\overset{||}{C}} - O - \overset{O}{\overset{||}{C}} - + \text{H}_2\text{O}$$

Similar oxidations of α-diketones have been summarized by Waters (33).

The action of ozone on the benzal compound in absolute methanol followed by decomposition of the ozonide with

hydrogen over platinum oxide yielded an enol, $C_{17}H_{24}O_2N_2$, which was identical to the enol XIII isolated previously in small yield by the oxidation of α-cyanolycopodine with sodium hypobromite or with selenium dioxide. This enol was hydrolyzed to the secondary enol-base, XVI, $C_{16}H_{25}O_2N$.

2. The Conversion of Benzal-α-cyanolycopodine to a Benzal-t-base.

Some Reactions of the Benzal-t-base

Acid hydrolysis of the benzal compound, XIV, produced the secondary base, benzal-α-des-dihydrolycopodine, XVII, which analyzed for $C_{23}H_{31}ON$ as the free base and as the hydrochloride. Methylation of XVII with formaldehyde and formic acid or with methyl sulfate produced the same benzal tertiary base, $C_{24}H_{33}ON$, XVIII, which analyzed for a single $N-CH_3$ group. Various attempts to form the methiodide of this tertiary base for further degradations were unsuccessful. The starting base was recovered quantitatively from a mixture with methyl iodide in various solvents.

This base also failed to react with cyanogen bromide under conditions which were successful with lycopodine. The failure of XVIII to undergo a von Braun cleavage is remarkable since the $N-CH_3$ linkage at least is expected to cleave very readily. The von Braun reaction probably proceeds through the formation of a quaternary ammonium intermediate between the tertiary nitrogen and cyanogen bromide (34). The failure of this base to undergo the von Braun fission or to

form a methiodide is probably due to steric effects hindering the formation of a quaternary salt from the tertiary base.

The base, XVIII, did react slowly with methyl sulfate in boiling benzene to yield a compound, $C_{26}H_{39}O_5NS \cdot \frac{1}{2}H_2O$, XIX. This reaction product formed an ether-soluble amorphous base, XX, on treatment with aqueous alkali. The product XX analyzed for $C_{25}H_{37}O_2N$. The isolation of this ether-soluble base indicates that the action of methyl sulfate on the benzal-t-base resulted in a bond fission rather than the usual formation of a quaternary methosulfate.

The ultraviolet spectra of the benzal compounds, XIV, XVIII and XX are shown in Figure III of the Appendix. The spectrum of the benzal-t-base, XVIII, is very similar to the spectrum of the neutral benzal-α-cyanolycopodine, XIV. The amorphous base, XX, lacks the strong band at $240\,m\mu$ present in the former benzal compounds. The significance of this is not altogether clear. It is noteworthy, however, that the selenium dioxide oxidation products of XIV and XVIII also lack the band at $240\,m\mu$. (Compare Figure IV of the Appendix.)

Unlike the benzal-t-base, the reaction product XX formed a methiodide, $C_{28}H_{40}O_2NI$, XXI, very readily on mixing an acetone solution of the base with methyl iodide. When subjected to a Hofmann degradation, the methiodide, XXI, yielded trimethylamine, identified as its picrate and methiodide. This result indicates that three separate N-methylations have taken place to form the methiodide and also con-

firms that a carbon-nitrogen bond has been cleaved in the re-
action of XVIII with methyl sulfate. Incidentally, the melt-
ing point of trimethylamine methiodide reported in the liter-
ature (35) is incorrect. The compound does not melt but
rather dissociates above 300°C. The ultraviolet spectrum of
the distillate from the Hofmann degradation is shown in Figure
IV of the Appendix.

The analysis of both the base, XX, and the methiodide,
XXI, indicated that an oxygen has been introduced into the
benzal-t-base in the reaction with methyl sulfate, in addition
to a carbon-nitrogen bond fission. It was not possible to
detect strong absorption in the hydroxyl region of the infra-
red for the amorphous base, XX. In chloroform solution,
there was weak, broad absorption in the 3400-3700 cm.$^{-1}$ region
which could conceivably be due to hydroxyl absorption. How-
ever, XX, did react with acetic anhydride to yield acetoxyl
derivatives. This acylation led to rather unusual results
and different products formed in various reaction runs. In
one case, a crystalline compound, analyzing approximately for
$C_{29}H_{41}O_4N$, was isolated which contained infrared absorption
bands at 1760, 1670 and 1570 cm.$^{-1}$. These were attributed
to acetoxyl, conjugated carbonyl and phenyl groups respectively.
In another reaction, a mixture of basic and neutral acetates
formed. Both of these compounds had double absorption in the
acetoxyl region at 1725 and 1750 cm.$^{-1}$. The usual conjugated
carbonyl band was absent. The neutral product had absorption

in the amide region which indicated an N-acetyl grouping as well. However, none of these acetates were definitely characterized. The infrared spectrum of the crystalline acetate with acetoxyl as well as carbonyl absorption provided some confirmation that a hydroxyl function was present in the amorphous base, XX. The amorphous acetates could have resulted from acetylation of this hydroxyl function accompanied by enolization of the carbonyl group in the presence of sodium acetate. The enol would then be acetylated and a diacetate would result. This would account for two absorption peaks in the acetoxyl region.

The benzal-t-base, XVIII, also reacted with acetic anhydride and was partially converted to an amorphous acetate which lacked the usual carbonyl absorption for XVIII but showed acetoxyl absorption at 1750 cm.$^{-1}$. This is most probably an enol acetate of the type shown below and establishes that XVIII has the partial structure as shown.

$$C_6H_5 - \overset{H}{\underset{|}{C}} = C - \overset{|}{\underset{OAc}{C}} = \overset{|}{C} - \qquad\qquad C_6H_5 - \overset{H}{C} = \overset{|}{C} - \underset{O}{\overset{|}{C}} - \overset{|}{\underset{H}{C}} -$$

XVIII

The amorphous base, XX, was quite obviously a mixture. A pure N, N-dimethylated base requires an N-CH$_3$ analysis of 15.0. The results obtained for the N-CH$_3$ analysis were low, varying around 8.2. One N-CH$_3$ group requires 7.5. This suggests that this base was a mixture of secondary and tertiary

bases. This would account for the difficulty in getting a pure acetylation product.

The pK_a values of the benzal bases were as follows:

benzal-α-des-dihydrolycopodine (XVII)   7.0

the benzal-t-base (XVIII)   6.0

$C_{25}H_{37}O_2N$ (XX)   8.8

The base, XX, shows a large increase in basicity over the benzal-t-base, XVIII. This suggests that the bond fission reaction of XVIII leading to XX has taken place between the nitrogen and carbonyl functions. The removal of the electron-attracting carbonyl function from interaction with the nitrogen is expected to increase the basicity of the nitrogen. The exact nature of this carbon-nitrogen fission is not known and will be difficult to formulate until the carbonyl-nitrogen relationship is definitely established.

3. Selenium Dioxide Oxidation Products of the Benzal-t-base and of Benzal-α-cyanolycopodine

In an effort to obtain more information concerning the carbonyl-nitrogen relationship in the benzal compounds, XVIII was oxidized with selenium dioxide. A β-piperidone structure, for example, would be expected to oxidize to a neutral lactam. The product from this oxidation, $C_{24}H_{33}O_2N$, XXII, proved to be a hydroxy base. It had hydroxyl absorption at 3400 cm.$^{-1}$ and was acetylated with acetic anhydride to yield an acetoxyl derivative, $C_{26}H_{35}O_3N$, with acetoxyl absorption at 1745 cm.$^{-1}$. The carbonyl band for

XXII appeared at 1690 cm.$^{-1}$ compared with 1680 cm.$^{-1}$ for XVIII. This small increase in the carbonyl frequency absorption would indicate that the new hydroxyl function in XXII entered alpha and axial to the carbonyl group (36).

The ultraviolet spectrum of XXII (Figure V of the Appendix) shows distinct differences from the starting material (Figure III of the Appendix). The band at 280 $m\mu$ in the latter is shifted to 285 $m\mu$ in XXII and the strong band at 240 $m\mu$ in the benzal-t-base is absent in XXII. These differences are attributed to a change in the chromophore as follows:

$$C_6H_5 - \overset{\shortmid}{C} = \overset{\shortmid}{C} - \underset{O}{\overset{\shortmid}{\underset{\shortparallel}{C}}} - \underset{H}{\overset{\shortmid}{C}} - \longrightarrow C_6H_5 - \overset{\shortmid}{C} = \overset{\shortmid}{C} - \underset{O}{\overset{\shortmid}{\underset{\shortparallel}{C}}} - \underset{OH}{\overset{\shortmid}{C}} -$$

Compound XXII failed to oxidize under the usual Oppenhauer conditions. This failure may well be due to the formation and precipitation of complexes of the type, $R_3\overset{+}{N}:\overline{Al}R_3$, described by Woodward (37). This base also failed to react with benzophenone and potassium-t-butoxide under the conditions of the modified Oppenhauer after eight hours' heating. The resistance of XXII to oxidation suggests that the hydroxyl function may be tertiary. Prolonged refluxing in xylene did cause a reaction accompanied by much resin formation. No definite crystalline product could be isolated from the reaction. The base was also recovered unreacted from attempted reactions with lead tetraacetate.

Benzal-α-cyanolycopodine, XIV, also reacted with

selenium dioxide to yield two oxidation products. One of
these products was a hydroxylated compound, XXIII, $C_{24}H_{30}O_2N_2$,
with hydroxyl absorption at 3580 and carbonyl absorption at
1695 cm.$^{-1}$ in carbon tetrachloride. The carbonyl absorption
frequency in the starting material appeared at 1685 cm.$^{-1}$
in the same solvent. This would indicate that the hydroxyl
function has entered alpha and axial to the carbonyl group
(36).

A second neutral oxidation product was isolated from
this oxidation by chromatography on alumina. This material
passed rapidly through the column and crystallized in
brilliant yellow prisms. It analyzed for $C_{24}H_{28}ON_2$, XXIV,
and has a markedly different ultraviolet spectrum than any
of the other benzal compounds. See Figure V of the Appendix.
The band at $280 m\mu$ for the benzal compound, XIV, has under-
gone a bathochromic displacement to $310 m\mu$ in the oxidation
product, XXIV. In the infrared, this product showed strong,
sharp bands at 1675, 1625 and 1595 cm.$^{-1}$ in nujol mull or
in carbon tetrachloride solution. The carbonyl absorption
in the starting material, XIV, appeared at 1681 cm.$^{-1}$ in
nujol and 1690 cm.$^{-1}$ in carbon disulphide. The low frequen-
cy shift of the carbonyl band in the oxidation product indi-
cates that the reaction occurred adjacent to the carbonyl.
The band at 1625 cm.$^{-1}$ is interpreted as being due to olefin
absorption and that at 1595 cm.$^{-1}$ due to phenyl absorption.
Thus the spectral and ultimate analyses indicate a chromo-

phore of the following type:

$$C_6H_5 - \overset{|}{C} = \overset{|}{C} - \overset{\overset{O}{\parallel}}{C} - \overset{|}{C} = \overset{|}{C} -$$
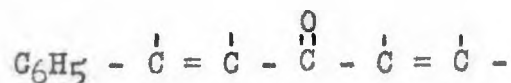
Infrared and ultraviolet spectra for similar chromophores have been reported in the literature. Fuson, Josien and Shelton (38) measured the infrared spectrum of 6-benzylidene-3,5-dimethyl-Δ^2-cyclohexenone:
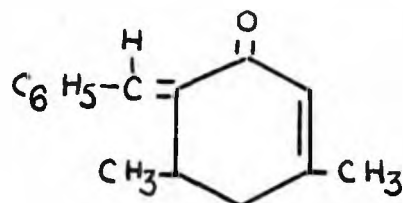
They found that the introduction of the endo-conjugated C=C group adds another absorption band in the 1600 cm.$^{-1}$ region. The carbonyl band was at 1664 cm.$^{-1}$ in carbon tetrachloride. French (39) measured the ultraviolet spectrum of this compound in absolute ethyl alcohol. She found two strong bands, λ max. 2378 Å, log ϵ = 3.73, and λ max. 3220 Å, log ϵ = 4.47. The absorption curve was similar to that shown in Figure V of the Appendix for XXIV, except for a bathochromic shift of approximately 100 Å in the maxima for the former.

French attempted to assign one of the two maxima observed to the endo-cyclic conjugation and the other to the exo-cyclic. She made a comparison of the spectrum of the above structure with that of the mother substance without the exo-double bond. In this way, the band at 2378 Å was

assigned to the endo-cyclic conjugation and the new intense long wavelength band at 3220 Å to the exo-cyclic conjugation. In the oxidation product, XXIV, the band at 2280 Å is probably due to the conjugation introduced during the oxidation and the band at 3100 Å is undoubtedly due to the exo-cyclic conjugation which has been shifted from 2800 Å observed for the starting material, XIV.

It is not surprising that the absorption maxima for these similar chromophores do not appear at the same wavelength. Mariella and Raube (40) examined an analogous straight chain system, styryl vinyl ketone, and found weaker absorption bands at $\lambda_{max.}$ 225 $m\mu$, $\log.\epsilon = 3.37$ and $\lambda_{max.}$ 289 $m\mu$, $\log.\epsilon = 3.54$. They consider that resonance forms such as $(+)\langle\underline{\quad}\rangle = CH - CH = C - O^{(-)}$ contribute to the excited state of the molecule. Where R = vinyl, the cross-conjugation effect causes weaker absorption. Thus, the positions of the maxima in XXIV would depend upon the degree of coplanarity of the conjugated systems as well as upon the number of substituents on the olefinic double bonds.

The following partial structures can be written for XXIV.
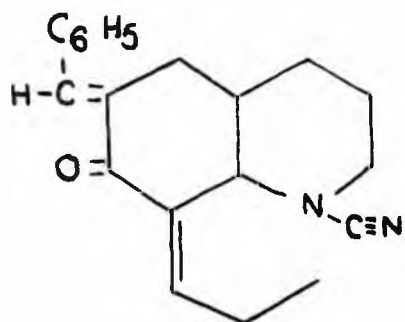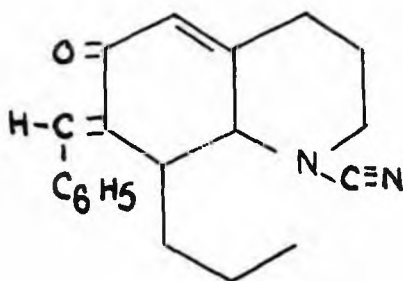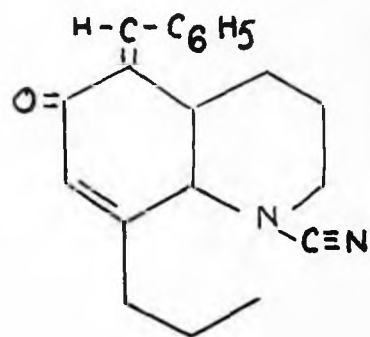
XXIV(a)   XXIV(b)   XXIV(c)

Structures with the nitrogen on a conjugated double bond have
been avoided for reasons discussed on pages 26 - 28. It can
be seen that this limits the position of the carbonyl group to
two possibilities. Further experiments are required on this
compound before a definite structure can be proposed, however.
Formulation XXIV(a) is considered the most likely one to repre-
sent this compound since it has the closer relationship of the
carbonyl to the nitrogen.

EXPERIMENTAL

Materials and Methods

The major source of lycopodine was the plant Lyco-
podium flabelliforme variety ambiguum (Victorin) indigenous
to the slopes of the Cobequids in Wentworth Valley, Nova
Scotia. The plant material was extracted by the method of
Manske and Marion (3). Lycopodine was derived from the crude
alkaloid by chromatography on alumina using either chloroform
or benzene as eluant. Lycopodine, the major constituent,
passed rapidly through the column. The yield from the above
plant was 2.3 gm. per kilogram of dried plant material. Final
purification was achieved through conversion to the per-
chlorate. The purified alkaloid melted at 115-116.5°C.
$[\alpha]_D^{27} = 23.6$ (c = 5% ethanol). The pK_a values were 9.06 and
9.07 as determined by titration of the perchlorate and hydro-
bromide respectively.

Melting points were determined on a hot stage equipped
with a microscope. Infrared spectra were measured on a Perkin-
Elmer No. 21 recording spectrophotometer. Ultraviolet spectra
using methanol solvent unless otherwise specified were de-
termined on a Beckman DU spectrophotometer. The pK_a values
were obtained by potentiometric titration using a Beckman pH
meter with a glass electrode and calomel reference electrode.

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The compounds were dissolved in 50 per cent methanol-water and the salts were titrated with 0.10 N sodium hydroxide while the bases were titrated with 0.10 N hydrochloric acid. The pH at the one-half point in the titration curve was taken as the pK_a value. The results from two such determinations were averaged to obtain each pK_a value.

Procedures

A. <u>Experiments on the Des-bases Derived from α-Cyanobromo-</u>
    <u>lycopodine</u>

   1. <u>Reaction of Lycopodine with Cyanogen Bromide</u>

   Cyanogen bromide was prepared as described in Organic Syntheses (41). The commercially available reagent was also used. In both cases, a final purification was carried out by distilling the cyanogen bromide through a tube filled with calcium chloride. A short condenser with a steam-heated jacket was found convenient for this operation. The purified cyanogen bromide was stored in a refrigerator until immediately before use and the benzene solution of the reagent was dried over calcium chloride before the reaction was started.

   Lycopodine (15 gm.) dissolved in 150 ml. of dry benzene was added over a period of ten hours with stirring to a solution of 50 gm. of cyanogen bromide in 150 ml. of dry benzene. The reaction mixture was then allowed to stand overnight. The benzene and the excess cyanogen bromide were removed <u>in vacuo</u>. The residue was taken up in chloroform,

washed with dilute acid, water, and dilute sodium bicarbonate.
The acidic and aqueous washings were saved and 1.2 gm. lyco-
podine was reclaimed therefrom. The chloroform solution was
concentrated and adsorbed on a column of alumina. Elution with
chloroform yielded a first fraction of cyanobromides (18.9 gm.)
which crystallized in contact with ether. Following the cyano-
bromides down the column was a distinct brown band which yielded
an amorphous residue. This residue showed strong absorption
in the hydroxyl region as well as the carbonyl and nitrile
regions. This residue (1.0 gm.), on acetylation, yielded a
crystalline O-acetyl derivative identical to α-cyanoacetoxy-
lycopodine reported previously (20).

The cyanobromide residues were crystallized from ether.
The first crop of crystals consisted of pure α-cyanobromo-
lycopodine, m.p. 140-141°C. The yield was 8.8 gm. Concen-
tration of the mother liquors yielded crystalline material
which melted over a wide range and was a mixture of the α-
and β-cyanobromides. By repeated recrystallizations it was
possible to isolate additional crops of the pure α- and in
some cases the pure β-isomer, although these cases were rare
and perhaps fortuitous. Pure β-isomer was obtained in many
cases by manual separation of the crystals of the two cyano-
bromides which have distinctly different forms; the α-isomer
crystallized in pyramidal form, the β-isomer in needles.
The pure β-cyanobromolycopodine melted at 108-109°C.

Both isomers exhibit strong absorption in the infra-

red in nujol mull at 1700 cm.$^{-1}$ in the carbonyl region, and
at 2210 cm.$^{-1}$ in the -C≡N region. There are distinct differ-
ences in the 600-1200 cm.$^{-1}$ region.

2. Hydrolysis of α-Cyanolycopodine, IV

α-Cyanolycopodine (0.5 gm.) prepared by the method
of MacLean, Manske, and Marion(20) was refluxed over-night
with 20 ml. of 2M hydrochloric acid containing 5 ml. of n-
propanol to ensure partial solution. The clear solution,
concentrated to remove the alcohol, deposited crystals of the
hydrochloride upon cooling. After recrystallization from
methanol, the hydrochloride melted above 300°C.

Calc. for $C_{16}H_{27}ON\cdot HCl$: C, 67.23; H, 9.81; N, 4.90.
Found: C, 66.88, 66.92; H, 9.76, 9.78; N, 4.84, 4.72.
pK_a = 9.05.

The free base (α-des-dihydrolycopodine, V), obtained
from the hydrochloride, was a solid, difficult to obtain in
pure form, which softened at 45°C. and melted at 49°C. after
repeated crystallizations from hexane. Its infrared absorp-
tion spectrum contained no bands in the nitrile region. A
film of the base had the usual carbonyl band at 1694 cm.$^{-1}$ and
a strong band at 3330 cm.$^{-1}$, indicative of an =NH grouping.

3. Reaction of α-Des-dihydrolycopodine, V, with Acetic
Anhydride

α-Des-dihydrolycopodine (0.1 gm.) was dissolved in
a few cubic centimeters of acetic anhydride and the solution
heated on the steam cone in the presence of anhydrous sodium

acetate. After removal of excess acetic anhydride in vacuo, the residue was treated with ether and the ether solution washed with dilute hydrochloric acid, sodium bicarbonate, and water. Upon distillation of the ether there remained an amorphous solid. This material did not crystallize from the usual solvents. However, the infrared absorption spectrum of a film of this compound contained a strong band at 1640 cm.$^{-1}$ which, together with the absence of absorption in the N-H region, is indicative of an acetyl derivative. The usual carbonyl band appeared at 1700 cm.$^{-1}$.

4. Alkylation of α-Des-dihydrolycopodine

A mixture of V (0.79 gm.), formic acid (0.16 ml., 90%), and formaldehyde (0.9 ml.) was heated under reflux on the steam bath for ten hours. The initial reaction, which was vigorous and accompanied with foaming, subsided after one to two hours. At the end of the reaction time the mixture was diluted with water, made strongly acid with hydrochloric acid, and extracted with ether. The aqueous layer was separated, made alkaline with ammonia, and extracted several times with ether. Distillation of the ether yielded a viscous oil. A film of this oil had no absorption in the 3300-3400 cm.$^{-1}$ region, indicative of transformation of the secondary base, V, to a tertiary base. The carbonyl band was not shifted.

This tertiary base, VI, was dissolved in a small volume of acetone and treated with concentrated hydrochloric acid, whereupon the hydrochloride crystallized in nearly colourless

prisms, m.p. 254°C. Recrystallization from acetone yielded
prisms, m.p. 256°C. The yield was 0.52 gm.

Calc. for $C_{17}H_{29}ON \cdot HCl \cdot H_2O$: C, 64.22; H, 10.14; N, 4.40;
NCH$_3$, 9.14.

Found: C, 64.49, 63.84; H, 9.94, 9.91; N, 4.65, 4.84;
NCH$_3$, 9.55, 9.65.

A mixture of 0.72 gm. of V and 0.5 ml. of freshly dis-
tilled methylsulfate was refluxed for six hours in benzene
solution and then allowed to stand over-night. The solvent
was removed in vacuo on the steam cone, the residue dissolved
in water, made alkaline with ammonia and extracted with chloro-
form. Distillation of the chloroform left 0.60 gm. of an oil.
This oil was dissolved in acetone and made acid with concen-
trated hydrochloric acid. Colourless prisms separated which
were identical to VI in melting point and mixed melting point.

5. Methiodide of the Tertiary Base

A sample of VI (0.33 gm.) was added to excess methyl
iodide and the solution refluxed on the steam bath. After
about three hours, a small yield of crystals was obtained.
After further refluxing for twenty hours, more crystals formed,
but the total yield was very low - approximately 10%. Re-
crystallization of the combined lots of crystals from a mixture
of methanol and ethylacetate produced colourless crystals, m.p.
192.5°C.

Calc. for $C_{18}H_{32}ONI$: C, 53.33; H, 7.96; N, 3.46;

N-CH$_3$, 14.32.

Found: C, 53.43, 53.30; H, 8.12, 7.95; N, 3.24, 3.14;

N-CH$_3$, 10.65, 11.76.

A small sample of the methiodide was dissolved in methanol, platinum oxide was added, and the mixture treated with hydrogen at 40 p.s.i.g. for eight hours. The unreacted methiodide was recovered on removal of the methanol and addition of ethyl acetate to the residue.

6. Lithium Aluminum Hydride Reduction of α-Des-dihydro-
   lycopodine, V

Lithium aluminum hydride (1.0 gm.) was added to an-hydrous ether in a three-necked flask fitted with a reflux condenser and dropping funnel, and the mixture refluxed for three hours. A solution of V (3.0 gm.) in anhydrous ether was then added over a one-hour period with vigorous stirring. The mixture was stirred for an additional two hours before decomposition - first with moist ether, then with water. The ether layer was separated and distillation of the ether pro-duced a crystalline product, α-des-tetrahydrolycopodine, VIII, (2.0 gm., 66%). Recrystallization from ether yielded colourless crystals, m.p. 168-169°C.

Calc. for $C_{16}H_{29}ON$: C, 76.43; H, 11.63; N, 5.58.

Found: C, 76.15, 76.05; H, 11.67, 11.55; N, 5.75, 5.79.

pK$_a$ = 9.80.

The infrared spectrum of this compound in nujol showed

broad absorption at 3150 cm.$^{-1}$ attributed to the N-H group.
There was no carbonyl absorption but the hydroxyl absorption
could not be detected in nujol mull in the usual region
(3500-3700 cm.$^{-1}$) for a free -OH group.

7. Lithium Aluminum Hydride Reduction of α-Cyanobromo-
    lycopodine

An ethereal solution of α-cyanobromolycopodine (3.0
gm.) was added slowly with stirring to 200 ml. of ether con-
taining 22 ml. of approximately 0.1% lithium aluminum hydride
solution. The stirring and refluxing were continued for
eight hours, and after the reaction mixture had been left for
fourteen hours, it was decomposed with moist ether. The
ether layer was extracted repeatedly with dilute hydrochloric
acid to remove the basic fraction. A small amount of non-
basic material (0.18 gm.) was isolated on evaporation of the
ether. A portion of this non-basic material was similar to
the Meerwein-Ponndorf reduction product of α-cyanolycopodine
reported below.

The above hydrochloric acid extract was made alkaline
with ammonia and extracted repeatedly with ether and finally
with chloroform in a continuous extractor. Removal of the
ether-chloroform solvent left a crystalline residue (1.75 gm.,
82%). Recrystallization from ether produced colourless
crystals, m.p. 168-169°C., which did not depress the melting
point of the alcohol formed on lithium aluminum hydride re-
duction of α-des-dihydrolycopodine.

8. <u>Dehydrogenation of ∝-Des-tetrahydrolycopodine, VIII</u>

The dehydrogenation apparatus consisted of a 15 ml. round-bottomed flask sealed to a 15 cm. glass tube which served as an air condenser for the refluxing mixture. The tube was fitted with a standard taper joint and a side arm just below this joint. The side arm was connected to a tube containing calcium chloride, a stopcock and thence to a gas trap containing dilute acid. Nitrogen, purified as described by Fieser (42), was introduced through a small inner-sealed tube which extended to just above the reaction mixture. Before starting the dehydrogenation, the system was evacuated through a three-way stopcock situated between the gas purifying apparatus and the reaction flask. Then the apparatus was flushed with nitrogen.

∝-Des-tetrahydrolycopodine (1.30 gm.) was intimately mixed with 0.50 gm. of palladium-charcoal and the mixture was heated in the dehydrogenation apparatus in a slow stream of nitrogen. The bath temperature was slowly raised to 250°C. where rapid decomposition set in. After heating at 280-300°C. for one hour, the reaction mixture was allowed to cool, then taken up into chloroform and chromatographed on alumina. The weakly adsorbed fraction (0.6 gm.) was dissolved in n-hexane and rechromatographed on neutral Woelm alumina. The major portion of this material was strongly adsorbed at the top of the column. Elution with n-hexane containing chloroform developed a narrow band which fluoresced bright yellow in ultra-

violet light. A film of this fraction had infrared absorption bands at 1605 and 1575 cm.$^{-1}$, and C-methyl absorption at 1460 cm.$^{-1}$. The ultraviolet spectrum is shown in Figure I of the Appendix.

9. Meerwein-Ponndorf Reduction of α-Cyanolycopodine

α-Cyanolycopodine (0.62 gm.) was dissolved in dry iso-propyl alcohol, freshly prepared aluminum isopropoxide (2 gm.) was added, and the solution heated under reflux. The top of the reflux condenser was fitted with a trap containing a side arm with a stopcock and a cold finger filled with ethanol. The cold finger served to condense most of the refluxing iso-propyl alcohol so that the distillation of the solvent along with any acetone formed was carried out at a slow, constant rate.

After several days, the reaction mixture was worked up to yield a semi-crystalline residue. On addition of ether, immediate separation of colourless crystals occurred. After recrystallization from ether, the dihydro-α-cyanolycopodine, IX, melted at 191-192°C.

Calc. for $C_{17}H_{28}ON_2$: C, 73.87; H, 10.21; N, 10.1.

Found: C, 73.84, 73.67; H, 9.77, 10.15; N, 8.99, 9.05.

The infrared absorption spectrum of this compound in nujol showed strong hydroxyl absorption at 3440 cm.$^{-1}$ and lacked carbonyl absorption.

10. Sodium Borohydride Reduction of α-Cyanobromolycopodine

A solution of α-cyanobromolycopodine (4.0 gm.) in

ethanol was added with stirring to a warm solution of sodium borohydride (6.0 gm.) in ethanol. After the mixture had been allowed to stand for one day, the excess sodium borohydride was destroyed with formaldehyde. The mixture was made just acid with hydrochloric acid, the solvent removed in vacuo, and the residue was extracted with chloroform. The chloroform extract was washed with dilute acid, sodium bicarbonate, and water. Evaporation of the chloroform yielded a crystalline product (3.0 gm., 97%) which was identical by mixed melting point and infrared spectrum to the product prepared by the reduction of α-cyanolycopodine with aluminum isopropoxide.

11. Sodium Borohydride Reduction of the Mixed Cyanobromides

An intimate mixture of the α- and β-cyanobromides (2.0 gm.) was reduced with sodium borohydride using the same procedure as described in the preceding section. The crude product (1.6 gm.) showed infrared absorption bands in nujol at 1675 and 3440 cm.$^{-1}$ and was evidently a mixture of IX and the β-cyclized compound studied by Harrison (22). This material was dissolved in benzene and chromatographed on alumina. The dihydro-α-cyanolycopodine, the major constituent, was easily separated by virtue of its stronger adsorption on the column.

12. Dehydration of Dihydro-α-cyanolycopodine

Dihydro-α-cyanolycopodine (1.0 gm.) was dissolved in

xylene containing p-toluene sulfonic acid (0.15 gm.) and the mixture was refluxed for four hours. The reaction mixture was cooled, washed with dilute acid, dilute sodium bicarbonate, and water. On removal of the xylene under reduced pressure on the steam bath there remained a mobile oil (0.75 gm.) which failed to crystallize from the usual solvents even after chromatography on alumina.

Calc. for $C_{17}H_{26}N_2$: C, 79.07; H, 10.08; N, 10.85.

Found: C, 78.39, 78.39; H, 10.02, 9.90; N, 9.75, 9.90.

The infrared absorption spectrum of a film of this compound showed weak absorption in the unsaturation region near 1650 cm.$^{-1}$ and lacked hydroxyl absorption. The cyanamide absorption appeared at 2210 cm.$^{-1}$.

A sample (0.64 gm.) of this amorphous anhydro compound, X, was dissolved in 25 ml. of anhydrous ethyl acetate. The solution was cooled to -20°C. in an ethanol-dry ice bath and ozone (3%) was passed through the mixture for one hour. The ozonide was then decomposed by shaking with hydrogen over a palladium-calcium carbonate catalyst. After removal of the catalyst and evaporation of the solvent under reduced pressure there remained 0.79 gm. of residue which was found to be a mixture of acid and neutral products. This material showed strong absorption in the infrared near 1700 cm.$^{-1}$ and had the usual strong cyanamide absorption at 2210 cm.$^{-1}$. This crude material was dissolved in acetone and a solution of potassium permanganate in acetone slowly added until approximately 1 gm.

of the oxidant was consumed. The excess permanganate was
destroyed by heating with a small amount of methanol and then
the solution was filtered and evaporated to dryness. Aqueous
alkali was added to the residue which was then extracted with
ether and 0.085 gm. of neutral material was recovered from the
ether extracts. The aqueous layer was made acid and extracted
with chloroform and 0.20 gm. of acidic material was recovered.
Additional acidic material (0.21 gm.) was obtained by de-
composing the manganese dioxide, which was filtered from the
original reaction mixture, with bisulfite and extracting con-
tinuously with ether for several days.

A sample of the amorphous acid was dissolved in
methanol and esterified with a freshly prepared ethereal
solution of diazomethane. An amorphous neutral fraction was
obtained from the reaction mixture. This product was dis-
tilled under reduced pressure from a Spath tube at 150°C. A
film of this distillate showed double carbonyl absorption in
the infrared at 1708 and 1733 cm.$^{-1}$.

13. Lithium Aluminum Hydride Reduction of X

The anhydro compound (1.6 gm.) prepared as described
in the preceding section was added to a solution of 1.0 gm.
of lithium aluminum hydride in boiling ethyl ether. The
mixture was refluxed in a nitrogen atmosphere over-night.
The excess lithium aluminum hydride was decomposed with moist
ether, water was added and the mixture extracted with chloro-
form. On distillation of the chloroform, there remained

1.2 gm. of an oil. This crude material was dissolved in ether and the basic fraction extracted with dilute hydrochloric acid. The acid extract was made alkaline with ammonia and the free base (0.95 gm.) removed by ether extraction. A sample of this amorphous base was dissolved in a small volume of acetone; concentrated hydrochloric acid was added and crystals of the hydrochloride formed. Recrystallization from acetone produced colourless needles, m.p. 245-247°C.

Calc. for $C_{16}H_{27}N \cdot HCl$: C, 71.19; H, 10.10; N, 5.19.

Found: C, 71.69, 71.48; H, 10.30, 10.20; N, 5.04, 5.00.

In carbon tetrachloride the free base showed infrared absorption in the unsaturation region at 1655 cm.$^{-1}$ and lacked cyanamide absorption. Although the free base lacked noticeable N-H absorption, the hydrochloride showed a strong band at 1585 cm.$^{-1}$ in nujol or in chloroform attributed to the ionized salt of the secondary amine.

B. <u>Bromination Experiments. Oxidations of α -Cyanolycopodine</u>

    1. <u>Reaction of α -Cyanolycopodine with Bromine in Carbon Tetrachloride</u>

α -Cyanolycopodine (0.72 gm.) was dissolved in dry carbon tetrachloride in a three-necked flask provided with a stirrer and dropping funnel. Bromine (5%) in carbon tetrachloride was added slowly with stirring. After a few minutes, the uptake of bromine was rapid and precipitation occurred. A total of 8 ml. of the bromine solution was added. At the

end of the reaction a portion of the yellow precipitate was
separated by filtration. This material rapidly became amor-
phous on standing and attempts to crystallize it from various
solvents were unsuccessful. Chloroform was added to make a
clear solution and the excess bromine was destroyed by wash-
ing with bisulphite solution. Removal of the solvent under
reduced pressure left an amorphous residue from which a
crystalline product (0.17 gm.) separated on the addition of
ether. Recrystallization from an acetone-ether mixture yielded
colourless crystals which began to decompose at 122°C. and
melted at 129°C.

> Calc. for $C_{17}H_{25}ON_2Br$: C, 57.79; H, 7.14; N, 7.94;
>> Br, 22.6.
>
> Found: C, 58.16, 57.99; H, 7.29, 7.16; N, 7.90, 7.82;
>> Br, 21.8, 22.0.

The infrared spectrum in nujol of this brominated
compound showed absorption in the nitrile region at 2210 cm.$^{-1}$
and the carbonyl region at 1710 cm.$^{-1}$, while the starting
material had carbonyl absorption at 1700 cm.$^{-1}$.

Upon distillation of the solvent from the mother
liquor of the above bromo compound, there was obtained 0.74
gm. of amorphous residue. The infrared spectrum of this
residue showed weak bands at 3400 and 1630 cm.$^{-1}$ in addition
to the bands at 1710 and 2210 cm.$^{-1}$ for the crystalline bromo
compound.

The crystalline monobromo compound reacted readily

with aqueous alkali and silver oxide to yield a mixture of products. Examination of the mixture in the infrared indicated the presence of hydroxyl and conjugated carbonyl groups.

2. The Action of Alkali in Aqueous Dioxane on Crude Bromination Product

The non-crystalline bromination product (0.6 gm.) was heated on the steam bath in 5% potassium hydroxide containing some purified dioxane to cause partial solution. The reaction mixture soon became very dark in colour and the heating was discontinued. The mixture was concentrated in vacuo to remove the dioxane and then extracted with ether. The ether extract was washed with water, dilute acid, and alkali to yield only 0.13 gm. of a non-crystalline product which was not further investigated. The aqueous layer was therefore acidified and chloroform extracted to yield a crystalline product (0.2 gm.) which melted at 157-158°C. after recrystallization from ether-petroleum ether.

Calc. for $C_{17}H_{24}O_2N_2$: C, 70.79; H, 8.39; N, 9.71.

Found: C, 70.76, 70.69; H, 8.35, 8.32; N, 9.25, 9.35.

The infrared spectrum of this compound in nujol had bands at 1640, 1660, 2210, and 3340 cm.$^{-1}$. The ultraviolet spectrum is shown in Figure II of the Appendix. The compound gave a deep blue coloration with ferric chloride in aqueous ethanol.

3. The Action of Sodium Hypobromite on α-Cyanolycopodine

α-Cyanolycopodine (0.50 gm.) was dissolved in puri-

fied dioxane. Then 10 ml. of 5% sodium hydroxide was added, followed by 0.30 ml. of bromine which was added dropwise with stirring. A small amount of crystalline material formed at the bottom on the flask. This was removed with a spatula and recrystallization from acetone yielded colourless needles which began to decompose at 120°C. and melted at 129°C. An admixture with the bromo compound reported above had the same behaviour.

After the bromine addition was completed, the reaction mixture was heated on the steam cone. The mixture which was originally strongly alkaline soon became neutral and another 2 ml. of 5% sodium hydroxide was added and the heating continued for one hour. Concentration of the reaction mixture under reduced pressure left an amorphous residue which was partially soluble in alkali. The alkali-soluble fraction was precipitated by addition of hydrochloric acid and extracted with chloroform. This chloroform-soluble material had absorption bands in the infrared at 1675 and 1648 cm.$^{-1}$ in nujol.

4. Oxidation of α-Cyanolycopodine with Selenium Dioxide

α-Cyanolycopodine did not react readily with selenium dioxide in boiling benzene, xylene or dioxane. By using the following conditions, a vigorous reaction was effected. α-Cyanolycopodine (0.20 gm.) was intimately mixed with 0.16 gm. of selenium dioxide and the mixture was heated in an atmosphere of pure nitrogen. A vigorous reaction started at 120°C. and the heating was continued for one hour; the temperature of the

bath being raised to 135°C. towards the end of the reaction.
The dark brown residue was extracted with ether and the ether
extract was in turn extracted repeatedly with 5% potassium
hydroxide. The aqueous alkaline extract was acidified and
the precipitate which formed was taken up into ether. On
evaporation of the ether, there remained 0.08 gm. of a crystal-
line residue. Recrystallization from ether yielded colourless
crystals, m.p. $137-140^{\circ}$C. The infrared spectrum of this
product in nujol was similar to that of the oxidation product
described in the preceding section. Both gave a deep blue
colour with ferric chloride.

5. Bromination of Lycopodine

A solution of 1.00 gm. of lycopodine was added with
vigorous stirring to an equimolar amount of bromine dissolved
in carbon tetrachloride. The uptake of bromine was very
rapid at room temperature and enough additional solvent was
added to redissolve the hydrobromide salt which initially
precipitated.

The reaction mixture was allowed to stand over-night
and the solvent removed in vacuo on the steam cone to pro-
duce a theoretical yield of bromolycopodinehydrobromide.
Recrystallization from acetone-methanol yielded colourless
crystals which melted at $290-295^{\circ}$C. (dec.).

Calc. for $C_{16}H_{24}ONBr \cdot HBr$: C, 47.20; H, 6.19; N, 3.44;
Br, 39.2.

Found: C, 48.64, 48.64; H, 6.25, 6.32; N, 3.67, 3.53;
Br, 37.3, 37.2.

The pK_a of this bromolycopodinehydrobromide was 7.30.
The infrared spectrum in nujol showed absorption in the amine
salt region 2500 to 2700 cm.$^{-1}$. The carbonyl band was at
1710 cm.$^{-1}$.

Although this bromination product of lycopodine formed
readily and in good yield, attempts to convert it to the free
base or to displace the substituted bromine through reactions
with silver oxide or potassium acetate, and alkaline or acid
hydrolysis, did not lead to any identifiable product.

6. Bromination of α-Des-dihydrolycopodine

α -Des-dihydrolycopodine (0.50 gm.) was treated with
bromine under conditions similar to those described for
lycopodine. After removal of the solvent in vacuo, there
remained a quantitative yield of partly crystalline bromo-
hydrobromide salt. Recrystallization from methanol yielded
colourless needles, m.p. 275-280°C. (dec.).

Calc. for $C_{16}H_{26}ONBr\cdot HBr$: C, 46.95; H, 6.66; N, 3.42;
Br, 39.2.

Found: C, 46.70, 47.51; H, 7.10, 7.04; N, 3.54, 3.55;
Br, 37.6, 38.1.

The infrared spectrum in nujol exhibited absorption
in the carbonyl region at 1713 cm.$^{-1}$. There was a strong
band at 1585 cm.$^{-1}$ attributed to the ionized salt of the
secondary amine.

C. The Reaction of α-Cyanolycopodine with Benzaldehyde.

Reactions and Degradations of the Benzal Compounds

1. The Reaction of α-Cyanolycopodine with Benzaldehyde

One gram of α-cyanolycopodine and 0.74 gm. of ben-
zaldehyde were dissolved in absolute methanol in a flask
equipped with a dropping funnel and reflux condenser. A
solution of sodium methoxide in absolute methanol (4 ml. of
a solution prepared from 12 gm. of sodium in 150 ml. of
methanol) was added to the refluxing solution over a period
of fifteen minutes. The reaction mixture was allowed to
stand over-night at room temperature and, after it had been
left for several hours in the refrigerator, crystallization
occurred. The first crop of crystals (0.40 gm.) was re-
crystallized from methanol, to give glistening yellow
crystals, m.p. 179.5-180.5°C.

The filtrate was concentrated on the steam cone and
the residue poured into water to yield an amorphous mass
which immediately solidified on warming on the steam cone.
The precipitate was collected and dried to yield an ad-
ditional 0.83 gm. of crude benzylidene derivative. The total
yield was 93%.

Calc. for $C_{24}H_{30}ON_2$: C, 79.50; H, 8.35; N, 7.74.

Found: C, 79.52, 79.36; H, 8.34, 8.19; N, 7.80, 7.85.

The infrared spectrum in carbon disulphide contained
aromatic absorption bands at 3050, 3017, and 1617 cm.$^{-1}$,
carbonyl absorption at 1690 cm.$^{-1}$, and nitrile absorption at

2215 cm.$^{-1}$. In nujol there was aromatic absorption at 1607 cm.$^{-1}$, carbonyl absorption at 1681 cm.$^{-1}$, and nitrile absorption at 2205 cm.$^{-1}$.

2. Ozonolysis of the Benzal Compound

A solution of 0.33 gm. of the benzal compound in anhydrous ethyl acetate was cooled to -20 to -30°C. in an acetone-dry ice trap. Ozone (3%) was passed through this solution (flow-rate, 10 mm. Hg) for fifteen minutes. The cold solution was transferred to a cooled hydrogenation bottle, a Pd-CaCO$_3$ catalyst added, and the mixture reduced with hydrogen (20 p.s.i.g.) over-night. On evaporation of the solvent under reduced pressure, there remained a semi-solid residue (0.37 gm.) with the odour of benzaldehyde. Recrystallization from ether yielded colourless crystals which softened at 150°C. and melted at 165°C. The infrared spectrum of this compound in nujol showed strong bands in the carbonyl region at 1780 and 1742 cm.$^{-1}$ and also a series of strong bands in the 1050-1120 cm.$^{-1}$ region.

Calc. for C$_{17}$H$_{24}$O$_3$N$_2$: C, 67.10; H, 7.89; N, 9.21.

Found: C, 67.25, 67.26; H, 7.89, 8.00; N, 8.00, 7.95.

The ozonolysis was repeated on another sample of the benzal compound (0.30 gm.) using a similar procedure to that described above. In this experiment, however, anhydrous methanol was used as the solvent and the ozonide was decomposed with hydrogen over a platinum oxide catalyst. Working up of the product in the usual way yielded a semi-solid

product (0.25 gm.) which crystallized on addition of ether. Recrystallization from ether yielded shiny prisms, m.p. 141-143°C.

Calc. for $C_{17}H_{24}O_2N_2$: C, 70.79; H, 8.39; N, 9.71.

Found: C, 70.68, 70.91; H, 8.41, 8.48; N, 9.40, 9.20.

The infrared spectrum of this compound in nujol had hydroxyl absorption at 3330 cm.$^{-1}$, cyanamide absorption at 2210 cm.$^{-1}$ and bands at 1675 and 1648 cm.$^{-1}$. In chloroform solution these bands appeared at 3500, 2220, 1680 and 1655 cm.$^{-1}$. This compound proved to be identical by mixed melting point and infrared spectrum to the sodium hypobromite and selenium dioxide oxidation product of α-cyanolycopodine.

A sample of the above compound was dissolved in propanol, then 2 N hydrochloric acid was added and the material hydrolyzed by refluxing over-night. The solution was concentrated to a small volume under reduced pressure, then diluted with water and extracted once with ether. The aqueous layer was made alkaline with ammonia and then extracted repeatedly with ether. The residue which remained on evaporation of the ether yielded colourless crystals, m.p. 142-146°C., on recrystallization from ether.

Calc. for $C_{16}H_{25}O_2N$: C, 73.00; H, 9.50; N, 5.32.

Found: C, 72.47, 72.49; H, 9.85, 9.68; N, 5.00, 5.10.

$pK_a = 7.2$.

In chloroform solution there were absorption bands at 3460, 1662, and 1632 cm.$^{-1}$.

3. Hydrolysis of Benzal-α-cyanolycopodine

The benzal compound (1.0 gm.) was dissolved in pro-
panol. Then, 30 ml. of 2 N hydrochloric acid was added and
the mixture was refluxed over-night. The solution was con-
centrated to dryness in vacuo on the steam cone and on the
addition of acetone, the product crystallized (0.8 gm.). Re-
crystallization from acetone produced colourless needles,
m.p. 271°C. (dec.).

Calc. for $C_{23}H_{31}ON \cdot HCl$: C, 73.84; H, 8.65; N, 3.75.

Found: C, 73.50, 73.70; H, 8.77, 8.80; N, 4.20, 4.05.

pK$_a$ = 7.0.

This salt had carbonyl absorption in nujol at 1680
cm.$^{-1}$. There was a broad band at 1580-1600 cm.$^{-1}$ attributed
to the unresolved peaks of the phenyl absorption and the
ionized salt absorption.

A sample of this salt was converted to the free base
which after crystallization from petroleum ether melted at
106-108°C.

Calc. for $C_{23}H_{31}ON$: C, 81.81; H, 9.25; N, 4.16.

Found: C, 81.89, 81.91; H, 9.60, 9.50; N, 3.66, 3.66.

The infrared spectrum of this secondary base (benzal-
α-des-dihydrolycopodine) in chloroform solution had a weak
band at 3320 cm.$^{-1}$, attributed to N-H absorption, and bands
at 1675 and 1615 cm.$^{-1}$.

4. Methylation of Benzal-α-des-dihydrolycopodine

Benzal-α-des-dihydrolycopodine (0.45 gm.) was cooled

in an ice-water mixture and then 0.1 ml. of 98% formic acid
was added, followed by 0.4 ml. of formaldehyde. The mixture
was heated on a steam cone. The initial reaction was vigorous
but soon subsided. The heating was continued for four hours
and then the reaction mixture was allowed to cool, made alka-
line with ammonia, and extracted with ether. Concentration
of the ether produced a quantitative yield of crystalline
material. Recrystallization from petroleum ether yielded
colourless crystals, m.p. 142-145°C.

Calc. for $C_{24}H_{33}ON$: C, 82.00; H, 9.46; N, 3.99;
NCH$_3$, 8.26.

Found: C, 82.22, 82.37; H, 9.84, 9.54; N, 4.07, 3.81;
NCH$_3$, 8.17.

The infrared spectrum of this tertiary base had ab-
sorption bands at 1685 and 1628 cm.$^{-1}$ in nujol.

A sample (0.10 gm.) of the secondary base was dis-
solved in a small volume of dry benzene. Freshly distilled
methyl sulfate (0.10 ml.) was added and the mixture was re-
fluxed for three hours. The benzene was removed under re-
duced pressure, the residue made alkaline with ammonia and
extracted with ether. The ether was distilled and the resi-
due crystallized from petroleum ether. The product thus
purified proved to be identical by mixed melting point and
infrared spectrum to the tertiary base prepared by alkylation
with formaldehyde.

This tertiary base failed to yield a methiodide when

mixed with methyl iodide in such solvents as acetone, benzene or ether at room temperature or at the boiling point. The unreacted tertiary base was recovered in all cases. A sample of the tertiary base when heated with methyl iodide in a sealed tube at 90°C. for six hours yielded an amorphous ether-insoluble product which was not characterized. This base failed to react with cyanogen bromide under conditions similar to those used with lycopodine.

5. The Action of Methyl Sulfate on the Benzal-t-base

The tertiary base (0.56 gm.) was dissolved in dry benzene and 0.45 ml. of freshly distilled methyl sulfate was added. The mixture was refluxed for five hours and upon cooling, crystals separated from the reaction mixture. Another lot of crystals was collected after the reaction was continued over-night. The total yield was 0.25 gm. This product was recrystallized from a comparatively large volume of benzene containing a small amount of methanol, m.p.141-143°C. On drying in vacuo over-night over phosphorus pentoxide, this compound lost 2% of its weight and this was rapidly taken up again when the compound was exposed to the atmosphere. A hemihydrate would contain 1.85% water.

Calc. for $C_{26}H_{39}O_5NS \cdot \frac{1}{2}H_2O$: C, 64.18; H, 8.27; N, 2.88.

Found: C, 63.93, 64.16; H, 8.29, 8.25; N, 2.88, 2.74.

The infrared spectrum of this compound in nujol had absorption bands at 3520, 3465, 1675, 1608 cm.$^{-1}$ and strong bands at 1230 and 1260 cm.$^{-1}$.

A sample of this substance was dissolved in water and on the addition of ammonia an amorphous precipitate formed. This proved to be soluble in ether but failed to crystallize.

Calc. for $C_{25}H_{37}O_2N$: C, 78.27; H, 9.72; N, 3.65.

Found: C, 77.59, 78.18; H, 9.88, 9.50; N, 2.61.

A film of this substance showed absorption bands at 1680 and 1620 cm.$^{-1}$. In carbon tetrachloride solution these bands were at 1685 and 1610 cm.$^{-1}$.

Addition of methyl iodide to a solution of this amorphous base, XX, in acetone gave immediate crystallization of a methiodide, XXI, which melted at 275°C. (dec.).

Calc. for $C_{26}H_{40}O_2NI$: C, 59.51; H, 7.66; N, 2.67;
   I, 24.14.

Found: C, 59.26, 59.26; H, 7.63, 7.64; N, 2.74, 2.84;
   I, 24.30, 24.50.

6. Hofmann Degradation of the Methiodide, XXI

The methiodide, XXI, was dissolved in water containing a small amount of methanol to aid solution. This solution was shaken with freshly prepared moist silver oxide, allowed to stand one-half hour and then the mixture, which was now strongly alkaline, was filtered and concentrated nearly to dryness under reduced pressure on the steam cone. The residue was heated in vacuo in a Späth tube which was connected to a gas trap containing a solution of a picric acid in methanol which was cooled in dry ice. Distillation commenced at 140°C. and 0.1 mm. pressure. At the end of the decom-

position, the solution in the gas trap was concentrated and yellow needles formed, m.p. 215°C. This material did not depress the melting point of authentic trimethylamine picrate.

This degradation was repeated on another sample of the methiodide (0.3 gm.). In this case, a solution of methyl iodide in methanol was used in the gas trap. Decomposition occurred at 140-160°C. and 0.05-0.1 mm. At the end of the reaction, the gas trap contained a fine crystalline precipitate which, like trimethylamine methiodide, did not melt on heating but decomposed to produce the characteristic odour of the base.

The distillate from the decomposition of the quaternary base (84 mg.) was dissolved in ether and this solution washed repeatedly with dilute hydrochloric acid. The ethersoluble neutral fraction was dissolved in benzene and chromatographed on alumina using chloroform as an eluant. The ultraviolet spectrum of the major fraction is shown in Figure IV of the Appendix.

7. Acetylation of the Base, XX

A mixture of the amorphous base with excess acetic anhydride and anhydrous sodium acetate was heated on the steam cone for three hours. The acetic anhydride was removed under reduced pressure and the residue dissolved in water. On addition of aqueous ammonia, a precipitate formed which crystallized on contact with petroleum ether. Recrystallization from petroleum ether yielded colourless prisms,

m.p. 155-157°C.

    Calc. for $C_{29}H_{41}O_4N$: C, 74.49; H, 8.84; CH_3CO(two), 18.4.

    Found: C, 73.72, 73.95; H, 8.80, 8.88; CH_3CO, 12.8.

    The infrared spectrum of this compound in chloroform solution had absorption bands at 1760, 1670 and 1570 cm.$^{-1}$. Its ultraviolet spectrum is shown in Figure IV of the Appendix.

    In a subsequent experiment to obtain more of this acetate, the product was an amorphous residue which failed to crystallize. It was only partially soluble in dilute hydrochloric acid and was separated into a basic and a neutral fraction by partition with ether. Both of these products were amorphous. The basic acetate in chloroform solution had strong infrared absorption bands at 1745 and 1720 and weak bands in the 1600-1640 cm.$^{-1}$ region. In carbon tetrachloride solution, the O-acetyl bands appeared at 1750 and 1725 cm.$^{-1}$. The neutral acetate in carbon tetrachloride solution had strong O-acetyl bands at 1750 and 1725 cm.$^{-1}$ and strong bands at 1675 and 1645 cm.$^{-1}$.

    8. <u>The Action of Acetic Anhydride on the Benzal-t-base</u>

    The base, XVIII, (50 mg.) was dissolved in 1 ml. of acetic anhydride, anhydrous sodium acetate was added and the mixture heated on the steam bath for three hours. The acetic anhydride was removed <u>in vacuo</u>, the residue treated with aqueous ammonia and extracted with ether. Removal of the ether left an amorphous residue which failed to crystallize.

This material had strong infrared absorption in the O-acetyl region at 1750 cm.$^{-1}$ and absorption in the unsaturation region at 1600-1620 cm.$^{-1}$ in carbon tetrachloride.

Another sample of the base, XVIII, was dissolved in a mixture of 1 ml. of pyridine and 1 ml. of acetic anhydride and the mixture refluxed for fifteen minutes and then allowed to stand over-night at room temperature. The mixture was worked up as before to yield an amorphous product with O-acetyl absorption as before at 1750 cm.$^{-1}$. A few crystals of the starting base were also isolated from the crude product by treating with petroleum ether. Both of these products had weak carbonyl absorption at 1675 cm.$^{-1}$ attributed to the starting base.

9. Oxidation of the Benzal-t-base with Selenium Dioxide

A solution of 0.430 gm. of XVIII in dioxane was added from a dropping funnel to 0.168 gm. of selenium dioxide partially dissolved in boiling dioxane. The solution was refluxed for eight hours after which time selenium was precipitated and the solution became deep red. The solution was filtered, concentrated to dryness in vacuo, and the residue dissolved in ether and filtered to remove a small amount of insoluble material. Removal of the ether left a crystalline product which, after recrystallization from ether-petroleum ether, separated in needles, m.p. 185-188°C.

Calc. for $C_{24}H_{33}O_2N$: C, 78.41; H, 9.05; N, 3.81;

active hydrogen (one), 0.28.

Found: C, 78.36, 78.25; H, 8.94, 9.06; N, 3.78, 4.13;

active hydrogen, 0.24.

In carbon tetrachloride solution, this compound, XXII, showed hydroxyl absorption at 3400 cm.$^{-1}$, carbonyl absorption at 1690 cm.$^{-1}$, and a band in the unsaturation region at 1615 cm.$^{-1}$.

A sample of XXII (100 mg.) was dissolved in a mixture of 2 ml. of acetic anhydride and 2 ml. of pyridine. This solution was refluxed for fifteen minutes, allowed to stand over-night and evaporated to dryness under reduced pressure. The residue was taken up into ether and the base recovered from the ether by washing with dilute acid. The acid extract was made alkaline with ammonia and the acetylated base extracted with ether again. The material thus purified melted at 138-148°C. Recrystallization from petroleum ether yielded colourless crystals, m.p. 150-155°C.

Calc. for $C_{26}H_{35}O_3N$: C, 76.28; H, 8.62; N, 3.32;

CH_3CO, 10.24.

Found: C, 75.77; H, 8.41; N, 3.66; CH_3CO, 10.11.

This acetyl derivative of XXII showed acetoxyl absorption at 1745 cm.$^{-1}$ and carbonyl absorption at 1700 cm.$^{-1}$, in carbon tetrachloride solution.

10. Attempted Oxidations of XXII

The base, XXII, failed to react under the conditions

of the Oppenhauer oxidation with acetone and aluminum iso-
propoxide in boiling benzene. Even after thirty hours'
refluxing, the starting material was recovered. In sub-
sequent oxidations described below, more vigorous conditions
were used.

A sample of 90 mg. of XXII was dissolved in a mixture
of 2.5 ml. of dry xylene and 2.5 ml. of purified cyclohexa-
none. Aluminum isopropoxide (0.50 gm.) was added and the
mixture refluxed. After one-half hour, a precipitate formed
and the mixture formed a gel.

Sufficient xylene was added to allow the mass to re-
flux and the boiling was continued for forty hours. The
xylene and excess cyclohexanone were removed in vacuo on the
steam cone and the residue partitioned between ether and
hydrochloric acid. The aqueous acid layer was made alkaline
with ammonia and extracted with ether. On working up, there
was recovered 30 mg. of the starting material from this basic
fraction.

The original ether extract yielded, on evaporation of
the solvent, a dark amorphous residue. This was evidently
contaminated with xylene, cyclohexanone and condensation pro-
ducts. It was dissolved in benzene and chromatographed on
alumina. Elution with chloroform containing methanol de-
veloped a coloured band which yielded 85 mg. of an amorphous
residue. This material had complex absorption in the carbonyl
region with bands at 1755, 1710 and 1675 cm.$^{-1}$.

In subsequent runs, a modified Oppenhauer oxidation using benzophenone and potassium-t-butoxide was tried. The catalyst was prepared as described by Woodward (37). The hydroxy base, XXII, (100 mg.), was dissolved in dry xylene containing 275 mgm. of benzophenone. Potassium-t-butoxide (100 mg.) was added, the apparatus flushed with pure, dry nitrogen and refluxed for eight hours, then allowed to stand over-night. The red solution was extracted with dilute hydro- chloric acid and the acid extracts made alkaline and ex- tracted with ether. Evaporation of the ether yielded crystals (90 mgm.) which melted at 182-187°C., either alone or mixed with the starting material.

The above recovered base was mixed with another sample of XXII and treated with benzophenone and potassium- t-butoxide under conditions similar to those described above except that a prolonged heating period (twenty-four hours) was used. The reaction mixture was very dark and contained a resinous precipitate. Working up of the basic fraction yielded only an amorphous residue. This material had bands in the ultraviolet at $530\,m\mu$ and $284\,m\mu$ and in the carbonyl region of the infrared at 1720 cm.$^{-1}$.

The compound XXII failed to react with lead tetra- acetate in 90% acetic acid after standing three days at room temperature. In a second attempt, a sample of XXII was dis- solved in a mixture of 5 ml. of glacial acetic acid and 1 ml. of absolute methanol and treated with excess lead tetraacetate

under refluxing conditions over-night and then at room temperature for four days. However, the starting material was recovered from this run also.

11. <u>Oxidation of the Benzal Compound, XIV, with Selenium Dioxide</u>

A solution of benzal-α-cyanolycopodine (2.00 gm.) in dioxane was added slowly to 0.760 gm. of selenium dioxide partially dissolved in boiling dioxane. The apparatus was flushed with pure, dry nitrogen and the mixture refluxed for eight hours and allowed to stand over-night. The mixture was filtered to remove precipitated selenium, the dioxane removed in <u>vacuo</u>, and the residue treated with boiling ether. A portion of the product (0.42 gm.) would not dissolve in ether. This insoluble material was subsequently found to be a mixture containing a small amount of the oxidation product (XXIII) and selenium dioxide. Concentration of the ether solution yielded 0.50 gm. of colourless crystals, XXIII. Recrystallization from ether-petroleum ether yielded colourless needles, m.p. 212-217°C.

Calc. for $C_{24}H_{30}O_2N_2$: C, 76.14; H, 7.99; N, 7.40.
Found: C, 76.08, 75.77; H, 7.90, 8.04; N, 7.40.

This compound showed hydroxyl absorption at 3580, cyanamide absorption at 2210, and carbonyl absorption at 1695 cm.$^{-1}$ in carbon tetrachloride solution. In chloroform the carbonyl absorption was at 1695 cm.$^{-1}$. The ultraviolet spectrum of this compound is shown in Figure V of the Appendix.

Concentration of the mother liquors from the re-
crystallization of XXIII yielded more of this compound along
with some orange prisms. This new compound, XXIV, could be
separated from XXIII by virtue of the greater solubility of
the latter in ether. A more convenient separation consisted
of dissolving an intimate mixture of the two compounds in
benzene and chromatographing on alumina. Compound XXIV
passed very rapidly down the column as a bright orange band
and elution with benzene containing methanol developed the
much more strongly adsorbed compound XXIII.

Recrystallization of XXIV from ether yielded brilliant
yellow prisms, m.p. 199-202°C.

Calc. for $C_{24}H_{28}ON_2$: C, 79.95; H, 7.84; N, 7.77.

Found: C, 79.37, 79.62; H, 7.84, 7.87; N, 7.72, 7.56.

This compound in carbon tetrachloride solution had
the usual cyanamide absorption at 2210, carbonyl absorption
at 1675, a strong sharp band at 1625 and a broad band re-
sembling the phenyl absorption at 1590 cm.$^{-1}$. In chloroform
solution, the latter bands appear at 1670, 1620 and 1590 cm.$^{-1}$.
The ultraviolet spectrum of this compound is shown in Figure
V of the Appendix.

SUMMARY

α-Cyanolycopodine was the starting material for a number of reactions and degradations. It was converted through a series of reactions to a methiodide but unfortunately the latter formed in very low yield. The reduction of α-cyanolycopodine and α-cyanobromolycopodine with hydride reagents provided convenient methods for the preparation of several useful derivatives for dehydrogenation and oxidation studies. In addition, a satisfactory method was developed for the separation of α- and β-cyanobromolycopodine as useful derivatives. One derivative, α-des-tetrahydrolycopodine, was dehydrogenated to a quinoline derivative. This provided some evidence for a reduced quinoline ring system in the α-compounds and together with other evidence indicated that three of the four rings of lycopodine are probably six-membered.
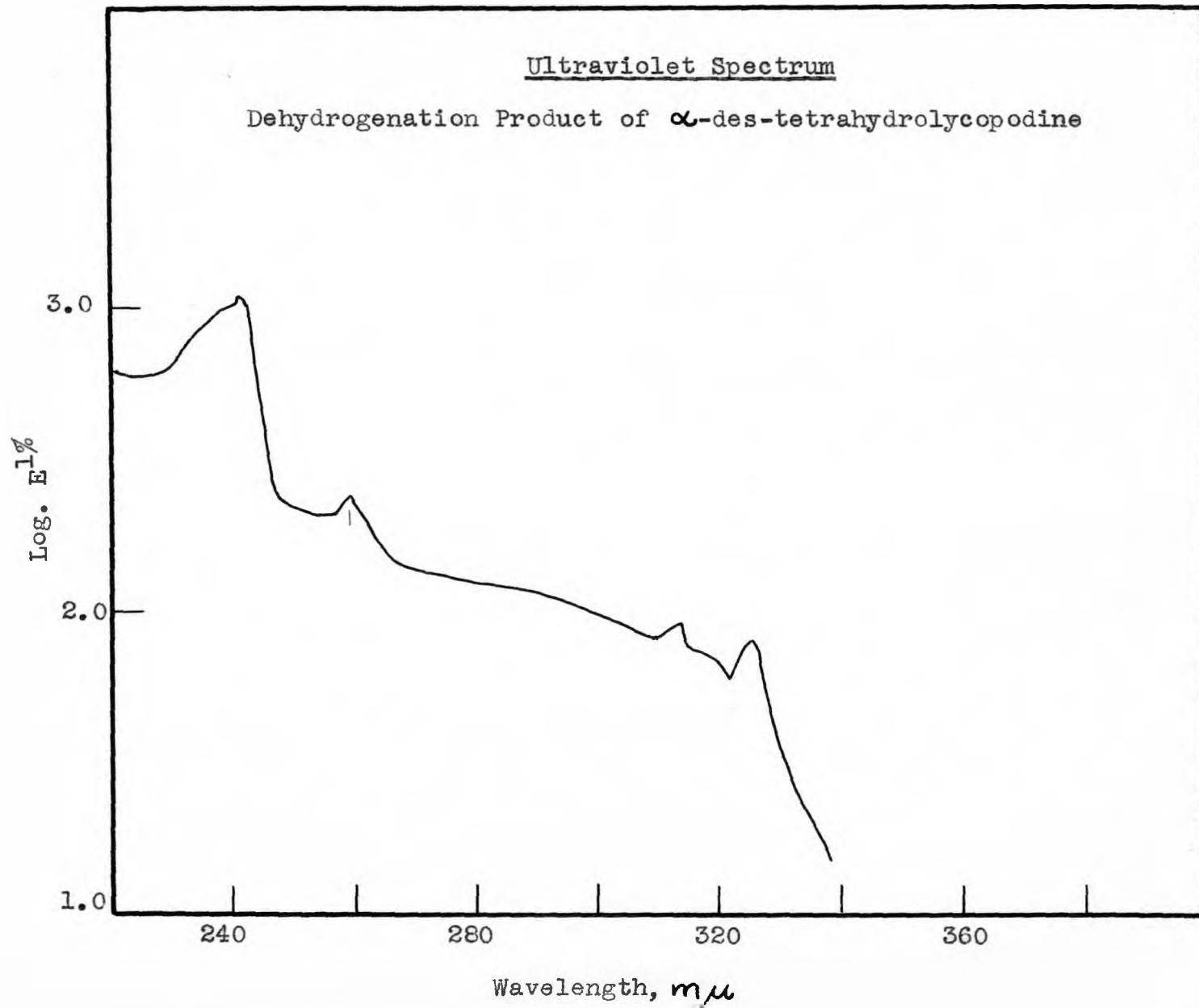
Bromination and oxidation experiments were carried out on α-cyanolycopodine and two conjugated enols were isolated. This was evidence for at least one active methylene group in lycopodine. From an examination of the spectra of these enols, it is unlikely that the carbonyl group and the nitrogen can be in the same six-membered ring.

Bromo derivatives were prepared from α-cyanolycopodine, lycopodine and α-des-dihydrolycopodine. Comparison

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of the pK_a values for the des-bases and the brominated bases
with the values for lycopodine and dihydrolycopodine suggests
that the relationship of the nitrogen to the carbonyl group
has not been altered in the formation of α-cyanobromolycopodine
during the von Braun reaction.

A benzal derivative was prepared from α-cyanolyco-
podine to confirm the presence of an active methylene group.
The benzal compound was converted to a N-CH$_3$ benzal-t-base
for further degradations but this base failed to react with
methyl iodide or cyanogen bromide. It did undergo an unusual
reaction with methyl sulfate and an amorphous base was iso-
lated from this reaction. This base readily formed a meth-
iodide and Hofmann degradation of the corresponding quaternary
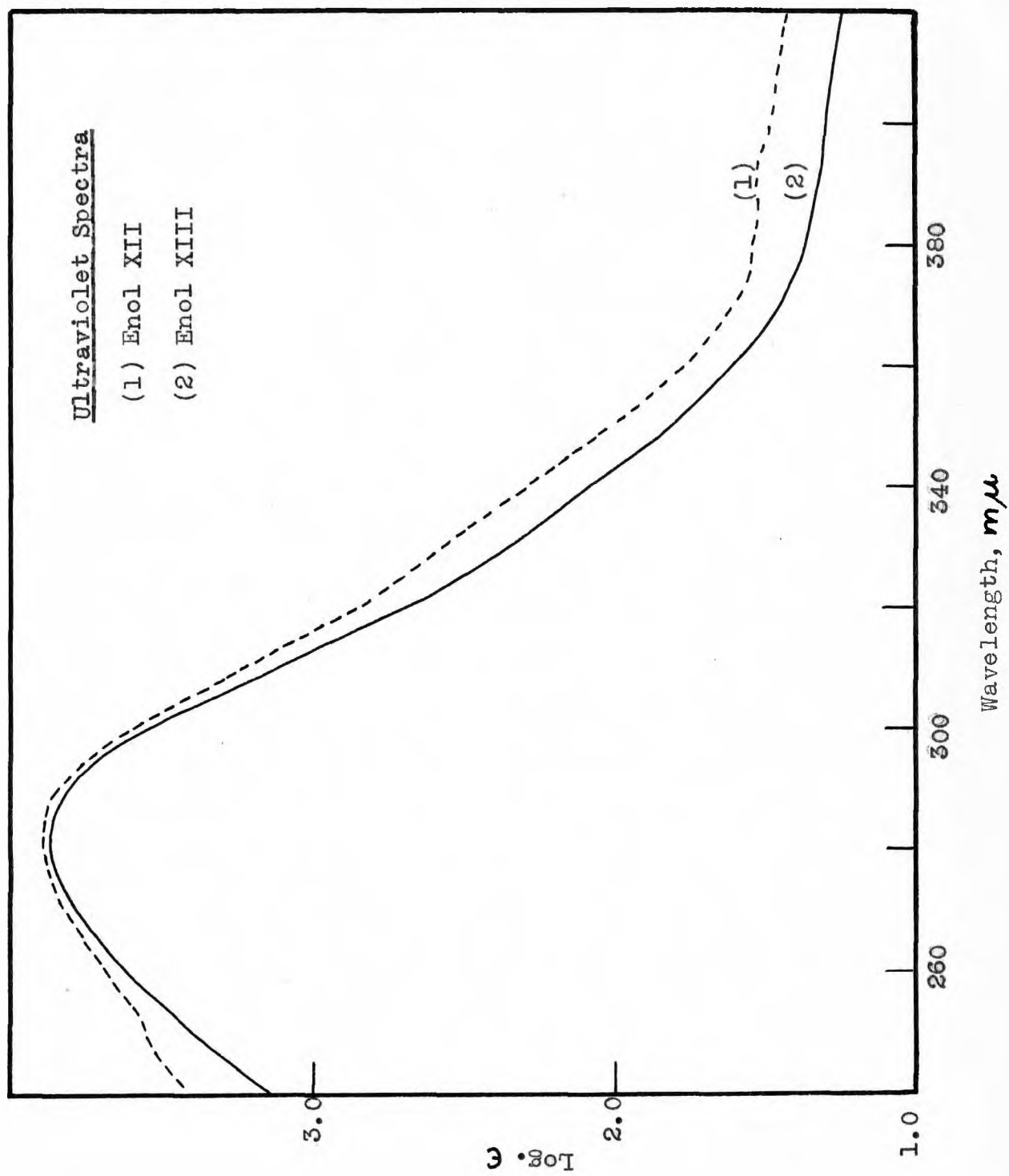hydroxide yielded trimethylamine.

The neutral benzal compound and the benzal-t-base were
oxidized with selenium dioxide. The benzal compound yielded
two oxidation products; one a hydroxylated derivative, and a
second formed by introduction of a double bond conjugated with
the carbonyl group. The nature of this product limits the
possible positions for the carbonyl group in a ring adjoining
the heterocyclic ring.

Ultraviolet Spectrum
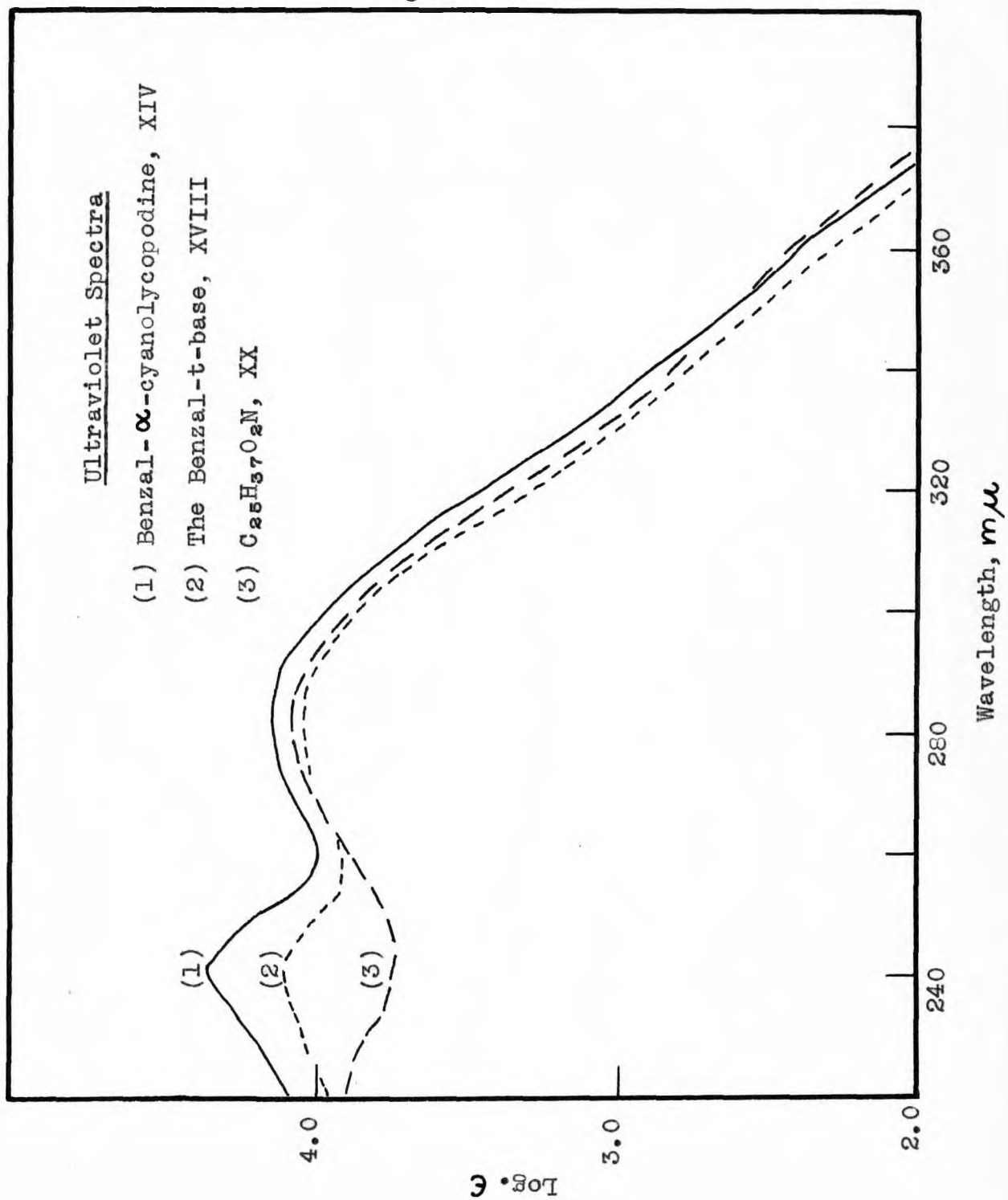
Dehydrogenation Product of α-des-tetrahydrolycopodine

APPENDIX

Figure II

Ultraviolet Spectra

(1) Enol XII

(2) Enol XIII

APPENDIX

Figure III

Ultraviolet Spectra

(1) Benzal-α-cyanolycopodine, XIV

(2) The Benzal-t-base, XVIII

(3) $C_{25}H_{37}O_2N$, XX

Wavelength, $m\mu$

Log. ε

Ultraviolet Spectra

(1) The Acetate, $C_{29}H_{41}O_4N$

(2) Distillate from Hofmann
    Degradation

Ultraviolet Spectra

(1) $C_{24}H_{33}O_2N$, XXII

(2) $C_{24}H_{30}O_2N_2$, XXIII
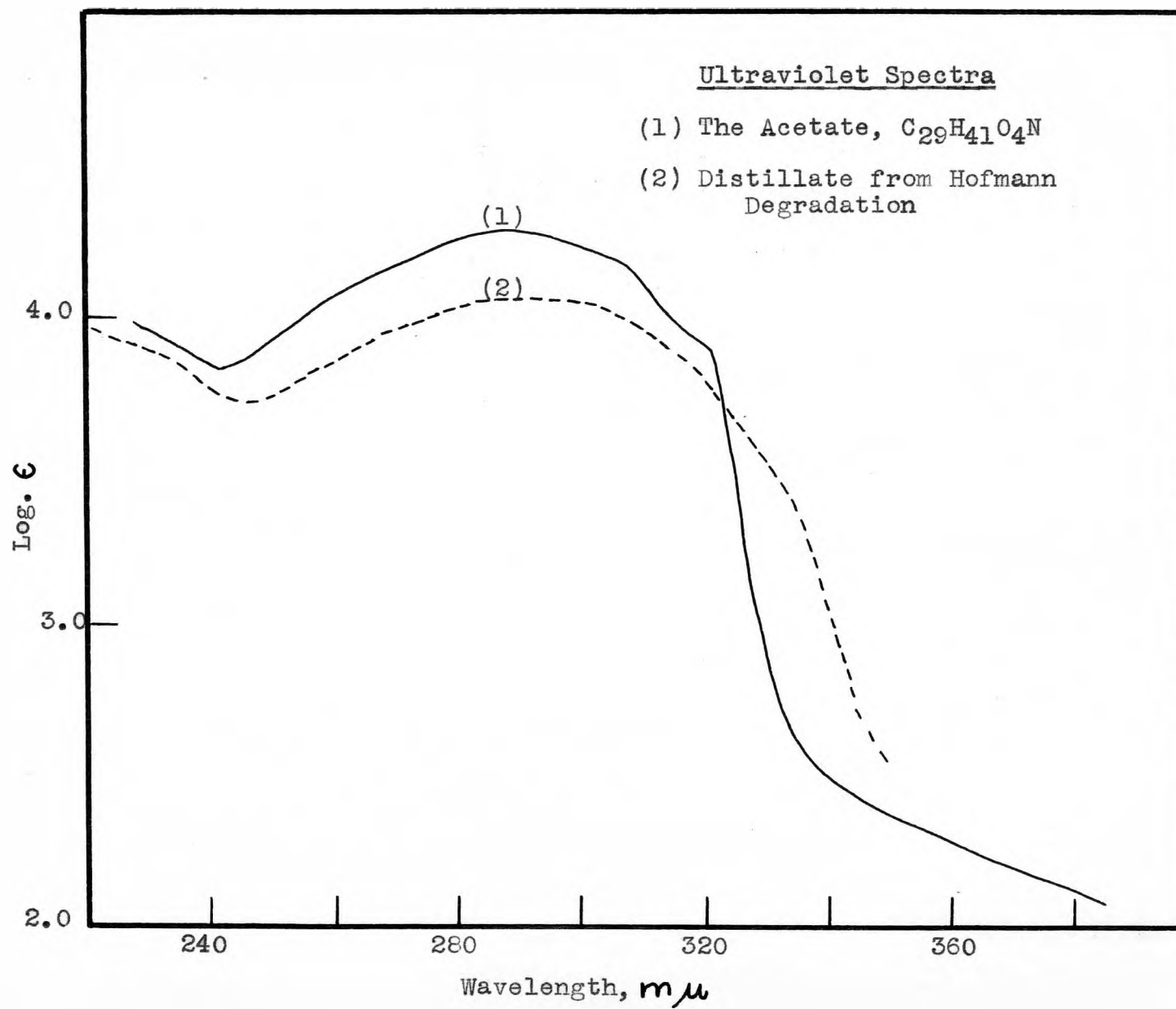
(3) $C_{24}H_{28}ON_2$, XXIV
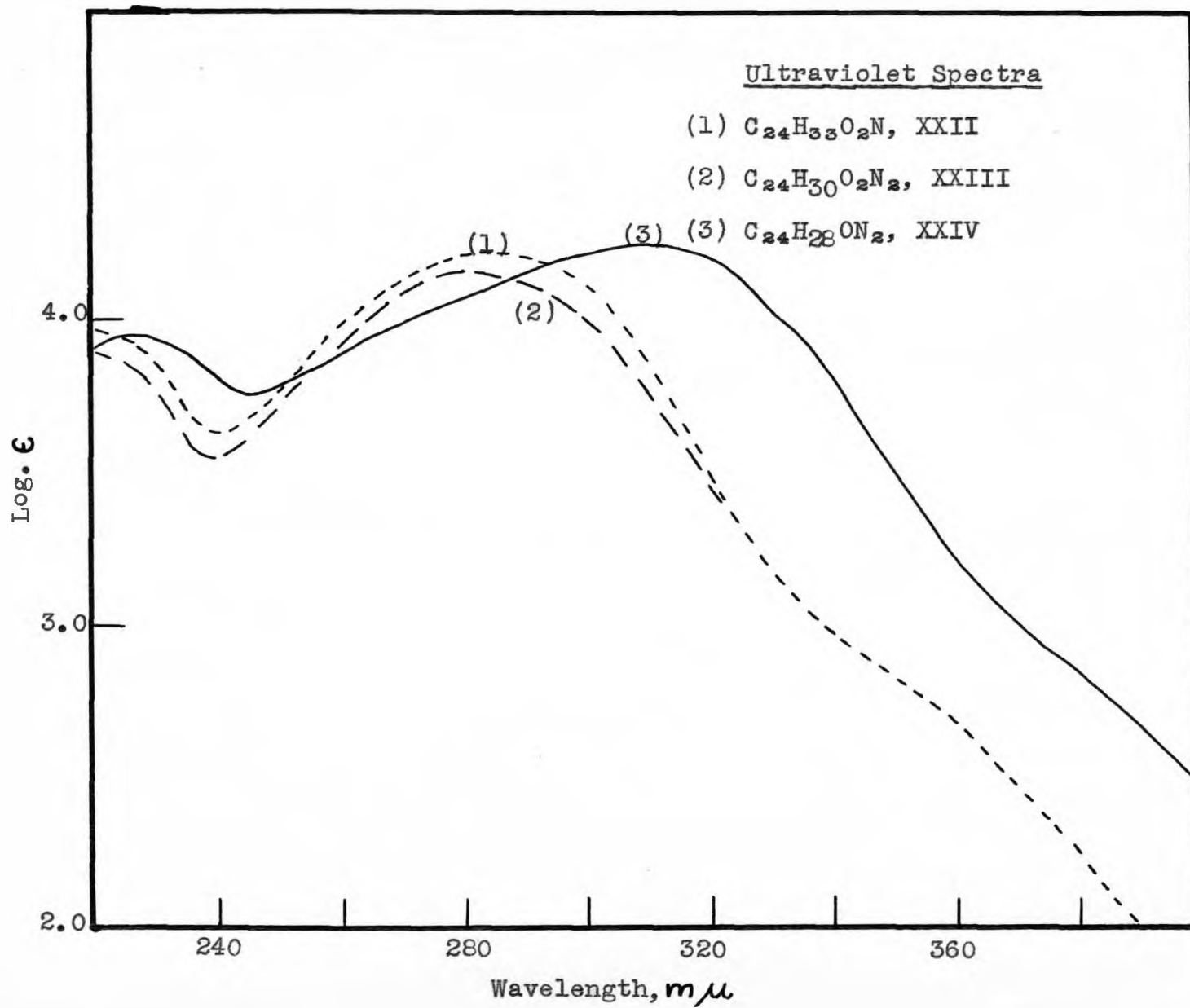
APPENDIX

Figure V

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