THE STRUCTURE OF LYCONNOTINE (PART I)

STUDIES OF SOME DERIVATIVES OF CYCLOHEXANE (PART II)

STUDIES OF SOME DERIVATIVES OF BICYCLO [2.2.1]HEPTANE (PART III)

by

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PREFACE

This thesis is divided into three parts. The work in Parts I and II was carried out under the guidance of Prof. F. A. L. Anet. The investigations presented in Part III were taken up under the supervision of Prof. R. R. Fraser, after Dr. Anet moved to the University of California, Los Angeles.

Part I is concerned with the isolation of a new alkaloid, now named lyconnotine and a lactone derived from lyconnotine; elucidation of the structure and stereochemistry of these alkaloids is included. An attempted interrelation of lyconnotine with acrifoline and dihydroacrifoline by photolysis of the latter two alkaloids is also described.

Part II deals with (i) the ring inversion in cyclohexene-*cis*-3,3,4,5,6,6-d_6, (ii) *cis*-1,2-dicarbomethoxy cyclohexane-*cis*-3,3,4,5,6,6-d_6 and (iii) cyclohexane-3,3,6,6-d_4.

Finally, the third part of this thesis includes preparation of some 7-substituted norbornane derivatives and the application of Nuclear Magnetic Resonance (N.M.R.) spectroscopy to establish their configurations. A study of the magnetic anisotropy of the double bond in these and similar systems is described.

ACKNOWLEDGMENTS

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ABSTRACT

PART I

Lyconnotine, an alkaloid of Lycopodium annotinum L. has been isolated by an improved method. Isolation of a derivative of lyconnotine has also been accomplished. The structure and stereochemistry of these alkaloids have been established on the basis of chemical and spectral evidence. Attempts to interrelate acrifoline and dihydroacrifoline to lyconnotine by photochemical cleavage of the former two alkaloids have been unsuccessful. On photolysis, a complicated mixture of a number of components is obtained. It has been shown that the major photoproducts cannot be readily converted to lyconnotine.

PART II

The preparation of (i) cyclohexene-cis-3,3,4,5,6,6-d_6, (ii) cis-1,2-dicarbomethoxy cyclohexane-cis-3,3,4,5,6,6-d_6, and (iii) cyclohexane-3,3,6,6-d_4 has been achieved. The N.M.R. spectra of these compounds at ambient and lower temperatures are discussed and various kinetic parameters for conformational changes in cyclohexene have been obtained. Values of the coupling constants in cyclohexane are furnished.

PART III

The syntheses of a number of 7-substituted bicyclo[2.2.1]heptane derivatives are described. Representative compounds include 7-isopropylidene bicyclo [2.2.1]hept-5-ene-exo-2,3-diol carbonate Ia, the corresponding endo isomer Ib, exo-2,3-dihydroxy-7-isopropylidene bicyclo[2.2.1]hept-5-ene IIa, the corresponding endo diol IIb, 7-isopropylidene bicyclo[2.2.1]hept-5-ene-exo-2,3-diol thionocarbonate, IIIa and its endo counterpart IIIb. Products of catalytic reduction of compounds Ia, IIa and IIIa have also been obtained. Configurations of these compounds have been established on the basis of their N.M.R. spectra. Attempts to obtain 7-isopropylidene bicyclo[2.2.1]hepta-2,5-diene have been unsuccessful. The anisotropic effect of the double bond in the above series and in the 7,7-dimethylene bicyclo [2.2.1]heptane derivatives is discussed and compared with the previous results in the literature.

PART I

INTRODUCTION

1. Scope of the Problem

The elucidation of the unusual structure of annotinine (1), an alkaloid of Lycopodium annotinum L., in 1957 has led to a great deal of interest in other Lycopodium alkaloids. The present investigation stems from previous work carried out in this laboratory (2,12,13,22,23,31,32). Khan (2) isolated from Lycopodium annotinum L., a small amount of a new alkaloid, $C_{17}H_{25}O_3N$, m.p. 117-118°; its infrared spectrum in carbon tetrachloride solution exhibited bands at 3662 cm^{-1} and 1740 cm^{-1}. This part of the thesis is concerned with the isolation of this alkaloid, now named lyconnotine, and of a derivative of lyconnotine from Lycopodium annotinum L. The elucidation of the structure and stereochemistry of lyconnotine and its derivative is described. This section of the work also includes an attempted interrelation of lyconnotine with acrifoline and dihydroacrifoline by photochemical cleavage of the latter two alkaloids.

2. Review of Pertinent Literature

(i) General Introduction

The genus Lycopodium belongs to the family Lycopodiaceae and is included in the group Pteridophyta. Lycopodium annotinum L. represents one of about one hundred species of the genus Lycopodium (4). These plants are well represented in North America and are variously known as "Ground Pines", "Club Mosses", or "Christmas Greens" because of the resemblance of the sporophyte with its small evergreen leaves to many species of coniferous trees. The genus Lycopodium occupies an intermediate position in the evolutionary history of plants and forms a link between the algae and fungi and the highly evolved flowering plants.

The presence of an alkaloid, lycopodine, in Lycopodium complanatum L., was first reported by Bodeker (5). In 1938, Achmatowicz and Uzieblo (6) isolated lycopodine and two other alkaloids, clavatine and clavatoxine, from Lycopodium clavatum L. The correct formula, $C_{16}H_{25}ON$, was assigned to lycopodine by these authors. This was followed by a series of papers by Manske and Marion who reported the isolation of a large number of new alkaloids from different species of Lycopodium. A review of this work is available (7).

Although alkaloidal constituents of various Lycopodium species have been investigated since the nineteenth century, the presence of alkaloids in Lycopodium annotinum L. was first noted in 1943 (8). Manske and Marion, in that year,

isolated from Lycopodium annotinum L., annotinine ($C_{16}H_{21}O_3N$), the principal alkaloid of this species. They also reported the isolation of the previously known lycopodine (5,6), the obscurines and several other alkaloids. Among other alkaloids which have been isolated from certain sub-species of Lycopodium annotinum L., are acrifoline ($C_{16}H_{23}O_2N$), annotine ($C_{16}H_{21}O_3N$), nicotine ($C_{10}H_{14}N_2$) and isolycopodine ($C_{16}H_{25}ON$) (9,10,11).

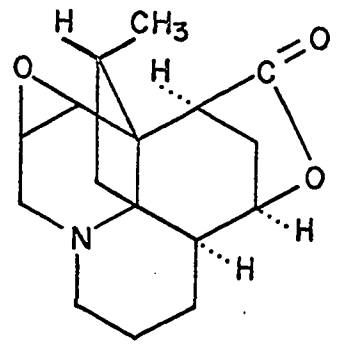
The methods of isolation and purification in the past were mainly fractional distillation and fractional crystallization of the bases or of their salts. These methods had the disadvantage of being cumbersome and were not always reproducible. Recently the procedures of countercurrent distribution have been successfully utilized by Anet and Eves (12) for concentration and purification of particular alkaloids; this technique in combination with suitable paper chromatographic procedures for their detection has proved to be efficient as well as reproducible. Employing these procedures, Anet and Eves succeeded in isolating lycodine from the crude alkaloids of Lycopodium annotinum L. Anet and Khan (13) further improved upon these methods and were able to isolate four other alkaloids, annofoline ($C_{16}H_{25}O_2N$), lycofoline ($C_{16}H_{25}O_2N$), lofoline ($C_{18}H_{29}O_3N$) and fawcettiine ($C_{18}H_{29}O_3N$). The aspects of distribution, isolation and characterization of alkaloids of various Lycopodium species have been reviewed extensively (7,10,14).

(ii) Reactions and Structural Studies of some Lycopodium Alkaloids

At the time the present work was undertaken, the chemistry of Lycopodium alkaloids was fairly well developed. In the following pages, a brief discussion of the structural studies and reactions of some of the Lycopodium alkaloids is presented.

(a) Annotinine

Annotinine ($C_{16}H_{21}O_3N$), the principal alkaloid of Lycopodium annotinum L., was first reported by Manske and Marion (8). It has been shown that this alkaloid has a different carbon skeleton from the others. Since the chemistry of annotinine has been reviewed in detail by Wiesner and co-workers (1,16), only the structure of annotinine is included in this discussion. Wiesner, Ayer, Fowler and Valenta (15) showed structure I to be the correct representation of the alkaloid. This was corroborated by X-ray crystallographic studies of Przybylska and Marion on annotinine bromohydrin (17). The relative stereochemistry implied in structure I for annotinine is also established by the X-ray analysis (18).



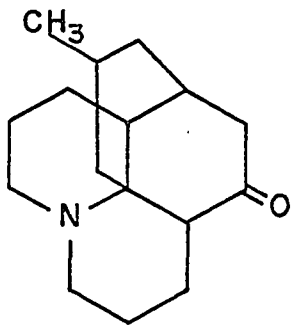
I

Annotinine

Recently, Wiesner and co-workers have deduced the absolute configuration(I)of annotinine (19).

(b) Lycopodine

Lycopodine is the major alkaloid of many Lycopodium species and occurs in small quantities in almost all the species. Bodeker (5) was the first to isolate lycopodine but the assignment of its correct molecular formula was made by Achmatowicz and Uzieblo (6). As a result of their degradative studies on lycopodine, MacLean and Harrison (20) have proposed structure II for lycopodine.



II

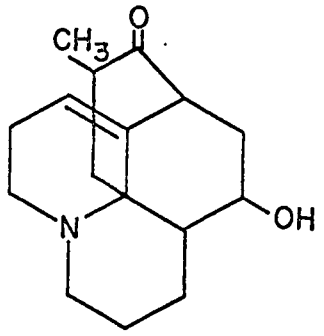
Lycopodine

MacLean and co-workers have recently published a detailed account of the degradation studies on lycopodine (21). Subsequent work of Anet (22) has lent further support to its proposed structure. Anet has been able to interrelate lycopodine to annofoline and establish their relative stereochemistry. The structure of annofoline was elucidated by Anet and Khan (23) independently.

(c) Acrifoline

Acrifoline ($C_{16}H_{23}O_2N$) is a minor alkaloid of Lycopodium annotinum L. It was first isolated from the plant Lycopodium annotinum var. acrifolium Fern by Manske and Marion (9).

From what follows, acrifoline has been shown (24,25) to possess the structure III.



III

Acrifoline

From the infrared spectral studies of acrifoline, its acetyl derivatives and of dihydroacrifolinol, Perry and MacLean (26) have deduced the nature of the functional groups in acrifoline. The infrared spectrum of acrifoline in Nujol showed an intense band at 3310 cm^{-1} for a hydroxyl group but a very weak band at 1700 cm^{-1} in the carbonyl region. However, when the spectrum was recorded in chloroform solution, acrifoline exhibited a strong carbonyl absorption at 1700 cm^{-1}. A weak band at 1670 cm^{-1} was also observed indicating the presence of a double bond. Acrifoline on catalytic hydrogenation was found to yield two dihydro derivatives, namely dihydroacrifoline ($C_{16}H_{25}O_2N$) and annofoline which are stereoisomeric at C_4 (see page 13 for the numbering used). Lithium aluminum hydride reduction of dihydroacrifoline afforded dihydroacrifolinol ($C_{16}H_{27}O_2N$) which showed a

band at 3300 cm^{-1} (hydroxyl group) but no absorption at 1700 cm^{-1} (keto group) in its infrared spectrum. Acrifolinol, the lithium aluminum hydride reduction product (25) of acrifoline, also yielded the same compound when subjected to catalytic hydrogenation. A monoacetyl derivative ($C_{18}H_{25}O_3N$) of acrifoline was obtained which in its infrared spectrum exhibited absorption bands at 1740 cm^{-1} (acetoxy group) and at 1700 cm^{-1} (keto group) but no band in the hydroxyl region. These observations confirmed the presence of a hydroxyl group, a double bond, a carbonyl group and a tertiary nitrogen atom in acrifoline. Acrifoline was *deduced* to be tetracyclic.

The carbonyl absorption in the infrared spectrum of acrifoline provided a clue to the spatial relationship of the carbonyl and the hydroxyl groups. The difference in behaviour in the solid state and in solution suggested the presence of a hemiketal form in the solid state. Since only five- and six-membered cyclic hemiketals form spontaneously, the carbon atoms having the hydroxyl group and the keto group should be separated by two or three atoms (24). The N.M.R. spectrum of acrifoline in chloroform exhibited absorptions of area equivalent to one proton at displacements of 3.35 and 2.04 parts per million (p.p.m.) (relative to chloroform) and were attributable to $>CHO-$ and $>C=C<^{H}$ groups respectively. A doublet of area equivalent to 3 protons occurred at displacement of 6.20 p.p.m. and this

established the presence of a $>CH\,CH_3$ group. The Kuhn-Roth analysis (24) of acrifoline had also shown the presence of a C-Me group. The above results were confirmed by the N.M.R. spectrum of acetylacrifoline (25). In the N.M.R. spectrum of acetylacrifoline, absorptions at displacements of 1.97, 2.64 and 6.30 p.p.m. were observed; these bands could be attributed to $>C=C<^{H}$, $>CHO-$ and $>CH\,CH_3$ respectively. The signal of the $-CO\,CH_3$ was seen as a sharp peak at a displacement of 5.50 p.p.m. The presence of an aldehyde group in acrifoline could be safely ruled out because of the absence of absorption at low field in both the above N.M.R. spectra. It therefore followed that the carbonyl group in acrifoline must be ketonic. Since the signal area of the CH-O- group corresponded to one proton, the hydroxyl group must be secondary.

Acrifoline and dihydroacrifoline (pKa 8.34 and 9.13 respectively) showed a considerable difference in their basic strengths, the latter being stronger base. This difference in basic strengths has been attributed (26) to an allylamine (-C=C-C-N-) structure in acrifoline.

Dihydroacrifolinol ($C_{16}H_{27}O_2N$), underwent Oppenauer oxidation to give a diketone ($C_{16}H_{23}O_2N$) (24). This compound in its infrared spectrum showed a band at 1705 cm^{-1} (carbonyl group) but no hydroxyl absorption. It appeared from the carbonyl frequency that the above oxidation product was a diketone with both the carbonyl groups located in rings that

were six membered or larger. Absorption at 1420 cm^{-1} in the infrared spectrum of the diketone and none in this region in the spectrum of acrifoline was indicative of the presence of a $-CH_2-CO-$ group in the above diketone but not in acrifoline. It follows therefore that the $-CH_2-CO$ group arose from a $CH_2-CH-OH$ group in acrifoline. The hydroxyl group in acrifoline did not appear to be allylic since attempts to replace it by halogen were not successful.

The structure of acrifoline proposed by French and MacLean explains all of the discussed information. This structure is corroborated by the work of Anet (22).

(d) Annofoline

Annofoline ($C_{16}H_{25}O_2N$) was isolated by Anet and Khan from Lycopodium annotinum L. (13) and was shown to contain a C-methyl group and a tertiary nitrogen. In the infrared spectrum it showed a hydroxyl group (band at 3400 cm^{-1}) and a carbonyl group (band at 1700 cm^{-1}). The intensity of the carbonyl band was much weaker when the spectrum was recorded in carbon tetrachloride solution and resembled that of acrifoline (24). This behaviour suggests that in solution there exists an equilibrium between the hydroxy ketone and the hemiketal forms of annofoline. Annofoline exhibited a doublet at τ 8.93 in its N.M.R. spectrum indicating that the C-methyl group is present as $>CH\ CH_3$. Annofoline on treatment with t-butyl nitrite

gave rise to an oximino acid which underwent smooth dehydrogenation to yield julolidine (23). This furnished evidence for the presence of a hexahydrojulolidine system in annofoline.

Annofoline yielded an α , β - unsaturated ketone on selenium dioxide oxidation. The N.M.R. spectrum of this compound exhibited a sharp band at τ 2.74 which was assigned to an olefinic hydrogen atom β to the keto group. The presence of a quaternary centre adjacent to the -CH= group was indicated by this unsplit peak. Also the singlet for the methyl group at τ 8.18 was unsplit. This implied that there was the system -CO-C(Me)=CH-$\overset{*}{C}$ where $\overset{*}{C}$ is a quaternary centre.

The structure III (see page 13) proposed by Anet and Khan for annofoline is consistent with all of the observed reactions.

(e) Fawcettiine

Fawcettiine ($C_{18}H_{29}O_3N$) was isolated from Lycopodium fawcettii (27) and Lycopodium annotinum (13). It has been shown to contain a hydroxyl group, an O-acetyl group, a tertiary nitrogen atom and a C-methyl group apart from the one in the acetyl group.

Fawcettiine, on oxidation with chromium trioxide, gave a keto acetate, dehydrofawcettiine, ($C_{18}H_{27}O_3N$) which could be hydrolyzed by base to yield annofoline (28). This deacetylation of dehydrofawcettiine was shown to be

accompanied by isomerization to annofoline (22).

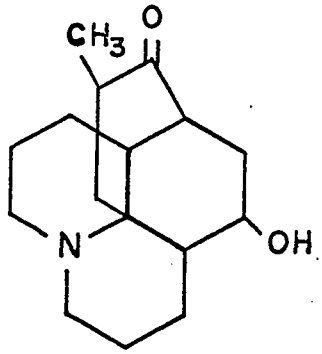
On hydrolysis of fawcettiine, deacetylfawcettiine ($C_{16}H_{27}O_2N$) was obtained; dehydration of the latter with thionyl chloride resulted in anhydrodeacetylfawcettiine (27). The remaining hydroxyl group was found to be resistant to further dehydration. The N.M.R. spectrum of anhydrodeacetylfawcettiine exhibited only one olefinic proton (τ 4.45) and a $>CHCH_3$ grouping (τ 9.00; J 5.9 c.p.s.). These observations can be accounted for by structures IV, V, and VI for fawcettiine, dehydrofawcettiine and anhydrodeacetylfawcettiine respectively (page 13).

(iii) Interrelation and Stereochemistry of some Lycopodium Alkaloids

An examination of the structures of lycopodine, acrifoline, annofoline and fawcettiine I, II, III, and IV respectively (page 13) suggests their close relationship to each other. Anet (22) has been able to interrelate these alkaloids and elucidate their relative stereochemistry.

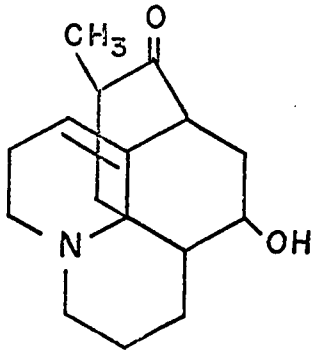
Acrifoline on catalytic hydrogenation afforded the previously known dihydroacrifoline and a small amount (about 10%) of annofoline. Thus annofoline and dihydroacrifoline are diastereoisomeric at C_4.

Wolff-Kishner reduction of annofoline followed by chromic acid oxidation (23) resulted in a compound $C_{16}H_{25}ON$, melting point 88-92°. This compound was designated as



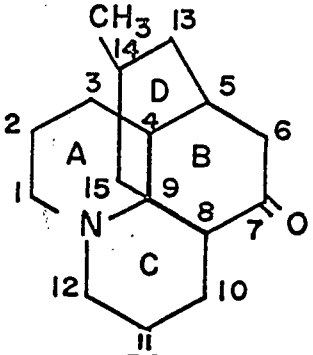
III

Annofoline



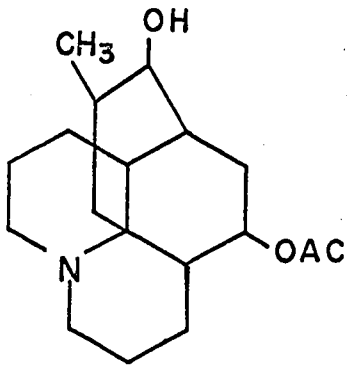
II

Acrifoline



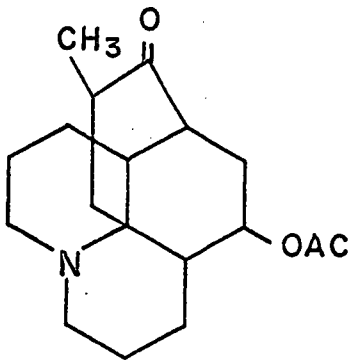
I

Lycopodine



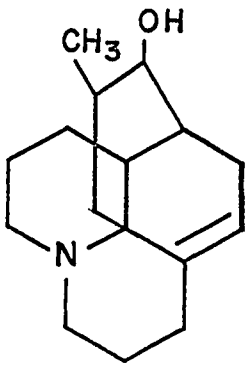
IV

Fawcettiine



V

Dehydrofawcettiine



VI

Anhydrodeacetylfawcettiine

deoxyannofoline having the structure I (page 13) but was not identical with lycopodine m.p. 115°. Anet showed that these two compounds differ only in the configuration of the carbon atom bearing the methyl group (C_{14}).

Sodium borohydride reduction of annofoline furnished a mixture of two isomeric diols α - and β - dihydroannofoline (23). The β -isomer was shown to be identical with deacetylfawcettiine (27). These α - and β -isomers were not merely epimeric alcohols but they differed in the configuration at C_{14}. Annofoline gave rise to the α -isomer only when the sodium borohydride reduction was carried out under neutral conditions. However, reduction in the presence of sodium hydroxide yielded up to 50% of the β -isomer (22). This suggests that the β -isomer is not a reduction product of annofoline but of a ketone having a methyl group at C_{14} in the opposite configuration to that of annofoline. The fact that 13-ketofawcettiine and O-acetylannofoline are not identical even though both yield annofoline on alkaline hydrolysis, further lends support to the above conclusion. These reactions suggest that in the reduction of annofoline under alkaline conditions, a base catalyzed equilibrium is rapidly established between annofoline and the less stable ketone (i.e. its C_{14} epimer). The hydride reduction of the less stable ketone proceeds at a much faster rate than the reduction of annofoline.

The fact that acrifoline and annofoline exist as mixtures of hemiketal and internally hydrogen-bonded hydroxy ketones indicates that ring D must exist predominantly in the boat form. The chair form suffers a very strong repulsion between C_{14} and the axial hydroxyl on C_7. The methyl group in ring D in annofoline is believed to be equatorial as annofoline was shown to be the stable isomer at C_{14}.

Compounds having no axial substituent at C_7 or possessing a double bond in ring B between C_6 and C_7 or C_7 and C_8, will be more stable with ring D in a chair conformation (22); thus in the stable isomer the configuration of the methyl at C_{14} is equatorial and is opposite to that encountered in annofoline.

The stability of lycopodine to base indicates that the rings B and C are fused <u>trans</u>. This is confirmed by the ready dehydration of dihydrolycopodine to $\Delta^{7,8}$ isomer, VIII (see Figure 1, page 17). Rings A and B must be fused <u>cis</u> since α -cyanobromolycopodine (20) was known to cyclize by base by internal alkylation in a position α - to the keto group at C_6 or C_8. This would be understandable if the ring residue in α -cyanobromolycopodine were axial on ring B. Deacetylfawcettiine, IX, dehydrated to give anhydrodeacetylfawcettiine which on oxidation yielded a ketone previously prepared by Burnell from deacetylfawcettiine (27). This ketone on Wolff-Kishner reduction afforded anhydrodihydro-

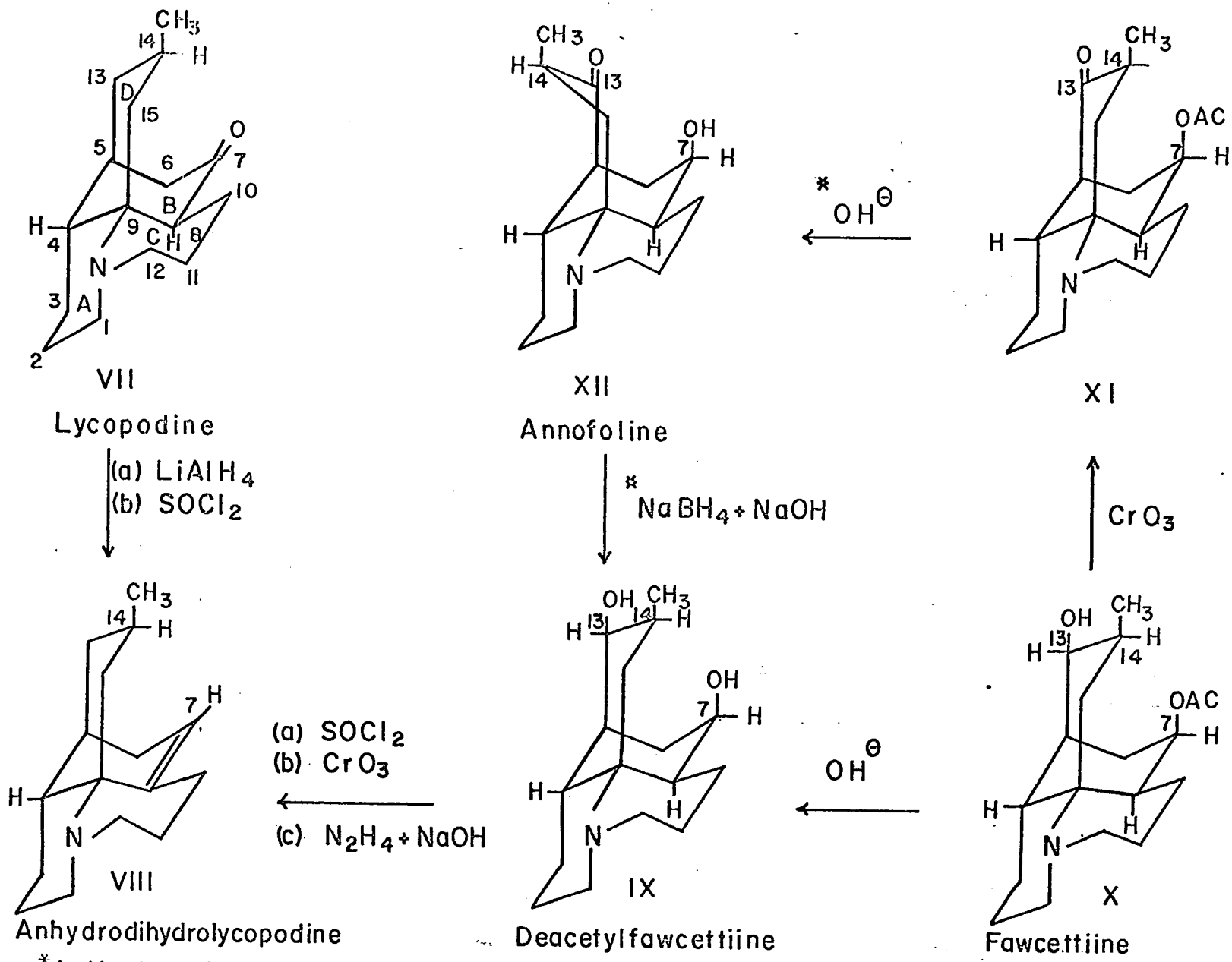
lycopodine VIII. Compound VIII could also be obtained from lycopodine on treatment with Lithium aluminum hydride followed by dehydration (29).

It is evident that in deacetylfawcettiine ring D should be in the chair form because the alternative boat form would place the methyl group at C_{14} in an extremely unfavorable flagpole position. The hydroxyl at C_{13} is trans to the methyl group and is equatorial. This also accounts for the stability of C_{13} hydroxyl group to dehydration. The interrelation of lycopodine, annofoline and fawcettiine is indicated graphically in Figure 1 (page 17).

(iv) Mass Spectra of some Lycopodium Alkaloids

Extensive studies on Lycopodium alkaloids have been carried out and have led to the structure elucidation of many of them. However, there are still many alkaloids whose structures are unsolved, particularly those occurring in minor amounts. In recent years, the mass spectrometric method has been employed (30) as a useful tool in solving these structural problems. This method is very well suited, in particular, to structural studies on substances available in small quantity.

MacLean (3) has recently investigated the mass spectra of a number of Lycopodium alkaloids of known structure to study their fragmentation pattern. This has been done by him with a view to applying the information so



*indicates that isomerization is involved at C_{14} in this step.

Figure 1 Interrelation and stereochemistry of some Lycopodium alkaloids

obtained, to the study of those alkaloids whose structures still await solution.

Among the Lycopodium alkaloids whose mass spectra have been examined by MacLean (3) are lycopodine, dihydrolycopodine, anhydrodihydrolycopodine, and acetyldihydrolycopodine. All these spectra showed peaks , which could be attributed to the loss of the bridge plus a hydrogen atom. Another peak that was common to all the spectra except that of lycopodine fell at m/e 146. MacLean has put forward a fragmentation scheme compatible with the observations and this scheme for dihydrolycopodine is shown in Figure 2 (page 20). In the transformation m/e 249 to m/e 192, the neutral fragment eliminated was postulated to be $(CH_3)_2CHCH_2$. A fluid rather than static situation with respect to the unsaturation was assumed in the ion of m/e 174 where the double bonds could occupy any of the positions shown in formulae A, B, and C (Figure 2, page 20). The formation of the ion of m/e 146 was considered to take place with the loss of an ethylene fragment. Although no direct evidence is available, MacLean proposed that the hydrogen lost with the bridge came from C_4. This conclusion was arrived at as a result of his labelling experiments on lycopodine; it was shown that the hydrogen lost did not come from C_6, another likely position for its abstraction.

The mass spectrum of acrifoline was also studied by MacLean (3). This was considered of interest as

acrifoline with a $\Delta^{3,4}$ double bond constituted a system lacking hydrogen at C_4. The spectrum had two intense peaks at m/e 191 and 174 and exhibited peaks of lesser intensity at m/e 190, and 172. The proposed mechanism for the fragmentation of acrifoline compatible with these observations is shown in Figure 3 (page 21). The lack of a hydrogen at C_4 in acrifoline prompted MacLean to postulate the loss of bridge as methyl cyclopropanone or as carbon monoxide and propylene from the molecular ion to leave the stable conjugated ion-radical (i.e. m/e 191). The peak at m/e 174, the most intense in the spectrum, was attributed to an ion formed by loss of hydroxyl radical from the ion m/e 191. Alternatively, it might arise directly from the molecular ion since acrifoline is known to exist as an equilibrium mixture of hydroxyketone and hemiketal isomers. A concerted elimination from the molecular ion involving the hemiketal is also shown in Figure 3 (page 21).

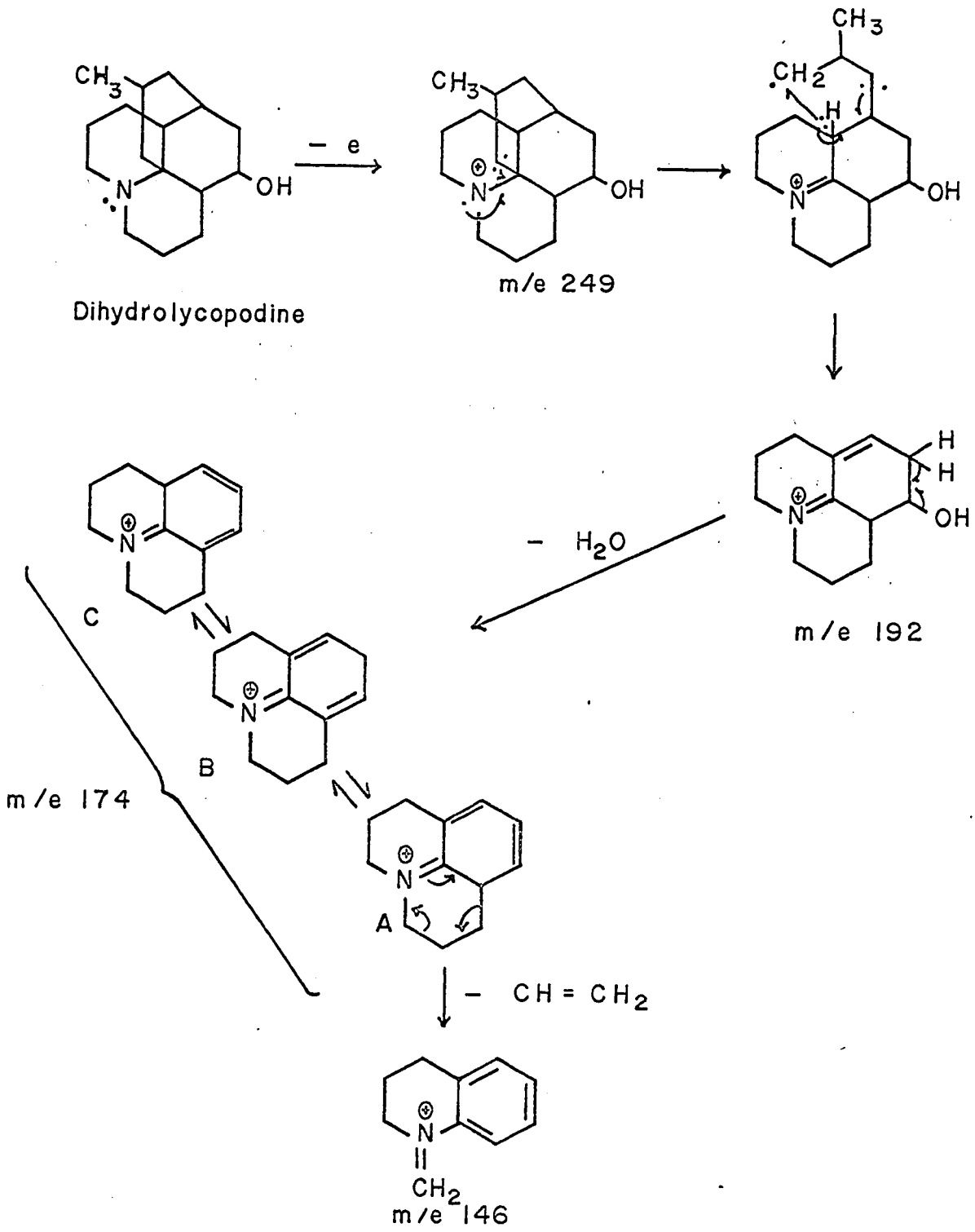
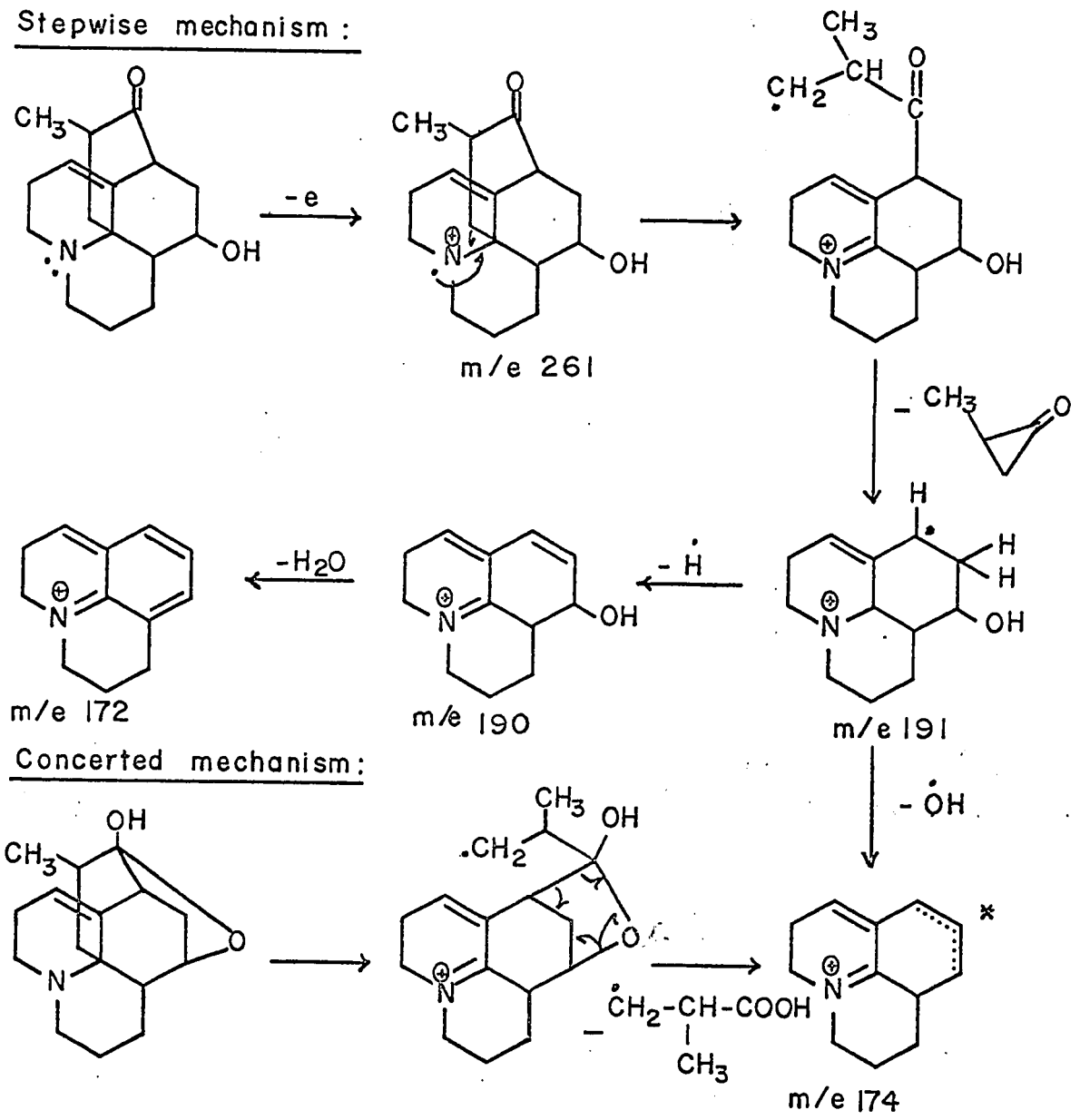


Figure 2 Fragmentation pattern of dihydrolycopodine



*indicates that the double bond in the ion may occupy 5, 6- or 6, 7- position as shown by dotted lines.

Figure 3 Fragmentation pattern of acrifoline

EXPERIMENTAL

1. Description of the General Methods

The melting points of the compounds reported here were determined on a "Leitz" hot-stage apparatus. The ultraviolet spectrum was recorded using a Beckman DK-2 Spectrophotometer in methanol solution in 1 cm cells. The infrared spectra in solution were measured in a micro cavity cell (ca. 1 mm path length; 0.04 ml volume) on a Perkin-Elmer Infracord double beam instrument. The nuclear magnetic resonance (N.M.R.) spectra reported in this part of the thesis were recorded on a Varian Model V-4302 high resolution spectrometer operating at 60 Mc/sec. The spectra were calibrated by the side band technique using tetramethylsilane (T.M.S.) as the internal standard. The coupling constants are expressed in cycles per second (c.p.s.) and the proton chemical shifts are expressed in τ values (33).

$$\tau \text{ in p.p.m.} = 10.0\text{-}10^6 \, (H_{Me_4Si}\text{-}H)/H_{Me_4Si}$$

where H = magnetic field at resonance

The double resonance ("spin decoupling") experiments on the lactone alkaloid reported in this section were kindly performed by Professor F.A.L. Anet. The mass spectrum of lyconnotine was very kindly determined by Dr. K. Biemann at Massachusetts Institute of Technology. Elementary analysis of a compound reported here was done by Midwest

Microlab Inc., Indianapolis. Nitrogen content of Lyconnotine was determined by Mrs. P. Revelle. Paper chromatography, unless otherwise stated, was carried out according to Anet and Khan (13) using Whatman No. 1 paper impregnated with citrate-phosphate buffer. The chromatograms were developed in n-butanol saturated with water and the spots were revealed by spraying with a modified Dragendorff's reagent (34). Buffers of different pH values (as mentioned within the text) were used depending on the nature of the alkaloidal mixture under investigation. At times the same reaction mixture was chromatographed at different pH values and the pH values yielding the best separation are represented in the text. Fluka Alumina (Type 5016A) was used for column chromatography.

A Hanovia Type L450 watt ultraviolet lamp was employed for irradiation. Depending upon the experimental results, photolysis was carried out with or without filter sleeves (Corex, Pyrex, Vycor and thin-walled Pyrex sleeves) placed in the immersion well. The material to be irradiated was contained either in a test tube held at a distance of about 2" from the outer wall of the immersion well or it was placed in an outer jacket that could be fitted directly on to the immersion well.

Acrifoline, used in this work, was either available or was isolated from the alkaloidal mixture from previous investigations.

The alkaloid mixture from which lyconnotine was isolated, was partitioned in the Craig's countercurrent distribution apparatus by Mrs. S. Osgerby.

2. Isolation of Lyconnotine

The crude alkaloids of Lycopodium annotinum L., remaining after the crystallization of annotinine, when partitioned between chloroform and buffer of pH 7.0 (13), could be divided into three fractions: I "chloroform soluble", II "buffer soluble" and III "middle fraction". The middle fraction contained alkaloids having nearly equal solubility in both phases.

The material available for the present work was a middle fraction, similar to III above but from a different batch of Lycopodium alkaloids. This fraction was submitted to a second countercurrent distribution. The alkaloid mixture (4 g) was dissolved in chloroform (120 ml) and the solution was placed in the first three tubes of a sixty tube Craig's countercurrent distribution apparatus (35) and partitioned, through 57 transfers, between chloroform and citrate-phosphate buffer of pH 7.0 (40 ml in each phase), with the buffer as the moving phase. Aliquots (2 ml), of each phase from every third tube, were withdrawn and the alkaloids from each of these tubes were isolated. Paper chromatography (pH 5.0) of materials from tubes 13-60 showed the presence of several alkaloids in each tube and were not investigated any further.

Paper chromatography (pH 5.0) of contents of tubes 4-12 revealed the presence of three components (R_f 0.21, 0.50 and 0.75). The mobilities of the main components corresponded to those of lyconnotine (R_f 0.50) and acrifoline (R_f 0.21). The contents of tubes 4-12 exhibited bands at 3700 cm^{-1}, 3500 cm^{-1}, 1735-40 cm^{-1} and 1700 cm^{-1} in their infrared spectra and were combined. On evaporation of the solvent, a syrup (1.22 g) was obtained which was dissolved in methanol (10 ml). This solution was divided into two equal parts, fractions A and B. The latter stood at room temperature for about a year.

Fraction A was concentrated to a syrup (0.61 g) which was taken up in methylene chloride three times and evaporated. The syrup was then dissolved in a minimum quantity of methylene chloride and applied to a column (12 mm internal diameter) of basic alumina (15 g). The column was eluted with methylene chloride and fractions (10 ml) were examined by paper chromatography (pH 5.0). Fractions 1 to 60 showed the presence of one component whose mobility was the same as that of lyconnotine (R_f 0.50). Fraction 61 showed the presence of another component whose mobility corresponded to that of acrifoline (R_f 0.21). Fractions 1-60 were combined and concentrated. The base so obtained was dissolved in dilute hydrochloric acid. The acid solution was made basic with aqueous sodium hydroxide solution and extracted several times with methylene chloride. The combined methylene chloride extracts were

washed with water and dried over anhydrous sodium sulfate. The filtered solution was concentrated to give a brown mass which was dissolved in ether. The brown crystals, which separated out overnight, were sublimed in a glass bulb at 100-110°/0.05 mm to give a pale yellow solid. A second sublimation afforded a white crystalline product (50 mg).

3. Characterization of Lyconnotine

Lyconnotine after resublimation melted at 118-119°. The formula $C_{17}H_{25}O_3N$ (M.W. 291.4) requires N, 4.8%; found N, 4.24%. The mass spectrum showed the molecular weight to be 291.

The ultraviolet spectrum of lyconnotine in methanol showed an absorption band at 234.5 m μ (ϵ 18,000). The infrared spectrum of lyconnotine in carbon tetrachloride solution showed bands at 3700 cm^{-1}, 1735-40 cm^{-1}, a little hump at 1665 cm^{-1} and a small shoulder at 3050 cm^{-1}. Its N.M.R. spectrum in deuterated chloroform exhibited, among other bands, a multiplet near τ 4.4, a singlet at τ 6.41 and a doublet at τ 8.93.

A. Catalytic Reduction of Lyconnotine

A solution of lyconnotine (5.3 mg) in ethanol (10 ml) was hydrogenated for 1/2 hour in presence of pre-activated Adam's Catalyst (2.4 mg) at atmospheric pressure. After removal of the catalyst by filtration, paper chromatography (pH 7.0) on the filtrate revealed the presence of two compounds with R_f values 0.92 and 0.73 respectively (R_f value

of lyconnotine itself at this pH was 0.85). Hydrogenation when continued for a period of six hours resulted in one spot on paper chromatogram (pH 5.0, R_f 0.66; R_f of lyconnotine at pH 5.0, 0.50).

B. Oxidation of Lyconnotine with Chromium Trioxide

Lyconnotine (6 mg) was dissolved in dry pyridine (0.50 ml) and the solution was added to a solution of chromium trioxide (100 mg) in pyridine (1.5 ml). The reaction mixture was shaken to ensure thorough mixing and was allowed to stand at room temperature for 28 hours. The pyridine-chromium trioxide complex was then decomposed with water. The solution was made alkaline with aqueous sodium hydroxide and was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulphate, filtered and concentrated. The infrared spectrum of the residue in carbon tetrachloride solution showed bands at 1690 cm^{-1}, 1740 cm^{-1}; no band was observed near 3700 cm^{-1}. An attempt to sublime the reaction product at temperatures between 90-100°/0.05 mm was not successful.

C. Attempted Manganese Dioxide Oxidation of Lyconnotine (36)

(a) Preparation of Active "Manganese Dioxide A" (37)

A small quantity of manganous carbonate was placed in a porcelain dish and heated at 220-280° for about 18 hours with concurrent air circulation. The initially tan powder turned black and was allowed to cool in air.

(b) (i) Treatment of Lyconnotine with Manganese Dioxide in Carbon Tetrachloride

Active "Manganese Dioxide A" (20 mg) prepared as above was added to a solution of lyconnotine (2 mg) in carbon tetrachloride (2 ml). The reaction mixture was shaken in a test tube for 1/2 hour at room temperature. The filtered solution was concentrated. The infrared spectrum of the base (in CCl_4) exhibited bands at 3700 cm^{-1}, 1735 cm^{-1} and at 1660 cm^{-1} (small shoulder). Paper chromatography (pH 5.0) of the product showed one spot (R_f 0.49) which corresponded to that of lyconnotine.

(ii) Treatment of Lyconnotine with Manganese Dioxide in Benzene

A suspension of manganese dioxide (20 mg) in benzene (2 ml) containing lyconnotine (2 mg) was refluxed for a period of two hours. The manganese dioxide was removed by filtration and the solvent was taken off from the filtrate under reduced pressure. The infrared spectrum of the resulting material in carbon tetrachloride was in no way different from that of lyconnotine itself. A paper chromatogram of this product (pH 5.0) revealed one spot which corresponded to the reference alkaloid, lyconnotine.

Lyconnotine (2 mg) in benzene (2 ml) with excess manganese dioxide (40 mg) was refluxed for 5 hours. The reaction mixture was filtered off and the solvent from the filtrate was evaporated on a flash evaporator. The residue, dissolved in carbon tetrachloride, showed bands at 3700 cm^{-1},

1735-40 cm^{-1} and at 1660 cm^{-1} in its infrared spectrum. Paper chromatography showed one spot (R_f 0.50 at pH 5.0).

D. Treatment of Lyconnotine with Strong Base (sodium ethoxide in ethanol)

Metallic sodium (3 mg) was added to a solution of lyconnotine (2 mg) in ethanol (1 ml) and the reflux was continued for half an hour. The solution was cooled and most of the liquid was removed at reduced pressure. The residue was dissolved in water (2 ml) and the alkaloid material extracted with methylene chloride. The methylene chloride solution was dried over anhydrous sodium sulphate, filtered and evaporated to dryness.

The infrared spectrum of the resulting product in carbon tetrachloride solution exhibited no band at 3700 cm^{-1} but did show bands at 1735 cm^{-1} and at 1660 cm^{-1} (little shoulder). A small shoulder near 3050 cm^{-1} was also discernible.

4. Isolation of Acrifoline (26)

The material available for the isolation of acrifoline was a fraction from the mother liqor remaining after the crystallization of annotinine from the crude alkaloids of Lycopodium annotinum L.

The solvent (methanol) from this fraction was removed under reduced pressure and the viscous residue was dissolved in acetone. On addition of concentrated hydrogen bromide (48%) to the alkaloid solution a precipitate was

obtained. Further concentration of the mother liquor yielded another crop of crystals. Acrifoline hydrobromide thus obtained was thoroughly washed with acetone. The hydrobromide was dissolved in water, extracted with ether and the ether washings were rejected. The aqueous solution was basified with sodium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulphate. The filtered solution, on evaporation of the solvent, yielded acrifoline which had a brown tinge. The base was next dissolved in ether and refluxed for 5 minutes. The ether solution was quickly filtered through a cotton plug in a funnel. On evaporation of the solvent from the filtrate, chromatographically pure acrifoline was obtained.

5. Attempted Interrelation of Acrifoline to Lyconnotine by Photolysis of Acrifoline

(A) Preliminary Micro Scale Experiments

(a) Ultraviolet Irradiation of Acrifoline in a Quartz Test Tube (with no filter sleeve), in Methanol

A solution of acrifoline (15 mg) in methanol (20 ml) was irradiated for periods of 2 and 4 hours, in a quartz test tube with 2 mm thick walls. The test tube was held at a distance of approximately 2" from the outer side of the immersion well and irradiation was continued after exclusion of oxygen from the methanolic solution under a stream of nitrogen. A portion of the irradiated solution was concentrated to give a small residue whose infrared

spectrum showed bands at 3662 cm^{-1} and 1700 cm^{-1}. Paper chromatography (pH 5.0) of this material revealed the presence of one compound whose mobility was the same as that of acrifoline.

(b) Ultraviolet Irradiation of Acrifoline in a Thin-Walled Pyrex Test Tube (with Pyrex filter sleeve) in Methanol

Irradiation of acrifoline (10 mg) in methanol (10 ml) was carried out for a period of 12 hours in a thin-walled Pyrex test tube (approx. 0.2 mm thick walls), in the absence of oxygen. A Pyrex filter sleeve (approx. 2 mm thick walls) was used in the immersion well. The infrared spectrum and the paper chromatogram of the product did not show an appreciable change in acrifoline.

(c) Ultraviolet Irradiation of Acrifoline in Thin-Walled Pyrex Test Tube (with thin-walled Pyrex filter sleeve) in Methanol

A solution of acrifoline (10 mg) in methanol (10 ml) was irradiated in a thin-walled Pyrex test tube, using a thin-walled Pyrex filter sleeve (approx. 0.2 mm thick walls). The photolysis was continued for 12 hours in the absence of oxygen. From the paper chromatography and the infrared spectrum, largely the presence of unchanged acrifoline in the reaction mixture was revealed.

(d) Ultraviolet Irradiation of Acrifoline in a Thin-Walled Pyrex Test Tube (with Corex filter sleeve) in Methanol and Ether

Irradiation of acrifoline (5 mg) in methanol (10 ml), in the absence of oxygen was carried out, using Corex filter sleeve in the immersion well. The reaction mixture, after 5 hours of photolysis, showed bands at 3662 cm^{-1} and 1705 cm^{-1} in its infrared spectrum. Paper chromatography (pH 5.0) exhibited one spot corresponding to acrifoline. The 12-hour irradiated product exhibited no band in the hydroxyl region, originally present in acrifoline; a band at 1735 cm^{-1} instead was observed. A fresh sample of acrifoline was irradiated under the above conditions using acetophenone as photosensitizer; this however did not give any different results from those obtained without any acetophenone.

Acrifoline (6 mg) was dissolved in ether (10 ml) and the oxygen was removed from the solution under a slow stream of nitrogen, as before. The solution was irradiated with the ultraviolet light for 2 1/2 hours. The solvent from a portion of the irradiated solution was removed. The infrared spectrum of the residue in carbon tetrachloride exhibited weak bands at 1735 cm^{-1} and at 1775 cm^{-1} together with moderately intense bands at 1700 cm^{-1} and at 3660 cm^{-1}. A small shoulder at 1670 cm^{-1} was also discernible. Paper chromatography (pH 5.0) revealed the presence of three compounds with R_f values 0.20 (acrifoline), 0.44 (major pro-

duct) and 0.76 (minor product). The concentration of the unchanged acrifoline appeared to be quite great in this mixture.

A fresh sample of acrifoline (10 mg) in ether solution was irradiated for a period of six hours. The reaction mixture after removal of ether showed in its infrared spectrum bands at 1670 cm^{-1}, 1700 cm^{-1}, 1735 cm^{-1}, 1775 cm^{-1} and at 3660 cm^{-1}. Several spots of this mixture were applied on paper buffered to pH 5.0, along the base line and were allowed to develop for about 17 hours. Paper strips from the edges of the chromatogram were then cut and sprayed. On spraying the presence of three compounds including the unchanged acrifoline was revealed. Portions of the paper chromatogram from the unsprayed part, corresponding to the major product with R_f 0.44 were cut and eluted off with 1% hydrochloric acid. The acid solution was made basic and extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate and filtered. On evaporation of the solvent, the residue was dissolved in carbon tetrachloride and infrared spectrum was recorded which showed bands at 1735 cm^{-1}, 3660 cm^{-1} and a weak shoulder at 1670 cm^{-1}.

B. Small Scale Photolysis of Acrifoline

(a) Ultraviolet Irradiation of Acrifoline in an Outer Jacket (with no filter sleeve) in Methanol

Acrifoline (100 mg) in methanol (150 ml) was subjected to photolysis for a period of 4 hours with constant bubbling of nitrogen through the solution, contained in a specially designed jacket that could be directly fitted on to the immersion well. The jacket was also provided with a condenser, to prevent the loss of the solvent during photolysis. The infrared spectrum of the mixture showed among others, a band at 1740 cm^{-1}. Paper chromatography (pH 5.0) revealed the presence of at least six components in the mixture.

(b) Ultraviolet Irradiation of Acrifoline in an Outer Jacket (with thin-walled Pyrex sleeve) in Methanol

Acrifoline (100 mg) was dissolved in methanol (150 ml) and the solution was irradiated in an outer jacket, using a Pyrex filter sleeve (approx. 2 mm thick walls) in the immersion well. The irradiation was continued for a total of 18 hours with interruption of the reaction after 6, 12 and 15 hours. The progress of the reaction was followed by the infrared and paper chromatographic studies. Acrifoline did not seem to have undergone much change during this experiment.

(c) (i) Ultraviolet Irradiation of Acrifoline in an Outer Jacket (with Corex filter sleeve) in Ether

Irradiation of acrifoline (300 mg) in ether (150 ml) was carried out in the outer jacket, making use of the Corex filter sleeve (approx. 2 mm thick walls). The photolysis was allowed to proceed for a total period of 10 hours. Samples (0.5 ml) were withdrawn after 1 1/2, 6, 8 and 10 hours and their infrared spectra were recorded. The relevant bands of these spectra are summarized in Table I. Paper chromatography (pH 5.0) of these samples revealed the presence of six compounds. The most intense spot on paper chromatogram was that of the product with R_f value 0.44.

(ii) Separation of the Photoproduct of Acrifoline by Preparative Chromatography

The ether from the mixture of the photoproducts of acrifoline obtained in (c,i) above was removed; the material was dissolved in a small amount of methanol and was uniformly applied along the base line of 4 sheets of Whatman No. 3 MM paper buffered to pH 5.0. Care was taken not to put more than 80 mg of the mixture at a time on one sheet of paper. After allowing the chromatograms to develop for 14 hours, small strips of paper from the centre and the two edges were cut and sprayed with a modified Dragendorff's reagent.

The portions, from the unsprayed part of the chromatogram, corresponding to the compound with R_f value

TABLE I

Infrared Spectra of the Photoproducts of Acrifoline

(with Corex filter sleeve)

Period of Irradiation	Infrared Bands
1 1/2 hours	1700 cm^{-1} (very intense); 3660 cm^{-1}; 1735 cm^{-1} (weak); 1770 cm^{-1} (weak).
6 hours	1700 cm^{-1}; 1735 cm^{-1}; 1770 cm^{-1}; 3660 cm^{-1}. All bands were moderately intense.
8 hours	1700 cm^{-1} (weak); 1770 cm^{-1} (moderate); 1735 cm^{-1} (moderate); 3660 cm^{-1}.
10 hours	1700 cm^{-1} (weak); 1770 cm^{-1} (moderate); 1735 cm^{-1} (intense); 3660 cm^{-1}.

0.44 were eluted with 1% hydrochloric acid. The acid solution was well shaken with chloroform; the chloroform extract was rejected. The acid solution was then made basic with sodium hydroxide solution and the alkaloid content was extracted with chloroform. This solution was dried over anhydrous sodium sulfate and filtered. Infrared spectrum of the chloroform solution showed a band at 1735 cm^{-1}. The N.M.R. spectrum of the compound in deuterated chloroform showed three broad bands in the region τ 7.49-8.84.

6. Preparation of Dihydroacrifoline

A solution of acrifoline hydrobromide (500 mg) in water (30 ml) was hydrogenated at atmospheric pressure in presence of platinum oxide (50 mg). The catalyst was activated before placing the acrifoline hydrobromide solution in the hydrogenation flask. Required amount of hydrogen was taken up in an hour. After removal of the catalyst, from the hydrogenation product, the solution was basified and extracted with chloroform. Paper chromatography (pH 7.0) showed the presence of two compounds, the R_f values of which corresponded to those of authentic annofoline and dihydroacrifoline respectively. Almost 90% of the product appeared to be dihydroacrifoline. Dihydroacrifoline was separated from annofoline by preparative paper chromatography (for procedure see page 35). The dihydroacrifoline was purified by sublimation at 105-115°/0.05 mm.

7. Attempted Interrelation of Dihydroacrifoline to Lyconnotine by Photolysis of Dihydroacrifoline

A. Preliminary Micro Scale Experiments

(a) Ultraviolet Irradiation of Dihydroacrifoline in a Thin-Walled Pyrex Test Tube (with Corex filter sleeve) in Methanol

A solution of dihydroacrifoline (10 mg) in methanol (10 ml) was irradiated for 12 hours in all, in a thin-walled Pyrex test tube (approx. ·2 mm thick walls) with Corex filter sleeve (approx. 2 mm thick walls) in the absence of oxygen. The reaction was interrupted at time intervals of 2, 4, 6 and 9 hours respectively and a small amount of the solution was withdrawn from the reaction medium to measure the infrared spectra. After removal of the solvent the infrared spectra in carbon tetrachloride exhibited among others, a band at 1715 cm^{-1} which was not very intense, at time intervals of 2, 4, and 6 hours. Paper chromatography (pH 5.0) showed the 9- and 12-hour irradiated solution of dihydroacrifoline to be a mixture of six components.

(b) Ultraviolet Irradiation of Dihydroacrifoline in a Thin-Walled Pyrex Test Tube (with no filter sleeve) in Methanol

Dihydroacrifoline (10 mg) was dissolved in methanol (10 ml) and the solution was placed in a thin-walled Pyrex test tube. The contents in the tube were then irradiated in

the absence of oxygen with no filter sleeve in the immersion well, for a total of 6 hours. The reaction was interrupted after the lapse of 1/2 hour and 1 1/2 hours respectively and a small amount of the alkaloid solution was withdrawn to measure the infrared spectra which showed a band at 1715 cm^{-1}. Paper chromatography on the 6-hour irradiated solution of dihydroacrifoline revealed the presence of three compounds, one of which being the unchanged dihydroacrifoline.

(c) Ultraviolet Irradiation of Dihydroacrifoline in an Outer Jacket (with no filter sleeve)

Photolysis of dihydroacrifoline (15 mg) in methanol in an outer jacket was allowed to proceed for 4 hours, without placing any filter sleeve in the immersion well. Paper chromatography (pH 5.0) of the resulting oily material showed the presence of at least six components. Same reaction when carried out in the above experimental conditions, in ether, again yielded an oily material of many components even on irradiation for nearly 1/2 hour.

(d) Ultraviolet Irradiation of Dihydroacrifoline in an Outer Jacket (with Corex filter sleeve)

Dihydroacrifoline (18 mg) in ether solution, on irradiation for 4 1/2 hours, gave rise to a mixture of six components as revealed by paper chromatography. The photolysis of dihydroacrifoline was in this case allowed to proceed using a Corex filter sleeve. The infrared spectra, however, showed a band at 1715-20 cm^{-1} together with the other

characteristic bands of unchanged dihydroacrifoline.

Using the same filter sleeve, photolysis of dihydroacrifoline (20 mg) was carried out in methanol for 5 hours. This again resulted in a mixture of six products as shown by paper chromatography. A band at 1715-20 cm^{-1} was, however, discernible in the infrared spectrum of the photoproduct.

(e) Ultraviolet Irradiation of Dihydroacrifoline in an Outer Jacket (with Vycor filter sleeve) in Methanol

A solution of dihydroacrifoline (10 mg) was irradiated for 2 hours using Vycor sleeve and methanol as the solvent. The irradiation was carried out in the atmosphere of nitrogen; paper chromatography (pH 5.0) of this solution revealed the presence of six components.

(f) Ultraviolet Irradiation of Dihydroacrifoline in an Outer Jacket (with Pyrex filter sleeve) in Methanol

Dihydroacrifoline (16 mg) was dissolved in methanol (100 ml) and the solution was irradiated in the outer jacket used above. A Pyrex filter sleeve was used in the immersion well surrounding the lamp. The total period of irradiation was 6 hours but the reaction was interrupted at time intervals of 1/2, 1, 1 1/2 hours; the products at these intervals were not very much different and there appeared to be little change in dihydroacrifoline. The reaction mixture after

photolysis for 6 hours exhibited the presence of four compounds on paper chromatogram (pH 5.0); one of these components was the unchanged dihydroacrifoline.

The infrared spectrum of the 6-hour irradiated solution exhibited a band at 1715-20 cm^{-1} in carbon tetrachloride solution, in addition to the bands of dihydroacrifoline.

B. (a) Small Scale Photolysis of Dihydroacrifoline in an Outer Jacket (with Pyrex filter sleeve) in Methanol

Dihydroacrifoline (400 mg) was irradiated in methanol in an atmosphere of nitrogen for 6 hours using the outer jacket. The actual irradiation was carried out in two batches of 200 mg of the alkaloid in 150 ml of methanol. A Pyrex filter sleeve was placed in the immersion well.

The reaction mixture showed the presence of four compounds on paper buffered to pH 6.0 having R_f values 0.22 (dihydroacrifoline), 0.35, 0.41 and 0.68.

The infrared spectrum of the mixture exhibited a band at 1715-20 cm^{-1} in carbon tetrachloride solution.

(b) Separation of the Photoproduct of Dihydroacrifoline by Preparative Paper Chromatography

On the basis of the intensity of the various photoproducts on paper chromatogram, the amount of the compound with R_f 0.35 appeared comparatively greater than the others.

This product was isolated by preparative chromatography using 4 sheets of Whatman No. 3 MM paper (for procedure see page 35).

The alkaloid material isolated from paper was sublimed at 100-110°/0.05 mm. The sublimate was used for infrared and nuclear magnetic resonance spectra.

(c) I.R. and N.M.R. Spectra of the Photoproduct of Dihydroacrifoline

The infrared spectrum of the main photoproduct showed a band at 1715-20 cm^{-1} in carbon tetrachloride solution.

The N.M.R. spectrum in deuterated chloroform exhibited bands at τ 0.5 and τ 4.18. The signal of the methyl group originally present in dihydroacrifoline was missing from the spectrum of the photoproduct.

8. Isolation of the Lactone Alkaloid

It may be recalled that the contents of tubes 4-12 from the countercurrent distribution were subdivided into two fractions A and B. While lyconnotine was isolated from the fraction A, fraction B stood at room temperature for about a year (see page 25).

Fraction B was concentrated to a syrup which was dissolved in methylene chloride three times and evaporated. The syrup was then taken up in a minimum quantity of methylene chloride and put uniformly on a column (12 mm internal diameter) of basic alumina (15 gm). The column was eluted

with methylene chloride and fractions (10 ml each) were examined by paper chromatography (pH 5.0). Fractions 1 to 60 from the column showed the presence of one component with R_f value 0.40. Fraction 61 showed the presence of the other component whose mobility was the same as that of Acrifoline (R_f 0.21). Fractions 1-60 were combined and concentrated to give pale crystals. Sublimation of the pale crystals at 110-120°/0.05 mm yielded a white crystalline product, m.p. 230°.

A sublimed sample of this product was used for elementary analysis.

Calc. for $C_{16}H_{21}O_2N$: C,74.10%; H,8.16%; N,5.40%

Found : C,73.95%; H,8.34%; N,5.94%

The infrared spectrum of this compound in carbon tetrachloride showed a band at 1735 cm^{-1} (intense) and small humps at 1665-60 cm^{-1} and 3100 cm^{-1}. Two distinct bands near 2900 cm^{-1} were also observed in this spectrum.

The N.M.R. spectrum of the lactone was recorded in deuterated chloroform. It showed among other bands, a multiplet near τ 4.2, and a doublet at τ 8.81. The de-coupling experiments on the lactone were also performed.

DISCUSSION

1. Isolation of Lyconnotine

Lyconnotine, first isolated by Khan (2) of this laboratory in 1959, is found in very small amounts in the crude alkaloids of Lycopodium annotinum L. From the previous countercurrent distribution studies using the system chloroform-buffer of pH 7.0, it was known that these Lycopodium alkaloids under these conditions could be divided into three classes: alkaloids with partition coefficient much greater than unity, alkaloids with partition coefficient near to unity and finally alkaloids with partition coefficient much smaller than unity. Lyconnotine was isolated from the second category above, employing successive countercurrent distributions.

A middle fraction from a previous countercurrent distribution experiment, with the system chloroform and buffer of pH 7.0 on alkaloids of Lycopodium annotinum L., was expected to contain lyconnotine and was available to the author. This particular fraction was subjected to a second countercurrent distribution in a 60-tube Craig's machine (35) with the system chloroform and buffer of pH 7.0 with buffer as the moving phase. Analysis of the contents of the various tubes was carried out by paper chromatography and infrared spectroscopy which revealed the presence of lyconnotine in tubes 4-12. The contents of tubes 13-60 were found by paper chromatography to be mixtures of bases and

were not investigated any further. The infrared spectra (in carbon tetrachloride) of material from tubes 4-12 showed bands at 3700 cm^{-1} and 1735-40 cm^{-1} for the hydroxyl and the carbonyl groups respectively.

Paper chromatography revealed that the material of tubes 4-12 contained lyconnotine and acrifoline together with a trace amount of some other alkaloid. Khan (2) had reported earlier the isolation of lyconnotine directly from a fraction of the countercurrent distribution on a different batch of alkaloids; a number of recrystallizations had to be done in order to obtain the base in sufficiently pure form and this also might have been responsible for the very small quantity of lyconnotine obtained by Khan. It was therefore considered desirable to affect the separation of lyconnotine from acrifoline on an alumina column. The alkaloid mixture of tubes 4-12 was divided into two equal portions which were designated as fractions A and B. The fraction A was utilized for the isolation of lyconnotine employing the alumina chromatography while the fraction B stood in methanol at room temperature for about a year. During this period in fact, some experiments on lyconnotine were carried out and an attempt was made to interrelate lyconnotine with acrifoline and dihydroacrifoline and this will be discussed later in this section. Lyconnotine obtained from the alumina column was free from acrifoline as shown by paper chromatography and was crystallized from ether. However, crystallization with ether resulted in a brownish product

that was further purified by sublimation at 100-110°/0.05 mm. On resublimation, a white crystalline product, m.p. 118-119° was obtained.

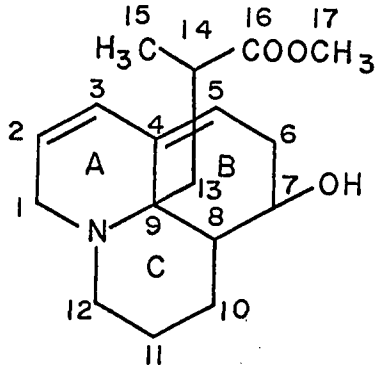
2. Isolation of the Lactone Alkaloid from Lyconnotine

Since the amount of lyconnotine obtained initially from the fraction A of tubes 4-12 (from the countercurrent distribution) was small and was almost exhausted in carrying out a few experiments, it was decided to isolate a further quantity of the base from the fraction B that had been kept at room temperature in methanol solution for about a year.

Surprisingly enough, the alkaloid obtained from the fraction B on alumina chromatography, showed entirely different physical properties from those of lyconnotine. The procedure for the isolation of the alkaloid from the column was exactly the same as that used for lyconnotine. The base from the fraction B was obtained in crystalline form even on evaporation of the solvent from the eluant from the column. Apart from its being much more readily crystallizable than lyconnotine, the alkaloid had a different m.p., and showed different infrared and N.M.R. spectra. As will be seen in the next section, that alkaloid has been proved to be a lactone derived from lyconnotine. Further purification of the lactone was accomplished by sublimation at 110-120°/0.05 mm. The sublimate melted at 230°.

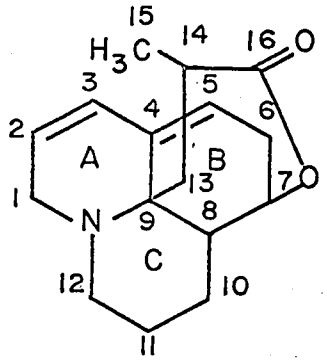
3. The Structure of Lyconnotine

Khan (2) proposed that lyconnotine m.p. 117-118° had the molecular formula $C_{17}H_{25}O_3N$; while the alkaloid analyzed correctly for C and H, the nitrogen content was low. The pK_a of the base was found to be 8.2. The infrared spectrum of lyconnotine showed the presence of a hydroxyl and a carbonyl group (bands at 3662 cm^{-1} and 1740 cm^{-1} respectively). The former absorption band was correctly assigned by Khan to a hydroxyl group but the latter band was erroneously attributed to a lactone group in the molecule. Khan also observed that lyconnotine on treatment with aqueous sodium hydroxide gave a compound that melted at 209-210°; this compound had no hydroxyl group although the carbonyl band was still observed at 1740 cm^{-1} in the infrared spectrum. These observations led Khan (2) to believe erroneously that lyconnotine was a lactone which on treatment with alkali was converted into a sodium salt and that the latter was converted into another lactone (m.p. 209-210° above) with concurrent dehydration of lyconnotine. As a result of our investigations, on lyconnotine, however, obtained from the fraction A of tubes 4-12 and on the derived lactone from lyconnotine, isolated from fraction B, it has been possible to establish their structures on a firm basis. From what follows, it will become evident that the structures I and II below, as proposed by us, could indeed be assigned to lyconnotine and to the derived lactone respectively.



I

Lyconnotine



II

Lactone from Lyconnotine

A. Presence of a Hydroxyl Group, a Carbonyl Group and Conjugated Double Bonds

The infrared spectrum of our lyconnotine sample in carbon tetrachloride (Figure 4, page 49) showed the presence of a hydroxyl group, a carbonyl group and of unsaturation in the molecule as revealed respectively by the bands at 3700 cm^{-1}, 1735-1740 cm^{-1} and 1655 cm^{-1} (small shoulder). A shoulder near 3050 cm^{-1} was also discernible for unsaturation in this spectrum.

In order to establish the presence of unsaturation, catalytic hydrogenation (1/2 hour) of lyconnotine was carried out in the presence of Adams catalyst. The hydrogenation, followed by paper chromatography (pH 7.0) revealed the presence of two compounds with R_f values 0.92 and 0.73

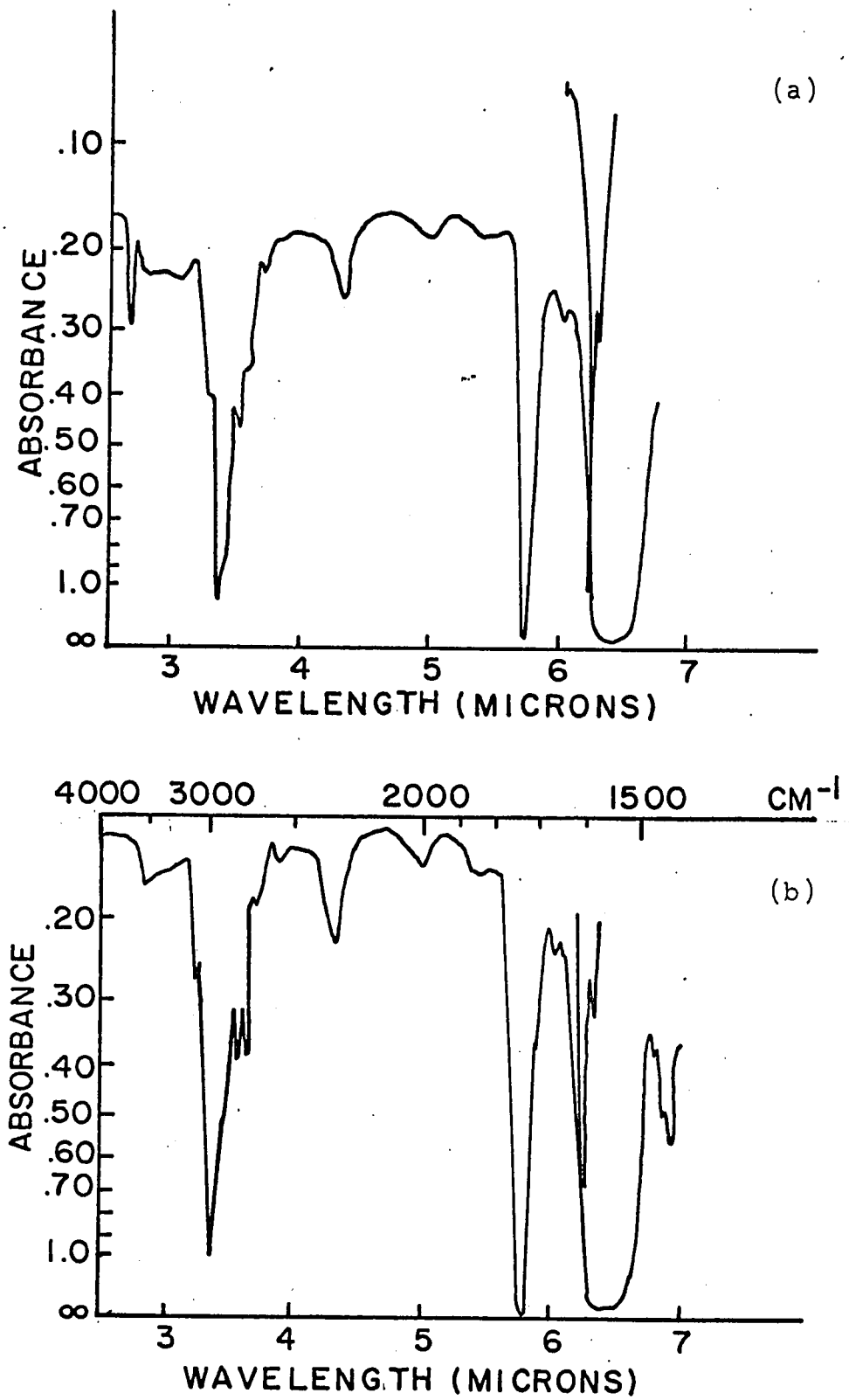


Figure 4 Partial infrared spectra in carbon tetrachloride solution: (a) lyconnotine; (b) the lactone from lyconnotine

respectively (R_f value of lyconnotine 0.85). This was taken as a probable indication of the presence of two double bonds which presumably did not reduce at the same rate and this could lead to a dihydro and a tetrahydro derivative of lyconnotine. This received further support from the fact that hydrogenation when continued for a longer time (6 hours) resulted in only one spot (R_f 0.66) on paper impregnated with buffer of pH 5.0 (R_f of lyconnotine 0.50). Due to the lack of material at our disposal, however, the isolation and characterization of these dihydro and tetrahydro derivatives were not pursued.

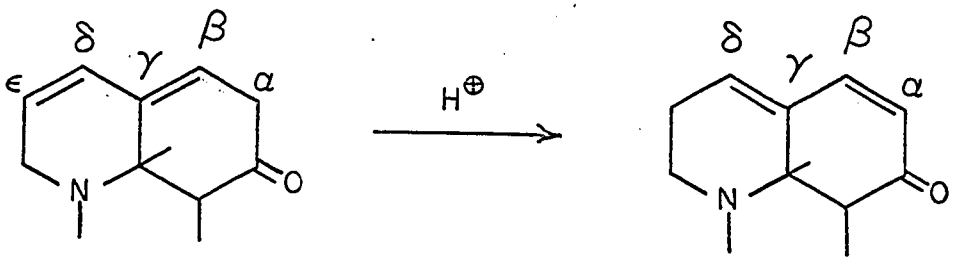
The ultraviolet spectrum of lyconnotine showed maximum absorption at 234.5 mμ (ϵ 18,000). This has been taken as an evidence of the presence of two double bonds which do not exist in the same ring, in lyconnotine. This conclusion was arrived at because steroid dienes containing the two ethylenic linkages in the same ring (usually in ring B) are known (39) to absorb in the region of 260-285 mμ; such dienes are known as homoannular and have low extinction coefficient (5000-15,000). On the other hand if conjugation is distributed over more than one ring, the absorption band is found at lower wavelengths (220-250 mμ); such dienes are referred to as heteroannular and have high extinction coefficient (14,000-28,000). Thus cyclic dienes fall into two groups depending upon whether the double bonds are in the same ring (homoannular) or in two rings (heteroannular). Woodward (40) analyzed the data on absorption spectra of

dienes and has shown that each exocyclic location produces a shift of 5 mμ in the direction of longer wavelength and that each alkyl group or ring residue linked to any of the four carbon atoms of the diene system also produces a bathochromic shift of 5 mμ. This empirical rule, often known as Woodward's Rule, has been of value in the elucidation of organic structures. An average value of 214 mμ has been arrived at (39) as the wavelength of absorption of a hypothetical parent heteroannular steroid diene with no exocyclic bonds and no substituents. In lyconnotine, ring residues extending to unsaturated C_2 from C_1, to C_4 from C_9 and to C_5 from C_6 count as a total of three alkyl substituents and since 4,5 double bond is exocyclic, the calculated maximum is 214 + (3x5) + 5 = 234 mμ (see page 48). This calculated value is in excellent agreement with the observed maximum absorption of 234.5 mμ in lyconnotine.

B. Oxidation of Lyconnotine

The nature of the hydroxyl group in lyconnotine was established by carrying out oxidation with chromium trioxide in pyridine. The reaction product exhibited bands at 1740 cm^{-1} and at 1690 cm^{-1} but no band in the hydroxyl region. The band at 1690 cm^{-1} in the infrared spectrum indicated the presence of an α , β -unsaturated ketone in a six membered ring (49). The observation was consistent with the presence of a secondary hydroxyl group in lyconnotine. The characteristic band of an α , β -unsaturated

ketone was initially misleading in the sense that the hydroxyl group was considered to be allylic to the double bond in ring B (see page 48). It was shown (36) earlier that allylic hydroxyl groups could be oxidized by active manganese dioxide in neutral media although oxidation of saturated alcohols could be also expected (37,38) at a slower rate. Attempts were therefore made to oxidize lyconnotine in carbon tetrachloride and benzene solution separately using excess manganese dioxide so as to be able to establish the allylic nature, if any, of the hydroxyl group. A lyconnotine suspension with manganese dioxide in carbon tetrachloride on shaking (1/2 hour) at room temperature was not oxidized. Similarly, no change in lyconnotine was observed even on refluxing lyconnotine solution in benzene in the presence of manganese dioxide for 5 hours. This observation was therefore taken as indirect evidence that the hydroxyl group was homoallylic. The production of the α , β-unsaturated ketone as a result of chromium trioxide oxidation of lyconnotine could be rationalized in terms of the isomerization of the double bond from the β , γ - to the α , β - and the δ , ϵ - to the γ , δ - positions as shown on the following page.



Isomerization of the ketone from lyconnotine (partial structures)

Indeed, the homoallylic nature of the hydroxyl group in lyconnotine has been further confirmed from the double resonance experiments on the derived lactone; this will be discussed later in the present section.

Lack of a sufficient quantity of lyconnotine prevented any attempts to isolate the oxidation product for further investigation.

C. Treatment of Lyconnotine with Base

The reaction product of lyconnotine obtained on treatment with sodium ethoxide in ethanol did not show a hydroxyl band in the infrared spectrum while the carbonyl frequency was observed at 1735 cm^{-1}. This was attributed to the formation of the lactone as a result of loss of a molecule of methanol from lyconnotine although lactones are known to open up in basic media. However, due to the very small amount of lyconnotine at our disposal, this product was not isolated on a larger scale for further characterization.

D. The N.M.R. Spectrum of Lyconnotine

The N.M.R. spectrum of lyconnotine is shown in Figure 5 (page 55). It exhibited, among others, bands of area equivalent to nearly three protons in the olefinic region, and a doublet at τ 8.93 (J 6 c.p.s.) which was compatible with the CH-CH_3 group. A single sharp peak of area equivalent to 3 protons at τ 6.41 was also observed and this could be assigned to the protons of the methyl group in the carbomethoxy group. The N.M.R. evidence is, therefore, consistent with the other facts observed. The carbonyl absorption in the infrared spectrum of lyconnotine could readily be explained now and could be attributable to the methyl ester group. Similarly, the presence of the three olefinic protons as indicated by the N.M.R. spectrum could also be accommodated by the proposed structure I for lyconnotine (page 48).

E. The Mass Spectrum of Lyconnotine

The mass spectrum not only confirmed the molecular weight of the alkaloid to be 291 but also gave further invaluable information regarding its structure. The fragmentation pattern formulated for lyconnotine, is borne out by the peaks obtained in the mass spectrum, and is shown in Figure 6 (page 56). In this fragmentation scheme, we have followed the recently proposed convention (41); the usual arrow denotes a two-electron shift while a fish hook implies one-electron shift.

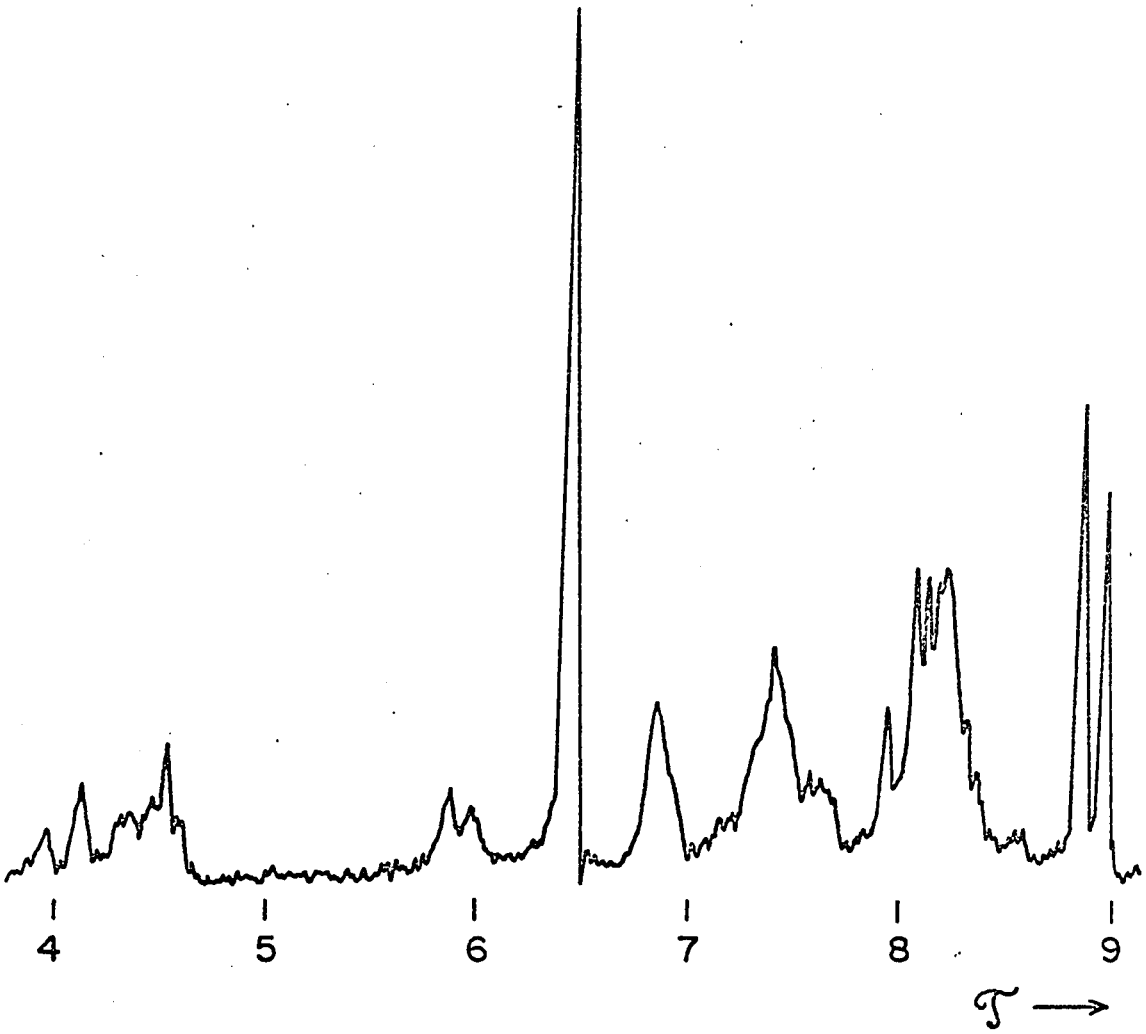


Figure 5. The N.M.R. spectrum of lyconnotine in deuterated chloroform

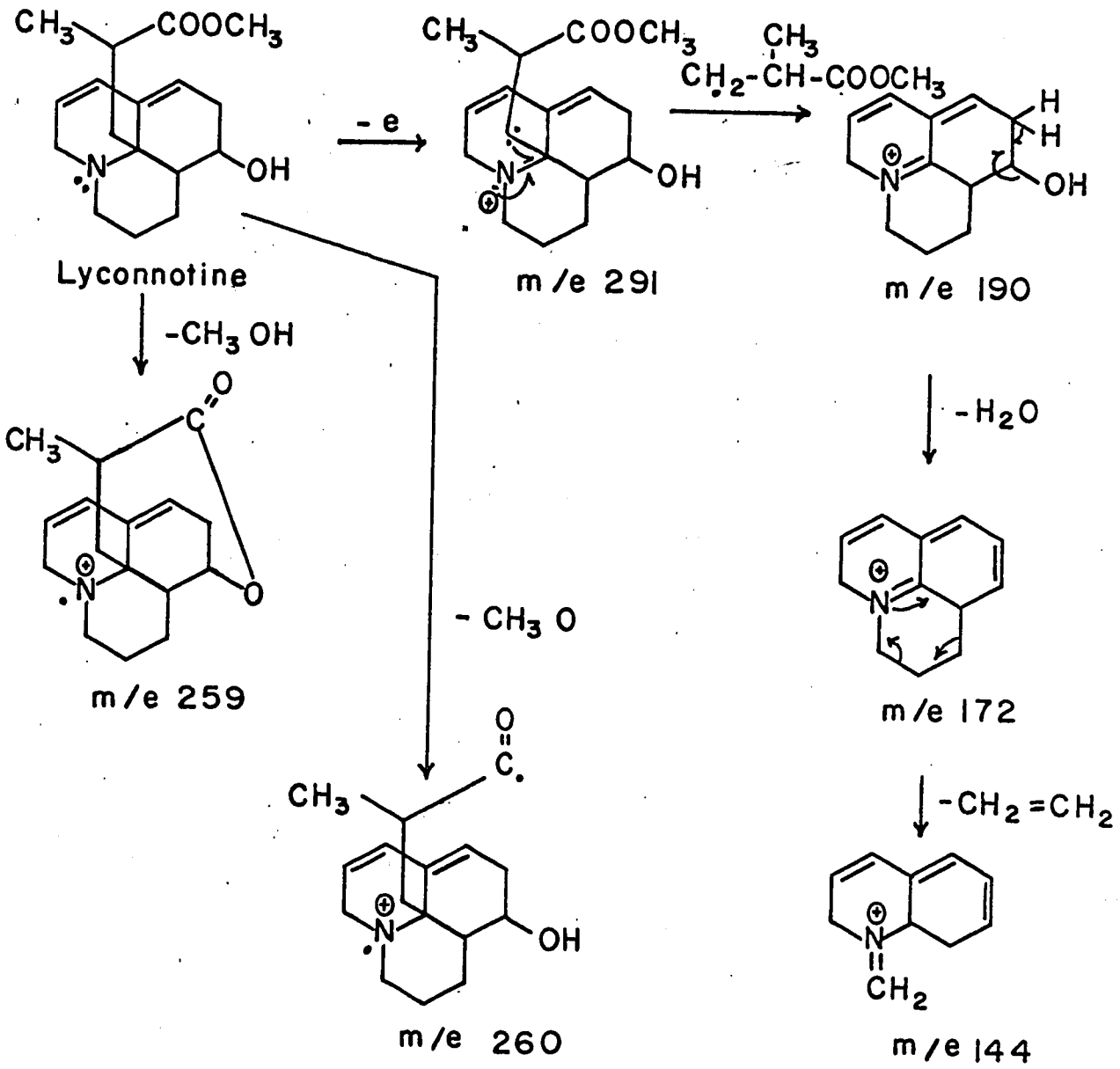


Figure 6. Fragmentation pattern of lyconnotine

In the mass spectrum of lyconnotine, intense peaks at m/e 291 and at 190 were observed. Whereas the peak at m/e 291 could be attributed to the main molecular ion, the peak at 190 would nicely account for loss of the entire chain comprising of $CH_3-O-\overset{O}{\overset{\|}{C}}-CH\begin{matrix}CH_3\\ \diagdown\\ CH_2\end{matrix}$.

The spectrum also showed peaks at m/e 172, and at 144 and these could be explained by the loss of molecules of water and ethylene, respectively. There was also evidence for the production of fragments of mass 259 and 260 which is in accordance with the loss of CH_3OH and CH_3O fragments. The peak at m/e 259 could be accounted for by the thermal cyclization of lyconnotine to the lactone.

It is believed that loss of an electron from the nitrogen atom of lyconnotine results in the formation of an ion radical (m/e 291) which is stabilized with the fission of a C-C bond resulting in the loss of the side chain to yield an ion of mass 190.

The fragmentation scheme presented in Figure 6 is also consistent with the one proposed recently by MacLean (3) for the alkaloids of Lycopodium of known structures.

The mass spectrum of lyconnotine also gives a clue with regard to the formation of the lactone alkaloid as is evidenced by a peak at m/e 259. Indeed, this lactone has been isolated from the fraction B of the tubes 4-12 of the countercurrent distribution as mentioned earlier. The lactone $C_{16}H_{21}O_2N$, m.p. 230°, analyzed correctly for C and H, although the nitrogen content was slightly on the high side. Since the

lactone was isolated from the same fraction of the counter-current distribution (i.e. tubes 4-12 of c.c.d.) from which lyconnotine was isolated under identical elution chromatographic conditions, it must be derived from lyconnotine. This observation is rather surprising because one would normally expect the equilibrium in the methanolic solution of lyconnotine to be shifted toward the lyconnotine side rather than toward the lactone side. This, however, could be explained only by assuming the geometry of lyconnotine to be very favorable for the formation of the lactone. In fact this point has been of some help in deducing the relative stereochemistry of lyconnotine. That the above lactone was derived from lyconnotine and that it had the structure II (page 48) was further supported by its infrared spectrum (Figure 4b on page 49) which did not show any absorption in the hydroxyl region; an intense band at 1735 cm^{-1} was compatible with the carbonyl absorption in a seven-membered lactone.

F. The N.M.R. Spectrum of the Lactone Alkaloid

The N.M.R. spectrum of the lactone derived from lyconnotine in deuterated chloroform is shown in Figure 7 (page 59). The spectrum is consistent with the proposed structure II for the lactone. Since the various protons in the molecule have different chemical environments, they will be expected to have different chemical shifts which is actually observed in the spectrum. The low field bands in

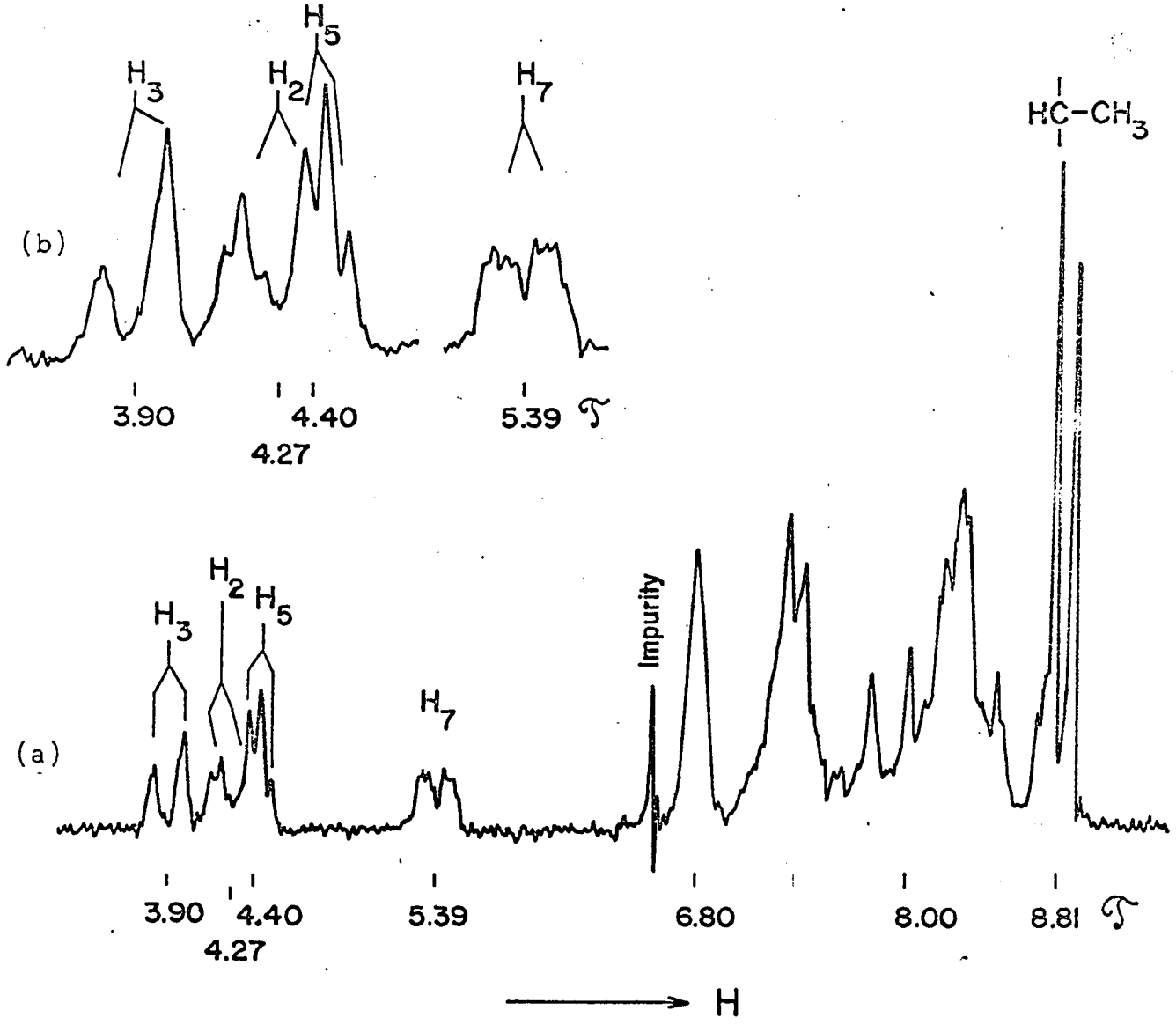


Figure 7. (a), The N.M.R. spectrum of the lactone in deuterated chloroform

(b), Slow sweep spectrum of H_3, H_2, H_5 and H_7 of the lactone

the olefinic region (τ 3.9 to 4.4) of the spectrum have been assigned to protons at C_3, C_2 and C_5 respectively. From a consideration of the effect of deshielding exerted by the lactone grouping, the octet of area equivalent to one proton is attributed to the proton on C_7. From a similar consideration, the protons on C_1 are considered to be represented by the band at τ 6.80 as these protons are on the carbon α to the nitrogen atom. The band at τ 8.81 is consistent with the environment of the protons of the methyl group and it is a doublet because of the coupling with the proton on C_{14} (J 6.4 c.p.s.). Thus it may be concluded that methyl group in the lactone is present as the $CH\text{-}CH_3$ group. The rest of the bands in the region of τ 7.35 to τ 8.47 account for the remaining protons in the molecule.

The olefinic region of the spectrum of the lactone shows lines of area equivalent to approximately three protons at τ 3.9, 4.27 and 4.4 and these are consistent with the environment of the protons on C_3, C_2 and C_5 respectively. The protons on C_3 and C_2 comprise an AB system and therefore an AB quartet is expected to arise. The complete quartet is not visible in the spectrum, instead only the low field component of the quartet is observed. This is because of the fact that the high field component of the quartet (from H_2) is superposed on the bands of the proton on C_5 as the protons on C_2 and C_5 are not very much chemically shifted from each other. From the low field component of the quartet attribu-

table to proton on C_3, it is observed that the coupling constant J is equal to 10 c.p.s. The proton on C_5 will be expected to couple with the two protons on C_6 and therefore a triplet of relative intensity 1:2:1 will be expected here. Indeed the spectrum shows a band at τ 4.4 which is very roughly a triplet (J=4 c.p.s.) but the relative intensity of the band is not in the ratio of 1:2:1. This is because of the fact that high field component of the quartet is superposed at least in part on the signal of proton at C_5. These observations therefore indicate the presence of the sequence $CH_2-\overset{H}{C}=C-\overset{H}{C}=C-H$ in the lactone. In the slow sweep spectrum of the olefinic protons (Figure 7b, page 59) the low field component of the quartet arising from the proton on C_3 shows a further splitting of 1.6 c.p.s. and this may be rationalized as being due to the coupling of a proton at C_3 with the protons on C_1. The line of the high field component of the quartet which is not superposed on the signal of the proton on C_5 appears as a triplet with a spacing of 3.4 c.p.s. This splitting of 3.4 c.p.s. is attributed to the coupling of a proton on C_2 with the protons on C_1. A single sharp line will be normally expected for the methylenic protons on C_1 provided the chemical shift of these two protons is almost the same. In the present situation, the signal of the protons on C_1 might be expected to be a quartet with unequal splittings of 3.4 and 1.6 c.p.s. because of the coupling of the methylenic protons with the protons on C_2 and the proton on C_3 respectively. However, since the line width of this band

at half height is 6.44 c.p.s., the quartet cannot be seen and a broad band in the spectrum for the protons on C_1 is observed. The broad signal for the methylenic protons on C_1 is attributed to the fact that the chemical shift of the two protons, although fairly close, is not quite the same.

The proton on C_7 appears in the beginning as a quartet centered at τ 5.39 in the N.M.R. spectrum (Figure 7a) but its slow sweep spectrum (Figure 7b) shows it to be an octet with splitting of 8.3, 3.1 and 1.8 c.p.s. The large, medium and small couplings of the proton on C_7 have been explained in terms of the Karplus relationship (46) of the dihedral angle and the coupling constant. This relationship is very helpful in determining the gross stereochemical relationship in that the magnitude of the vicinal coupling is known to vary from a maximum of 0 and 180° to a minimum at 90°. A model of the lactone shows that the dihedral angle defined by the planes $H_7C_7C_6$ and H_6 (quasiequatorial) C_6C_7 is about 30° while the one between the planes of $H_7C_7C_6$ and H_6 (quasiaxial) C_6C_7 is nearly 120°. In view of this observation the large splitting of 8.3 c.p.s. is considered to be due to the coupling of the proton on C_7 with the quasi-equatorial proton on C_6 and the small coupling of 1.8 c.p.s. is attributed to the coupling of the proton on C_7 with the quasiaxial proton on C_6. From a similar consideration, the splitting of 3.1 is concluded to be due to the coupling of H_7 with H_8.

The N.M.R. spectrum of the lactone does not show any signal for the methyl protons of the carbomethoxy group, which is observed in the spectrum of lyconnotine at τ 6.41, further affording evidence for the lactone formation.

G. Double Resonance (45) Spectra of the Lactone Alkaloid

Further support with respect to the assignments of the various bands to the respective protons was lent by the double irradiation experiments on the lactone alkaloid. From the decoupled spectra of H_3 and H_2 (Figure 8b, page 64) it can be seen that irradiation of the signal of the protons on C_1 in the region τ 6.82-6.85 results in sharpening of the lines of protons on C_3 (Figure 8b) and C_2 (Figure 8c), giving rise to a simple AB quartet. The irradiation of protons on C_1 does not affect the band of the proton on C_5 to an appreciable extent. This conclusively proves that the protons on C_3 and C_2 are coupled with the protons on C_1 and that these couplings are removed on irradiation of the band of the latter. Thus the presence of the sequence $>N-CH_2-CH=CH$ in the lactone is concluded.

Irradiation of the protons on C_6, over a range of frequencies centered on τ 7.3 led to only a partially collapsed signal of H_5 which was originally a triplet (Figure 8b). This means, then, that the two protons on C_6 have different chemical shifts and that their mean position is about τ 7.3. This difference of the chemical shift of the protons on C_6 has been attributed to the magnetic

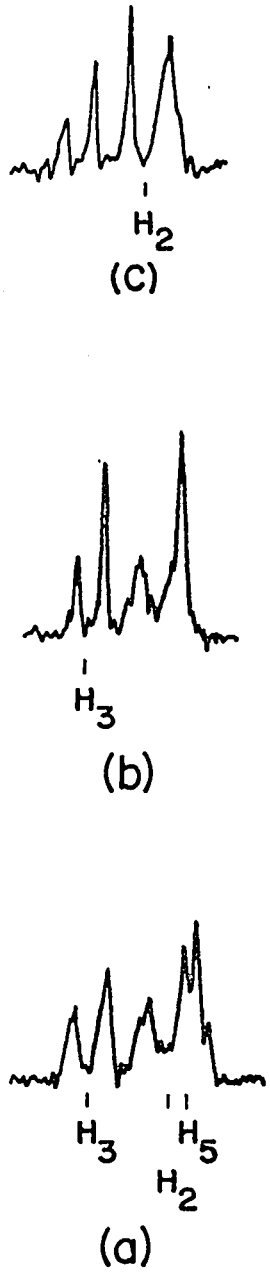


Figure 8. The N.M.R. signals of H_3, H_2 and H_5 of the lactone: (a), the undecoupled bands; (b), the decoupled signal of H_3 and partially decoupled signal of H_5; (c), the decoupled signal of H_2

anisotropy of the lactone group. It seems probable that the quasiequatorial proton on C_6 is shifted to low field while the quasiaxial proton is shifted to high field. This implies that the quasiequatorial proton probably lies in the plane of the lactone group while the quasiaxial proton on C_6 is below the plane of the lactone group and hence will be shifted up field. The proton on C_7 (i.e. H_7) in the lactone gives rise to an octet having large, medium and small splitting of 8.3, 3.1 and 1.8 c.p.s. respectively, as mentioned earlier. Figure 9 (page 66) shows that the medium coupling of H_7 which is attributed to the proton on C_8, is removed on irradiation at τ 7.95 giving rise to a rough quartet for H_7. This implies that the chemical shift of the proton on C_8 is τ7.95 which is consistent with its environment in the lactone molecule. The octet of H_7 could also be collapsed to a broad singlet on irradiation at τ 6.97 as a result of the disappearance of the larger coupling of 8.3 c.p.s. For this purpose, the mean irradiation frequency of the spectra (d) and (e) in Figure 9 was taken to be the correct one. Since it is probably the quasiequatorial proton on C_6 that is responsible for the larger coupling, the chemical shift of this proton must be τ 6.97 as indicated by the double irradiation of the signal of H_7. This is consistent with the Karplus relationship of dihedral angle and coupling constant as mentioned earlier. That the proton on H_7 is not allylic is confirmed by the fact that irradiation of the vinylic protons does not produce any change in the band of H_7.

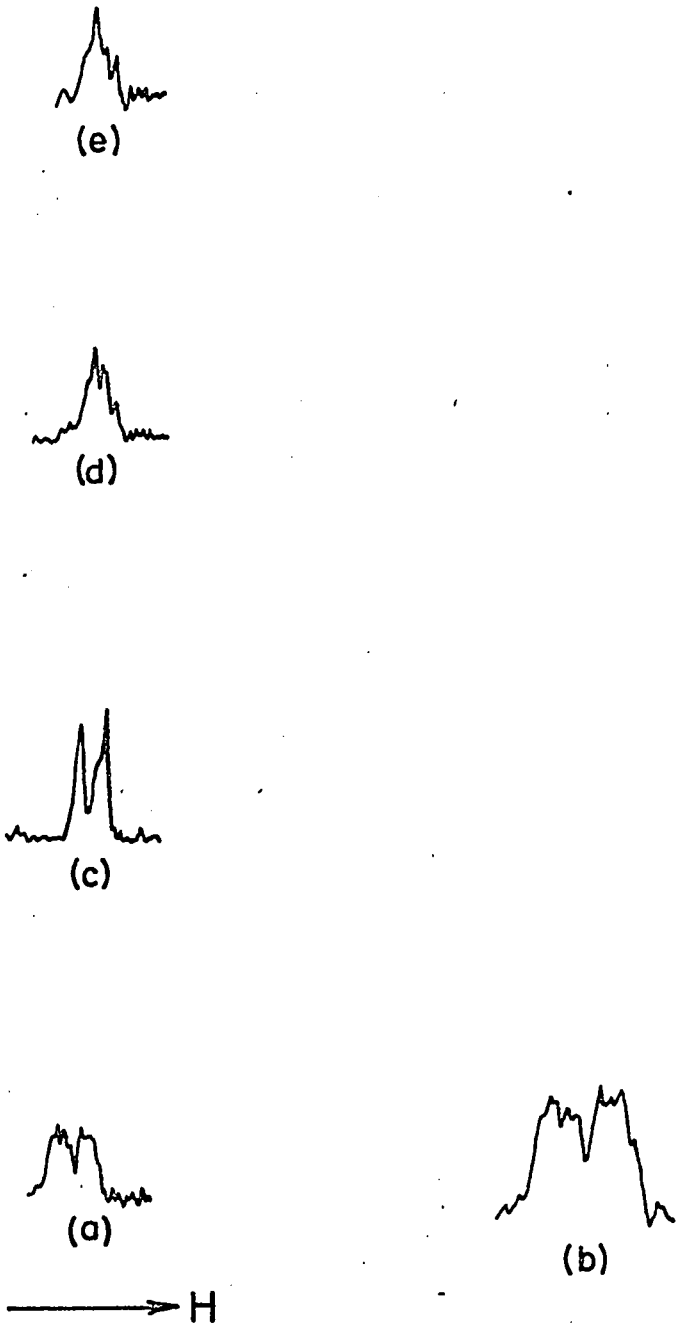
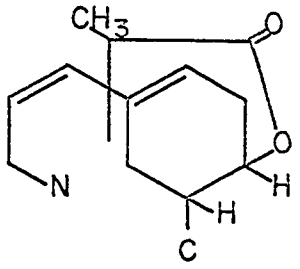


Figure 9. The N.M.R. signals of H_7 of the lactone: (a), and (b), the undecoupled signals; (c), (d), and (e), the decoupled signals

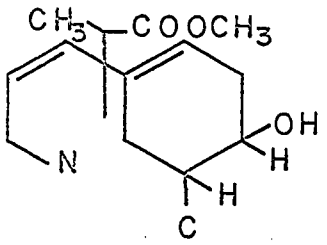
This therefore also proves the homoallylic nature of H_7 in the lactone and hence the homoallylic nature of the hydroxyl group on C_7 in lyconnotine.

The methyl group in the N.M.R. spectrum of the lactone appears as a doublet because it is coupled with a proton on C_{14}. This shows the presence of the grouping $>CH\text{-}CH_3$ in the lactone. The doublet of the methyl protons could be collapsed into a singlet on irradiation at τ 7.37 (Figure 10, page 68). Thus the chemical shift of H_{14} must be τ 7.37. The low chemical shift of this proton is compatible with its environment as it would be deshielded by the lactone group adjacent to C_{14}.

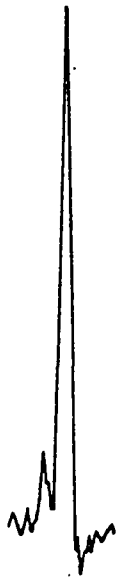
The N.M.R. data presented above therefore establishes the presence of the partial structure III in the lactone and hence structure IV in lyconnotine.



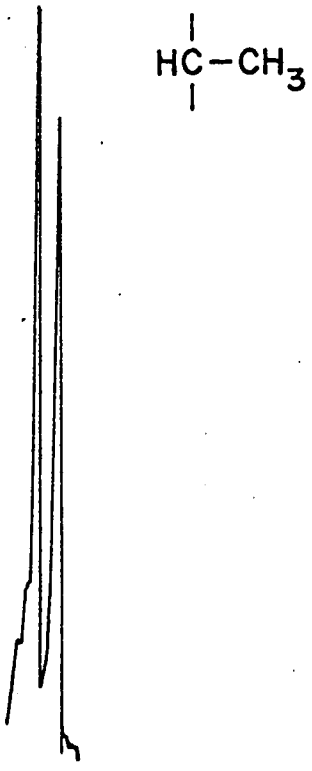
III



IV



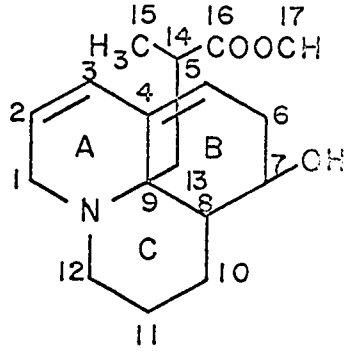
(b)



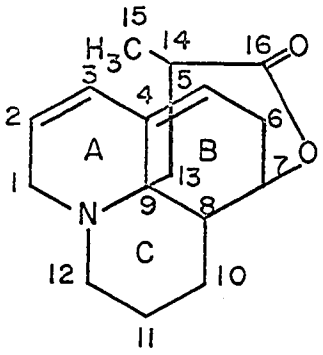
(a)

Figure 10. The N.M.R. signals of the methyl group of the lactone: (a), the undecoupled signal; (b), the decoupled signal

The mass spectral evidence in support of the structures I and II for lyconnotine and the derived lactone respectively has already been presented which proves beyond any doubt the presence of the hydrojulolidine skeleton and an ester side chain in lyconnotine. The infrared spectrum of lyconnotine and the lactone together with some chemical evidence presented earlier lends support to these structures. In view of the foregoing, therefore, the following structures for lyconnotine and the lactone have been proposed:



Lyconnotine



Lactone from Lyconnotine

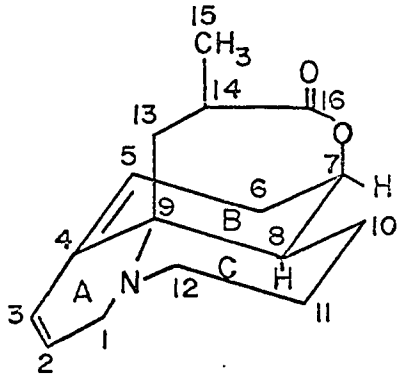
After the completion of this work, it was found that Valenta and co-workers (43) had also been engaged in the structural elucidation of lyconnotine. As a result of their studies, these workers have also arrived at the same structure for lyconnotine. The above structure of lyconnotine is therefore rigorously established (48) which receives further support from the synthesis of lyconnotine transformation products achieved recently by Valenta and co-workers (47).

4. Stereochemistry of Lyconnotine and of the Lactone Alkaloid

On the basis of the physical and chemical evidence, structures I and II for lyconnotine and the derived lactone respectively were established. However, the relative configuration at C_7, C_8, C_9 and C_{14} was still undecided.

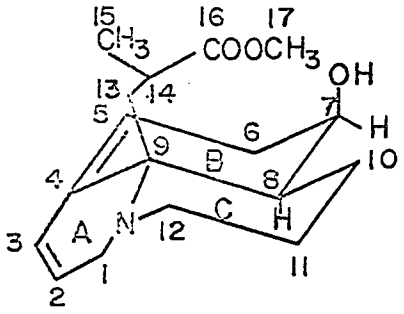
The relative stereochemistry at C_7, C_8 and C_9 in lyconnotine was deduced as follows:

Since lyconnotine gave rise to a lactone alkaloid with the loss of a molecule of methanol, the configuration of the derived lactone is believed to be represented by structure V on the following page. It can be seen that the relative configurations at C_7 and C_9 have to be cis to allow the formation of the lactone. The rings B and C are trans fused, a fact which is supported by the infrared spectrum of the lactone. Two Bohlmann bands in the region near 2900 cm^{-1}, characteristic of trans fused quinolizidine ring system (42) were exhibited in the infrared spectrum of the lactone. This is also consistent with similar observation of Valenta (43) on the tetrahydrolactone. Thus it is only the configuration V that satisfies these observations. The configuration at C_{14} could not be established.



V

Lactone



VI

Lyconnotine

5. Attempted Interrelation of Acrifoline to Lyconnotine

It was considered probable from the structural and stereochemical features of acrifoline that lyconnotine might have arisen from acrifoline or a close derivative of it.

Attempts were therefore made to interrelate acrifoline to lyconnotine. With this end in view, the ultraviolet irradiation studies on acrifoline were carried out under a variety of conditions. Ketones were already known to undergo photolytic disproportionation (44) to aldehydes and ketenes.

The two most probable pathways for the photolytic cleavage of acrifoline, envisaged by us are shown in Figure 11 (page 72). It may be seen that either one of the two products, A and B, in this scheme could be related to a tetrahydro derivative of lyconnotine provided the cleavage took place in the right direction as indicated in Figure 11. The product B (i.e. the aldehyde) could, in principle, also be

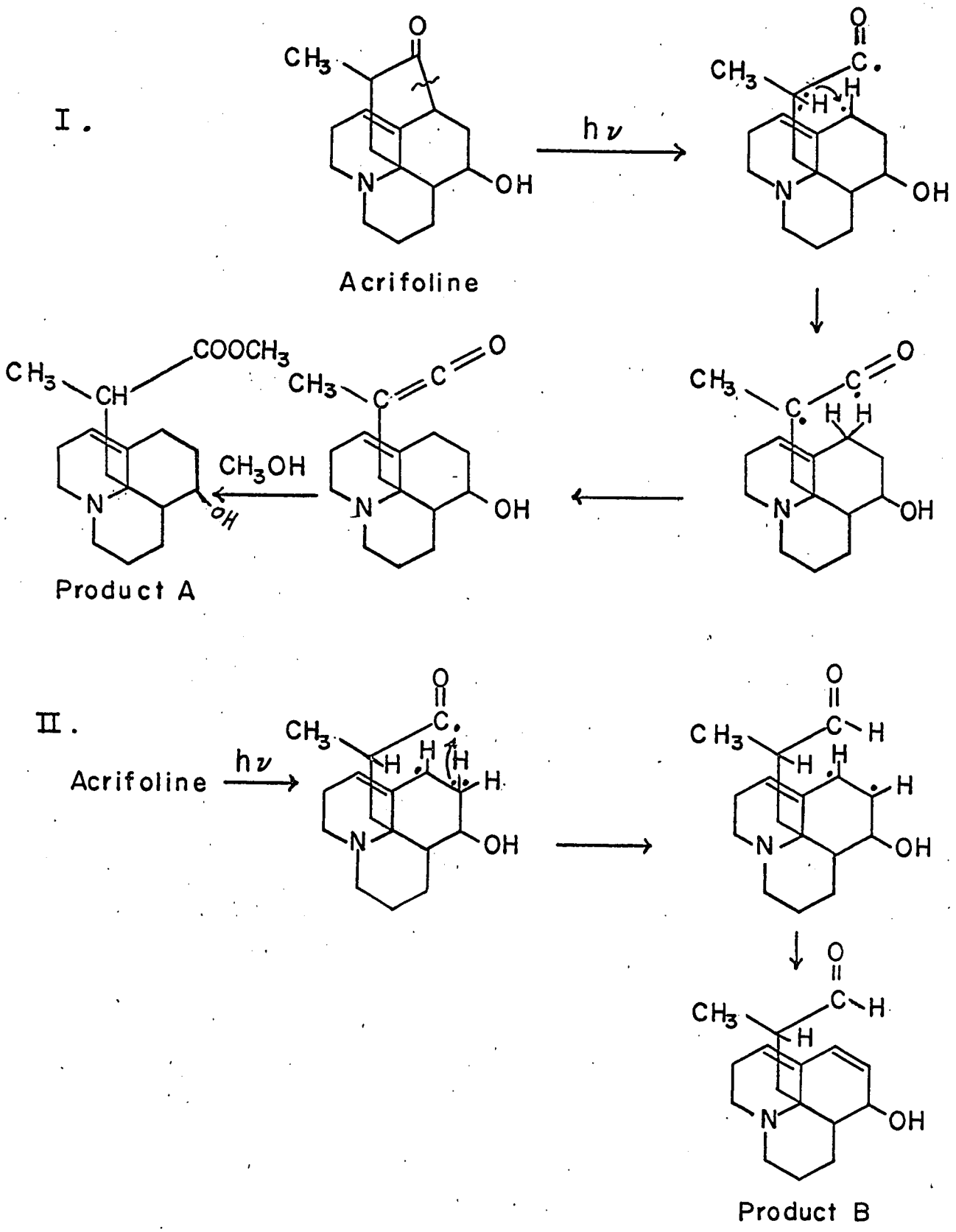


Figure 11. Envisaged pathways for photolytic cleavage of acrifoline

converted easily to the dihydro derivative of Product A.

After the isolation of acrifoline from the crude alkaloids of Lycopodium annotinum L., the preliminary experiments were performed on acrifoline on a micro scale. Ultraviolet irradiation of acrifoline in the absence of oxygen was first carried out in methanolic solution in a quartz tube without using a filter sleeve in the immersion well. It was found by infrared and paper chromatographic studies that there was mostly unchanged acrifoline at the end of photolysis. This was attributed to the insufficient transmission of the intense radiations from the lamp to the reaction medium.

Acrifoline was then irradiated in a thin-walled Pyrex test tube with Pyrex filter sleeve using methanol as the solvent. Again, there did not seem to be much change in acrifoline.

Irradiation of acrifoline was next carried out in a slightly different way, that is, this time a thin-walled Pyrex sleeve was placed in the immersion well. This experiment also did not show any appreciable change in acrifoline. It appeared that the radiations transmitted to the reaction medium, through the Pyrex filter sleeve were not of appropriate energy for our purpose.

Next, we decided to use a Corex filter sleeve in the immersion well which had the advantage of transmitting the ultraviolet radiations better than Pyrex.

Acrifoline was therefore irradiated in a thin-walled Pyrex test tube using Corex filter sleeve in methanol and ether. It seemed that irradiation of acrifoline in ether under the above conditions was probably the best; this gave rise to three compounds including the unchanged acrifoline as shown by paper chromatogram. The principal photo product appeared to be the component with the R_f value 0.44 (pH 5.0). The infrared spectrum of the mixture of the photo products showed bands at 1700 cm^{-1}, 1735 cm^{-1} and at 1775 cm^{-1}, together with the hydroxyl group absorption at 3660 cm^{-1}. The product with R_f 0.44 was isolated from the unsprayed part of the chromatogram and showed bands at 1735 cm^{-1} (carbonyl absorption), 3660 cm^{-1} (hydroxyl absorption) and at 1670 cm^{-1} (C=C). This product was thought to be the likely compound to be related to lyconnotine.

From the preliminary experiments, it became evident that the use of the Corex filter sleeve and ether as the solvent could make a suitable combination for the small scale irradiation of acrifoline in the outer jacket. Irradiation of acrifoline in ether solution was therefore carried out in a specially designed outer jacket making use of the Corex filter sleeve (Figure 12 on page 75). The use of the outer jacket was preferred; firstly it could hold greater volume of acrifoline solution (about 150 ml) and secondly, it had an arrangement for bubbling the nitrogen through the solution as the photolysis proceeded so as to avoid quenching by oxygen. As in the previous experiments,

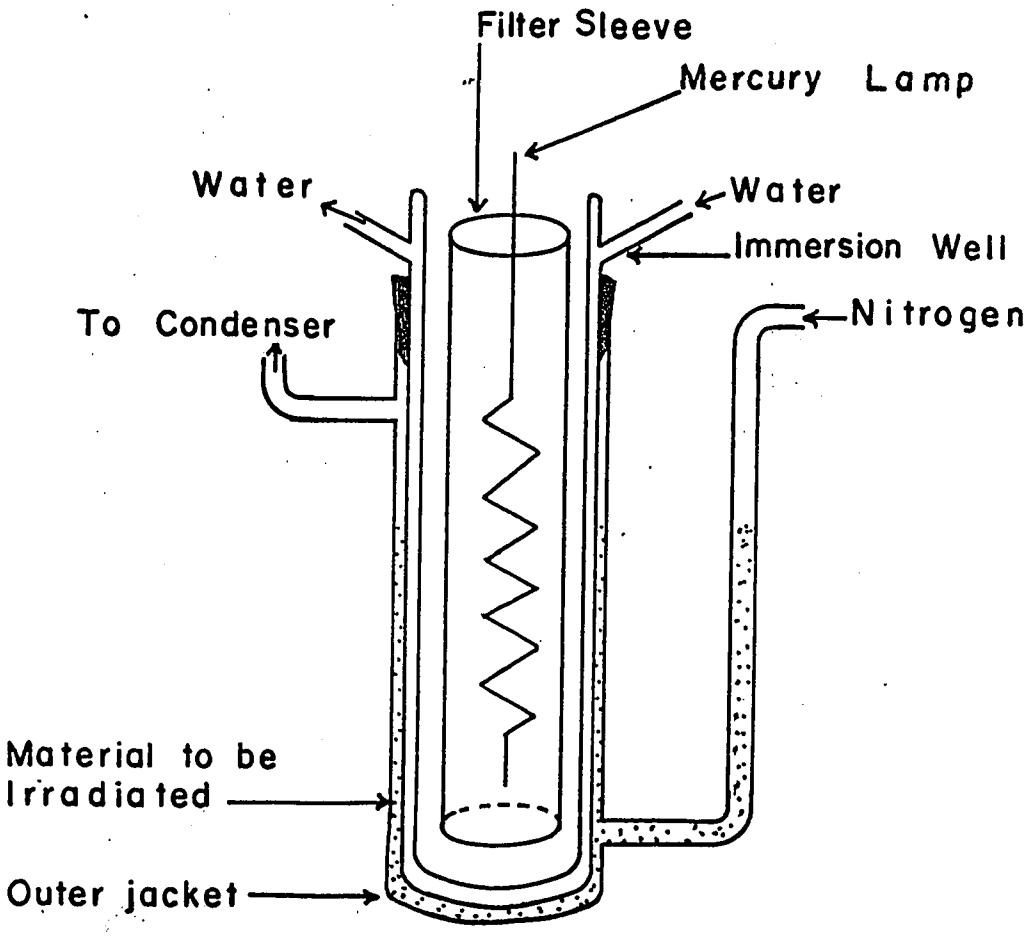


Figure 12. Apparatus for U.V. irradiation of acrifoline and dihydroacrifoline

the progress of the reaction was followed by the intensities of the various bands in the infrared spectra. Paper chromatography (pH 5.0) of the irradiated solution showed the presence of six compounds including the unchanged acrifoline. The major product, as judged by the intensity of the spots on paper chromatogram, appeared to be the compound with R_f value 0.44 which had also been obtained on micro scale photolysis.

This compound was separated from other products by preparative paper chromatography. The photo product (with R_f 0.44) thus obtained showed a band in the infrared spectrum at 1735 cm^{-1} and no band at 1700 cm^{-1}. The N.M.R. spectrum of this compound showed three broad bands in the region τ7.49-8.84. The doublet of the methyl group originally present in the spectrum of acrifoline was not clearly seen; instead a broad band centred at τ 8.84 was observed. It became evident from the N.M.R. spectrum of the major product of acrifoline that it was not of interest to us and that it could not be readily related to lyconnotine. Because of the limited amount of acrifoline at our disposal, and also because of the very low yield of the compound with R_f 0.44, no attempt was made to isolate this product in greater quantity for characterization.

Since photolysis of acrifoline in an outer jacket with Corex filter sleeve in ether solution did not prove as promising as it appeared from the micro scale experiment, irradiation of acrifoline on a small scale without a filter sleeve was considered worth trying. This experiment was

also performed in the outer jacket with continuous bubbling of nitrogen through the solution during photolysis; a mixture of many components was obtained as shown by paper chromatography. This complex mixture could be attributed to very intense radiations transmitted to the reaction medium in the absence of a filter sleeve.

Irradiation of acrifoline in methanol in the outer jacket using a thin-walled Pyrex sleeve did not produce much change in acrifoline as revealed by infrared and paper chromatographic studies.

As a result of these unsuccessful attempts of interrelating acrifoline to lyconnotine, photolysis of acrifoline was abandoned at this stage.

6. Attempted Interrelation of Dihydroacrifoline to Lyconnotine

Since the photolysis of acrifoline itself did not prove fruitful for the purpose of interrelation of acrifoline to lyconnotine, it was considered of interest to undertake photolysis of dihydroacrifoline and see if the latter could be interrelated to lyconnotine.

Dihydroacrifoline was prepared from acrifoline by the catalytic hydrogenation of the latter.

Photolysis of dihydroacrifoline in methanol, in the thin-walled Pyrex test tube, with Corex filter sleeve in the immersion well, did not show much change initially but when irradiation was continued for 9-12 hours, a complex

mixture was obtained. The mixture had a moderately intense band at 1715 cm^{-1} in its infrared spectrum that could be assigned to an aldehydic carbonyl group.

Dihydroacrifoline was next irradiated for a much shorter period of 1/2 hour and 1 1/2 hours without using any filter sleeve this time, in methanolic solution placed in the thin-walled Pyrex test tube. The reaction mixture showed a band at 1715 cm^{-1} in the infrared spectrum; paper chromatography revealed the presence of two compounds in addition to the unchanged dihydroacrifoline.

Photolysis of dihydroacrifoline in methanol was then carried out in the outer jacket used earlier for acrifoline too. This time, again, no filter sleeve was used. The same experiment was repeated using ether as the solvent. In both cases, an oily product was obtained which turned out to be a complex mixture.

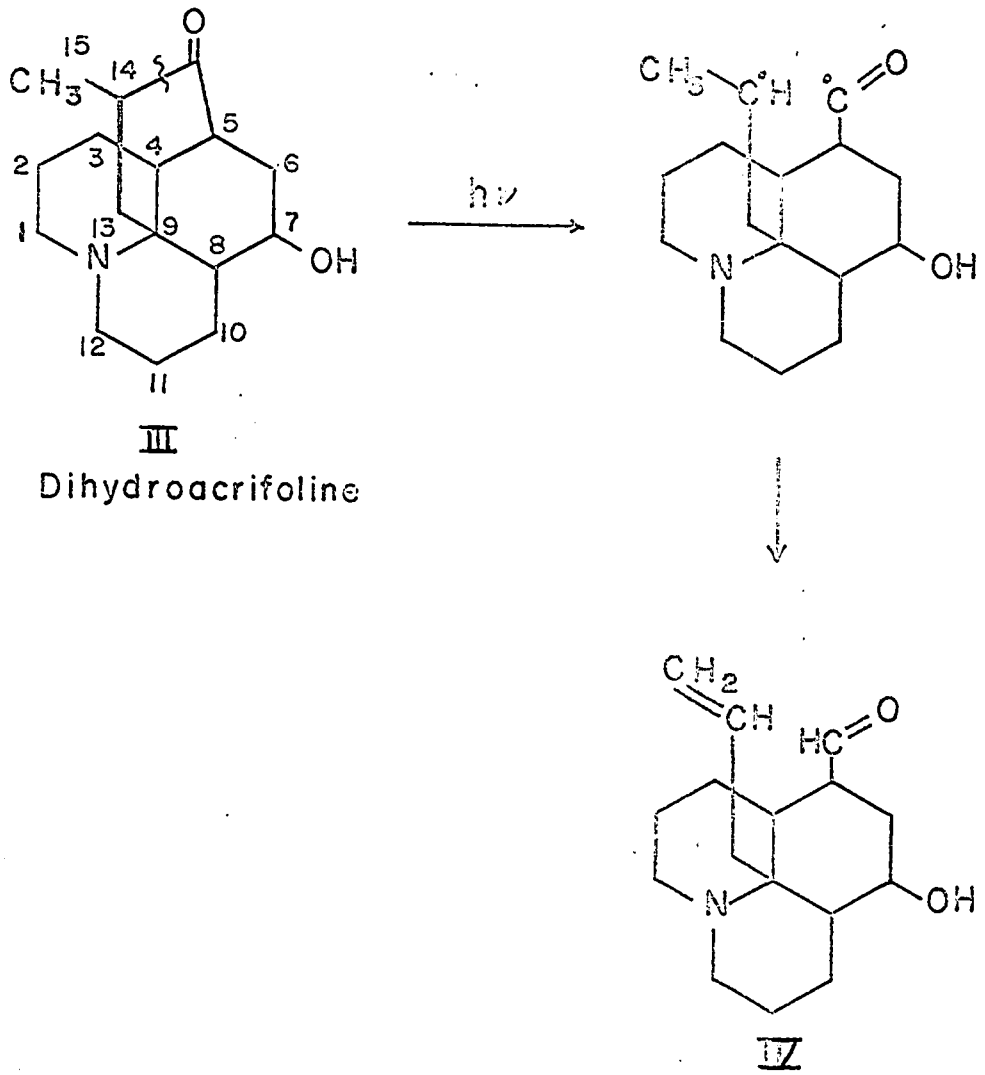
Since irradiation of dihydroacrifoline without any sleeve resulted in a bad mixture, photolysis using Corex filter sleeve was carried out, in the outer jacket using methanol as well as ether separately. The infrared spectra of the photo products in both the cases exhibited bands at 1715-20 cm^{-1}; paper chromatography (pH 5.0) showed them to be mixtures of at least 6 compounds including the unchanged starting material.

Irradiation of dihydroacrifoline in methanol in the outer jacket was carried out, using Vycor filter sleeve but this time also, a complex mixture was obtained.

Dihydroacrifoline in methanol was irradiated in the outer jacket using Pyrex filter sleeve in the immersion well. The paper chromatography (pH 5.0) indicated the formation of at least three products.

From the preliminary experiments, it was evident that photolysis of dihydroacrifoline could probably be best accomplished using Pyrex filter sleeve in a methanolic solution. Dihydroacrifoline was therefore irradiated in the outer jacket. The paper chromatography (pH 6.0) showed the presence of four components with R_f values 0.22 (dihydroacrifoline), 0.35, 0.41 and 0.68. The major product appeared to be the compound with R_f 0.35 which was isolated employing preparative paper chromatography. The base thus obtained, after sublimation, showed a band in its infrared spectrum at 1715-20 cm^{-1} indicating the carbonyl function as an aldehyde. The N.M.R. spectrum of this product gave, among others, signals at τ 0.5 and τ 4.18. While the former signal could be attributed to an aldehydic proton, the latter could be assigned to the olefinic protons. The band for the methyl protons present originally in dihydroacrifoline was no longer observed in the N.M.R. spectrum of this product. This could be rationalized by assuming that the product formed as a result of photolytic cleavage of dihydroacrifoline was compound **IV** as shown on the following page.

The formation of product **IV** would arise from the cleavage of the C_{14}-C_{15} bond in dihydroacrifoline (**III**), to give rise to a biradical, followed by the abstraction of a hydrogen atom by the radical at C_{15} from the methyl protons.



III

Dihydroacrifoline

IV

Unfortunately this product was contrary to our expectation and could not be interrelated to lyconnotine. Thus the attempts to interrelate dihydroacrifoline to lyconnotine have not been successful.

PART II

INTRODUCTION

1. Scope of the Problem

In recent years, nuclear magnetic resonance (N.M.R.) spectroscopy has been extensively applied to conformational problems. This section of the thesis deals with its application to (i) cyclohexene-cis-3,3,4,5,6,6-d_6, (ii) cis-1,2-dicarbomethoxy-cis-cyclohexane-3,3,4,5,6,6-d_6 and (iii) cyclohexane-3,3,6,6-d_4. The methods of preparation of these compounds are also described.

2. Brief Review of Pertinent Literature

The first significant studies of conformations were concerned with the cyclohexane ring which is known (50,51) to be more stable in the chair (I) than in the boat form. The boat (IIa) and the twisted boat (IIb) forms (page 82) have been calculated (52) to be 6.9 kcal/mole and 5.3 kcal/mole less stable, respectively, than the chair form.

The introduction of an endocyclic double bond in a six-membered ring results in a change of conformation from a chair to a half-chair (53) at least in a carbocyclic compound (54). The half-chair conformation of cyclohexene exists in dl forms. Ring inversion results in an interchange of the two forms and thus provides a mechanism for racemization. An unsuccessful attempt to resolve cyclohexene-cis-4,5-

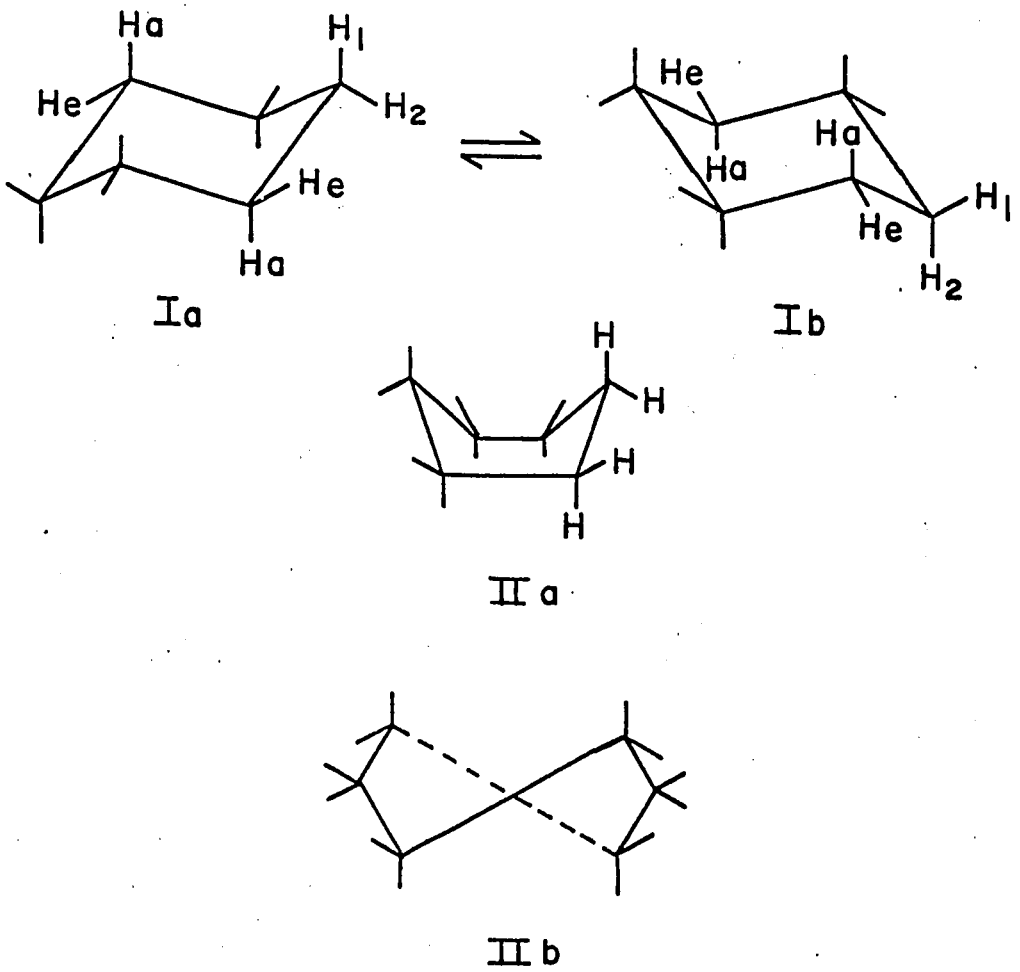


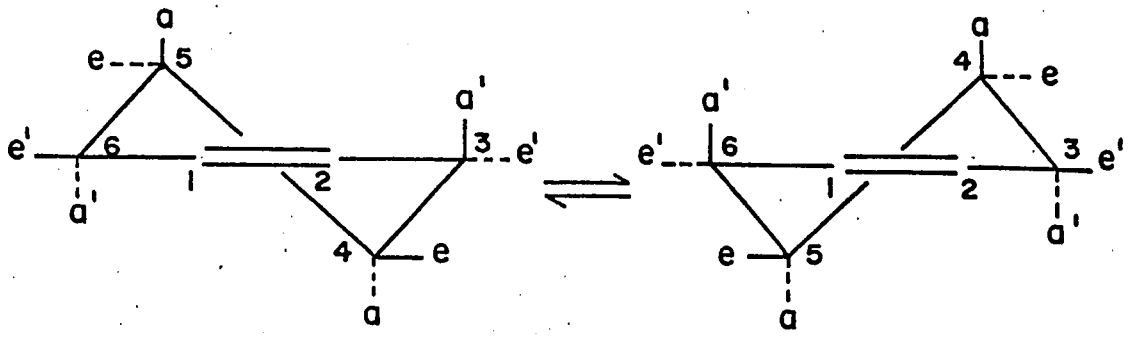
Figure 13. Conformations of Cyclohexane

dicarboxylic acid was interpreted (55) in terms of rapid ring inversion.

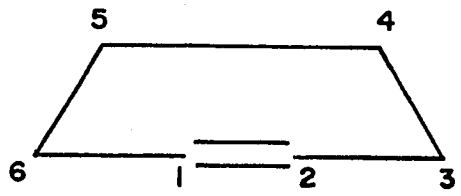
Theoretical calculations by Beckett, Freeman and Pitzer (56) favor the half-chair conformation (IIIa, IIIb; page 84) of cyclohexene by about 2.7 kcal/mole over the alternate half-boat conformation (IV). X-ray and electron diffraction studies (57) on some substituted cyclohexenes have confirmed this geometry. Substituents on C_3 and C_6 are designated as quasi-axial ($\acute{a}$) and quasi-equatorial ($\acute{e}$). Substituents on C_4 and C_5 occupy normal axial and equatorial positions. Several 3,4-, 3,5- and 3,6- disubstituted cyclohexenes have been studied which favor the diequatorial conformation (58). Garbisch (59) has investigated a number of 6-substituted 1-phenyl (and methyl) cyclohexenes. The preferred conformations of C_6 substituents have been determined, using N.M.R. techniques.

Rate Processes by N.M.R. Spectroscopy

N.M.R. spectroscopy provides a method for the study of processes involving no permanent chemical change and can be applied to determine the rates of interchange of stable forms of molecules. The method depends on the observed shape of the signals obtained from nuclei, on sites chemically shifted from each other, which are undergoing mutual exchange. The shape and the width of the signals change with the exchange rates, in a regular fashion, if the mean lifetimes of nuclei on sites are of the order of magnitude of the inverse



III a III b



IV

Figure 14. Conformations of Cyclohexene

frequency separation which would be observed between the peaks in the absence of an exchange process. If the rate of exchange is much greater than this, i.e., if the life time on a site is short, the signals are averaged to give a single line. On the other hand, if the rate of exchange is much smaller, separate signals arise with their normal chemical shifts and any fine structure due to spin-spin interactions. Reviews on the factors influencing the signal shape and application of N.M.R. to molecular conformations are available (60,61,135). The line shapes are related to rates by mathematical treatments suggested by Gutowsky, McCall and Slichter (62). The line shape equation developed by Gutowsky and co-workers has been extended by others (63,64,65) to similar problems. Following Kaplan's theory of exchange broadening (69), Alexander has put forward (70) a more general method of analysis. Additional methods of obtaining kinetic data from the spectrum are available (66-68, 138-140). The recent double resonance technique of Forsen and Hoffman (136) enables much smaller rate constants to be measured than the conventional line shape method. Eigen (137) and others have done much recently to develop relaxation methods for obtaining kinetic data.

Ring Inversion in Cyclohexanes and other Six-membered Rings

The chair-chair interconversion in cyclohexanes at room temperature is rapid and thus precludes the isolation of

separate conformers. Shoppee (71), from consideration of qualitative aspects of energetics, estimated the energy of activation for this process to be 9-10 kcal/mole. On the basis of their spectroscopic data, Beckett, Pitzer and Spitzer (72) suggested a value of 14 kcal/mole. The conformation of the transition state is considered (52,73) to be halfway between the chair and the twist-boat forms. Hendrickson (52) calculated the energy barrier for the ring inversion in cyclohexane to be 12.7 kcal/mole.

The kinetics of this process has been studied (73) by N.M.R. spectroscopy. Cyclohexane exhibits a sharp band in its N.M.R. spectrum at room temperature (60 Mc/sec.). Jenson and co-workers obtained a rough doublet for the axial and equatorial resonances at -70°; due to spin-spin interactions, a complex, incompletely resolved pattern, was observed. The rate of ring inversion at the temperature of half-peak separation (-66.7) was found to be 52.5 sec^{-1}. These workers assumed the boat form as the unstable intermediate. The free energy of activation, ΔF^{*}, for this process was calculated to be 10.1 $\pm$ 0.1 kcal/mole.

Harris and Sheppard (74) studied the rate of broadening of the single peak of cyclohexane over the temperature range -20 to -70° at 40 Mc/sec and obtained a value of 10.6 kcal/mole for ΔF^{*} at -66.5. Also, the values for ΔH^{*} and ΔS^{*} were evaluated to be 9.2 $\pm$ 0.2 kcal/mole and -7.9 $\pm$ 1.0 e.u., respectively.

Anet, Ahmad and Hall (75) have used cyclohexane-d_{11}, instead of cyclohexane itself, to obtain easily interpretable spectra over a wide temperature range (-32^{o} - -94^{o}) and have obtained a value of 11.3 ± 0.6 kcal/mole for the energy of activation. The values of $\triangle F^{*}$, $\triangle H^{*}$ and $\triangle S^{*}$ were calculated to be 10.3 kcal/mole, 10.9 ± 0.6 kcal/mole and 2.9 ± 2.3 e.u., respectively, which are in good agreement with those obtained by Bovey and co-workers (76).

The free energy of activation for ring inversion in perfluorocyclohexane has been calculated to be 9.9 kcal/mole by Tiers (77). Reeves and Stromme (78) studied the change of 1-H (i.e., the carbon atom bearing the substituent group) with temperature in cyclohexyl chloride and cyclohexyl bromide and obtained a value of 10.85 kcal/mole for the free energy of activation. Similar studies have been carried out (79) on 1,2-trans-dibromo- and 1,2-trans-dichloro-cyclohexanes. A very clear coalescence pattern in the F^{19} resonance spectrum of 1,1-difluorocyclohexane afforded (80) a value of 12 kcal/mole for the energy of activation. The N.M.R. spectra of 1-H of chloro-, bromo-, iodo- cyclohexane and cyclohexanol have been studied at low temperatures. Niekam and Dailey (81) calculated the activation energy for the ring inversion processes to be 11.7 kcal/mole. Similar studies have also been extended to derivatives of piperidine (82), piperazine (83), 1,2-dioxane and 1,2-dithiane (84,85,86); all these compounds exist in chair conformations.

Ring Inversion in Cyclohexene

Ring inversion can take place in the half-chair conformation of cyclohexene but there was no report in the literature on the determination of the rate of this process prior to our work (87). The N.M.R. spectrum of cyclohexene as measured (88) at room temperature has been found to be consistent with rapid inversion. Apart from the olefinic protons at τ 4.41, it showed two peaks of equal intensities at τ 8.04 and 8.35 which can be assigned to the allylic and homoallylic protons, respectively. The peaks of the methylene protons were very complex multiplets because of the complicated spin-spin coupling. It is obvious that separate bands for the axial and equatorial homoallylic protons would be observed if the averaging effects resulting from the rapid inversion could be removed. This can be done at very low temperatures.

EXPERIMENTAL

1. Description of the General Methods

Methods described in the Experimental section of Part I were used. The infrared spectra of liquids were recorded as films. A Perkin-Elmer gas chromatograph was used for purification of deuterated cyclohexene and cyclohexane.

The low temperature N.M.R. spectra were kindly determined by Dr. F. A. L. Anet using a temperature controlling device similar to that described previously (89). An N.M.R. specialties SD60 decoupler was used for double irradiation at the deuteron resonance frequency. Calculations of the A_2B_2 spectrum of cyclohexane-d_4 were carried out on an IBM 1620 computer using the FREQINT IV A program which was kindly provided by Miss O. Boshko and Mrs. D. Toop.

Butadiene-d_6 and cyclohexene-3,3,6,6-d_4 were obtained from Merck Sharp and Dohme of Canada Ltd.

2. Synthetic Procedures

cis-1,2-Dicarbomethoxy cyclohexane-cis-3,3,4,5,6,6-d_6

A mixture of butadiene-d_6 (2 ml) and maleic anhydride (1.8 g) in benzene (15 ml) was heated in a bomb at 105-110° for 6 hours. The crude product, cis-cyclohex-4-ene-1,2-dicarboxylic anhydride-d_6 (I), was recrystallized from benzene-petroleum ether. Compound I, m.p. 100-101°, reported 101-103° (90), was boiled with water for 1/2 hour.

On cooling, cis-cyclohex-4-ene-1,2-dicarboxylic acid-d_6 (II), crystallized out, m.p. 164°; reported 166° (91). The diacid II (2.0 g) was heated with hydrazine hydrate (3 ml) (92,93) in water-ethanol (14:1) at 65-70° for 16 hours while a stream of oxygen was passed through the solution. The reaction mixture was then cooled and treated with excess dilute hydrochloric acid. The acid solution was extracted, four times, with ether (20 ml). The ether extracts were combined and dried over anhydrous sodium sulfate. On evaporation of the solvent, cis-cyclohexane-1,2-dicarboxylic acid-cis-3,3,4,5,6,6-d_6 (mixture of III and IV) was obtained. The product melted at 191°; reported 192° (91). An ether solution of diazomethane was added drop-wise to a solution of the diacid III and IV (100 mg) in ether (10 ml) containing 2 drops of methanol, until the solution became pale yellow. The solvent was then evaporated and the product purified by bulb to bulb distillation to get cis-1,2-dicarbomethoxy cyclohexane cis-3,3,4,5,6,6-d_6 (V and VI). Diazomethane (94) was produced by treating nitrosomethylurea with aqueous potassium hydroxide solution (60%) under constant stirring and was taken up in ether placed over the layer of the alkali solution.

Cyclohexene-cis-3,3,4,5,6,6-d_6 (VII)

A mixture of the dicarboxylic acids III and IV (1.0 g), lead tetraacetate (3.0 g), and pyridine (12 ml) was heated (95-97) to 50-60° while a stream of nitrogen was passed through the solution. The gas stream was passed

through a receiver cooled in a Dry Ice-acetone bath. About 3 to 4 ml of a pyridine solution of the deuterated cyclohexene was thus collected. The product was treated with excess dilute hydrochloric acid and extracted with methylene chloride (1 ml). The methylene chloride extract was dried over anhydrous sodium sulfate and its volume was reduced to about one-third by distillation. The concentrated extract was injected, in portions of 0.03 ml, in a gas chromatograph. A column of diisodecyl phthalate at 97° was used and the peak corresponding to cyclohexene was collected in a receiver cooled in liquid nitrogen. Experiments with undeuterated substrate showed that the product thus obtained was identical with cyclohexene as shown by infrared and N.M.R. spectroscopy and that the yield was about 20%.

The deuterated product which collected in the receiver was transferred to an N.M.R. tube on a vacuum line. Bromotrifluoromethane was then condensed in the tube, which was cooled by Dry Ice. Tetramethylsilane was then added and the solution was stirred with a small glass rod. The loosely stoppered tube was then quickly transferred to the previously cooled probe of the N.M.R. spectrometer.

Cyclohexane-3,3,6,6-d_4

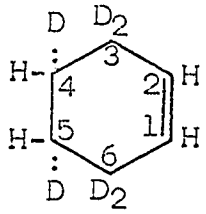
Cyclohexene-3,3,6,6-d_4 (0.5 g), p-toluene-sulphonylhydrazine (1.95 g), and diglyme (1.5 ml) were heated (98) under reflux for two hours; a brown coloration appeared and a white solid separated. After allowing the reaction mixture

to cool, water (5 ml) and carbon disulfide (5 ml) were added. The carbon disulfide layer was separated from the water layer and was thoroughly washed with water (5 ml) three times and the washings were discarded. The solution was dried over anhydrous sodium sulphate and filtered. The filtrate was heated to 50-60° and a stream of nitrogen was passed through the solution. The gas stream was passed through a receiver cooled in a Dry Ice-acetone mixture. A carbon disulfide solution of deuterated cyclohexane was thus collected and its volume was reduced to about 0.5 ml by distillation. The concentrated solution was injected, in portions of 0.03 ml, in a gas chromatograph using a column of diisodecyl phthalate at 99°; three peaks were observed which were readily identified by comparison with authentic samples of carbon disulfide, cyclohexane and cyclohexene. Cyclohexane-3,3,6,6-d_4 was collected from the gas chromatograph in a receiver cooled in Dry Ice-acetone mixture. Experiments with undeuterated substrate showed that the product thus obtained was identical with cyclohexane as shown by infrared and N.M.R. spectroscopy, and that the yield was about 20%. Cyclohexane-d_4 collected in the receiver was transferred to an N.M.R. tube on a vacuum line.

RESULTS

Cyclohexene-cis-3,3,4,5,6,6-d_6

The N.M.R. spectrum of VII at about -50° in bromotrifluoromethane consisted of two peaks (τ 4.40 and 8.42) of equal intensities, as expected. The peaks were broad because of proton-deuteron coupling; they became much sharper when the proton spectrum was observed with simultaneous strong irradiation at the deuteron resonance frequency of 9.2 Mc/sec. All the low temperature spectra of VII were taken under the latter condition i.e., with the protons decoupled from the deuterons.



VII

The peak at τ 8.42 broadened appreciably at temperatures below -150°. At -164°, the peak became a doublet whose separation gradually increased and was 19.8 c.p.s. at -170° (Figure 15, page 94). The mean chemical shift at -170° was τ 8.39. The line width at half-height of the internal tetramethylsilane reference was 6 c.p.s. at -170°.

The free energy of activation at the coalescence temperature (-164°) was calculated from Eyring's equation (116)

$$k = \kappa \frac{KT}{h} e^{-F^*/RT}$$

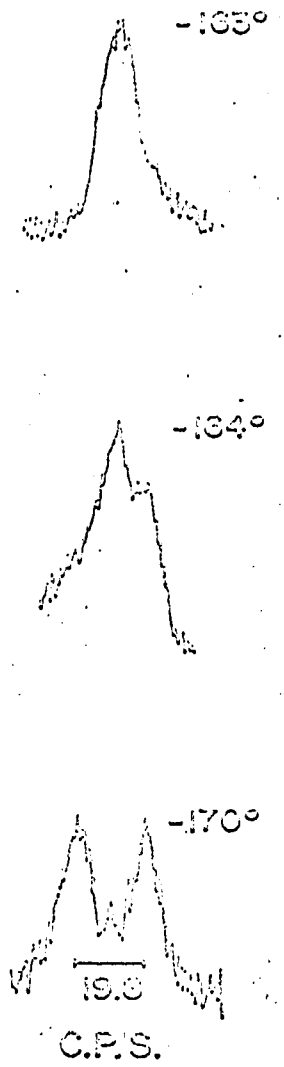


Figure 15: Peaks of H_4 and H_5 in cyclohexene cis,3,3,4,5,6,6-d_6 in bromotrifluoromethane solution at low temperatures.

where κ = transmission coefficient (assumed to be one)

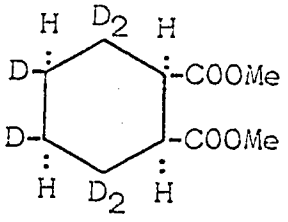
K = Boltzmann constant (1.38×10^{-16} ergs/degree)

h = Planck's constant (6.624×10^{-27} ergs-second)

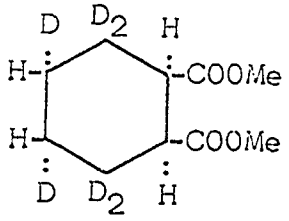
R = Gas constant (1.987 calories/degree/mole).

cis-1,2-Dicarbomethoxy cyclohexane-cis-3,3,4,5,6,6-d_6

The N.M.R. spectrum of a mixture of V and VI at room temperature in carbon disulfide solution showed peaks of unequal intensities at τ 6.47, 7.38, 8.60 and 8.71. The latter three peaks, which were broad at room temperature, became much sharper when the proton spectrum was observed with simultaneous strong irradiation at the deuteron resonance frequency of 9.2 Mc/sec (Figure 16, page 96). The low temperature spectra of V and VI were taken in the presence of deuterium decoupling frequency.



V



VI

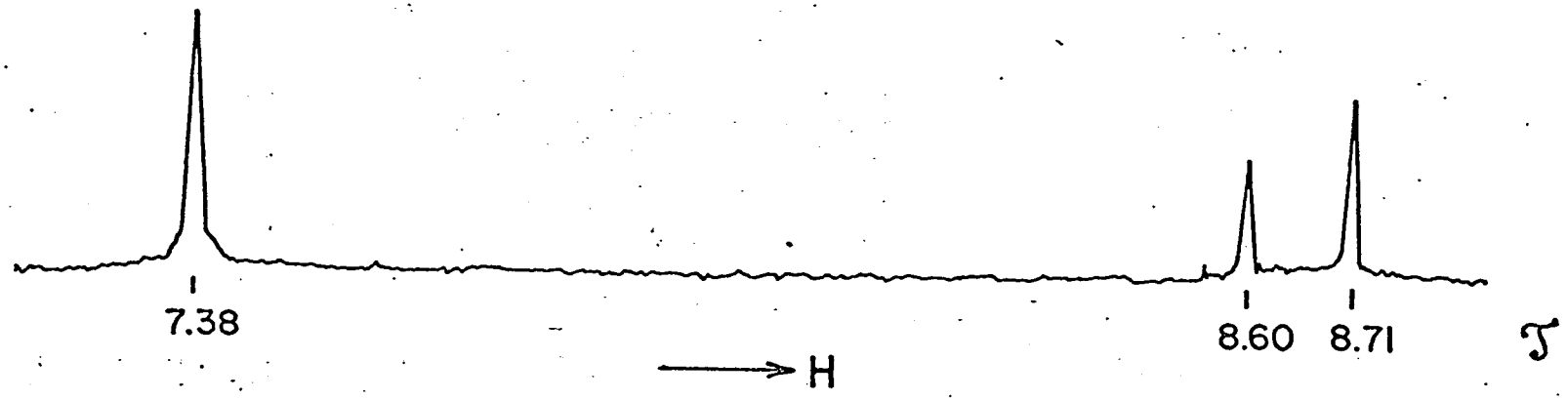


Figure 16 The N.M.R. spectrum of H_1, H_2, H_4 and H_5 in cis-1,2-dicarbomethoxycyclohexane-cis-3,3,4,5,6,6-d_6, V and VI, in carbon disulfide solution at room temperature

The peaks at τ 7.38, 8.60 and 8.71 began to broaden as the temperature was lowered. At -105° three distinct sets of quartets were discernible as shown in Figure 17 (page 98). Also two signals centred at τ 6.49 and 6.52, respectively, not shown in Figure 17, were observed.

Cyclohexane-3,3,6,6-d_4

The proton N.M.R. spectrum of cyclohexane-3,3,6,6-d_4 in carbon disulfide solution at room temperature showed a broad singlet at τ 8.63 which became sharper when the proton spectrum was observed under simultaneous strong irradiation at the deuteron resonance frequency. The low temperature spectra were recorded in the presence of deuteron decoupling frequency. The experimental spectrum of cyclohexane-d_4 at -112° is shown in Figure 18 (page 99) together with the calculated spectrum. The spectrum displayed the characteristic symmetry expected of an A_2B_2 system.

Analysis of the Spectrum

The original analysis (99) of A_2B_2 spectra has been extended (100-102) and applied to a number of such systems (103-112) and hence the details of the treatment of A_2B_2 spectra will not be repeated here. The pertinent terms to be considered and the structure of cyclohexane-d_4 are given:

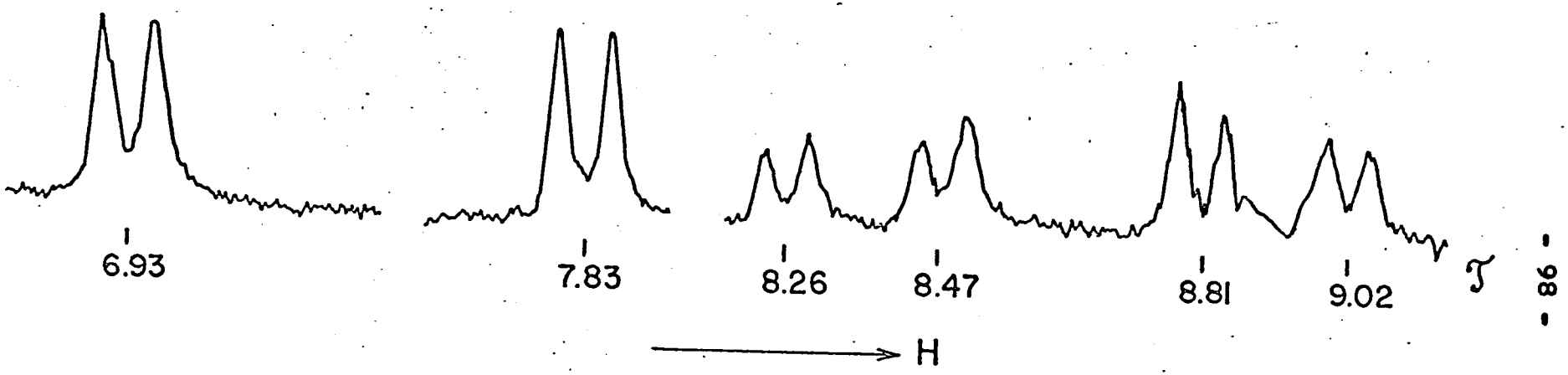


Figure I7 The N.M.R. spectrum of H_1, H_2, H_4 and H_5 in cis-1,2-dicarbomethoxycyclohexane cis-3,3,4,5,6,6-d_6, V and VI, at -105° in carbon disulfide solution

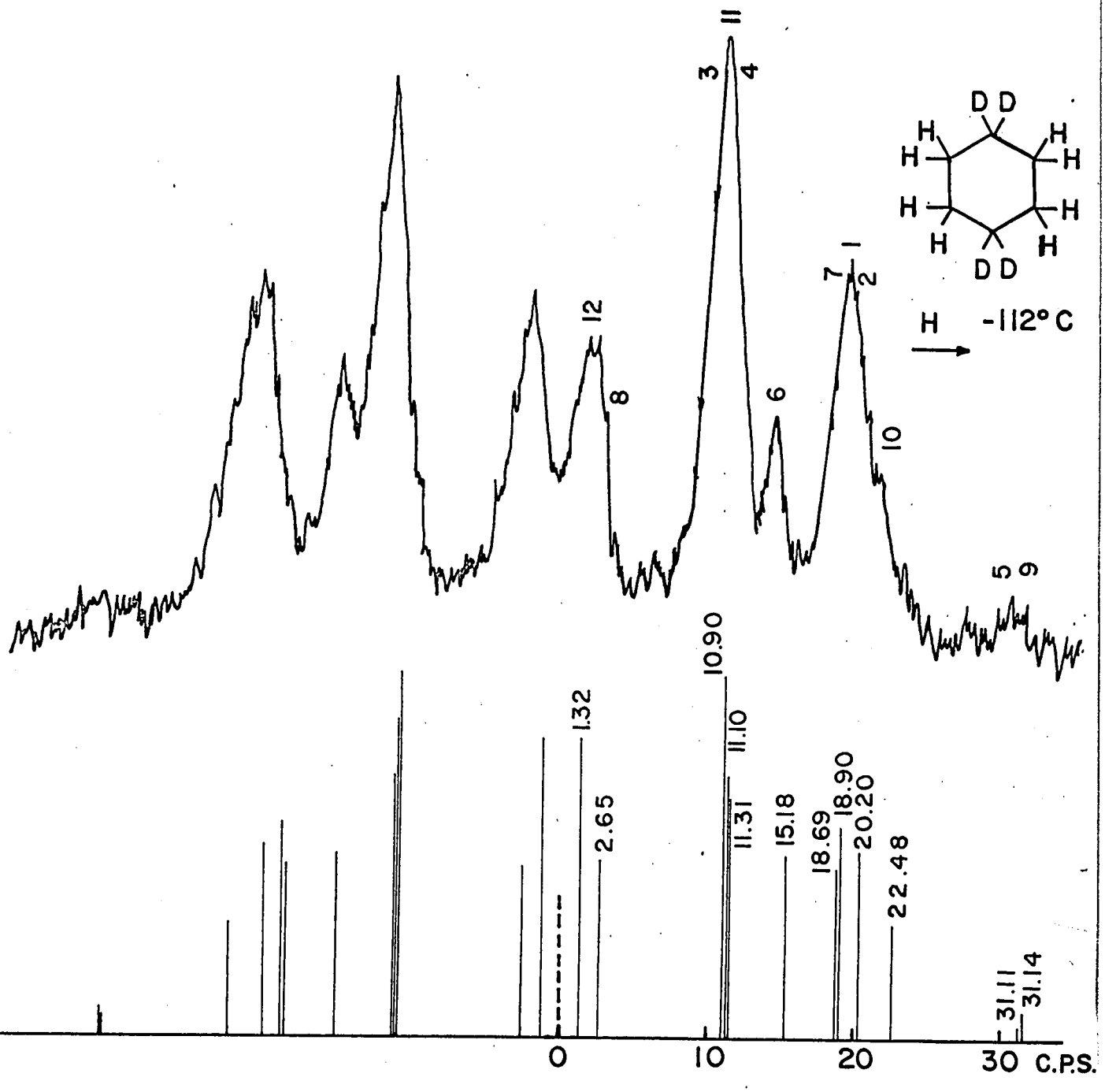
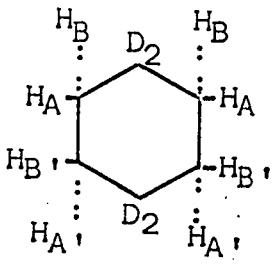
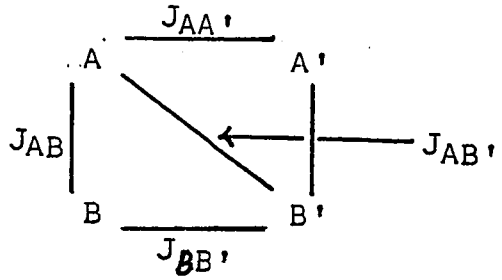


Figure 18: The observed (top) and calculated (bottom) proton N.M.R. spectrum of cyclohexane 3,3,6,6-d_4 in carbon disulfide solution. The mid point of the spectrum lies at 74.40 c.p.s. downfield with respect to T.M.S. and is represented by the dotted line.





$$\Delta AB = \nu_A - \nu_B$$

$$K = J\,AA' + J\,BB'$$

$$M = J\,AA' - J\,BB'$$

$$N = J\,AB + J\,AB'$$

$$L = J\,AB - J\,AB'$$

Calculations of the theoretical spectra were carried out with the aid of an IBM 1620 computer, using the FREQINT IV A 1620 program. A theoretical spectrum, on the basis of which various lines in the experimental spectrum could be assigned, was calculated. The assignment of lines is shown in Figure 18 for the up field half of the spectrum. From the positions of lines 1, 3, 9, 11, 2, 4, 7 and 8 numerical values for parameters N, L, M and K were evaluated utilizing the following expressions (99,100)

$$N = E_1 - E_3 \qquad \text{(i)}$$

$$[(\Delta AB)^2 + N^2]^{1/2} = E_1 + E_3 \qquad \text{(ii)}$$

$$(M^2 + L^2)^{1/2} = E_9 - E_{11} \qquad \text{(iii)}$$

$$(\Delta AB + M)^2 + L^2 = E_9 + E_{11} \qquad \text{(iv)}$$

$$K = E_2 - E_4 + E_7 - E_8 - N \qquad \text{(v)}$$

General inspection of the spectrum permitted picking out lines 1 and 3 unambiguously because of their large intensity. The splitting of this pair of lines is N. An internal check of the value of Δ AB was carried out using equation (ii). The value of K was obtained from the Equation V due to Dischler (100). The J-values and the value of Δ AB which gave the best fit with the experiment are given in Table II.

TABLE II

Spectral Parameters of Cyclohexane-3,3,6,6-d_4

Δ AB = 28.7 c.p.s.

J AB = -12.5 c.p.s.

J AB' = +4.5 c.p.s.

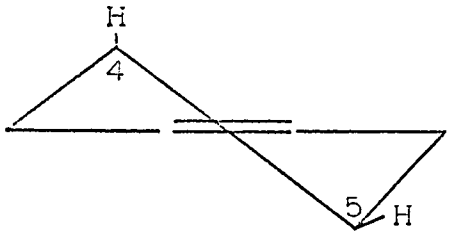
J AA' = +12.8 c.p.s.

J BB' = +2.6 c.p.s.

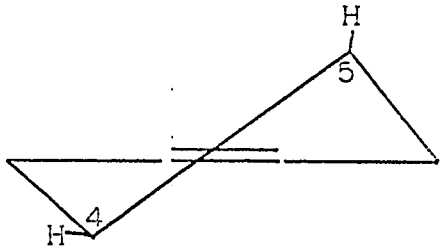
DISCUSSION

Cyclohexene-cis-3,3,4,5,6,6-d_6

The two half-chair conformations of VII are VIIa and VIIb. Only the homoallylic protons on C_4 and C_5 are shown.



VIIa



VIIb

In VIIa H-4 is axial while H-5 is equatorial and vice versa in VIIb. At about -50°, the N.M.R. signals of these protons are averaged due to rapid ring inversion and only one peak at τ 8.42 is observed. Separate signals would be observed for the axial and equatorial homoallylic protons in the absence of ring inversion. The allylic protons in cyclohexene would also be of two types, namely quasi-axial and quasi-equatorial. Since very complex multiplets (resulting from complicated spin-spin coupling) are observed (88) for the methylene protons in cyclohexene itself, we have synthesized cyclohexene-cis-3,3,4,5,6,6-d_6 (VII) and have studied its N.M.R. spectrum at various temperatures. The choice of this compound was a compromise

between spectral simplicity (75,76) and ease of synthesis. Compound VII was obtained as a result of cis reduction (92, 93) of the double bond in II by diimide, followed by lead tetraacetate decarboxylation of a mixture of III and IV (see page 90).

The coupling constants between H-4 and H-5 in either VIIa or VIIb should be small probably in the range of 2 to 4 c.p.s., in analogy (113) with other gauche vicinal coupling constants. The chemical shift between H-4 and H-5 is difficult to predict. In cyclohexane, the axial-equatorial shift is (75,76) 28.7 c.p.s. (at 60 Mc/sec). If a similar chemical shift exists in VIIa and VIIb, the spectrum of H-4 and H-5 in the absence of ring inversion will be approximately of the AX type. Since the inherent line widths at significantly low temperatures are greater than 4 c.p.s., the splitting which results from the coupling of H-4 and H-5 is not expected to be resolved. Under these conditions, the spectrum is essentially a doublet, whose separation is the H-4 and H-5 chemical shift.

The fact that the spectrum of H-4 and H-5 in VII consists of two peaks below -164° shows that the rate of ring inversion at these temperatures is sufficiently low and that the spectrum is no longer the average of VIIa and VIIb. At -170° the separation of the two peaks is 19.8 c.p.s. but has not yet reached a constant value. The true chemical shift between H-4 and H-5 is estimated to be 24 ± 2 c.p.s.

The rate constant (k, in units of sec^{-1}) for the ring inversion VIIa $\rightleftharpoons$ VIIb can be calculated at the coalescence temperature from the expression (114) $k = \pi \nu / \sqrt{2}$, where ν is the chemical shift (in c.p.s.). This expression is actually valid only when the spectrum consists of two sharp lines of equal intensities when $k \ll \nu$ and one sharp line when $k \gg \nu$, conditions which are not well satisfied in the present instance. The value of k at -164° using this expression has been found to be 53 sec^{-1}. The free energy of activation (ΔF^{*}) calculated with a transmission coefficient of one, is 5.3 kcal/mole.

The effect of deuterium substitution on the rate of ring inversion of the half-chair is expected (75) to be negligible compared to the likely errors in the present measurements. The remaining discussion therefore deals with the data with respect to undeuterated cyclohexene.

The spectra of VII are hardly suitable for obtaining k with any accuracy over a reasonable range of temperature. The peak separation method below the coalescence temperature cannot be utilized due to lack of accurate chemical shift in the absence of ring inversion. Furthermore the temperature range at which the measurements can be made in this instance is very limited; also the signal-to-noise ratio at very low concentrations is unfavorable. It is, therefore, not possible (117) to obtain the energy of activation for the ring inversion in cyclohexene. For a simple process such as ring inversion which

is taking place in an inert solvent, ΔS^* can be estimated. The contributions to ΔS^* from changes in vibrational and rotational frequencies and in solute-solvent interactions on going from the initial state to the transition state should be very small (118). The only factor which is expected to make a significantly different contribution in the ground and the transition states is symmetry. The contribution of symmetry to ΔS^* can be calculated (119) easily if the geometry of the transition state is known.

Two transition states can be envisaged for the ring inversion of cyclohexene. One possibility is a structure with a planar carbon skeleton but because this has a large number of eclipsed CH bonds, as well as large angle distortions, it is undoubtedly much higher in energy than the structure AB in Figure 19 with only five carbon atoms in one plane. This latter structure leads to the boat form (B) of cyclohexene. From specific heat measurements the boat form has been deduced (56) to be 2.7 kcal/mole less stable than the half-chair form. The boat is thus an intermediate in the ring inversion of the half-chair (Figure 19, page 106). The symmetry number of the half-chair is 2, and that of the transition state discussed above is 1. Both, the ground state and the transition state, exist in pairs of nonsuperposable mirror images. This effect contributes $+R \ln 2$ to ΔS^*. In terms of the structures in Figure 19, there are two ways that A can go to the transition state, namely A $\longrightarrow$ AB and A $\longrightarrow$ AB' (note

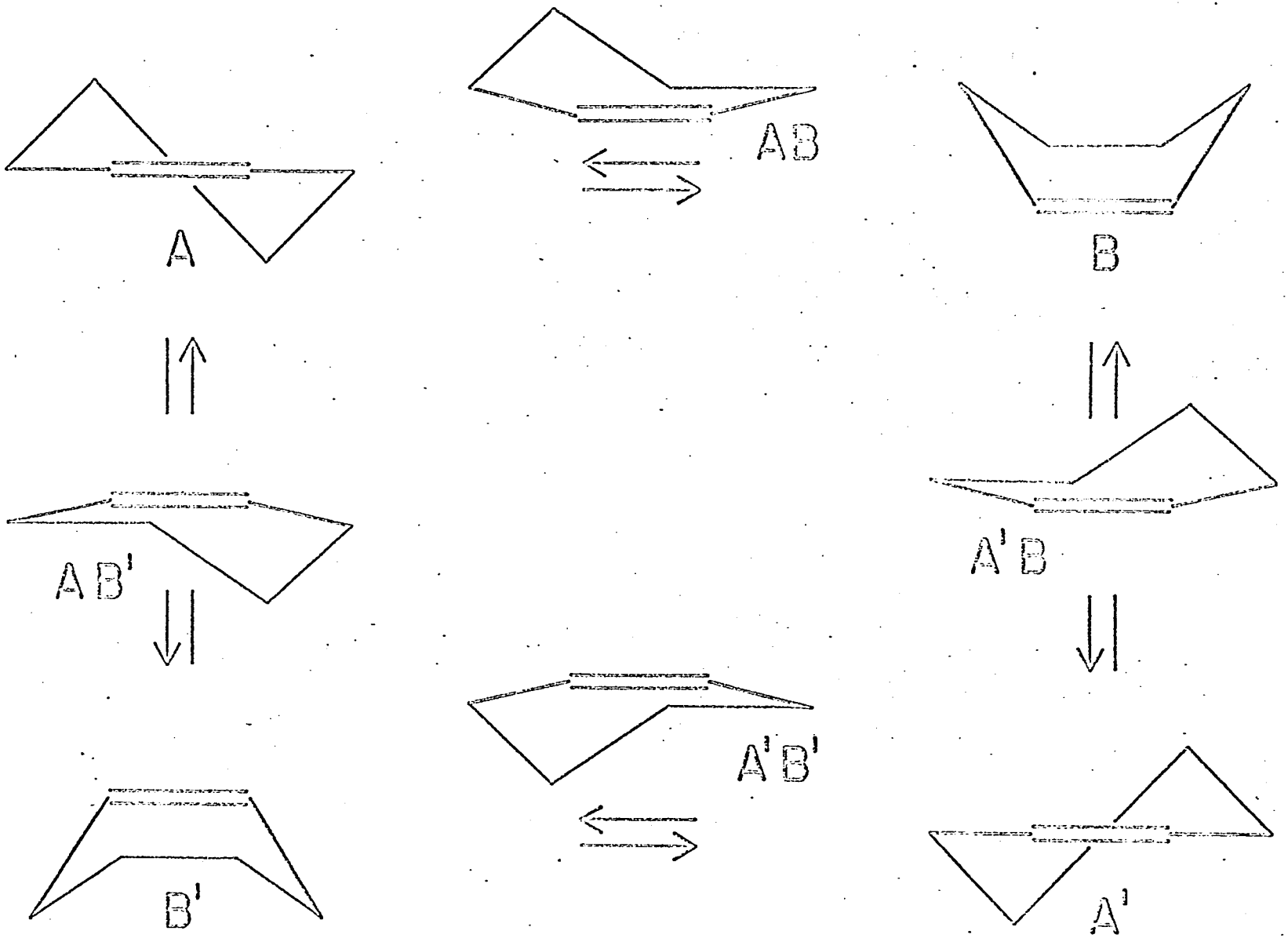


Figure 19: Interrelationship of various forms of cyclohexene; A and A' (half-chairs), B and B' (boats), AB, A'B, A', B', and AB' (transition states). Only the carbon skeleton are shown.

that AB and AB' are superposable, although the out-of-plane carbon atom in AB is different from that in AB').

Because the boat form is a necessary intermediate in the ring inversion, a molecule starting at A and passing over transition state AB to the boat form B on its way to A' has an equal probability of coming back to A as of going to A'. Thus k for the half-chair to boat process is twice that for the full inversion of the half chair. This effect is equivalent to a contribution of -R ln 2 to ΔS^*. The two effects therefore cancel as can be seen from Figure 20 (page 108).

Thus ΔF^* for the process A $\longrightarrow$ A' is 5.3 kcal/mole and for this process $\Delta S^* = 0$ from symmetry contributions. Therefore, ΔH^* is 5.3 kcal/mole as shown in Figure 20. An identical statement is that ΔF^* for the half-chair to boat process (e.g., A $\longrightarrow$ B and B' in Figure 19) is 5.2 kcal/mole, now $\Delta S^* = +R \ln 2$ from symmetry effects, so that ΔH^* has the same value as previously calculated. The various kinetic parameters for the half-chair to boat and for the complete inversion processes are given in Table III.

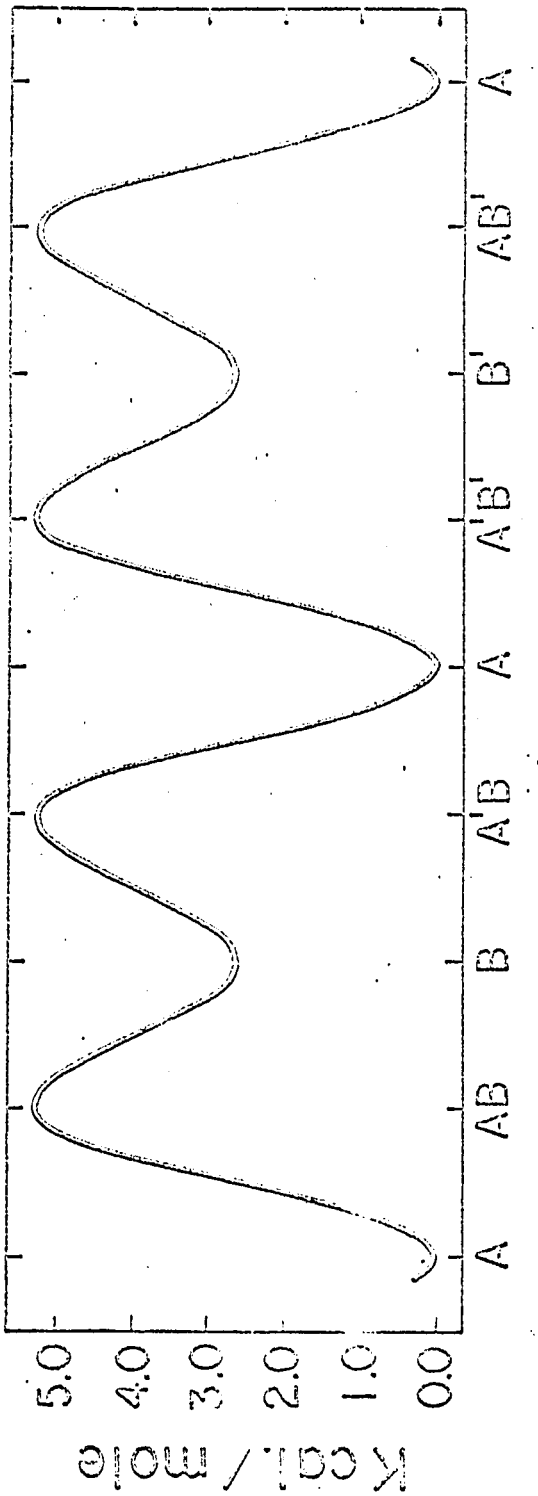


Figure 20: Diagrammatic representation of the energies of the various forms of cyclohexene shown in Figure 19.

TABLE III

Kinetic Parameters for Conformational Changes in Cyclohexene

Process	k sec^{-1}	ΔF^* kcal/mole	ΔH^* kcal/mole	ΔS^* e.u.
Half-chair to boat	106	5.2[a]	5.3[b]	+1.3[c]
Inversion of half-chair	53	5.3[a]	5.3[b]	0[c]

a At -164°
b Calculated from $\Delta H^* = \Delta F^* + T\Delta S^*$
c Calculated from theoretical considerations

If these values of ΔH^* and ΔS^* are accepted, the average lifetime at 25° of a cyclohexene molecule before inversion can be calculated to be of the order of 10^{-9} sec., using the following expressions:

$$k = \kappa \frac{KT}{h} e^{-\Delta H^*/RT} e^{\Delta S^*/R}$$

where $\Delta S^* = 0$

and $T = 298^\circ K$

$$\tau = \frac{1}{2k}$$

τ = average lifetime

The spectrum of VII at -170° gives no evidence for an equilibrium mixture of boat and half-chair forms where substantial amounts of both forms are present. This does not rule out such a possibility because the spectrum is consistent with any proportion of the two forms, provided that the axial-equatorial chemical shifts are roughly the same in the boat as in the half-chair.

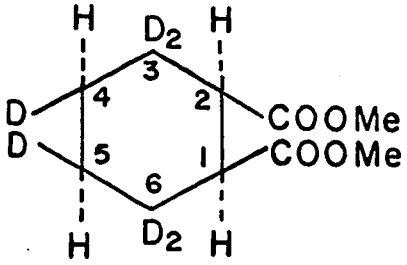
Finally, the high- (τ 8.59) and low-field (τ 8.19) signals are assigned to the axial and equatorial protons. The magnetic anisotropy (120,121) of the double bond is not expected to reverse the normal shift of axial and equatorial protons.

Jensen and Bushweller (115) have carried out a similar conformational investigation on substituted cyclohexene i.e. 4-bromocyclohexene. Their findings are similar to those of ours for cyclohexene. The signal of HCBr was found to broaden below -145° and to separate completely into two peaks at -159°. The high field peak was assigned to the axial hydrogen and the low field signal to the equatorial proton. The values of ΔF^*, ΔH^* and ΔS^* for ring inversion were calculated to be 5.93 $\pm$ 0.10 kcal/mole, 6.1 kcal/mole and 1.4 e.u., respectively.

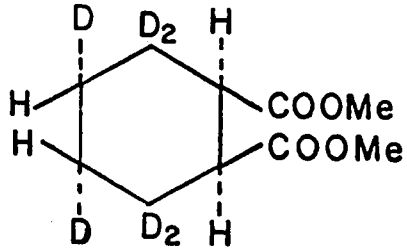
cis-1,2-Dicarbomethoxy cyclohexane-cis-3,3,4,5,6,6-d_6

The N.M.R. spectrum (Figure 16) of cis-1,2-dicarbomethoxy cyclohexane-cis-3,3,4,5,6,6-d_6 at room temperature exhibiting four peaks at τ 6.47, 7.38, 8.60 and 8.71, is consistent with structures V and VI (page 95). The singlet at τ 6.47 of area equivalent to 12 protons which is not shown in Figure 16 is attributed to the methyl groups of the carbomethoxy groups. The peak (of area equivalent to 4 protons) at τ 7.38 is consistent with the environment of H-1 and H-2 in V and VI and represents the mean absorption of these protons. This is because the chair-chair intercon-

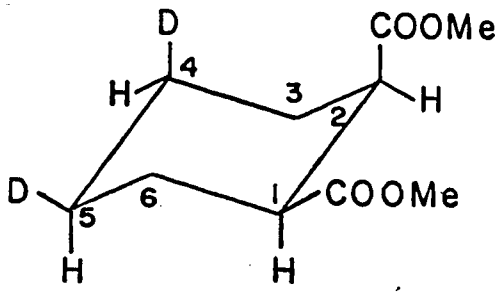
version of Va to Vb (page 112) at room temperature is rapid and hence the axial and equatorial protons experience average local field giving rise to only one signal. For the same reason H-4 and H-5 are expected to exhibit a single peak. The signal at τ 8.60 is attributed to the mean position of H-4 and H-5 in VIa and VIb whereas the average position of H-4 and H-5 in Va and Vb is represented by the peak at τ 8.71. Since the area under the peak at τ 8.60 and 8.71 is unequal, it is believed that compounds V and VI are present in unequal amounts. This is reasonable to assume because compound V and VI were obtained via diimide reduction (92,93) of cis-cyclohex-4-ene-1,2-dicarboxylic acid-3,3,4,5,6,6-d_6 (II), followed by methylation. Since diimide reduction is known to be stereospecific and gives rise to cis addition of hydrogens, it becomes obvious that saturation of the double bond in compound II would lead to two isomers of cis-cyclohexane-1,2-dicarboxylic acid-cis-3,3,4,5,6,6-d_6 (III and IV) depending on whether the hydrogen attack at the double bond in II takes place from the side of the carboxyl group or from the side opposite to it. On steric grounds, the attack should be more favoured from the least hindered side and thus the amount of the isomer III formed during diimide reduction of II should be greater than that of IV. Methylation of III and IV should, then, lead to predominance of isomer V rather than VI. Thus isomer V in turn gives rise to a more intense peak at τ 8.71 (at room temperature) for H-4 and H-5 than the



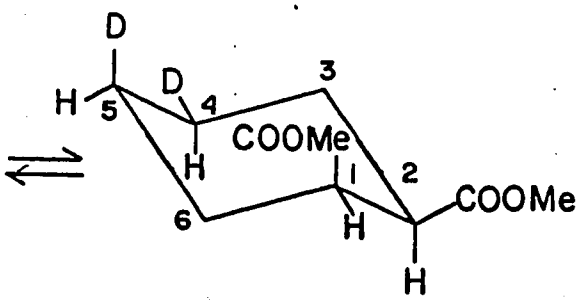
V



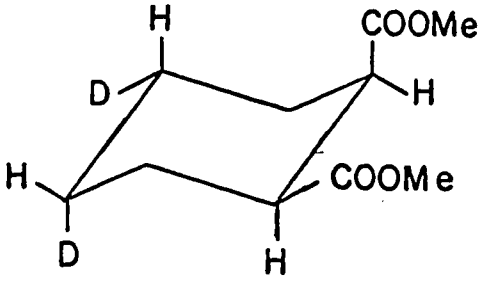
VI



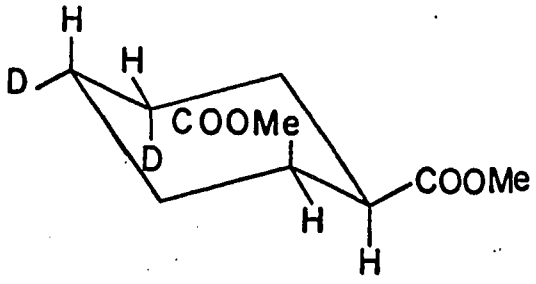
Va



Vb



VI a



VI b

signal of the corresponding protons in VI. From the area under these peaks it appears that the isomers V and VI are formed in the ratio of 3:2, respectively.

These foregoing conclusions receive support from the low temperature spectrum (Figure 17, page 98) of H_1, H_2, H_4 and H_5 in V and VI. At low temperature (e.g. -105°), the chair-chair interconversion of V and VI becomes very slow (73-76), so that separate signals for axial and equatorial protons result. For convenience, the three sets of quartets in Figure 17 have been designated as A, B and C (see also Table IV, page 114). It can be seen that at -105° when the various conformers of V and VI are "frozen", there should be three different sets of axial and equatorial protons. One such set of protons is represented by H_1 and H_2. H_4 and H_5 in Va and Vb and VIa and VIb (see page 112) constitute the other two sets.

The data on the chemical shift of the various protons at -105° and the vicinal coupling constants between axial and equatorial protons in V and VI together with the average chemical shift of axial and equatorial protons at room temperature are summarized in Table IV. The quartet "A" due to H_1 and H_2 in the absence of ring inversion is of the AX type where the two doublets are well separated and all the four lines have equal intensity. The high-field component of this quartet is assigned to the axial proton and the low-field half is attributed to the equatorial proton. The mean chemical shift of these protons at room

TABLE IV

Chemical Shift and Coupling Constant data of

cis-1,2-dicarbomethoxy cyclohexane cis-3,3,4,5,6,6-d_6

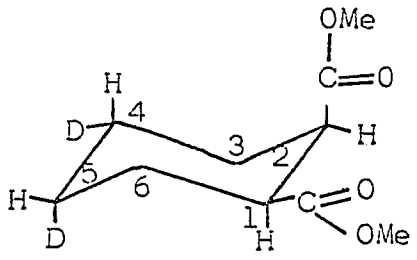
Quartet	Protons	Average $\nu_o\delta$ in τ units at room temp.	$\nu_o\delta$ at -105° in τ units		$J_{a\,e}$	Chemical Shift difference between a e protons in c.p.s.
			Axial	Equatorial		
A	H_1 and H_2 in V and VI	7.38	7.83	6.93	4.3	54 c.p.s.
B	H_4 and H_5 in Va and Vb	8.71	8.81	8.47	3.6	20.4 c.p.s.
C	H_4 and H_5 in VIa and VIb	8.60	9.02	8.26	3.6	45.6 c.p.s.

temperature (τ 7.38) is sufficiently low compared to that of cyclohexane (τ 8.57) (122). This down-field shift of H_1-H_2 is explicable in terms of the electronegative effect of the carbomethoxyl groups which should be expected to deshield these protons. At -105° separate axial (τ 7.83) and equatorial (τ 6.93) signals are consistent with the slow ring inversion. The chemical shift difference of 54 c.p.s. between axial-equatorial protons, H_1-H_2, is larger than what is encountered in cyclohexane (28.7 c.p.s.) (75) and is rationalized in terms of the strong magnetic anisotropy of the carbonyl (123) groups at C_1 and C_2. It seems probable from models that these groups exist predominantly in such a way that the equatorial proton lies in about the same plane as the carbonyl group (H_2 in Va and VIa, and H_1 in Vb and VIb). This should exert a deshielding effect on the equatorial proton. On the other hand the axial proton (H_1 in Va and VIa, and H_2 in Vb and VIb) lies in a plane below the carbonyl group and hence it should be shielded. The coupling constant of 4.3 c.p.s. between H_1 and H_2 seems reasonable, in analogy (113) with other gauche vicinal coupling constants.

The quartet B is attributed to H_4 and H_5 (equatorial and axial in Va respectively and vice versa in Vb). Again, the high-field component of the quartet (τ 8.81) represents the axial proton whereas the low-field component (τ 8.47) is due to the equatorial proton. The coupling

constant of 3.6 c.p.s. between H_4 and H_5 is consistent with other gauche vicinal coupling constants. The fact that quartet B is more intense than quartet C in the spectrum can be accounted for by considering the predominance of isomer V rather than VI.

The quartet C at -105° is assigned to axial-equatorial protons, H_4 and H_5 in VI. The chemical shift difference between axial and equatorial proton is quite large (45.6 c.p.s.) which can be accounted for in terms of the long range shielding and deshielding effect of the carbonyl groups.



VI

The probable preferred orientation of the carbonyl groups at low temperatures is shown above; it seems that the axial proton H_4 lies within the regions extending above and below the plane of both the carbonyl groups on C_1 and C_2 whereas the equatorial proton H_5 experiences the deshielding effect being in nearly the same plane as that of the carbonyl groups. At room temperature the orientation of the two

carbonyl groups represent the average of all possible orientations arising from rotation around the C_1 - CO and C_2 - CO bonds.

Finally, the axial (τ6.52) and equatorial (τ6.49) methyl groups appear as a closely spaced doublet at -105° in the spectrum.

The long range coupling of H_4 and H_5 with H_2 and H_1, respectively, is not expected to be resolved because the line-widths of these bands are about 2 c.p.s.; the magnitude of this coupling should be small as has been shown for some saturated systems (124,125). While visible spin-spin coupling through more than three bonds is common in unsaturated systems (126-131), it was assumed to be negligible in saturated systems (132-134) until recently. A study of this compound was originally undertaken to investigate the long range coupling, if any, in the cyclohexane series.

Cyclohexane-3,3,6,6-d_4

At room temperature, the chair-chair interconversion in cyclohexane-d_4 is rapid and hence its N.M.R. spectrum consists of a single sharp line (τ 8.63) because of the averaging of axial-equatorial protons. At low temperatures when the rate of ring inversion is slow, the two sets of protons (i.e. A and B) should be expected to resonate at different field strengths. This is, indeed, shown at low temperatures in the spectrum of cyclohexane-d_4.

The proton N.M.R. spectrum of cyclohexane-3,3,6,6-d_4 which exhibits a symmetrical multiplet, has been analyzed as an A_2B_2 system. Strictly, the protons of this compound constitute an A_4B_4 system but they can be dealt with as a superposition of two A_2B_2 sets if there are no long range couplings. The two axial protons are labelled A and the two equatorial protons B. While the chemical shift difference between the axial and equatorial protons in cyclohexane is known (75) to be 28.7 c.p.s., the J-values in this compound are still not known. The calculated spectrum, which makes use of the parameters listed in Table II, agrees with the experimental spectrum. Since the lines of this spectrum are broad, the coupling constants used to calculate the spectrum can not be considered very accurate. Because of the broadening which seems to be due to long range coupling between the two sets of A_2B_2 protons, more accurate coupling constants could not be obtained. For this purpose cyclohexane-3,3,4,4,5,5,6,6-d_8 would be a more suitable compound. This investigation, however, affords approximate values of the coupling constants in cyclohexane.

PART III

INTRODUCTION

A great deal of interest has been shown recently in the nuclear magnetic resonance spectra of bicyclo[2.2.1] heptane ring systems (norbornane and norbornene derivatives). These compounds possess fixed geometry and can be readily synthesized from the Diels-Alder reaction between cyclic dienes and derivatives of ethylene.

The initial investigations furnished relations between spin-spin coupling constants of ring protons and the stereochemistry (141-149). For example, it has been shown that in α and α' chlorocamphor (141), in 3,8-cyclocamphor (142) and in the camphane 2,3-diols (143) the magnitude of the coupling of an exo-proton with the adjacent bridgehead proton is larger (4-5 cycles/sec) than when the proton is endo (0-1 cycle/sec). Examples of various types of long range couplings are known (143,145,146,148-151), for which a theoretical explanation (152) has been proposed.

Fraser (153) established a method of configurational assignment in the 5- and 6- substituted 2-norbornene series. It was shown that upon hydrogenation of the double bond, the signal for a 5- or 6-exo hydrogen moves upfield while a signal due to a 5- or 6-endo hydrogen shifts to lower field. Fraser attributed this behaviour to the known fact that a double bond possesses an appreciable

magnetic anisotropy (120). By this effect the N.M.R. signals of neighboring protons which lie above the plane of the double bond* in a molecule are shifted upfield (shielding) whereas a downfield shift (deshielding) is experienced by protons located in the plane of the double bond (120). Other workers (121,154-159) have established the configuration of substituents in these systems, by evaluating diamagnetic shielding effects of a double bond or a benzene ring.

In general, the magnitude of the shielding and deshielding effects depends on two factors a) the distance of a proton and b) the orientation of the proton with respect to the double bond. These effects can be calculated employing Nakagawa and co-workers' equation (162) provided the molecular geometry is known. In terms of a three dimensional picture, a proton may be considered to lie on or near one of the three principal axes of the double bond. Figure 21 (page 121) defines the various axes, where the z-axis coincides with the bond axis, the y-axis is perpendicular to the z-axis and in the plane of the double bond, and the x-axis is perpendicular to both (i.e. in the plane of the orbitals). Different views regarding the shielding

*The "plane of the double bond" means the plane passing through the two carbon atoms of the double bond and the four atoms bonded to them.

and deshielding effects of a proton along or near these axes have been proposed. Jackman (120) for example suggests

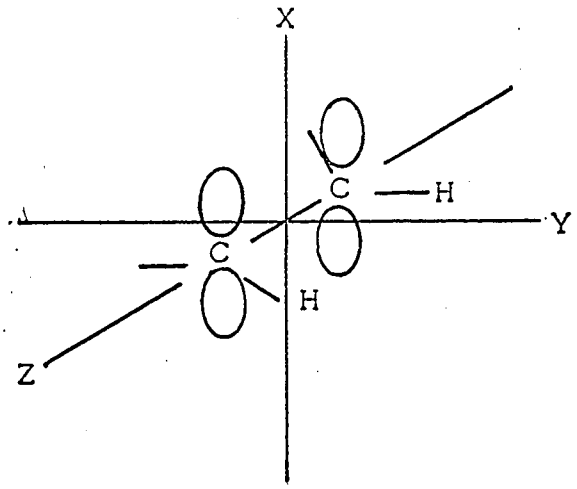


Figure 21: A diagrammatic illustration of the three principal axes of a double bond.

that protons which lie in the x-axis are shielded whereas those in the y- and z-axes are deshielded. Pople (174) on the basis of his theoretical calculations proposed that a proton is deshielded in the y-direction centered on the carbon atoms rather than in the middle of the bond and that it is shielded near the x- and z-axes. In contrast, Conroy (175) has suggested a strong shielding in the y direction. According to the recent work of ApSimon and co-workers (176), protons on the x- and y-axes are shielded whereas those on the z-axis are deshielded. Thus, there is no consistent picture regarding the magnetic anisotropy of a double bond. Most N.M.R. measurements support the suggestions of Jackman and Pople. Ayer, McDonald and Stothers (121) find that in the adduct of maleic anhydride and maleopimaric acid, a

double bond is rigidly held in such a position that an angular methyl group is close to the x-axis; it is shielded in accord with the Pople and Jackman, and in this instance in accord with ApSimon et al (176) too. A similar conclusion was reached by Meyer and Huffman (158). Fraser's investigation (153) on substituted norbornenes also lends support to Jackman's and Pople's suggestions. More recently, several epimeric 7-substituted norbornenes and norbornadienes have been examined by Snyder and Franzus (160), in order to study the effects of anisotropy of the double bond on syn and anti protons at the 7-position. This hydrogen was found to be more shielded when syn than when anti to the double bond, an observation which is consistent with both Jackman (120) and Pople (174). Analysis of the N.M.R. spectra of a number of substituted norbornene derivatives has been carried out by Laszlo and Schleyer (161). They noted that of the two C_7 protons, the hydrogen syn to the double bond absorbed at lower field than the hydrogen anti to it whereas the reverse effect should be expected according to Jackman (120), Pople (174) and ApSimon et al (176). Tori and co-workers (162) pointed out that the introduction of a double bond in norbornane induces a difference in the chemical shift between the bridge methylene protons (these protons in norbornane absorbed at τ 8.80 whereas in norbornene, resonances were observed at τ 8.67 and τ 8.92). The signal of the methylene protons in norbornadiene at τ 8.05 showed an extraordinarily larger

downfield shift than that expected from the additive shielding due to each π electron system (163). This anomaly was not shown by bicyclo[2.2.2]octane ring series. These authors (162), initially assigned the high field band at τ 8.92 to the proton syn to the double bond and the low-field absorption at τ 8.67 to that anti to it. On the basis of their recent investigations on norbornene and benzonorbornane (164), these assignments have been reversed (i.e. the high-field signal in norbornene is now assigned to the C_7 proton anti to the double bond and low-field absorption is attributed to the proton syn to it). Thus in norbornene, the double bond exerted a deshielding effect on the C_7 proton syn to it and a shielding effect on the proton anti to it whereas the reverse should be expected according to Jackman's (120), Pople's (174) and ApSimon and co-workers' (176) suggestions. The observed chemical shift values in this case were quite different from those calculated from Nakagawa and co-workers' equation (155,162,163).

These reports on the anomalous shielding and deshielding effects of C_7 protons by the double bond in norbornene and norbornadiene prompted us to undertake the present investigation. It was considered desirable to study the anisotropic effect of the double bond in similar systems. (The theoretical relation of $\Delta\sigma$, the contribution of anisotropy to the total screening due to a double bond can be (177) written as

$$\Delta\sigma = \Delta\chi \left(\frac{1}{R^3}\right) (1 - 3\cos^2\theta)$$

where R is the distance of an affected proton from the center of the double bond, θ is the angle which the line joining the proton to the center of the double bond makes with the π orbitals (X-axis) and $\Delta\chi$ is the difference in the magnetic susceptibilities ($\chi_{xx} - \chi_{yy}$), assuming that $\chi_{yy} = \chi_{zz}$. This then is the mathematical expression for Jackman's proposal.). For this purpose, 7-isopropylidene bicyclo[2.2.1]heptane and 7,7-dimethylene bicyclo[2.2.1] heptane ring systems appeared suitable because in these compounds the effect of the double bond on the chemical shifts of the methyl protons of the isopropylidene group and the C_7 methylene protons, respectively, could be studied. We wished to see if anomalies similar to those occurring in norbornadiene, took place in the above ring systems. This section of the thesis, therefore, deals with an attempted synthesis of 7-isopropylidene bicyclo [2.2.1]hepta-2,5-diene and a study of the spectra of all the intermediate compounds. An examination of the spectra of 7,7-dimethylene bicyclo[2.2.1]heptane derivatives is also included.

EXPERIMENTAL

1. Description of the General Methods

Methods of Part I and Part II were employed. The ultraviolet spectra were recorded using a Perkin-Elmer Ultraviolet Visible spectrophotometer.

2. Synthetic Procedures

Monochloroethylene carbonate and vinylene carbonate

Monochloroethylene carbonate and vinylene carbonate were prepared according to the procedure of Newman and Addor (165). While the former boiled at 110-115/15 mm, reported 106-107/10-11 mm (165), the latter showed a boiling point of 55-60°/15 mm, reported 73-74°/32 mm.

Dimethylfulvene

Dimethylfulvene, b.p. 58-65°/17 mm, reported 46°/11 mm, was prepared by the method of Thiele and Balhorn (166).

7-Isopropylidene bicyclo[2.2.1]hept-5-ene-2,3-diol carbonate (mixture of exo- and endo-isomers, Ia and Ib)

A solution of vinylene carbonate (8.6 g) in p-xylene (40 ml) was brought to reflux under an atmosphere of nitrogen. Dimethylfulvene (10.6 g) was added to this solution dropwise. The mixture was heated under reflux for 18 hours. At the end of this period, the reaction mixture

had lost its yellow color and was light brown. The solvent was then removed under vacuum; the residual syrup was distilled at 110-130/0.05 mm, to give a pale yellow crystalline material (6.66 g; yield 35%).

The N.M.R. spectrum of this material in carbon tetrachloride containing a trace amount of deuterated chloroform exhibited two sets of absorptions in the intensity ratio of 2:3. The weaker set of signals consisted of triplets at τ 3.70 and 5.20 (spacing: 2 c.p.s.; 2 protons each), a quintet at τ 6.31 (spacing: 2 c.p.s.; 2 protons) and a singlet at τ 8.41 (6 protons). The more intense absorptions included a triplet at τ 3.81 (spacing: 2 c.p.s.; 2 protons), a singlet at τ 5.58 (2 protons) and a triplet at τ 6.49 (spacing: 2 c.p.s.; 2 protons) and a singlet at τ 8.33 (6 protons).

7-Isopropylidene bicyclo[2.2.1]hept-5-ene exo-2,3-diol carbonate i.e. the exo-adduct, Ia

The pale yellow material obtained above was recrystallized from carbon tetrachloride-petroleum ether (30-60°) to yield white needle-like crystals, m.p. 108-109°. This material possessed the following spectral properties.

Infrared: $\nu_{max}^{CHCl_3}$ 3050cm^{-1} (weak); 1850cm^{-1}, 1810cm^{-1} (intense)

N.M.R. (CCl_4): τ 3.81 (triplet; spacing: 2 c.p.s., 2 protons)

τ 5.60 (singlet; 2 protons)

τ 6.50 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 8.33 (singlet; 6 protons)

U.V.: λ_{max} 207 mμ (ε 2564)

Mol.Wt.: 192 (mass spectrum)

Anal. Calcd. for $C_{11}H_{12}O_3$: C,68.73; H,6.29

Found: C,68.99; H,6.18

7-Isopropylidene bicyclo[2.2.1]hept-5-ene-endo-2,3-diol carbonate i.e. the endo-adduct, Ib

Compound Ib was obtained by sublimation of the mixture of exo- endo-carbonate at 35-40°/0.05 mm, followed by recrystallization from ether. The compound melted at 74-76° and exhibited the following spectral properties.

Infrared: $\nu_{max}^{CCl_4}$ 3050cm^{-1} (weak); 1850cm^{-1}, 1810cm^{-1} (intense)

N.M.R. (CCl_4): τ 3.70 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 5.22 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 6.32 (quintet; spacing: 2 c.p.s.; 2 protons)

τ 8.42 (singlet; 6 protons)

U.V.: λ_{max} 207.5 mμ (ε 3109)

Mol.Wt.: 192 (mass spectrum)

Analysis: An elemental analysis of compound Ib could not be obtained because it was available in very small quantity

why ? 2.C.I !

exo-2,3-Dihydroxy-7-isopropylidene bicyclo[2.2.1] hept-5-ene, IIa

Compound IIa was obtained by hydrolysis of the exo-carbonate Ia. The exo-adduct (358 mg) was stirred with a 10% potassium hydroxide solution at room temperature for about 2 hours. The clear solution was made acidic with 10% hydrochloric acid and extracted with ether. The ether extracts were combined, washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent, a crude crystalline residue (300 mg; yield 84%) remained. The compound, after recrystallization from carbon tetrachloride melted at 124-26° and gave the following spectral data.

Infrared: $\nu_{max}^{CHCl_3}$ 3600-3300cm^{-1}; 3050cm^{-1} (shoulder)

N.M.R.: ($CDCl_3$) τ 3.82 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 6.34 (singlet; 2 protons)

τ 6.84 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 7.12 (broad band; 2 protons)

τ 8.34 (singlet; 6 protons)

U.V.: λ_{max} 207 mμ (ε 5081)

Anal. Calcd. for $C_{10}H_{14}O_2$: C,72.26; H,8.49

Found: C,72.14; H,8.32

endo-2,3-Dihydroxy-7-isopropylidene bicyclo[2.2.1] hept-5-ene, IIb

The endo-diol, IIb, was obtained by the hydrolysis of the endo-carbonate, Ib, in exactly the same way as the exo-diol from the exo-carbonate. Compound IIb, after recrystallization from ethanol or sublimation at 100-110°/ 0.05 mm, afforded white crystals, m.p. 132-33°. The following absorption bands were exhibited in the various spectra.

Infrared: $\nu_{max}^{CHCl_3}$ 3600-3300cm^{-1}; 3050cm^{-1} (shoulder)

N.M.R.: ($CDCl_3$)

τ 3.62 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 5.92 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 6.50 (quintet; spacing: 2 c.p.s.; 2 protons)

τ 7.46 (broad band; 2 protons)

τ 8.46 (singlet; 6 protons)

U.V.: λ_{max} 207 mμ (ε 5401)

Anal. Calcd. for $C_{10}H_{14}O_2$: C,72.26; H,8.49

Found: C,72.20; H,8.46

7-Isopropylidene bicyclo[2.2.1]hept-5-ene-exo-2,3-diol thionocarbonate, IIIa

A solution of the exo-diol, IIa, (166 mg) in p-xylene (5 ml) was heated under reflux with a solution of thiocarbonyl diimidazole* (178 mg) in p-xylene (5 ml), for 1/2 hour. The reaction mixture was cooled and filtered to remove any crystalline material. The solvent from the filtrate was evaporated to give crystalline product (200 mg; yield 96%). After sublimation at 110-15/0.05 mm, needle-like crystals, m.p. 176-78°, were obtained. The material had the following spectral properties.

Infrared: $\nu_{max}^{CHCl_3}$ 3050cm^{-1} (shoulder); 1330cm^{-1}, 1300cm^{-1}, 1275cm^{-1} (intense)

N.M.R.: ($CDCl_3$)
- τ 3.78 (triplet; spacing: 2 c.p.s.; 2 protons)
- τ 5.18 (singlet; 2 protons)
- τ 6.37 (triplet; spacing: 2 c.p.s.; 2 protons)
- τ 8.35 (singlet; 6 protons)

U.V.: λ_{max_1} 205 mμ (ε 13384)
λ_{max_2} 241 mμ (ε 19922)

*Thiocarbonyl diimidazole was prepared according to the method of Staab and Walther (167).

Anal. Calcd. for $C_{11}H_{12}O_2S$: C,63.45; H,5.81; S,15.37

Found: C,63.63; H,5.73; S,15.38

Mixture of 7-isopropylidene bicyclo[2.2.1]hept-5-ene exo-2,3 and endo-2,3-diol thionocarbonate, IIIa and IIIb

Starting from a mixture of Ia and Ib, a mixture of diols, IIa and IIb, was obtained as described in the preceeding pages. This mixture was then converted into a mixture of the corresponding thionocarbonates, IIIa and IIIb. The crude crystalline material, on sublimation at 120-130°/0.05 mm, afforded a mixture of the exo- and endo-thionocarbonates in the ratio of 3:2 respectively, as shown by the following spectrum.

N.M.R.: ($CDCl_3$)

1st set (Exo-isomer)

τ 3.78 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 5.17 (singlet; 2 protons)

τ 6.36 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 8.34 (singlet; 6 protons)

2nd set (Endo-isomer)

τ 3.64 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 4.82 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 6.21 (quintet; spacing: 2 c.p.s.; 2 protons)

τ 8.41 (singlet; 6 protons)

Attempted Desulfurization-Decarboxylation of 7-isopropylidene bicyclo[2.2.1]hept-5-ene-exo-endo-2,3-diol thionocarbonate mixture. using trimethyl phosphite

The mixture of thionocarbonates, IIIa and IIIb, (1.04 g) in trimethyl phosphite (10 ml), in a two-necked flask equipped with a gas inlet tube and a reflux condenser, was heated under reflux, under a nitrogen atmosphere for 84 hours. The condenser, in turn, was connected to two traps containing carbon tetrachloride. A white solid deposited in the tubing of the first trap. A potassium hydroxide solution (30 ml of 20%) was next added to the reaction mixture and the contents were refluxed for 1/2 hour. The solution was extracted with ether several times and the combined ether extracts were washed with water and dried over anhydrous sodium sulfate. After evaporation of the ether from the filtrate, a dark brown residue (50 mg) was obtained. The N.M.R. spectrum of the dark residue, in deuterated chloroform showed the absorption bands of the starting material.

The white solid deposited in the first trap, exhibited 11 bands in the region τ 5.7-8.4 in its N.M.R. spectrum.

The first carbon tetrachloride trap showed about 9 bands between τ 5.2-9.1 in addition to the absorption of trimethyl phosphite at τ 6.58.

The second trap, in its N.M.R. spectrum gave two very broad bands at τ 8.65 and 9.05 in addition to 5

bands between τ 5.8-7.9.

Attempted Desulfurization-Decarboxylation of 7-isopropylidene bicyclo[2.2.1]hept-5-ene-exo-endo-2,3-diol thionocarbonate mixture, using Raney nickel

A solution of the exo-endo-thionocarbonate mixture, IIIa and IIIb, (95 mg) in ether (10 ml) was stirred with Raney nickel* (60-90 mg), for 12 hours. The filtered ether solution, on evaporation, gave only the starting material as shown by its N.M.R. spectrum.

A complicated N.M.R. spectrum of the reaction product was observed (about ten bands from τ 5.50-9.00) when the reaction was carried out for 2 hours in refluxing tetrahydrofuran or dioxane.

7-Isopropylidene bicyclo[2.2.1]heptane-exo-2,3-diol carbonate, Va

A solution of 7-isopropylidene bicyclo[2.2.1] hept-5-ene-exo-2,3-diol carbonate (50 mg) in ethanol (10 ml) was hydrogenated in the presence of Adam's catalyst (9 mg) at atmospheric pressure. One equivalent of hydrogen was taken up in about 5 minutes. After removal of the catalyst by filtration, the solvent was evaporated. A white residue (48 mg; yield 95%) was obtained. The product after sub-

*Raney nickel was prepared according to the procedure described by Vogel (168).

limation at 90-100°/0.05 mm, melted at 113-14°.

Compound V had the following spectral properties.

Infrared: $\nu_{max}^{CCl_4}$ 1845cm^{-1}, 1810cm^{-1}

N.M.R.: (CCl_4)
- τ 5.57 (singlet; 2 protons)
- τ 7.20 (triplet; spacing: 2 c.p.s.; 2 protons)
- τ 8.27 (singlet; 6 protons)
- τ 8.57 (multiplet)
- τ 8.79 (multiplet)

U.V.: λ_{max} 205 mμ (ε 3188)

Anal. Calcd. for $C_{11}H_{14}O_3$: C,68.02; H,7.27

Found: C,68.02; H,7.12

exo-2,3-Dihydroxy-7-isopropylidene bicyclo[2.2.1] heptane, VIa

A solution of exo-2,3-dihydroxy-7-isopropylidene bicyclo[2.2.1]hept-5-ene (60 mg) in ethanol (10 ml) was reduced in the presence of Adam's catalyst (8 mg) at atmospheric pressure. The up-take of hydrogen was over in 5 minutes. The catalyst was removed by filtration and the filtrate after evaporation of the solvent, afforded white amorphous material (56 mg; yield 92%); this substance sublimed at 80-90°/0.05 mm to give white crystals, m.p. 96-97°.

The following spectral absorptions were observed.

Infrared: $\nu_{max}^{CCl_4}$ 3500cm^{-1} (broad)

N.M.R.: ($CDCl_3$) τ 6.31 (singlet; 2 protons)
τ 7.43 and 7.47 (i.e. a distorted triplet, high field portion of which was overlapped by another band; 4 protons)
τ 8.29 (singlet; 6 protons)
τ 8.63 (multiplet)
τ 8.82 (multiplet)

U.V.: λ_{max} 205 mμ (ε 4371)

Anal. Calcd. for $C_{10}H_{16}O_2$: C,71.39; H,9.59
Found: C,71.61; H,9.47

7-Isopropylidene bicyclo[2.2.1]heptane-exo-2,3-diol thionocarbonate, VIIa

A solution of 7-isopropylidene bicyclo[2.2.1]hept-5-ene-exo-2,3-diol thionocarbonate (66 mg) in ethyl acetate (15 ml) was hydrogenated in the presence of platinum oxide (10 mg) at atmospheric pressure. The up-take of hydrogen was extremely slow and was complete after 24 hours. The solvent after filtering off the catalyst, was evaporated to yield a residue (60 mg; yield 90%). The product after sublimation at 100-110°/0.05 mm, melted at 145-46°.

Compound VIIa showed the following spectral properties.

Infrared: $\nu_{max}^{CHCl_3}$ 1340cm^{-1}, 1305cm^{-1}, 1275cm^{-1}

N.M.R.: ($CDCl_3$) τ 5.22 (singlet; 2 protons)
τ 7.05 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 8.29 (singlet; 6 protons)

τ 8.51 (multiplet)

τ 8.77 (multiplet)

U.V.: λ_{max_1} 205 mμ (ε 8338)

λ_{max_2} 241 mμ (ε 14362)

Anal. Calcd. for $C_{11}H_{14}O_2S$: C,62.84; H,6.71; S,15.22

Found: C,62.68; H,6.57; S,15.09

Attempted Hydrogenation of 7-isopropylidene bicyclo[2.2.1] hept-5-ene-endo-2,3-diol carbonate, Ib

A solution of the above endo-carbonate (60 mg) in ethanol (10 ml) was hydrogenated in the presence of Adam's catalyst for 5 minutes. The clear filtrate on evaporation of the solvent yielded a crystalline residue (55 mg; yield 90%). This material on sublimation at 44-55°/0.05 mm, afforded white crystals, m.p. 61°.

The compound exhibited the following spectral absorptions.

Infrared: $\nu_{max}^{CCl_4}$ 1850cm^{-1}, 1810cm^{-1}

N.M.R. (CCl_4): τ 5.38 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 7.50 (broad rough quintet; 2 protons)

τ 8.33 (broad band with width at half height of 5-6 c.p.s.; 5 protons)

τ 9.04 (doublet; spacing: 6 c.p.s.; 6 protons)

τ 8.77 (multiplet)

endo-2,3-Dihydroxy-7-isopropylidene bicyclo[2.2.1] heptane, VIb

Hydrogenation of a solution of endo-2,3-dihydroxy-7-isopropylidene bicyclo[2.2.1]hept-5-ene, IIb, (30 mg) in ethanol (10 ml) was carried out in the presence of Adam's catalyst (5 mg) for 5 minutes. The filtrate, after removal of the catalyst, gave white crystalline material which sublimed at 90-100°/0.05 mm. The sublimate melted at 129-30°.

Compound VIb gave the following spectral data.

Infrared: $\nu_{max}^{CCl_4}$ 3600-3300cm^{-1}

N.M.R.: ($CDCl_3$)
- τ 6.15 (triplet; spacing: 2 c.p.s.; 2 protons)
- τ 7.14 and 7.28 (a broad band intermingled with another broad band; 4 protons)
- τ 8.36 (singlet; 6 protons)
- τ 8.68 (multiplet)
- τ 9.12 (multiplet)

U.V.: λ_{max} 205 mμ (ε 3798)

Anal. Calcd. for $C_{10}H_{16}O_2$: C,71.39; H,9.59

Found: C,71.21; H,9.71

7-Isopropylidene bicyclo[2.2.1]hept-5-ene-exo-2,3-dicarboxylic acid, IX, and its anhydride, VIII

The method followed in the preparation of compound VIII was that of Craig and co-workers' (169). The anhydride, VIII, melted at 138-40°; reported 140° (169), and showed the following spectral properties.

Infrared: ν_{max}^{Nujol} 1850cm^{-1}, 1760cm^{-1}

N.M.R.: ($CDCl_3$)
- τ 3.76 (triplet; spacing: 2 c.p.s.; 2 protons)
- τ 6.30 (triplet; spacing: 2 c.p.s.; 2 protons)
- τ 7.00 (singlet; 2 protons)
- τ 8.60 (singlet; 6 protons)

Compound IX was obtained by the procedure of Alder and Ruhrmann (170). The melting point of this compound was 157°; reported 157° (170). It showed the following spectral absorptions:

Infrared: ν_{max}^{Nujol} 3200cm^{-1} (broad); 1725, 1705cm^{-1}

N.M.R.: (pyridine)
- τ 3.64 (triplet; spacing: 2 c.p.s.; 2 protons)
- τ 6.20 (triplet; spacing: 2 c.p.s.; 2 protons)
- τ 7.03 (singlet; 2 protons)
- τ 8.23 (singlet; 6 protons)

Attempted Decarboxylation of 7-isopropylidene bicyclo [2.2.1]hept-5-ene-exo-2,3-dicarboxylic acid, IX, using lead tetraacetate

A solution of compound IX (1.93 g) in dry pyridine (15 ml) was stirred and heated with lead tetraacetate (3.85 g) (95-97,171), under nitrogen, in a three-necked flask equipped with a gas inlet tube and a reflux condenser which, in turn, was connected to a receiver kept at Dry Ice-acetone temperature. Brisk effervescence, which continued for about 15-20 minutes, was observed as the temperature was raised to 60-70°. When no more gas was evolving, the temperature of the reaction mixture was raised to 80-100°; a distillate collected in the receiving flask which was treated with 10% hydrochloric acid and extracted with chloroform several times. The chloroform extracts were combined, washed with water and dried over anhydrous sodium sulfate.

The clear filtrate (yellow) in its N.M.R. spectrum showed bands at τ 2.73, 3.50 and 7.80. The yellow liquid was identified as dimethylfulvene by vapor phase chromatography.

The reaction was, next, done in a slightly different way.

A mixture of the diacid, IX (5.55 g) in dimethylsulfoxide (10 ml) (173) and lead tetraacetate (11.55 g) in dimethyl sulfoxide (30 ml) was kept at stirring for 8 hours at room temperature under nitrogen using a trap immersed in

a Dry Ice-acetone bath. A small amount of the liquid collected in the receiver which was dimethyl sulfoxide. The trap was replaced by another and the reaction mixture was heated for 2 hours at 60-80° under nitrogen. The temperature was then raised to 95-100° to obtain a small amount of the liquid in the receiver. The distillate was taken up in carbon tetrachloride, washed with water and dried. The N.M.R. spectrum of the filtered solution gave bands at τ 3.7 and 7.87.

Spiro[2.4]hepta-1,3-diene

Spiro[2.4]hepta-1,3-diene, b.p. 43-45°/70 mm, reported 57°/100 mm was prepared according to the method of Alder and co-workers (172). The following absorption bands were observed for this compound.

Infrared: ν_{max}^{film} 3120cm^{-1}; 3050cm^{-1}

N.M.R. (CCl_4): τ 3.66 (two symmetrical closely spaced
τ 4.07 multiplets; 4 protons)
τ 8.51 (singlet; 4 protons)

Adduct, X, of Spiro[2.4]hepta-1,3-diene with dibromoethylene

Compound X and rest of the compounds in this series (XI - XIV) were prepared by the method of Alder et al (172). This reaction was done in a Carius combustion tube, sealed under high vacuum. The adduct sublimed at 40-50°/

0.05 mm, m.p. 73°; reported 75° (172).

Compound X possessed the following spectral properties.

Infrared: $\nu_{max}^{CCl_4}$ 3110cm^{-1}; 3050cm^{-1}

N.M.R. (CCl_4): τ 3.71 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 5.48 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 7.43 (quintet; spacing: 2 c.p.s.; 2 protons)

τ 9.46 (singlet; 4 protons)

7,7-Dimethylene bicyclo[2.2.1]hepta-2,5-diene, XII

Purification of compound XII, b.p. 30-31°/18 mm, reported 37°/20 mm (172) was achieved by vapor phase chromatography, using silicone oil column at 91°. It exhibited the following spectral absorptions.

Infrared: $\nu_{max}^{CCl_4}$ 3100cm^{-1}; 3010cm^{-1} (shoulder)

N.M.R. (CCl_4): τ 3.26 (triplet; spacing: 2 c.p.s.; 4 protons)

τ 7.08 (quintet; spacing: 2 c.p.s.; 2 protons)

τ 9.57 (singlet; 4 protons)

Catalytic Reduction of 2,3-dibromo-7,7-dimethylene bicyclo[2.2.1]hept-5-ene, X

Hydrogenation of compound X afforded 2,3-dibromo-7,7-dimethylene bicyclo[2.2.1]heptane, XI which was purified by sublimation at 80-90°/0.05 mm. The white crystals melted at 104°; reported 76° (172). Compound XI gave the following spectral data.

Infrared: $\nu_{max}^{CCl_4}$ 3100cm^{-1} (shoulder)

N.M.R. (CCl_4): τ 5.33 (rather broad band with width at half height of 5 c.p.s.; 2 protons)

τ 8.27 (broad unsymmetrical multiplet; 6 protons)

τ 9.39 (singlet; 4 protons)

7,7-Dimethylene bicyclo[2.2.1]hept-2-ene, XIII

Purification of compound XIII, b.p. 57-60°/50 mm, reported 63°/60 mm (172) was accomplished on a vapor fractometer using a column of silicone oil at 98°. The compound possessed the following spectral properties.

Infrared: $\nu_{max}^{CCl_4}$ 3100cm^{-1}; 3020cm^{-1} (shoulder)

N.M.R. (CCl_4): τ 3.97 (triplet; spacing: 2 c.p.s.; 2 protons)

τ 7.92 (rather broad band of a width at half height of 6 c.p.s.; 2 protons)

τ 8.22 and 8.98 (Two well separated multiplets; 4 protons)

τ 9.62 and 9.71 (two closely spaced multiplets merged into each other; 4 protons)

7,7-Dimethylene bicyclo[2.2.1]heptane, XIV

Compound XIV, m.p. 40-42°, reported 44° (172) exhibited the following spectral properties.

Infrared: $\nu_{max}^{CCl_4}$ 3100cm^{-1} (shoulder)

N.M.R. (CCl_4): τ 8.5 (a broad multiplet; 10 protons)

τ 9.58 (singlet; 4 protons)

DISCUSSION

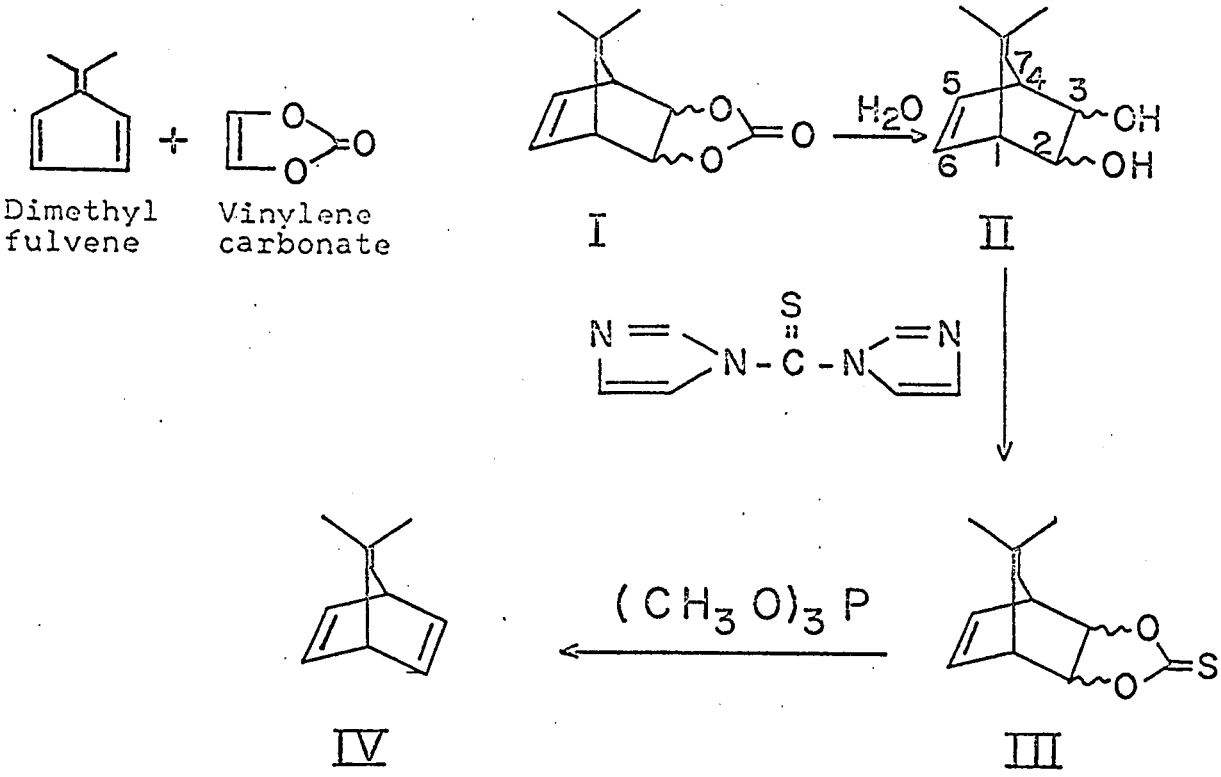
Our interest in the field was to investigate the anisotropic effect of the double bond in 7-isopropylidene bicyclo[2.2.1]heptane and 7,7-dimethylene bicyclo[2.2.1] heptane ring systems as outlined in the Introduction of Part III. While the synthetic procedure for the latter is known, no reports on the preparation of 7-isopropylidene bicyclo[2.2.1]hepta-2,5-diene, IV, were available. It was, therefore, necessary to attempt to synthesize this compound and to characterize any new compounds in this series. The two routes planned by us for the synthesis of compound IV are shown in Figure 22 (Scheme I and II, page 145). Scheme I makes use of the recent work of Corey and Winter (178) who reported that olefinic bonds could be obtained smoothly from 1,2-diols. Numerous examples of oxidative decarboxylation (95-97,171) of dicarboxylic acids to produce double bonds including examples in the bicyclic systems have led us to consider Scheme II.

1. A. Scheme I

(i) Configurational Assignments of 7-isopropylidene bicyclo[2.2.1]hept-5-ene-2,3-diol carbonate I And Its Derivatives

The reaction of dimethyl fulvene with vinylene carbonate afforded a mixture of two diastereoisomers, i.e. the exo and the endo isomers of the adduct I. This conclusion

Scheme I:



Scheme II:

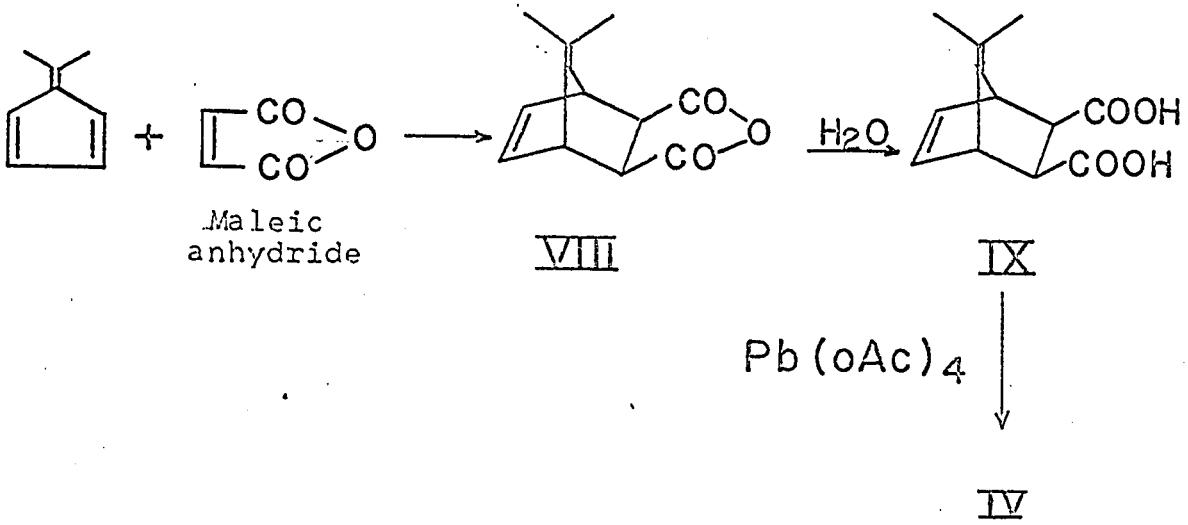


Figure 22 Synthetic routes for 7-isopropylidene bicyclo [2.2.1]hepta-2,5-diene

was arrived at on the basis of the N.M.R. spectrum of the product which showed two sets of bands (four peaks each) in the intensity ratio of 3:2. Fractional crystallization of the mixed adduct I afforded pure carbonates Ia and Ib, respectively.

The identity of the more abundant isomer, compound Ia, was proved in the following way. The mass spectrum of the needle-like crystals, m.p. 108-109°, showed its molecular weight to be 192, indicating that the compound Ia is a 1:1 adduct of dimethyl fulvene and vinylene carbonate. Its infrared spectrum exhibited bands at 3050 cm^{-1} (C=C-H stretch) and 1850 cm^{-1} and 1810 cm^{-1} (C=O stretch), thus the presence of a double bond and a carbonate group in the molecule is indicated. The <u>exo</u> isomer Ia gave the correct elemental analysis and thus confirmed its gross structure. The N.M.R. data of compound Ia which is summarized in Table V, (page 147), confirms the bicyclic nature of the compound as well as the <u>exo</u> configuration of the carbonate group. Two triplets at τ 3.81 and 6.50 are assigned to the vinylic and the bridgehead protons, respectively. A singlet at τ 5.60 must be the two protons at C_2 and C_3 since these protons being in the <u>endo</u> configuration will have no coupling with the bridgehead protons. Finally, a singlet at τ 8.33 represents the methyl protons of the isopropylidene group.

Structure of the minor isomer Ib, m.p. 74-76°, was proved similarly. The molecular weight of the compound was found to be 192 (as shown by its mass spectrum), indicating

TABLE V

Chemical Shift Data in τ Units* of some 7-Isopropylidene bicyclo[2.2.1]heptane Derivatives

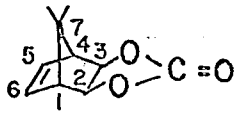
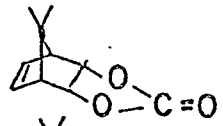
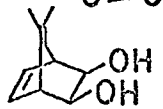
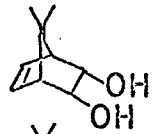
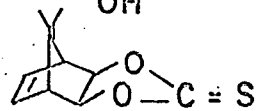
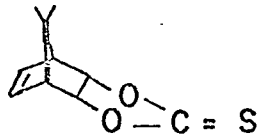
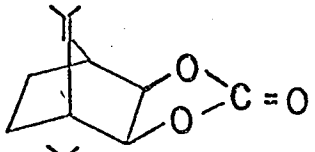
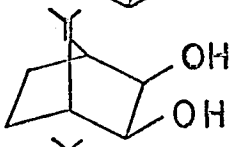
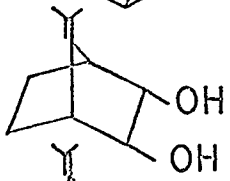
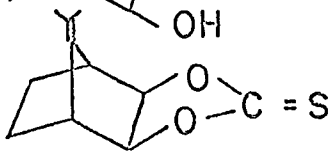
Compound	Olefinic Protons	Hydroxyl Protons	Protons at C_2 and C_3	Bridge-head Protons	Exo Protons at C_5 and C_6	Endo Protons at C_5 and C_6	Methyl Protons
Ia 	3.81(t)		5.60(s)	6.50(t)			8.33(s)
Ib 	3.70(t)		5.22(t)	6.32(qi)			8.42(s)
IIa 	3.82(t)	7.12 (br.s.)	6.34(s)	6.84(t)			8.34(s)
IIb 	3.62(t)	7.46 (br.s.)	5.92(t)	6.50(qi)			8.46(s)
IIIa 	3.78(t)		5.18(s)	6.37(t)			8.35(s)
IIIb 	3.64(t)		4.82(t)	6.21(qi)			8.41(s)

Table V continued

Compound	Olefinic Protons	Hydroxyl Protons	Protons at C_2 and C_3	Bridge-head Protons	Exo Protons at C_5 and C_6	Endo Protons at C_5 and C_6	Methyl Protons
Va 			5.57(s)	7.20(t)	8.57(m)	8.79(m)	8.27(s)
VIa 		7.47(br)	6.31(s)	7.43 (distorted t)	8.63(m)	8.82(m)	8.29(s)
VIb 		7.28(br)	6.15(t)	7.14 (br)	8.68(m)	9.12(m)	8.36(s)
VIIa 			5.22(s)	7.05(t)	8.51(m)	8.77(m)	8.29(s)

*All these assignments are confirmed by the integrated areas of the various peaks.

Peak multiplets are represented by, t = triplet; s = singlet; qi = quintet;

br = broad band; m = multiplet.

that it is a 1:1 adduct of dimethyl fulvene and vinylene carbonate. The presence of a double bond and a carbonyl function in the carbonate group in the molecule was indicated by its infrared spectrum where bands at 3050 cm^{-1} (C=C-H stretch) and 1850 cm^{-1} and 1810 cm^{-1} (C=O stretch) were discernible. The positions of the N.M.R. resonances of compound Ib are listed in Table V. This isomer gives rise to a triplet at τ 3.70 characteristic of the vinylic protons. A triplet at τ 5.22 is assigned to the two <u>exo</u> protons at C_2 and C_3 since the <u>exo</u> protons are known to couple with the bridgehead protons (141-143,153,160-162). Thus the carbonate group in this compound should have the <u>endo</u> configuration. A quintet at τ 6.32 is assigned to two bridgehead protons (153). A singlet at τ 8.42 represents the methyl protons of the isopropylidene group. In this way, compound Ib has been shown to be the <u>endo</u> adduct of dimethyl fulvene and vinylene carbonate. An elemental analysis of Ib itself was not obtained since it was available in rather small quantity but the diol IIb, which was derived from Ib on hydrolysis, was found to analyze correctly. This, therefore, establishes the structure of Ib as well. It is interesting to note that the methyl protons in the <u>endo</u> carbonate Ib absorb at higher field than the methyl protons in the corresponding <u>exo</u> isomer Ia whereas all other protons in the latter resonate at higher field than in the former.

The exo adduct Ia on hydrolysis gave rise to exo-2,3-dihydroxy-7-isopropylidene bicyclo[2.2.1]hept-5-ene, IIa, m.p. 124-26°. Its configuration follows from that of Ia and from its spectral data. Compound IIa in its infrared spectrum exhibited a shoulder at 3050 cm^{-1} for the double bond and a broad band from 3600 cm^{-1} - 3300 cm^{-1} for the hydroxyl groups and no band in the 1800 cm^{-1} region for the carbonyl group. The positions of its N.M.R. resonances are listed in Table V. A broad signal at τ 7.12 is assigned to the hydroxyl protons whereas a triplet at τ 3.82 is attributed to protons attached to a carbon-carbon double bond. A singlet at τ 6.34 represents the two protons at C_2 and C_3. The fact that it is a single sharp peak indicates that these protons are not coupled with the adjacent bridgehead protons and hence they must occupy endo positions. In other words the hydroxyl groups at these carbon atoms should be in the exo configuration. A triplet at τ 6.84 and a signal at τ 8.34 are assigned to the bridgehead and methyl protons, respectively. Further characterization of compound IIa was afforded by its correct elemental analysis.

Similarly, endo-2,3-dihydroxy-7-isopropylidene bicyclo[2.2.1]hept-5-ene, IIb, m.p. 132-33°, was obtained by the hydrolysis of the endo carbonate, Ib. The hydroxyl groups at C_2 and C_3 must, therefore, occupy the endo positions. The infrared spectrum of compound IIb lacked a band for the carbonyl group around 1800 cm^{-1}. Instead the com-

pound showed an absorption between 3600-3300 cm^{-1} (O-H stretch) and a shoulder at 3050 cm^{-1} (C=C-H stretch), indicating that hydrolysis of the carbonate Ib was complete. Compound IIb possesses five types of protons, whose τ values are given in Table V. Two triplets at τ 3.62 and 5.92 are assigned to the two vinylic protons and the two protons at C_2 and C_3, respectively. The two hydroxyl groups have to be in the endo configuration as the protons at C_2 and C_3 appear as a triplet due to coupling with the adjacent bridgehead protons. A quintet centered at τ 6.50 is attributable to the two bridgehead protons. A singlet at τ 8.46 is assigned to the protons of the methyl groups while a broad band at τ 7.46 represents the two hydroxyl protons.

7-Isopropylidene bicyclo[2.2.1]hept-5-ene-exo-2, 3-diol thionocarbonate, IIIa, m.p. 176-78°, was prepared by the reaction between the diol IIa and thiocarbonyldiimidazole. Its configuration follows from the configuration of IIa and is confirmed by its spectral data. The infrared spectrum of compound IIIa exhibited a shoulder at 3050 cm^{-1} for the double bond and three intense bands at 1330 cm^{-1}, 1300 cm^{-1} and 1275 cm^{-1} characteristic of cyclic thionocarbonates (178,179). In its N.M.R. spectrum, four well separated bands for the four types of protons were observed. These are listed in Table V. The fact that the protons at C_2 and C_3 appear as a singlet again confirms the exo configurational assignment. A mixture of the two isomers of thionocarbonate IIIa and IIIb was obtained in comparatively

larger quantity from the corresponding mixture of exo-endo diols IIa and IIb. The thionocarbonate mixture, in its N.M.R. spectrum exhibited two sets of bands in the intensity ratio of 3:2 for the exo and the endo thionocarbonate, respectively. Since the peaks for the exo isomer have been assigned, the signals due to endo isomer were readily recognized. They consisted of a triplet at τ 3.64 (vinylic protons), triplet at τ 4.82 (protons at C_2 and C_3), a quintet at τ 6.21 (bridgehead protons) and a singlet at τ 8.41. Integrated areas of these peaks confirmed these assignments.

(ii) Reduction Products of 7-isopropylidene bicyclo [2.2.1]hept-5-ene-2,3-diol carbonate, I, And Its Derivatives

We wished to study the effect of removal of the double bond on the chemical shift of the methyl protons, and the protons at C_2 and C_3, in compound I and its derivatives. Catalytic reduction of these compounds was, therefore, carried out and their N.M.R. spectra were recorded. The compounds thus obtained and their N.M.R. data are shown in Table V (page 148). These compounds are discussed in that order.

7-Isopropylidene bicyclo[2.2.1]heptane exo-2,3-diol carbonate, Va, m.p. 113-14°, exhibited in its infrared spectrum bands at 1845 cm^{-1} and 1810 cm^{-1} for the carbonyl group and no shoulder at 3050 cm^{-1} for the double bond. The N.M.R. spectrum of Va shows no peak for the vinylic

protons indicating that hydrogenation of Ia was complete. A singlet at τ 5.57 is assigned to the protons at C_2 and C_3 and a triplet at τ 7.20 represents the bridgehead protons as they are coupled with the exo protons at C_5 and C_6. Of the four protons at C_5 and C_6, two are in the exo and two in the endo configuration. Strictly speaking, these should constitute the A_2B_2 portion of an $A_2B_2M_2X_2$ system. The spectrum shows a multiplet for these protons where the band centered at about τ 8.57 is assigned to the two exo protons at C_5 and C_6 and the one at τ 8.79 to the two endo protons in accordance with the known chemical shifts of these protons in similar systems (164). The exact resonances of these protons is considered to be within $\pm$0.05 p.p.m. of the above values. A singlet at τ 8.27 is attributed to the protons of the two methyl groups. A correct elemental analysis of compound Va confirmed its structure.

The remaining hydrogenation products were characterized in a manner analogous to that described for compound Va. Only the salient features of their N.M.R. spectra will be discussed. The N.M.R. spectrum (see Table V) of exo-2,3-dihydroxy-7-isopropylidene bicyclo [2.2.1] heptane, VIa, m.p. 96-97°, is explicable in the same way as the spectrum of compound Va except that in this case the triplet of the bridgehead protons at τ 7.43 is overlapped by the signal of the hydroxyl protons at τ 7.47. A correct elemental analysis confirmed the identity of compound VIa.

7-Isopropylidene bicyclo[2.2.1]heptane exo-2,3-diol thionocarbonate, VIIa, m.p. 145-46°, exhibited characteristic bands of cyclic thionocarbonate at 1340 cm^{-1}, 1305 cm^{-1} and 1275 cm^{-1}. The N.M.R. absorption bands listed in Table V are assigned, following the arguments previously discussed. The identity of this compound is confirmed by its correct elemental analysis.

An attempt to hydrogenate 7-isopropylidene bicyclo [2.2.1]hept-5-ene-endo-2,3-diol carbonate, Ib, resulted not only in the saturation of the double bond between C_5 and C_6 but also in the reduction of the double bond at the 7-position. The evidence supporting this view is mainly spectroscopic. A carbonyl function is indicated by bands at 1850 cm^{-1} and 1810 cm^{-1} in its infrared spectrum. A triplet at τ 5.38 in the N.M.R. spectrum is assigned to the exo protons at C_2 and C_3 whereas a quintet at τ 7.50 is attributable to the bridgehead protons. A doublet at τ 9.04 (J = 6 c.p.s.) is assigned to the methyl protons of the isopropyl group as they will be coupled to the proton at the carbon bearing the methyl groups. This proton which should be expected to be a heptet because of the coupling with the six methyl protons, is not identifiable in the spectrum. The heptet may further be split due to coupling with the proton at C_7. It is therefore understandable that this proton at C_8 will be obscured by the bands between τ 8.33-9.04. A broad band with a width at half height of 6 c.p.s. (area equivalent to 5 protons) may account for the four exo protons at C_2, C_3, C_5 and C_6.

and a proton at C_7. A doublet at τ 8.77 represents the two endo protons. On steric grounds, saturation of the isopropylidene group in the endo carbonate Ib can be easily explained because here the carbonate group will exert no steric hindrance for the attack of the hydrogen atoms at the C_7 position.

Hydrogenation of the corresponding endo diol IIb, however, reduced only the double bond between C_5 and C_6 to give endo-2,3-dihydroxy-7-isopropylidene bicyclo[2.2.1] heptane, VIb, m.p. 129-30°. Table V shows the N.M.R. resonances of the various protons of compound VIb. Here, again, assignments of peaks can be made as before. The signals of the bridgehead and the hydroxyl protons seem to intermingle. Perhaps the low field band at τ 7.14 represents the bridgehead protons and the peak centered at τ 7.28, the hydroxyl protons. Compound VIb gave the correct elemental analysis, thus confirming its identity.

(iii) Attempted Desulfurization-Decarboxylation of 7-isopropylidene bicyclo[2.2.1]hept-5-ene-2,3-diol thionocarbonate, III

The mixture of thionocarbonate IIIa and IIIb was used for the reaction with trimethylphosphite (178). The expected product, 7-isopropylidene bicyclo[2.2.1]hepta-2,5-diene, IV, could not be isolated. The only isolable product was a white solid which deposited in one of the traps. It exhibited a complicated pattern of 11 bands in the

region τ 5.7-8.4 in its N.M.R. spectrum. The contents of the two traps containing carbon tetrachloride also showed quite complicated N.M.R. spectra (τ 5.2-9.1) which in no way could be attributed to compound IV. The reaction mixture after treatment of IIIa - IIIb with Raney nickel, gave an N.M.R. spectrum which lacked the olefinic absorptions expected for compound IV. These attempts to synthesize compound IV have been unsuccessful.

B. Scheme II

Attempted Decarboxylation of 7-isopropylidene bicyclo [2.2.1]hept-5-ene-exo-2,3-dicarboxylic acid, IX

Since compound IV could not be obtained via Scheme I, decarboxylation of compound IX was attempted. The melting points of the diacid IX and its anhydride (VIII) were in agreement with those reported in the literature (170,169). Their structures were further confirmed by their N.M.R. spectra (see Experimental, page 138).

Attempts to decarboxylate the diacid IX using lead tetraacetate (95-97,171) in pyridine or in dimethyl sulfoxide (173) afforded only dimethyl fulvene as shown by vapor phase chromatography. Thus attempts to synthesize compound IV have been unsuccessful. The failures may be due, at least in part, to the inherent instability of the desired triene. One should probably attempt its synthesis by a method which avoids the presence of any possible radicals. One such approach would consist of reacting dimethyl

fulvene with 1,2-dibromoethylene, followed by debromination with zinc dust.

In order to examine further the shieldings in the norbornadienes and hydrogenation products, the 7,7-dimethylene derivatives of norbornane, norbornene and norbornadienes were made according to the method in the literature (172) and their N.M.R. spectra were recorded. These are discussed on page 159.

We will now discuss the anisotropic effect of the double bond on the methyl groups and on the endo and exo protons at C_2 and C_3 in the reduction products of compound I and its derivatives. In view of the previous anomalies in shielding, we will examine the data qualitatively at the outset since a consistent behaviour must be observed if quantitative calculations are to be meaningful. Changes in the chemical shifts of various protons upon hydrogenation are obtained from the data in Table V and are shown in Table VI (page 158). It can be seen that the methyl groups in all the dihydro compounds absorb at lower field than in their unsaturated counterparts. This means that the double bond between C_5 and C_6 has a shielding effect on the methyl groups and that this effect is removed upon hydrogenation of the double bond. From the molecular models it would seem that the methyl protons lie in a region where they should be insensitive to $\chi_{xx}-\chi_{yy}$ as θ is approximately 50° but sensitive to the difference between χ_{xx} and χ_{zz}. The shielding by the double bond

TABLE VI

Changes in Chemical Shift ($\Delta\tau$) on Hydrogenation

Compounds	Protons at C_2 and C_3 (Exo)	Protons at C_2 and C_3 (Endo)	Methyl Protons
Ia ⟶ Va		-0.03	-0.06
IIa ⟶ VIa		-0.03	-0.05
IIIa ⟶ VIIa		+0.04	-0.06
IIb ⟶ VIb	+0.23		-0.10

$\Delta\tau = \tau_2 - \tau_1$, where τ_1 = the chemical shift in the unsaturated compound

τ_2 = the chemical shift in the dihydro compound

indicates $\chi_{xx} < \chi_{zz}$ in accord with the hypothesis of Jackman (120). The exo protons at C_2 and C_3 lie near the y-axis and should, therefore, be expected to be shifted downfield, whereas the endo protons (near the x-axis) should be expected to be shifted upfield by the double bond. If τ_1 represents the chemical shift in the unsaturated compounds and τ_2 in the dihydro compounds, then $\Delta\tau$ should be positive for the exo protons and negative for the endo protons as Fraser (153) suggested. The present investigation shows that in three cases out of four, the endo protons at C_2 and C_3 experience a downfield shift whereas the corresponding exo protons experience an upfield shift upon hydrogenation of the double bond. This behaviour is in accordance with Fraser's predictions (or in accordance with Jackman's and Pople's hypotheses). The fact that compound IIIa on removal of the double bond shows a positive rather than negative $\Delta\tau$ may result due to the anisotropic effect of the thionocarbonate group. A previous exception had also been noted by Wong and Lee (154). A sensible modification to the original proposal would be as follows: exo protons would be expected to show an appreciable positive $\Delta\tau$ while endo protons exhibit only a very small $\Delta\tau$ (positive or negative).

2. N.M.R. Spectra of 7,7-dimethylene bicyclo[2.2.1] heptane series

It was considered of interest to synthesize compounds XII, XIII and XIV and to study the effect of the

double bond on the chemical shift of C_7-methylene protons. Following the procedure of Alder and co-workers (172), 2,3-dibromo-7,7-dimethylene bicyclo[2.2.1]hept-5-ene, X, was prepared by the reaction of spiro[2.4]hepta-1,3-diene with 1,2-dibromoethylene. Compounds XI-XIV were then obtained by debromination of X with zinc dust and hydrogenation.

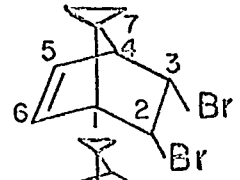
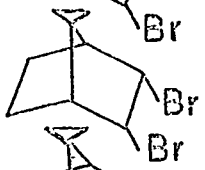
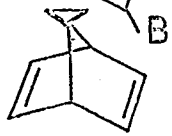
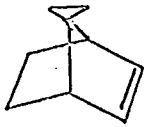
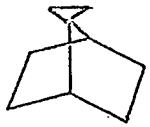
The structure assigned to compound X, m.p. 73°, reported 75° (172), was consistent with its infrared and N.M.R. spectra (see Experimental and Table VII). Since the band at τ 5.48 for the protons at C_2 and C_3 is a triplet, it indicates that these protons are in the exo configuration and hence the two substituents have to be in the endo configuration. Thus the endo configuration of compound X is established; Alder et al (172) who reported this compound, did not comment on its configuration.

Compound XI melted 28° higher than the temperature reported in the literature (172). The τ values of the assignable protons in this compound are given in Table VII (page 161). A broad band at τ 5.33 is assigned to the protons at C_2 and C_3. These protons being in the exo configuration should be expected to be deshielded by the double bond and should resonate at higher field on hydrogenation while they appear at lower field. This surprising result appears to be the most serious exception yet noted to Fraser's rule.

τ values of the assignable proton signals in compounds XII-XIV are given in Table VII. A singlet at τ 9.57

TABLE VII

Chemical Shift Data in τ Units* of some 7,7-Dimethylene bicyclo[2.2.1]heptane Derivatives

Compound	Olefinic Protons	Protons at C_2 and C_3	Bridge-head Protons	Exo Protons at C_5 and C_6	Endo Protons at C_5 and C_6	Cyclopropyl Protons	
						syn or anti	anti or syn
X 	3.71(t)	5.48(t)	7.43(qi)			9.46(s)	
XI 		5.33(br)				9.39(s)	
XII 	3.26(t)		7.08(qi)			9.57(s)	
XIII 	3.97(t)		7.92(br)	8.22(m)	8.98(m)	9.62 (m)	9.71 (m)
XIV 						9.58(s)	

*All these assignments are confirmed by the integrated areas of various peaks, t = triplet; qi = quintet; s = singlet; br = broad band; m = multiplet.

is assigned to the four cyclopropyl protons in compound XII. In compound XIII, two cyclopropyl protons are syn and the other two anti to the double bond. These protons give rise to multiplets centered at τ 9.62 ± 0.02 and 9.71 ± 0.02. It is not certain as to which of these protons absorb at higher field and thus the assignment of these signals to syn and anti protons is not possible. The signal of the cyclopropyl protons in compound XIV appears at τ 9.58.

We can now examine the anisotropic effect of the double bond on the chemical shifts of the cyclopropyl protons in 7,7-dimethylene bicyclo[2.2.1]heptane ring systems. It may be seen that these protons in compounds XII and XIV absorb at τ 9.57 and τ 9.58, respectively. Thus no deshielding of the cyclopropyl protons is observed in going from compound XIV to XII, although in proceeding from norbornane to norbornadiene, the C_7 protons are unusually deshielded. Molecular models indicate that the angle θ (i.e. the angle which the line joining the affected protons to the center of the double bond makes with the x-axis) in 7,7-dimethylene bicyclo[2.2.1]hepta-2,5-diene is smaller than in norbornadiene. This should make the effect of χ_{xx} predominant. However, the protons are also more distant from the double bond which will reduce the magnitude of this effect. The observed chemical shifts unfortunately indicate that $\chi_{xx} < \chi_{yy}$ for XIV - XIII (since both the syn and anti protons in XIII are shielded) but $\chi_{xx} > \chi_{yy}$ for

XIII - XII. Thus the shieldings are anomalous in this series too.

To summarize, ten new compounds (listed in Table V) have been prepared during the synthetic approach according to Scheme I. Nine of these compounds have been fully characterized. The stereochemical assignments of all the compounds in Table V are based on the known fact that the bridgehead protons couple more strongly (143,148, 160,180) to the adjacent exo protons than to their endo counterparts. These assignments receive further support from the modified $\Delta\tau$ rule of Fraser. Most of our observations support the view of Jackman and Pople according to which protons near the x-axis are shielded and those near the y-axis are deshielded. However, several serious exceptions have been noted. In view of this and previous contrasting behaviour in the literature, it is apparent that shielding effects of the double bond vary widely and cannot be reliably employed for configurational assignments. One possible explanation for this would be that the magnetic susceptibilities of a double bond in the x, y and z directions are not constant.

CLAIMS TO ORIGINAL RESEARCH

1. Lyconnotine has been isolated from the alkaloids of Lycopodium annotinum L., by an improved method.
2. Isolation of a lactone derived from lyconnotine has also been achieved.
3. The structure and stereochemistry of lyconnotine and the derived lactone have been established.
4. Cyclohexene-cis-3,3,4,5,6,6-d_6, cis-1,2-dicarbomethoxy-cyclohexane-cis-3,3,4,5,6,6-d_6 and cyclohexane-3,3,6,6-d_4 have been prepared.
5. From the N.M.R. spectra of cyclohexene-d_6 at low temperatures, kinetic parameters for the rate of ring inversion in cyclohexene have been determined.
6. The temperature-dependent N.M.R. spectra of cis-1,2-dicarbomethoxy cyclohexane-cis-3,3,4,5,6,6-d_6 and cyclohexane-3,3,6,6-d_4 were analyzed from which the values of various coupling constants in cyclohexane were obtained.
7. The following new compounds have been prepared and characterized.
   a) 7-Isopropylidene bicyclo[2.2.1]hept-5-ene-exo-2,3-diol carbonate.
   b) 7-Isopropylidene bicyclo[2.2.1]hept-5-ene-endo-2,3-diol carbonate.
   c) exo-2,3-Dihydroxy-7-isopropylidene bicyclo[2.2.1]hept-5-ene.

d) endo-2,3-Dihydroxy-7-isopropylidene bicyclo[2.2.1] hept-5-ene.

e) 7-Isopropylidene bicyclo[2.2.1]hept-5-ene-exo-2,3-diol thionocarbonate.

f) 7-Isopropylidene bicyclo[2.2.1]heptane exo-2,3-diol carbonate.

g) exo-2,3-Dihydroxy-7-isopropylidene bicyclo[2.2.1] heptane.

h) endo-2,3-Dihydroxy-7-isopropylidene bicyclo[2.2.1] heptane.

i) 7-Isopropylidene bicyclo[2.2.1]heptane exo-2,3-diol thionocarbonate.

8. The effect of the magnetic anisotropy of the double bond in the above compounds (i.e. a - i) and in the 7,7-dimethylene derivatives of norbornane, norbornene and norbornadiene was determined.

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