
Linda Ledbetter Green
Louisiana State University and Agricultural & Mechanical College

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GREEN, Linda Ledbetter, 1937-
THE CHEMISTRY OF endo-TRICYCLO-
[6.2.1.0²,7]UNDEC-9-EN-3,6-DIONE:
PRECURSOR FOR THE SYNTHESIS OF THE
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THE CHEMISTRY OF _endo-_TRICYCLO[6.2.1.0^{2,7}]UNDEC-9-EN-3,6-DIONE: PRECURSOR FOR THE SYNTHESIS OF THE BCD RING SYSTEM OF PHYLLOCIADENE

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in

The Department of Chemistry

by

Linda Ledbetter Green
B.S., Louisiana Polytechnic Institute, 1962
M.S., Louisiana Polytechnic Institute, 1965

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This work could not have been carried out without the loving patience and the assistance of the author's husband, Ernest E. Green.

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The use of endo-tricyclo[4.2.1.0\textsuperscript{27}]undec-9-en-3,6-dione, LIV, as a precursor in the synthesis of a member of the class of diterpenes containing the BCD ring system with a trans BC ring juncture was attempted. It was expected that this precursor would provide an effective means of directing the stereochemistry of important steps in the synthesis leading ultimately to the formation of phyllocladene, XI.

Specifically, the presence of the methylene bridged ring in LIV would be used to direct the stereochemistry of the addition of a functional group, CX, at the position which would become the BCD ring juncture of the diterpene. After this was accomplished, it was anticipated that the methylene bridged ring would be removed from the system as cyclopentadiene through a retro-Diels-Alder reaction. With the functional group, CX, inserted with the proper orientation, construction of the remainder of the molecule could be accomplished through known procedures.

However, at an early stage in the planned synthesis, unexpected results were obtained which prompted a more thorough study of the chemistry of LIV and its derivatives. The expected 9,10-dihalo derivative from the halogenation of LIV was not obtained, and instead a new series of 6,9-epoxy-10-halotricyclo-[6.2.1.0\textsuperscript{27}]undecanes (LVII, LX, LXI, LXXI, and LXXII) was formed.

During the course of structure proof of these compounds, striking similarities were noted in the nmr spectra of this series
and a series of well known and apparently structurally unrelated lactones. Thorough study and comparison of the ir and nmr spectra of the two series lead to the suggestion that the structures of the compounds described in the literature as 5-substituted-2,6-
bicyclo[2.2.1]heptanecarbolactones (γ-lactones) are in error. It was shown that the ir and nmr spectra of these compounds are much better accommodated by δ-lactone structures (6-substituted-
2,5-bicyclo[2.2.1]heptanecarbolactones). Additional chemical evidence has been obtained in support of this conclusion.
INTRODUCTION

The first systematic investigation of the essential oils was initiated by Wallach in the mid-nineteenth century. For his studies he obtained a series of compounds from the steam volatile fraction of various plants. His work toward the structural determination of these substances included molecular weight determinations, elemental analyses, and careful observations of the chemical reactivities of the compounds. The striking discovery that he made was that while the molecular weights of the hydrocarbons seemed to place them in different groups according to a set weight unit, the elemental analyses for all the substances were identical. This led to the determination that these essential oils all contained multiples of some pentene unit, $\text{C}_5\text{H}_8$. Further studies by Wallach aimed at determining the actual structures of these compounds included measurements of uptake of hydrogen halides and observations of optical activity both before and after the addition of bromine. He was able, through acid catalyzed isomerizations, to interconvert some of the different compounds within one molecular weight group. As a result of these experiments, and based on the structural similarities which he had observed, Wallach was able to propose a series of formulas for these oils. It was his idea that the structures could be explained through the polymerization and cyclization of some five carbon unit which was structurally equivalent to isoprene, $\text{I}$. In most of the structures which were known to Wallach, a head-to-tail type polymerization of isoprene would explain the arrangement of the alkyl
groups. Although his work was concentrated on the ten and fifteen carbon compounds, he proposed the same type polymerization for higher molecular weight products.

Although Wallach thought the head-to-tail arrangement of isoprene units was the only possible direction of polymerization, later studies\(^2\) have shown other possibilities, including tail-to-tail as well as other so-called "abnormal" arrangements. Any compound whose structure can be related directly to isoprene has been classified as a terpene, and, according to the number of isoprene units present, the terpenes have been subdivided. These subgroups are defined in Figure 1, which also illustrates the directions of polymerization of isoprene.

Based upon these studies, Wallach formulated the isoprene rule\(^3\) which states, in its most general form, that the terpene carbon skeleton is divisible into isoprene units. Because this rule is followed with remarkable regularity, its use in assigning structures to terpenes has been very successful. A review of carbon skeletons from the mono-, sesqui-, and diterpene groups in Figure 2 will illustrate the application of the rule. The few exceptions to the isoprene rule known among the terpenes are explained as being due to a molecular rearrangement involving a methyl migration.\(^4\)

Although many of the diterpenes have been known for longer than a century and have considerable commercial importance, significant structural elucidations of these compounds were not
NORMAL ISOPRENE POLYMERIZATION

2 \times \text{sesquiterpene} \rightarrow \text{a triterpene}

FIGURE 1
begun until the 1920's. It was then that Ruzicka and his co-workers began their studies employing sulfur dehydrogenation as a means to aromatize these natural products in order to determine their basic carbon skeleton. Actually, the first application of this method to diterpenes was made by Vesterberg in 1903 when he obtained retene, III, from the diterpene, abietic acid, II, as
shown in Figure 3. However, it was the broad application of the method by Ruzicka that led to the classification of terpenes in groups according to basic structures. He was able to show that the diterpenes could all be derived from four isoprene units, and that they belonged to the basic structural types according to dehydrogenation products.$^{3,5}$

Once the structures of these compounds had been determined, the question of how they were synthesized in the plant systems arose. Wallach had very early recognized the existence of some five carbon unit which was biologically equivalent to isoprene, although he did not assume that isoprene as such was involved. Evidence that the five carbon fragment is actually derived from acetate was shown by the work of Rittenberg and Bloch.$^8$ By using isotopically labeled acetic acid, these investigators
discovered that cholesterol was extensively labeled. More recently, workers at the Merck Laboratories have isolated mevalonic acid in the form of the δ-lactone, IV, and have been able to characterize it as an intermediate in cholesterol biosynthesis. When labeled o,l-acid was incubated with a cell extract, 43% of the label was incorporated into cholesterol. This represented an almost quantitative consumption, assuming only the natural enantiomer was biologically active. The nature of the biosynthesis of cholesterol and of related terpenes has been clarified by continued investigations by such workers as Bloch, Lynen, Cornforth, and Popjak. The current status of the terpene biosynthesis is summarized in Figure 4.

The diterpenes can be readily derived from geranylgeraniol, V, or some closely related substance. For example, manool, VI, is easily obtained upon cyclization of geranylgeraniol, followed by an allylic rearrangement (see Figure 5). Further similar transformations can lead to other di- and tricyclic diterpenes. Wenkert and Ruzicka have both suggested that the diterpenes which possess the abietic acid type structure, II, are actually formed biogenetically through a concerted Wagner-Meerwein type rearrangement (see Figure 6). This rearrangement occurs quite readily only when the vinyl group occupies a quasi-equatorial position, VII. This has led Wenkert to suggest that the pimaradienes which do not readily undergo methyl migration possess a quasi-axial vinyl group, IX, and these are
$2 \text{SCoA} \rightleftharpoons \text{SCoA}$

TPNH $\xrightarrow{\text{H}_2\text{O}}$ MEVALONIC ACID

-SCoA = Coenzyme A
-PP = Pyrophosphate
TPNH = Triphosphopyridine Nucleotide
ATP = Adenosine Triphosphate

FIGURE 4
naturally occurring. This idea, or at least the idea of a unique stereochemistry for the vinyl group, is supported by the fact that dehydrogenation of all diterpenes of the pimaradine type yield only pimanthrene.16

A quite different acid catalyzed rearrangement should take place with the naturally occurring pimaradiene isomer than that described for VII. Preferred protonation at the $\Delta_{8:14}$ in this case would lead to the type intermediate, X, proposed by Wenkert. The reaction sequence suggested in Figure 7 not only

![Figure 7](image-url)
indicates the possible biological origin of phyllocladene, XI, but also suggests pathways to isophyllocladene, XII, mirene, XIII, and other tetracyclic diterpenes.

The final proof of the structure of a natural product lies, of course, in the total synthesis of the compound. For this reason, with the elucidation of the structures of many terpenes, interest shifted to the synthesis of these compounds. Since the cyclic terpenes are apparently produced biosynthetically through the cyclization of the open-chain isoprene polymers, attempts to duplicate these reactions have been made. Indeed, under acidic conditions, some derivatives have been shown to produce bi- and tricyclic species. For example, the twenty carbon system, 9-m-isopropylphenyl-2,6-dimethylnon-trans-6-en-2-ol, XIV, cyclizes on treatment with polyphosphoric acid. (Fig. 8)

However, this process, as is the case with many similar syntheses,

![Diagram](image)

**FIGURE 8**

has two major problems. The products are left without any functional
group in ring A, which is a serious deterrent to any further synthetic work. The second major problem is that the control of the stereochemistry at the AB ring juncture is incomplete. In order to overcome these difficulties, Johnson has developed a more desirable system. By using an olefinic acetal as the acyclic substrate, cyclized products should result which still contain a functional group.

Careful selection of the stereochemistry of di- and trienic acyclic starting materials lead to highly stereoselective products. These reactions are summarized in Figure 9. By using an optically active substrate in the formation of the acetal, Johnson has been able to carry out reactions which indicate that considerable asymmetric induction is taking place in the course of the cyclization. These developments are relatively new. Most of the work in establishing synthetic routes to the polycyclic terpenes has been done through cyclization reactions involving cyclohexanone derivatives or ring extensions of naphthalene derivatives.

Among the early work done in the synthesis of these compounds was the now classical annelation reaction developed by Sir Robert Robinson. Because of the tendency of \(\alpha,\beta\)-unsaturated ketones to polymerize in the presence of base, attempts to condense these compounds with cyclic ketones were not very successful. Robinson developed the use of quaternary ammonium salts which would readily decompose in base to yield the desired condensation
\[ \text{S n C I} \]

\[ \text{V J} \]

\[ \text{X V} \]

\[ \text{v}_y \]

\[ \text{X V I} \]

\[ \text{S n C l}_4 \]

\[ \phi H \]

\[ \text{F I G U R E 9} \]

\[ \text{X V} \]

\[ \text{X V I} \]

\[ \text{X V I I} \]
reaction but at a rate insufficient for the polymerization to occur. An example of such a cyclization reaction is shown in Figure 10. This process offers a stereoselective synthesis at the ring juncture since catalytic hydrogenation of the resulting $\alpha,\beta$-unsaturated ketone can be influenced by the presence of an alkyl group on an adjacent cyclic carbon atom.\textsuperscript{22}
The importance of this annelation reaction was illustrated by Stork and Schulenberg who employed it in 1955 in the first successful total synthesis of a diterpenic resin acid. Their synthesis of \( \text{d,\text{,l-dehydroabietic acid, } XXI,} \) was carried out according to the sequence in Figure 11. The methylated
β-tetralone, XVIII, was treated with 1-diethylamino-3-pentanone methiodide to effect a ring extension to the tricyclic compound, XIX. The presence of the β oriented C₁₀ methyl group directed both the alkylation of XIX with ethyl bromoacetate to yield XX and the catalytic hydrogenation of XX to occur from the unhindered rear face of the molecule. The synthesis was then completed by removal of the carbonyl group and Barbier-Wieland degradation to the next lower homolog of the acid. Since this first total synthesis was completed, more than thirty syntheses of diterpenes have been carried out using numerous synthetic pathways.

Another method for building cyclic structures was successfully employed by Haworth and Baker. Their approach was to first prepare a compound in which the portions of the molecule which would ultimately become the A and C rings (see Figure 12) were already coupled. This compound was then converted into a tricyclic system through the use of a Bogert-Cook type synthesis. This procedure has proved to be very useful since two cyclic materials containing the proper substituents can be chosen as starting materials. The final ring closure is accomplished by the action of acid on some site of activation, usually a double bond or a hydroxyl group, on ring A to accomplish a Friedel-Crafts type alkylation of ring C. The stereochemistry involved in this ring closure is known to yield a trans AB ring closure. Stork and Burgstahler have suggested that Hagemann's Ester (3-methyl-4-ethoxycarbonyl-2-cyclohexen-1-one) is a useful starting material for
this process. It allows the ready synthesis of hydrophenanthrene ketones containing the C\textsubscript{10} methyl substituent common to the diterpenes.

Church, Ireland, and Marshall have employed this procedure in connection with the Robinson annelation reaction in order to develop an elegant synthesis of a degradation product of phyllocladene.\textsuperscript{28} In their work, an aldol type condensation of simple starting materials produces an unsaturated ketone, XXII,
which is condensed, in turn, with a quaternary ammonium salt to prepare the A ring containing all the desired methyl substituents. After reduction, this compound is treated with polyphosphoric acid to effect the ring closure.

Using the basic A to C to B ring formation, Ireland and Kierstead have developed a plan for the construction of the
pimaric acid structure, XXIII, which enables the separation of the various synthetic problems that are present. Starting with a simple phenylcyclohexanone, their plan (see Figure 14) involved

an elegant synthesis of the B ring. Aromatization of the C ring enabled the use of more direct approaches in the development of
the stereochemical features of the AB ring system. By retention of an oxygen function in the aromatic ring, its reduction and substitution in the pimaric acid pattern could be made by following previously developed procedures.\textsuperscript{30}

A third formally different route to the synthesis of compounds which have the basic hydrophenanthrene structure involves condensation of unsaturated ketones with 1-methyl-2-naphthol derivatives. In this BC to A ring approach, the naphthol nucleus becomes rings B and C of the final product. Ring A is added through the condensation reaction. Much of the work along these lines has been done by Wenkert and co-workers. Attempts by this group to cyclize methyl vinyl ketone with 1-methyl-2-naphthol, XXIV, in base did not lead to the desired products, but rather to a second, intramolecular, Michael addition. In order to block this reaction and create the necessary intermediate, XXVb, for product formation, XXVI, a solvent was needed which was acidic enough to promote a protonic exchange between XXVa and solvent. For this reason the reaction was carried out in glacial acetic acid with p-toluenesulfonic acid catalyst.\textsuperscript{31} The use of methyl-\beta-chlorovinyl ketone did not prove to be successful; however, when methyl ethynyl ketone was reacted with XXIV in a t-butyl alcohol medium with potassium t-butoxide catalyst, an unsaturated hydrophenanthrene, XXVII, resulted which had a cis AB ring junction. Through a series of reactions (see Figure 16), this compound could be successfully converted into a saturated trans-
hydrophenanthrone, XXVIII. An extension of this type condensation is the more recent work by Wenkert in which a β-keto unsaturated ester is the reagent of choice. Methyl acrylylacetate, XXIX, condensed with 1-methyl-2-tetralone, XXX, in high yields under the influence of sodium methoxide catalyst to produce the ketoester, XXXI. This reagent, while unusual and still rarely used, appears to be extremely useful, particularly in the preparation of the resin acids.

Several important tetracyclic diterpenes possess the bridged bicyclic CD ring structure, either as a bicyclo[3.2.1]- or bicyclo[2.2.2]octane system. The challenge represented by the bridged structural feature and complex stereochemical aspects of these terpenes has generated much interest in the development of synthetic schemes directed toward their total synthesis.
Church, Ireland, and Marshall have suggested the creation of some intermediate compound which could be used as a starting point for the synthesis of this general type system. Their idea was to prepare a compound in which the basic hydrophenanthrene system had been alkylated at C-8 by some group containing functional activity. Another requirement of the proposed intermediate was some activation in ring C which would permit cyclization to C-12 or C-13. The reagent of choice for the preparation of this intermediate was the α,β-unsaturated ketone, XXXII, which was available in large quantities through standard reaction procedures. From this ketone, the vinyl ether, XXXIII, was prepared according to the scheme outlined in Figure 19. A Claisen type rearrangement of this ether produced the C-8 substituted aldehyde, XXXIVa. This aldehyde contained the necessary carbon atoms for the formation of the D ring bridge. The reaction was carried out with the isomer of XXXIII which would yield the rearrangement product possessing a cis BC ring juncture. Although recyclization of the
C ring was required to obtain the opposite configuration at C-8, this intermediate did offer an entrance into the two stereochemical series found in the tetracyclic diterpenes.

The use of XXXIV directly in the formation of cis BC tetracyclic diterpene systems was demonstrated in the synthesis of kaurene. This was done through introduction of a carbonyl function at C-14 via the double bond (see Figure 20). Acid hydrolysis of the ethylene acetal of the C-8 aldehyde, XXXVb, yielded the desired bridged system XXXVI, through an aldol-type condensation. It was found that a modified Wolff-Kishner reaction to remove the C-14 carbonyl, followed by oxidation and a Wittig olefin synthesis, accomplished the synthesis of the diterpene, XXXVII, with the desired stereochemical features.

Actually, when the carbonyl function was introduced at C-14, a mixture of C13 and C14 ketones was obtained. The ease of
the cyclization of the C₁₄ ketone to kaurene, XXXVII, gave the idea that the same type reaction on the C₁₃ ketone would perhaps yield the bicyclo[2.2.2]octane system of the same stereochemistry. With this in mind, the same steps were carried out on this isomer, XXXVb, and the desired bridged system was obtained to produce atisirene, XXXVIII.

The use of this same intermediate, XXXIV, in the formation of the tetracyclic diterpenes with the opposite stereochemistry, that is, a trans BC ring juncture, was illustrated by Turner and co-workers in the synthesis of phyllocladene.³⁶ By alternate routes, both Ireland's and Turner's groups arrived at a C₈ substituted system (XXXIVa and XXXIX, respectively) in which the C ring could be recycled to obtain the opposite stereochemistry. Oxidation of either of these compounds yielded the same triacid, XLₐ, for this purpose. Ring closure of the corresponding methyl ester, XLₚ, by a Dieckmann cyclization resulted preferentially in the six-membered ring β-keto ester, XLI. This step, then, completed the reversal of configuration at C-8. After a Reformatsky condensation of XLI with methyl bromoacetate and treatment of the resulting ester-lactone, XLII, with methoxide, Turner's group was able to obtain the diacid, XLIII. On pyrolysis of the barium salt of this acid, the bridged D ring system was produced. The ketone obtained, XLIV, was readily converted to phyllocladene, XI.

Another approach which has been used to gain access to the CD ring system of phyllocladene terpenes is through an acid
\begin{figure}
\centering
\begin{tikzpicture}
  \node (XXXIX) at (0,0) {XXXIX};
  \node (XXXIV) at (3,0) {XXXIVa};
  \node (XL) at (3,-3) {XL};
  \node (XLI) at (0,-3) {XLI};
  \node (XLII) at (-3,-6) {XLII};
  \node (XLIII) at (-3,-3) {XLIII};
  \node (XLIV) at (3,-6) {XLIV};
  \node (XI) at (0,-6) {XI};

  \draw[->] (XXXIX) -- node[above] {[O]} (XXXIV);
  \draw[->] (XXXIV) -- node[above] {[O]} (XL);
  \draw[->] (XL) -- node[above] {t-BuOK} (XLI);
  \draw[->] (XLII) -- node[left] {Zn} (BrCH₂CO₂CH₃)
  \draw[->] (XLII) -- node[right] {1) OCH₃ \quad 2) H₃O⁺} (XLIII);
  \draw[->] (XLIII) -- node[above] {Δ} (XLIV);
  \draw[->] (XLIV) -- node[above] {} (XI);

  \node at (1.5,-2.5) {XL a \quad R=H \quad XL b \quad R=CH₃};
\end{tikzpicture}
\caption{FIGURE 21}
\end{figure}
catalyzed rearrangement of a bridgehead hydroxy olefin, L. The nature of the desired compound made it impractical to attempt the introduction of a hydroxyl function at the bridgehead of the already cyclized system. A more suitable approach was to cyclize the system with the hydroxyl group already in place. Figure 22 shows how the same intermediate keto acetal, XXXVb, used by Ireland and co-workers in previous work was used as a precursor to this desired system. Conversion of this starting material to the C₁₃ ethylene derivative, XLV, through a Wittig olefin synthesis was followed by hydroboration and oxidation to yield a C₁₃ acetyl group. This was isomerized with base to the more stable β position, XLVI. The cyclization of ring D was accomplished through an aldol type condensation during hydrolysis of the acetal under mild acidic conditions. The resulting bridgehead acetyl compound, XLVII, was converted to its oxime, which was allowed to undergo the Beckmann rearrangement to the amide, XLVIII. On treatment with nitrogen dioxide in acetic acid-sodium acetate buffer, XLVIII formed the N-nitroso derivative which rearranged to the diacetate, XLIX. Hydrolysis and oxidation of XLIX, followed by use of the Wittig synthesis, yielded the desired hydroxy olefin, L. The carbon skeletal rearrangement of this system was achieved by treatment of L with dilute acid in methanol. In this manner, the ketone, LII, was obtained through some type intermediate, Xb, common to the various tetracyclic diterpenes as proposed by Wenkert.
EXPERIMENTAL

In all the experiments which will be described, the chemicals used were reagent grade and, unless otherwise indicated, no further purification was considered necessary.

A Fisher-Johns Melting Point Apparatus was used for all melting points, which are reported uncorrected.

The ultraviolet (uv) spectra were run on a Beckman, Model DB, double beam spectrophotometer. Solvent was 95% ethanol. Infrared (ir) spectra were run on a Beckman, IR-10, double beam spectrophotometer. All absorptions are indicated as wavelength, $\lambda$, in microns. The 60 MHz nmr spectra were run on a Varian, Model A60A, nmr spectrometer. The 100 MHz nmr spectra were run on a Varian, Model NA-100, nmr spectrometer by Mr. W. E. Wegner of the Louisiana State University Department of Chemistry. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) internal standard. The mass spectrograms were run on a Varian, double focusing, M-66 mass spectrometer by Cheryl White, Louisiana State University Department of Chemistry staff member.

All carbon-hydrogen analyses were performed by Mr. Ralph Seab of the Louisiana State University Department of Chemistry.

Preparation of endo-Tricyclo[6.2.1.0$^2$7]undeca-4,9-dien-3,6-dione, LIII.

Technical grade dicyclopentadiene was distilled into an
ice cooled container at a slow rate, while the distillation head temperature was kept between 42° and 47°C. The freshly distilled cyclopentadiene (41 ml., 33 g., 0.5 mole) was added dropwise to a stirred suspension of p-benzoquinone (54 g., 0.5 mole) in 95% ethanol (500 ml.). After the reaction had been allowed to proceed for 12 hours, the solvent was removed at room temperature (reduced pressure) to the saturation point. The solution was then cooled in an ice bath and the yellow crystals collected. Repetition of the above process yielded second and third crops from the mother liquor. The product was obtained in almost quantitative yield; m.p. 67-69°C; \( \lambda_{\text{max}}^{\text{CHCl}_3} = 5.95, 6.15 \mu \). The 60 MHz nmr spectrum (in CDCl\(_3\)) showed multiplets at 1.58 (2H), 3.25 (2H), 3.55 (2H), 6.07 (2H), and a singlet at 6.58 ppm (2H). (See NMR-1.)

Preparation of endo-Tricyclo[6.2.1.0\(^2\)7]undec-9-en-3,6-dione, LIV.

Zinc dust (15 g., 0.25 mole) was added to a stirred suspension of the Diels-Alder adduct, LIII, (10 g., 0.54 mole) in water (100 ml.). Glacial acetic acid (5 ml.) was added to this mixture and the stirring continued for 2 hours. At the end of this time, the zinc was removed by filtration and washed with ethyl ether. The filtrate was saturated with sodium chloride and then extracted four times with ether. The combined ether extracts and washings were evaporated, leaving an oily residue. Chloroform was added to this oil, and any precipitate which formed was filtered out. The chloroform was evaporated, leaving a pale
yellow oil, LIV, in 55% yield; $\lambda_{\text{max}}^\text{CHCl}_3$ 5.90 μ. The 60 MHz nmr spectrum (in CDCl₃) showed multiplets at 1.43 (2H), 2.47 (4H), 3.21 (2H), 3.43 (2H), and 6.17 ppm (2H). (See NMR-2.)

The precipitate was identified as hydroquinone; m.p. 171-173° C. The 60 MHz nmr spectrum (D₂O) showed a singlet at 6.82 (aromatic) and a singlet at 4.61 ppm (HDO).

Deuterium Exchange on LIV.

200 mg. of LIV was stirred in 10 ml. D₂O for four days with no evidence of exchange. Three crystals of trichloroacetic acid were then added to the solution and stirring was continued for six days. At the end of this time, exchange on the carbons alpha to the carbonyl groups was complete. The 60 MHz nmr spectrum showed multiplets at 6.21 (2H), 3.40 (2H), and 1.43 ppm (2H).

Attempted Formation of the Pyrrolidine Enamine of LIV.

A solution of the dione, LIV, (5g., 0.028 mole) and pyrrolidine (1.98 g., 0.028 mole) in benzene was connected through a Dean-Stark apparatus to a reflux condenser and refluxed for 96 hours. At the end of this time, dark red-black crystals were caked on the flask walls. The solvent was separated from the crystals and evaporated to yield only the same crystalline material; m.p. 171-172° C. The 60 MHz nmr spectrum (D₂O) shows a singlet at 6.82 and one at 4.61 ppm (HDO). The crystals were identified as hydroquinone.
Preparation of 4-Diethylamino-2-butanone Methiodide, LV.

The 4-diethylamino-2-butanone was prepared according to the procedure of Robinson\textsuperscript{21} with one modification. The Mannich base was not distilled under vacuum, but rather distillation of the reaction mixture up to 60° C was carried out at atmospheric pressure. The oily residue (13 g., 41%) was dissolved in a small amount of benzene and an equal weight of methyl iodide was added dropwise to the cooled solution. After it had stirred for 12 hours, a viscous oil formed. It was stored under benzene until used; $\lambda_{\text{max}}^{\text{neat}}$ 5.97 μ. The 60 MHz nmr spectrum ($D_2O$) showed a quartet centered at 3.20, a singlet at 2.95, and a broad singlet at 1.25 ppm.

Attempted Preparation of Tetracyclo[10.2.1.0\textsuperscript{2,5}.0\textsuperscript{10}.0\textsuperscript{11}]pentadeca-9,13-dien-3,8-dione, LVI.

The diketone, LIV, (5 g., 0.028 mole) was dissolved in absolute ethanol (50 ml.) under a nitrogen atmosphere. The methiodide salt, LV, (7.98 g., 0.028 mole), and sodium methoxide (3.024 g, 0.056 mole) were added to the solution, with stirring, and the system was refluxed for six hours. The pH of the system was adjusted to 5 with dilute hydrochloric acid. The solution was filtered and then extracted with ether. After removal of solvent, a thick, dark oil remained. It could not be purified; however, ir data indicated an $\alpha,\beta$-unsaturated carbonyl system. $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.8, 6.0 μ.
Preparation of 10-Bromo-6,9-epoxy-6-hydroxy-endo-tricyclo- 
[6.2.1.0^2,7]undecan-3-one, LVII.

To a stirring solution of the dione, LIV, (10 g., 0.056 mole) and pyridine (4.5 ml., 4.42 g., 0.056 mole) in 300 ml of carbon tetrachloride (0°) was added dropwise a solution of bromine (2.87 ml., 8.96 g., 0.056 mole) in 100 ml. carbon tetrachloride. The solution stirred cold for two hours after the addition was complete. It was then filtered and the solvent removed at reduced pressure. The white solid obtained was extracted with ethyl ether in a Soxhlet extractor. When extraction was complete, the ether volume was reduced and the white crystalline product collected; yield 35%; m.p. 127-129° C; \( \lambda_{\text{KBr}}^{\text{max}} \) 2.94, 5.87 \( \mu \); \( \lambda_{\text{EtOH}}^{\text{max}} \) 290°, 250 \( \mu \). The 100 MHz nmr spectrum (CDCl\(_3\)) showed a complex upfield system including multiplets centered at 1.65 (1H), 2.20 (2H), 2.25 (1H), 2.50 (2H), 2.55 (1H), 2.75 (1H), and 2.83 ppm (1H). Further downfield were multiplets at 3.37 (1H), 3.72 (1H), and 4.71 (1H).

(See NMR-3.)

Analysis. Calculated for C\(_{12}\)H\(_{18}\)O\(_3\)Br: C, 48.17; H, 4.74.

Found: C, 48.77; H, 5.01.

When LVII (5 g., 0.02 mole) was refluxed for 24 hours with zinc dust (6.5 g., 0.10 mole) in a 10:1 95% ethanol-water solution (100 ml.) and the zinc removed by filtration, an oil and a crystalline product resulted. These were identified as the dione, LIV, and hydroquinone.
LXXII, X = I

LVII, X = Br

NMR 3
The corresponding iodo compound, 6,9-epoxy-6-hydroxy-10-iodo-endo-tricyclo[6.2.1.0^2>7]undecan-3-one, LXXII, was prepared in 44% yield from equimolar amounts of pyridine and iodine in carbon tetrachloride by a procedure identical to that for the bromination. The 60 MHz nmr spectrum (CDCl_3) showed a complex multiplet from 1.65 to 2.83 and multiplets at 3.25 (1H), 3.78 (1H), and 4.89 ppm (1H). (See NMR-3.)

Preparation of 9,10-Epoxy-endo-tricyclo[6.2.1.0^2>7]undecan-3,6-dione, LVIII.

Sodium ethoxide was prepared from 0.42 g. (0.018 mole) of sodium in 50 ml. absolute ethanol under nitrogen. The base was added dropwise to a stirred solution of the bromo ketone, LVII, (5 g., 0.018 mole) in 100 ml. of absolute ethanol at 0°C in a nitrogen atmosphere. After the addition was complete, the system was allowed to warm gradually to room temperature. After refluxing for 5 hours, the solution was neutralized with concentrated hydrochloric acid, filtered, and the solvent was removed on a rotary evaporator. An oily residue remained. On standing, crystals separated from the oil and were recrystallized from ether; m.p. 74-75°C. The 60 MHz nmr spectrum (CDCl_3) showed a complex upfield region which included a triplet at 1.18 (3H), and downfield, a quartet centered at 3.41 (2H), and two broad doublets at 4.28 (1H) and 4.53 ppm (1H). The crystals were assigned the structure relating to 6,9-epoxy-10-ethoxy-6-hydroxytricyclo[6.2.1.0^2>7]-undecan-3-one.
The 60 MHz nmr spectrum (CDCl\textsubscript{3}) of the oil, LVIII, showed a complex upfield region and a multiplet at 4.11 ppm (2H). \(\lambda_{\text{max}}^{\text{CHCl}_3} = 5.8 \mu\). On standing for two months, the oil crystallized into a white solid; m.p. 136-138° C. The nmr spectrum of the crystals was identical to that of the oil.

**Analysis.** Calculated for C\textsubscript{11}H\textsubscript{22}O\textsubscript{3}: C, 68.74; H, 6.24.

Found: C, 68.59; H, 6.29.

**Preparation of endo-Tricyclo[6.2.1.0\textsuperscript{2,7}]undec-9-en-3,6-diol, LIX, and Deuterated Analog, LXVI.**

A stirred solution of the dione, LIV, (20 g., 0.11 mole) dissolved in 400 ml. of ethanol was cooled to 15° and 3.6 g. of sodium borohydride (0.095 mole) added. After the reaction had stirred for 16 hours, 200 ml. of water was added and the mixture heated to boiling. After the ethanol evaporated, the solution was cooled and the precipitate was collected. Soxhlet extraction of the precipitate with ether gave white crystals in 95% yield; m.p. 136-137° C; \(\lambda_{\text{max}}^{\text{CHCl}_3} = 2.78, 2.92 \mu\). The 60 MHz nmr spectrum (CDCl\textsubscript{3}) showed multiplets at 1.40 (2H), 1.72 (4H), 2.40 (2H), 2.93 (2H), 4.10 (2H), and 6.20 ppm (2H). (See NMR-4.)

When the dione, LIV, (5 g., 0.028 mole) was treated with sodium borodeuteride (2 g., 0.048 mole) under identical conditions, the product obtained was 3,6-dideuterio-endo-tricyclo[6.2.1.0\textsuperscript{2,7}]undec-9-ene-3,6-ol, LXVI. The 60 MHz nmr spectrum (CDCl\textsubscript{3}) indicated complete deuteration at the 3 and 6 positions. Multiplets
occurred at 1.40 (2H), 2.40 (2H), 2.93 (2H), 6.23 (2H), and a singlet appeared at 1.70 ppm (4H). A signal due to hydroxyl is observed shifting with temperature. (See NMR-4.) Yield, 4.8 g., 94%.

Preparation of 10-Bromo-6,9-epoxy-endo-tricyclo[6.2.1.0²,7]undecan-3-ol, LX, and Deuterated Analog, LXVII.

To a stirred solution of the diol, LIX, (20 g., 0.11 mole) and pyridine (9.2 ml., 9.0 g., 0.11 mole) in 300 ml. of chloroform at 0° C was added dropwise a solution of 5.85 ml. of bromine (18.3 g., 0.11 mole) in 100 ml. chloroform. The temperature was maintained at 0-5° C for two hours after addition was complete. The white solid remaining after solvent evaporation was purified by ether Soxhlet extraction to yield crystals; m.p. 162-163° C; yield 100%; \( \nu_{\text{CHCl}_3}^{\text{max}} 2.92, 6.73, 10.65 \mu; \lambda_{\text{EtOH}}^{\text{max}} 210 \mu \). The 100 MHz nmr spectrum (CDCl₃) showed a series of complex multiplets upfield which represent 11 protons. Downfield are multiplets centered at 2.89 (1H), 4.10 (2H), 4.25 (1H), and 4.55 ppm (1H). (See NMR-5.)

Analysis. Calculated for C₁₁H₁₅O₂Br: C, 50.96; H, 5.79.

Found: C, 50.90; H, 5.80.

When this compound, LX, was refluxed with excess zinc dust in 10:1 ethanol-water solution, the starting diol, LIX, was obtained.

The corresponding iodo compound, 6,9-epoxy-10-iodo-endo-tricyclo[6.2.1.0²,7]undecan-3-ol, LXXI, was prepared in 98% yield.
LXXI, $X = I$

LX, $X = Br$

NMR 5
by an identical procedure, using equimolar amounts of pyridine and iodine in chloroform; m.p. 115-117°C. The 60 MHz nmr spectrum (CDCl₃) showed a complex multiplet from 1.46 to 3.03 (10H) and multiplets at 4.0 (2H), 4.31 (1H), and 4.60 ppm (1H). (See NMR-5.)

When the deuterated diol, LXVI, was treated with bromine under conditions identical to those described above, 10-bromo-3,6-dideuterio-6,9-epoxy-endo-tricyclo[6.2.1.0²⁷]undecan-3-ol, LXVII, was obtained in 69% yield. The 100 MHz nmr spectrum (CDCl₃) showed a compound identical to LX (NMR-5) with the exception that the multiplet centered at 4.10 ppm was absent. (See Figure 30.)

Preparation of 10-Bromo-6,9-epoxy-endo-tricyclo[6.2.1.0²⁷]undecan-3-one, LXI, and Deuterated Analog, LXVIII. The alcohol, LX, (10 g., 0.039 mole) was dissolved in acetone (250 ml.) and cooled with stirring to 0°C. A solution of chromium trioxide (4.25 g., 0.0425 mole) and sulfuric acid (2.3 ml., 4.25 g., 0.0425 mole) in 100 ml. of water was added drop-wise. The rate of addition was controlled to insure the temperature of the reaction mixture did not rise above 10°C. The system was stirred cold for 3 hours after the addition was complete and then allowed to warm slowly to room temperature. After the addition of water (250 ml.), the solution was extracted 5 times with ether. The combined ether extracts were washed with saturated sodium chloride solution twice and then with distilled water until the ether layer was almost colorless. The ether solution was dried over anhydrous sodium sulfate and reduced in volume by
rotary evaporation, yielding white crystals; m.p. 136-137° C; yield 67%; $\lambda_{\text{max}}^{\text{KBr}}$ 5.92, 9.50 μ. The 100 MHz nmr spectrum (CDCl₃) showed a complex multiplet from 1.0 to 3.0 (9H) and other multiplets at 3.67 (1H), 4.18 (1H) and 4.50 ppm (1H). (See NMR-6.)

**Analysis.** Calculated for C₁₁H₁₃O₂Br: C, 51.36; H, 5.06.

Found: C, 51.28; H, 5.55.

The oxime of LXI was prepared according to the procedure of Shriner, Fuson, and Curtin. M.p. 148-150° C; $\lambda_{\text{max}}$ 6.15, 3.05, 2.79 μ.

The 60 MHz nmr spectrum (CDCl₃) showed a complex multiplet from 1.36 to 3.1 (9H), multiplets at 3.51 (1H), 3.83 (1H), 4.30 (1H), 4.60 (1H), and a broadened singlet at 7.75 ppm.

The deuterated alcohol, LXVII, was treated with a chromium trioxide-sulfuric acid solution (10% molar excess) under conditions which were identical to those described above with one exception. The oxidation appeared to occur at a slower rate and the reaction time was extended to six hours stirring at room temperature. The product, 10-bromo-6-deuterio-6.9-epoxy-endo-tricyclo[6.2.1.0²,7]undecan-3-one, LXVIII, was obtained in 56% yield.

The 100 MHz nmr spectrum (CDCl₃) was identical to that of LXI with the exception that the multiplet centered at 4.18 ppm was absent. There was a complex multiplet from 1.0 to 3.0 (9H) and other multiplets occurred at 3.67 (1H) and 4.50 ppm (1H).

**Preparation of 4,10-Dibromo-6.9-epoxy-endo-tricyclo[6.2.1.0²,7]-undecan-3-one, LXII.**

A solution of bromine (1 ml., 3.14 g., 0.019 mole) in
25 ml. acetic acid was added dropwise to a stirred solution of the ketone, LXI, (5 g., 0.019 mole) in 60 ml. of acetic acid, at such a rate that a temperature of 15° C was maintained. When the addition was complete, the solution was allowed to slowly warm to room temperature, neutralized with potassium hydroxide, and extracted 3 times with ether. After being dried over anhydrous sodium sulfate, the ether was removed on a rotary evaporator to yield a white solid; recrystallized from ether; yield, 3.6 g., 56%; m.p. 164-166° C; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.82, 9.55, 9.90, 10.50 &. The 100 MHz nmr spectrum showed a complex multiplet from 1.56 to 3.40 (8H), and multiplets at 3.74 (1H), 4.15 (1H), and 4.49 (2H) ppm.

The dehydrohalogenation of LXII was attempted by refluxing with calcium carbonate in N,N-dimethylacetamide for 45 minutes. The starting dibromo compound was recovered. When reflux time was extended to 24 hours, there was some evidence of a reaction. The 60 MHz nmr spectrum (CDCl$_3$) indicates a mixture of compounds. A complex multiplet from 0.66 to 2.53 and multiplets at 2.75, 4.25, and 4.43 occur. There is a doublet at 5.95 and a quartet at 6.87 (ethylenic hydrogens) and an aromatic multiplet at 7.58 ppm.

Preparation of 6-Hydroxy-endo-tricyclo[6.2.1.0$^2$.7]undec-9-en-3-one, LXIII.

The ketone, LXI, (5 g., 0.019 mole) was refluxed for 24 hours with zinc dust (6.5 g., 0.10 mole) in a 10:1 ethanol-water
solution (60 ml.). The zinc was removed and the ethanol evaporated on the rotary evaporator. An oily residue remained; yield, 2.9 g., 85%; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.85, 5.88, 6.1 μ. The 60 MHz nmr spectrum (CDCl$_3$) showed an ethylenic hydrogen multiplet at 6.13, a broad multiplet at 4.25, and a complex multiplet between 3.30 and 1.30 ppm. When the oil was extracted with petroleum ether (b.p. 50-80°C) on a Soxhlet extractor, white crystals were obtained; 250 mg.; m.p. 128-129°C. The nmr spectrum of the crystals was identical to that of the oil. (See NMR-7.)

**Analysis.** Calculated for C$_{11}$H$_{14}$O$_2$.H$_2$O: C, 68.36; H, 8.16.

Found: C, 68.89; H, 8.47

Preparation of 3,14;10,13-Diepoxytetracyclo[10.2.1.0$^{3,8}$,0$^{2,11}$]-pentadecan-5-one, LXIV.

A solution of sodium ethoxide, from 0.92 g. (0.04 mole) of sodium in 75 ml. of absolute ethanol, was prepared in a nitrogen atmosphere. The ketone, LXI, (5.17 g., 0.02 mole) and the methiodide, LV, (5.70 g., 0.02 mole) were added, and the system was refluxed for 24 hours. After cooling, the solution was neutralized with concentrated hydrochloric acid, filtered, and the solvent was removed on the rotary evaporator. The thick, dark oil which remained was extracted with petroleum ether (b.p., 50-80°C) on a Soxhlet extractor. White crystals and a yellow oil obtained in this way proved, by spectral analysis, to be the same compound; m.p. 201-203°C; yield, 2.76 g., 56%; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.85, 9.08, 9.30 μ.
6.22

4.39

2.64

NMR 7
The 60 MHz nmr spectrum (CDCl₃) showed multiplets centered at 4.58 (1H), 4.38 (2H), 2.60 (2H), 2.40 (5H), 2.11 (3H), and 1.73 ppm (5H). (See NMR-8.)

**Analysis.** Calculated for C₁₅H₁₈O₃: C, 73.17; H, 7.31.

*Found: C, 72.50; H, 6.68.*

Preparation of 6,9-Epoxy-endo-tricyclo[6.2.1.0²7]undecan-3-ol, LXIX.

The diol, LIX, (15 g., 0.083 mole) in 100 ml. of methanol was cooled to 0°C and sulfuric acid was added dropwise until the pH of the solution was one. The solution was allowed to stir as the temperature slowly increased, and stirring at room temperature was continued for 6 days before there was indication of reaction. The solution was neutralized with 6N sodium hydroxide, filtered, and then concentrated. The remaining oil was extracted with petroleum ether (b.p. 50-80°C) on a Soxhlet extractor. White crystals were obtained from the petroleum ether; m.p. 105-106°C; yield 9.6 g., 64%; \( \lambda_{\text{max}}^{\text{CHCl}_3} 2.96, 6.80, 9.5, 10.1 \mu \). The 60 MHz nmr spectrum (CDCl₃) showed a complex multiplet between 1.13 and 2.50 (1H), multiplets at 2.86 (1H) and 3.93 (2H), and a broad triplet at 4.40 ppm (1H). A signal due to hydroxyl was observed with position dependent upon temperature.

**Analysis.** Calculated for C₁₁H₁₆O₂: C, 73.34; H, 8.89.

*Found: C, 72.54; H, 9.01.*
Preparation of 6,9-Epoxy-endo-tricyclo[6.2.1.0²,7]undecan-3-one, LXX.

The alcohol, LXIX, (1 g., 0.0056 mole) was dissolved in 25 ml. of acetone and cooled to 0°. A solution of chromium tri-oxide (0.61 g., 0.0061 mole) and sulfuric acid (0.4 ml., 0.61 g., 0.0061 mole) in 30 ml. of water was added at such a rate that the temperature did not rise above 10° C. After the addition was complete, the solution was allowed to slowly warm to room temperature and stir for 3 hours. Water (30 ml.) was added to the reaction mixture, and it was extracted 3 times with ether. The combined ether extracts were washed twice with saturated sodium chloride solution and with water until the ether layer was almost colorless. The ether solution was dried over anhydrous sodium sulfate, and the solvent removed to give a yellow oil; yield 0.52 g., 52%; λ_max 5.87, 9.09, 9.30 μ. The 100 MHz nmr spectrum (CCl₄) showed a complex multiplet from 1.04 to 2.54 (1H), multiplets at 2.85 (1H), 4.14 (1H), and a broad triplet at 4.30 ppm (1H). (See NMR-9.)

Preparation of Bicyclo[2.2.1]hept-5-en-2-carboxylic Acid. 40

Acrylic acid (68 ml., 72 g., 1 mole) was mixed with an equal volume of ether and freshly distilled cyclopentadiene (82 ml., 66 g., 1 mole) was added dropwise. The temperature was controlled so that it did not rise above 40° C. When the addition was complete, the reaction mixture was allowed to stir until it cooled.
to room temperature. It was then made basic with 10% sodium carbonate and extracted 3 times with ether. The water layer was acificed with hydrochloric acid. An oily layer separated. It was extracted into ether, dried over anhydrous sodium sulfate, and concentrated on the rotary evaporator. The remaining oil was vacuum distilled and the fraction boiling at 101°C at 0.7 mm was collected; yield, 102 g., 74%; $\lambda_{\text{max}}^{\text{CHCl}_3} 5.85 \mu$. The 60 MHz nmr spectrum (CDCl$_3$) showed a singlet at 11.65 (1H), and complex multiplets centered at 6.07 (2H), 3.05 (2H), 1.91 (1H), 1.40 ppm (4H). This was a mixture of the endo and exo acids.

Preparation of 5-Iodo-2,6-bicyclo[2.2.1]heptanecarbolactone, LXVa, or 6-Iodo-2,5-bicyclo[2.2.1]heptanecarbolactone, LXVb.*

The mixture of endo and exo acids (100 g., 0.725 mole) was neutralized with 10% sodium hydroxide solution and sodium hydrogen carbonate was added until pH 8 was attained. A solution of iodine (203 g., 0.798 mole) and potassium iodide (111 g., 0.870 mole) in 500 ml. of water was added dropwise to the stirred solution of the acid salt. When the addition was complete, saturated sodium thiosulfate solution was added until the solution was almost colorless. It was extracted with chloroform 3 times.

*Since the structure of the lactone described here and the structures of all related compounds are in question, a definite assignment of the position of the substituent and the size of the lactone (δ or γ) cannot be made. However, where a choice must be made for utility, structures will be drawn to concur with the current literature.
The combined chloroform extracts were washed with water and dried over
anhydrous sodium sulfate. After the chloroform was removed, a
viscous oil remained which crystallized on standing several days;
m.p. 57-59\(^\circ\) C; yield, 140 g., 73\%; \(\lambda_{\text{max}}^{\text{CHCl}_3}\) 5.63 \(\mu\) (See IR-2). The
100 MHz nmr spectrum (\(\text{CDCl}_3\)) showed broad doublets at 5.10 (1H)
and 3.93 (1H), a broad triplet at 3.21 (1H) and a complex multi­
plet from 2.96 to 1.30 ppm (6H). (See NMR-10.)

When the reaction was carried out under conditions
altered from light to dark, 0\(^\circ\) C to room temperature, and reaction
times of 5 minutes to several hours, and analysis made of crude pro­
duct or of clean, worked-up product, the lactone of identical
spectral properties was always obtained.

Preparation of endo-Bicyclo[2.2.1]hept-5-en-2-carboxylic Acid,
LXXIII.\(^{42}\)

The iodo lactone, LXV, (140 g., 0.53 mole), in 320 ml.
glacial acetic acid was cooled to 15\(^\circ\) C while being stirred with
a mechanical stirrer. Zinc dust (65 g., 1 mole) was added very
slowly to ensure that the temperature did not rise above 15\(^\circ\) C.
After the addition was complete, the reaction mixture was stirred
an additional 3 hours at 15\(^\circ\) and at room temperature for 2 hours
longer. The zinc was removed by filtration and washed with acetic
acid and water. The combined filtrate and washings were diluted
with 100 ml. of water and extracted 3 times with ether. The com­
combined ether extracts were washed 4 times with water, dried over
IR 2
5.63 μ

LXXIV

LXV

4000 cm⁻¹ 3000 2000 1000
anhydrous sodium sulfate, and the ether was removed on the rotary evaporator. The residue was vacuum distilled and the fraction boiling at 115°C at 5 mm was collected; yield, 43.4 g., 59%; \( \lambda_{\text{max}}^{\text{CHCl}_3} 5.85 \mu \). The 60 MHz nmr spectrum (CDCl\(_3\)) showed a singlet at 11.56 (1H) and multiplets at 6.10 (2H), 3.07 (2H), 1.90 (1H), and 1.40 ppm (4H).

Preparation of 5-Bromo-2,6-bicyclo[2.2.1]heptanecarbolactone, LXXIVa, or 6-Bromo-2,5-bicyclo[2.2.1]heptanecarbolactone, LXXIVb.

A mixture of endo- and exo-bicyclo[2.2.1]hept-5-en-2-carboxylic acid (5 g., 0.036 mole) and pyridine (5.18 ml., 5.688 g., 0.072 mole) in chloroform (100 ml.) was cooled to 0°C with stirring, and a solution of bromine (1.55 ml., 5.76 g., 0.036 mole) in 50 ml. chloroform was added dropwise. The temperature of the solution was allowed to rise slowly to room temperature after the addition of bromine was complete. After filtration, the solution was washed with water, 6N hydrochloric acid, 3N sodium hydroxide, and with water again. The chloroform layer was then dried over anhydrous sodium sulfate, and the chloroform was removed on the rotary evaporator. An oily residue remained; yield, 4.2 g., 74%; \( \lambda_{\text{max}}^{\text{CHCl}_3} 5.63 \mu \). (See IR-2.) The 100 MHz nmr spectrum (CDCl\(_3\)) showed broad doublets at 4.87 (1H) and 3.88 (1H), a broad triplet at 3.26 (1H), and a complex multiplet from 2.81 to 1.13 ppm (6H). (See NMR-10.)
Preparation of 2,6-Bicyclo[2.2.1]heptanecarbolactone, LXXVa, or 2,5-Bicyclo[2.2.1]heptanecarbolactone, LXXVb.

10 g. (0.073 mole) of a mixture of endo and exo-bicyclo[2.2.1]hept-5-en-2-carboxylic acid in 55 ml. of 50% sulfuric acid was stirred cold for 3 hours and then diluted with 40 ml. water. This solution was extracted 4 times with ether. The combined ether extracts were washed 3 times with 10% aqueous sodium carbonate solution and once with water and dried over anhydrous sodium sulfate. The ether was removed on the rotary evaporator to give white crystals; recrystallized from petroleum ether, m.p. 152-153°C; yield 8.7 g., 87%; $\lambda_{\text{max}}^{\text{CHCl}_3} 5.62 \mu$. (See IR-3.) The 100 MHz nmr spectrum (CDCl3) showed a broad triplet at 4.95 (1H) and 3.23 (1H), and complex multiplets at 2.52 (2H), 1.80 (2H), and 1.60 ppm (4H). (See NMR-9.)

Preparation of Methyl Bicyclo[2.2.1]hept-5-en-endo-2-carboxylate, LXXVI.

The endo acid, LXXIII, (43.4 g., 0.314 mole) was dissolved in 30 ml. of dry benzene and cooled to 5-10°C in a system under calcium chloride. Pyridine (26.3 ml., 27.3 g., 0.345 mole) which had been distilled from calcium oxide and stored over potassium hydroxide was added. Thionyl chloride (24.0 ml., 39.260 g., 0.33 mole) was added dropwise to this system. When the addition was complete, the reaction mixture was allowed to stir and gradually warm to room temperature. Then it was filtered
and the filtrate was returned to the vessel. The gases were removed by suction and the reaction mixture again cooled to 5-10° C. Methanol (13.5 ml., 11.04 g., 0.345 mole) and an additional 27 ml. pyridine were added to the solution and it was allowed to warm slowly to room temperature and was stirred for 2 hours. At the end of this time the solid salts were removed and the filtrate was washed with dilute hydrochloric acid until the wash water was red to litmus. It was then washed 4 times with water and dried over magnesium sulfate, and the benzene was removed on the rotary evaporator. An oily residue remained; 45.6 g. (89.5%). The 60 MHz nmr spectrum (benzene) showed no acidic hydrogen signals, but showed a vinyl multiplet at 6.0, a methyl singlet at 3.53, multiplets at 3.11 and 2.73, and a complex multiplet from 2.0 to 0.96 ppm.


Tetrahydrofuran for this reaction was distilled from lithium aluminum hydride and stored over magnesium sulfate.

The methyl ester, LXXVI, (45.6 g., 0.3 mole) in 225 ml. of THF was cooled in an ice bath in a dry nitrogen atmosphere. The system was attached through a mercury trap to an acetone trap. A solution of diborane in THF (350 ml. of a 1 M solution) was added dropwise to the stirred solution. After the addition was complete, the solution was allowed to stir cool for one hour.
60 ml. 2 N sodium hydroxide was added, followed by 40 ml. of 30% hydrogen peroxide. The temperature was maintained between 20 and 40° C during these additions. After these additions were complete, the system was left in a nitrogen atmosphere in the ice bath for an additional hour. It was then diluted with water and extracted 3 times with ether. The combined ether extracts were washed with 1 N sodium hydrogen carbonate and then with water and dried over magnesium sulfate. The ether was removed on the rotary evaporator to give 25.6 g. (50%) of an oil; $\lambda_{\text{max}}^{\text{CHCl}_3} = 2.91, 5.75 \mu$. The 60 MHz nmr spectrum (CDCl$_3$) showed two singlets (methyl) at 3.65 and 3.70 overlapping a multiplet centered at 3.71. A complex multiplet occurred between 2.90 and 0.90 ppm. A signal due to hydroxyl was observed shifting with temperature.


The mixture of alcohols, methyl 5-hydroxybicyclo[2.2.1]-heptane-endo-2-carboxylate and methyl 6-hydroxybicyclo[2.2.1]heptane-endo-2-carboxylate, (25.6 g., 0.15 mole) in 250 ml. of acetone was cooled to 0° C, with stirring. A solution of chromium trioxide (16.5 g., 0.165 mole) and sulfuric acid (9 ml., 16.5 mole) in 250 ml. of water was added dropwise to the alcohol solution. A temperature of 0-10° was maintained. After the addition was complete, the solution was allowed to warm slowly to room temperature and stir for 2 hours. Water was added to the reaction mixture which
was then extracted 3 times with ether. The combined ether extracts were washed twice with saturated sodium chloride solution and with distilled water until almost colorless. After drying over magnesium sulfate, the ether was removed on the rotary evaporator to give 15.6 g. (60%) of an oily residue; $\lambda_{\text{max}}^{\text{CHCl}_3} 5.7-5.8 \mu$. The 60 MHz nmr spectrum (CDCl$_3$) showed 3 singlets (methyl) at 3.70, 3.66, and 3.65, a multiplet at 4.10, and a complex multiplet from 3.13 to 0.76 ppm.

Preparation of 2,6-Bicyclo[2.2.1]heptanecarbolactone, LXXVa, and 2,5-Bicyclo[2.2.1]heptanecarbolactone, LXXVb.

The mixture of ketones, methyl 6-oxobicyclo[2.2.1]-heptane-endo-2-carboxylate and methyl 6-oxobicyclo[2.2.1]heptane-endo-2-carboxylate, (15.6 g., 0.0093 mole) in 150 ml. of ethanol was chilled in an ice-water bath and 0.9 g. (0.023 mole) of sodium borohydride was added. The solution was stirred for 16 hours, 100 ml. of water was added, and the solution was boiled for 15 minutes. After cooling, the ethanol was removed on the rotary evaporator. An oil which separated from the water layer was extracted into ether. The ether layer was dried over magnesium sulfate and the ether removed to give 8.31 g. of an oily residue; $\lambda_{\text{max}}^{\text{CHCl}_3} 5.63$, 5.79 $\mu$. The 60 MHz nmr spectrum (CDCl$_3$) indicates a 1:5 ratio of lactone, LXXV, to methyl ester. This is a 20% yield of product. Separation of the oil by column chromatography on neutral alumina resulted in isolation of hydroxy esters and one lactone. The 100
MHz nmr spectrum of the lactone is identical to that described for LXXV. $\lambda_{\text{CHCl}_3}^{\text{max}}$ 5.62 μ.

Catalytic Reduction of 5-Iodo-2,6-bicyclo[2.2.1]heptanecarbollactone, LXVa, or 6-Iodo-2,5-bicyclo[2.2.1]heptanecarbollactone, LXVb.

The iodolactone, LXV, (5 g., 0.019 mole), triethylamine (2.63 ml., 1.919 g., 0.019 ml.), and Adam's Catalyst (PtO$_2$·H$_2$O, 0.2 g., 0.00082 mole) were mixed in 100 ml. of ethanol and placed in a Parr Hydrogenation Apparatus under 36.5 pounds of H$_2$ pressure at room temperature for 30 minutes. A pressure drop of 1.5 pounds was observed. The mixture was filtered and the filtrate was extracted with ether. The ether layer was washed with dilute hydrochloric acid, dilute sodium hydrogen carbonate solution, and water. The ether solution was dried over anhydrous sodium sulfate and the ether was removed on the rotary evaporator to give an oil which crystallized on standing. The 60 MHz nmr spectrum (CDCl$_3$) was identical to the spectrum of the lactone, LXXV, prepared according to the procedure of Alder and Stein.$^{40}$


A mixture of the endo and exo acids (5 g., 0.02 mole), platinum oxide (0.2 g., 0.00082 mole), and triethylamine (2.63 ml., 1.919 g., 0.019 mole) in 50 ml. of ethanol was placed in the Parr Hydrogenation Apparatus under 40 pounds of H$_2$ at room temperature for 30 minutes. After filtration, the solution was extracted with
ether. The ether layer was washed with dilute hydrochloric acid, dilute sodium hydrogen carbonate solution, and water. After drying over anhydrous sodium sulfate, the ether was removed on the rotary evaporator to give an oily residue. The 60 MHz nmr spectrum (CDCl₃) showed a singlet at 9.90 and multiplets at 4.36, 2.70, 2.25, and 1.40 ppm. By comparison to spectra of authentic samples of the saturated endo and exo acids, this spectrum revealed that the oil contained the saturated endo acid and what must be decomposition products of the exo isomer. There was no evidence of lactone formation.

Reduction of the Lactone, LXXV, to endo-6-Diphenylhydroxymethyl-endo-2-bicyclo[2.2.1]heptanol, LXXVIIa, or endo-5-Diphenylhydroxy-methyl-endo-2-bicyclo[2.2.1]heptanol, LXXVIIb.

Phenylmagnesium bromide was prepared in a dry, nitrogen atmosphere by the slow addition of bromobenzene (33.5 ml., 50.083 g., 0.319 mole) in 200 ml. of ether to magnesium turnings (7.75 g., 0.319 mole) in 30 ml. of ether. After the reaction had started, ether was added periodically. After the reaction had subsided, the lactone, LXXV, (20 g., 0.145 mole) in ether solution was added dropwise. When the addition was complete, the system was refluxed for 2 hours and allowed to stand at room temperature under nitrogen for 36 hours. When the ether was removed, a white solid remained. This solid was stirred in glacial acetic acid-water solution (12.5:1) for 2 hours at room temperature and then the solution
was diluted with water. The solution was extracted 4 times with ether. The combined ether extracts were washed with 10% sodium carbonate solution until the wash water was basic, then 3 times with water. The ether layer was dried over anhydrous sodium sulfate and the ether removed on the rotary evaporator to yield a gummy residue. Recrystallization from chloroform gave white crystals, m.p. 125-126°C; yield 7.2 g., 36%; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.79, 2.99, 6.85, 9.80, 14.2 μ (see IR-4); $\lambda_{\text{max}}^{\text{EtOH}}$ 2.58 μ. The 60 MHz nmr spectrum (CDCl$_3$) showed an aromatic signal centered at 7.36, a complex multiplet from 4.40 to 3.13, and other multiplets at 2.58, 2.33, and from 1.83 to 0.90 ppm. When the magnesium salt from the Grignard reaction was refluxed for 3 hours in the acetic acid-water solution, white crystals were obtained (recrystallized from ethanol); m.p. 122-123°C; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 6.85, 9.30, 14.2 μ. (See IR-5.) The 60 MHz nmr spectrum (CDCl$_3$) showed an aromatic signal centered at 7.30 (10H), a broad triplet at 4.55 (1H), and multiplets at 2.96 (1H), 2.60 (1H), 2.05 (1H), and 1.40 ppm (6H). (See NMR-11.)

**Analysis.** Calculated for C$_{20}$H$_{20}$O: C, 86.95; H, 7.34. Found: C, 86.58; H, 7.34.

This compound was resistant to treatment with 50% sulfuric acid for 24 hours. On the basis of experimental evidence, it has been assigned the structure related to 3,3-diphenyl-2-oxatricyclo-[6.1.0.0$^4,8$]nonane, LXXVIIIa, or 3,3-diphenyl-2-oxatricyclo-[5.1.1.$^8$]nonane, LXXVIIIb.
LXXVII

2.99 μ

LXXIX

5.73 μ

IR 4

10.90 μ

LXXVII

HO
φ
φ

LXXIX

OH
φ
φ

IR 4
Oxidation of LXXVII.

The diol, LXXVII, (1.58 g., 0.006 mole) in 40 ml. of acetone was cooled to 0° C and a solution of chromium trioxide (1.4 g., 0.014 mole) and sulfuric acid (0.9 ml., 1.4 g., 0.014 mole) in 50 ml. of water was added dropwise, while the temperature was between 0-10° C. After the addition was complete, the reaction mixture was allowed to warm slowly to room temperature and stir for 3 hours. The solution was extracted 3 times with chloroform. The combined chloroform extracts were washed with water until almost colorless. The chloroform layer was dried over anhydrous sodium sulfate and the solvent was removed on the rotary evaporator to give a gummy residue which crystallized out of a small amount of chloroform; m.p. 166-167° C; yield 58%; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.90, 5.75, 10.9, 14.2, 15.3 μ. (See IR-4.) $\lambda_{\text{max}}^{\text{EtOH}}$ 2.52 μ. The 100 MHz nmr spectrum (CDCl₃) showed an aromatic region centered at 7.30 (10H), a broad singlet (hydroxyl) at 3.84, and multiplets at 3.10 (1H), 2.72 (1H), 1.78 (2H), 1.23 (3H), and 0.68 ppm (2H). (See NMR 12.) Mass spectrum (70 ev) m/e (rel intensity) 292 (28.6), 232 (64.3), 205 (50), 165 (57.1), 105 (53.6), 51 (64.3), and 77 (100).

Analysis. Calculated for C₃₀H₂₀O₂: C, 82.19; H, 6.85.

Found: C, 81.48; H, 6.90.

When this ketone, endo-6-diphenylhydroxymethyl-2-bicyclo[2.2.1]-heptanone, LXXIXa, or endo-5-diphenylhydroxymethyl-2-bicyclo[2.2.1]heptanone, LXXIXb, was refluxed in benzene in the presence
of p-toluenesulfonic acid catalyst in a Dean-Stark Apparatus, a
dark oil was obtained. The 60 MHz nmr spectrum (CDCl₃) of this
oil indicated a compound other than starting ketol. The aromatic
region was considerably simplified with a multiplet centered at
7.11. Other multiplets occurred at 3.20, 1.45, and 0.96 ppm.

Ozonolysis of this oil was carried out in the follow­ing manner: 800 mg. of the oil in 75 ml. of chloroform was cooled
to -20° C. O₃ in O₂ at 8 psi was bubbled through the solution for
18 hours. A solution of 1 g. of potassium iodide in glacial acetic
acid (15 ml.) was added dropwise to the cold solution. After the
addition was complete, the reaction mixture was allowed to war­
to room temperature and was washed with aqueous sodium thiosul­
fate solution until the color of iodine was gone. The chloroform
layer was then washed with aqueous sodium carbonate until the wash
water was basic. After washing twice with water, the chloroform
solution was dried over anhydrous sodium sulfate and the solvent was
removed on the rotary evaporator. A gummy yellow residue remained
which crystallized in a slight amount of chloroform; m. p. 120-121° C;
λₘₚ₃ 3.42, 6.78, 10.40 μ. The 60 MHz nmr spectrum (CDCl₃) of the
oil before crystallization showed a broad aromatic region centered
at 7.33, and multiplets at 3.08, 2.40, and 1.25 ppm. The crystals
could not be put into solution in sufficient concentration in any
of various solvents tried to obtain a suitable spectrum.
A study of the dependency of the nmr spectrum of endo-tricyclo[6.2.1.02,7]undec-9-en-3,6-dione, LIV, on temperature was made over the range of -80 to +110° C. The studies were conducted on dilute solutions of the dione in methylene chloride on the A-60-A spectrometer. The area of the spectrum studied was 1.66 to 3.08 ppm. The results of this study are summarized in Figure 29.

100 MHz NMR Decoupling Experiments.

Decoupling was carried out in the usual way on the following compounds: 10-bromo-6,9-epoxy-6-hydroxy-endo-tricyclo-[6.2.1.02,7]undecan-3-one, LVII; 10-bromo-6,9-epoxy-endo-tricyclo-[6.2.1.02,7]undecan-3-one, LXI; 5-bromo-2,6-bicyclo[2.2.1]heptane-carbolactone, LXXIVa, or 6-bromo-2,5-bicyclo[2.2.1]heptanecarbolactone, LXXIVb; 2,6-bicyclo[2.2.1]heptanecarbolactone, LXXVa, or 2,5-bicyclo[2.2.1]heptanecarbolactone, LXXVb. From the data obtained in these experiments, chemical shifts were assigned for these compounds. These data are tabulated in Tables I and II.
### Table I

<table>
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<tr>
<th>COMPOUND:</th>
<th>LVII</th>
<th>LX</th>
<th>LXI</th>
<th>LXXIVb</th>
<th>LXXV</th>
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<tr>
<td>δ(ppm)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>2.83</td>
<td>2.65</td>
<td>2.44</td>
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<tr>
<td>3</td>
<td>3.91</td>
<td></td>
<td></td>
<td>2.04(ex)</td>
<td>2.04</td>
</tr>
<tr>
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<td>2.20</td>
<td>2.20</td>
<td></td>
<td>2.61</td>
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<td>5</td>
<td>2.50</td>
<td>1.95(ex)</td>
<td>2.30(en)</td>
<td>3.83</td>
<td>1.75</td>
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<tr>
<td>6</td>
<td>4.10</td>
<td>4.18</td>
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<td>7</td>
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<td>2.55</td>
<td>2.53</td>
<td>1.72(b)</td>
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<tr>
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<td>3.31</td>
<td>2.89</td>
<td>2.95</td>
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<td>9</td>
<td>4.71</td>
<td>4.55</td>
<td>4.50</td>
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<tr>
<td>10</td>
<td>3.72</td>
<td>4.25</td>
<td>3.67</td>
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<tr>
<td>11</td>
<td>2.25(a)</td>
<td>2.18</td>
<td>2.15(a)</td>
<td>1.63(b)</td>
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</tr>
</tbody>
</table>

**Diagrams:**

LVII: R = OH  
X, Y = \( \emptyset \)

XL: R = H  
X = OH  
Y = H

LXI: R = H  
X, Y = \( \emptyset \)

LXXIVb: R = Br

LXXV: R = H
<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>APPARENT COUPLING CONSTANTS (Hz)</th>
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</tr>
<tr>
<td>LXI</td>
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</tr>
<tr>
<td></td>
<td>$J_{hex-4en} = 13$</td>
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</tr>
<tr>
<td>LXXIVb</td>
<td>$J_{7a-7b} = 11.5$</td>
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<tr>
<td></td>
<td>$J_{3ex-3en} = 11$</td>
</tr>
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<td></td>
</tr>
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<td></td>
</tr>
<tr>
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<td>$J_{7a-7b} = 11.5$</td>
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(Cont.)
<table>
<thead>
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<th>Vicinal</th>
<th>Long Range</th>
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<tr>
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<td>$J_{1-7b} = 1.5$</td>
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<tr>
<td></td>
<td></td>
<td>$J_{1-7a} = 1.5$</td>
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</tr>
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<td>$J_{3-4} = 4$</td>
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<td></td>
<td>$J_{4-7a} = 1$</td>
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DISCUSSION

The tetracyclic diterpenes which belong to the phyllocladene family contain a trans BC ring juncture. This feature dictates a $\beta$ orientation of the D ring, as well as a $\beta$ oriented C-10 methyl group. The preparation of systems which have this stereochemistry has been a challenge to synthetic organic chemists for many years. Only recently have syntheses of these compounds been successful. The basic approach which has been employed has been to synthesize the basic ABC ring structure, and to add the remaining ring D at a later stage of the synthesis. Since the C$_{10}$ methyl group is in a $\beta$ orientation on the ABC ring unit, subsequent addition of a substituent at C-8 occurs from the unhindered rear side of the molecule. This is the opposite stereochemistry from that needed for the D ring in phyllocladene. For instance, in the synthesis of phyllocladene developed by Turner,
et al.,36 (see page 25) it was necessary to rupture oxidatively
the C ring and reform it through a Dieckmann cyclization of the
resulting triacid in order to reverse the stereochemistry about
the BC ring juncture. (See Figure 21.) This cumbersome procedure
involved the addition of many extra steps in the synthesis. The
recyclization process was carried out on optically active material
in approximately 9% yield.

The recent synthetic approaches developed by Ireland
and co-workers37 to gain access to the CD ring system of phyllo-
cladene have also been plagued by this stereochemical problem.
In their procedure, starting again with the basic ABC ring struc-
ture, the entire D ring was constructed in the configuration op-
posite to that desired, and then the carbon skeleton was rearranged
through a Wagner-Meerwein type reaction to the desired stereo-
chemical modification. (See Figure 22.) This very elegant
rearrangement proceeded in 46% yield; however the overall yield
from the keto acetal, XXXVb, in Figure 22 to hibaene was only 10%.

One synthetic approach that has not been investigated
involves the initial construction of the BC to D rings with sub-
sequent annelation of ring A to this system. This reaction
sequence would circumvent the stereochemical problem since a
Michael reaction between the BCD ring unit (LXXXVI in Figure 24)
and methyl vinyl ketone (or its equivalent) could be expected to
afford the desired β orientation of the C-10 methyl group. For
the accomplishment of this sequence (see Figure 24), the reduced
Diels-Alder adduct, LIV, was used as the starting material. The over-all plan involved the addition of what would ultimately become ring C of the diterpene through some standard cyclization reaction. A thermal retro-Diels-Alder reaction to remove cyclopentadiene from the system was anticipated after its presence had directed the orientation of the addition of some functional group at the BC ring juncture. In 1906, Albrect had observed such a reverse reaction at 140°C. He reported the recovery of hydroquinone diacetate when the p-benzoquinone-cyclopentadiene adduct was refluxed in acetic anhydride. Since that time, the thermal reversibility of the Diels-Alder reaction has been observed repeatedly. Berson and Reimanick have reported that the thermal isomerization of the endo cyclopentadiene-methyl methacrylate adduct to the exo isomer actually proceeds through a fragmentation to the dissociated diene and dienophile. Their studies, based on experiments involving C14 labeling, have indicated that a diradical intermediate for intramolecular isomerization can be ruled out in this case. More recently, the dissociation involved in thermal isomerizations has been demonstrated through the use of tetracyanoethylene as a trap for any diene which is released. Workers at the Eastman Kodak Laboratories have been able to show that the isomerization of 4,5-epoxytricyclo[6.2.1.02,7]undec-9-en-3,6-dione at 220°C proceeds through dissociation of the diene and dienophile. Isomeric dimethyl dicyclopentadienedicarboxylates have also been shown to dissociate thermally by use of the reaction of the diene with trapping reagents.
Figure 2 outlines the reaction scheme which was proposed for the diterpene synthesis, using the cyclopentadiene "side-chain" to direct the stereochemistry initially. After ring C had been added through a Robinson annelation reaction, the introduction of a functional group at the BC ring juncture should be from the unhindered, front side of the molecule. This would then be the first example of such a group entering in the proper orientation for the formation of the phyllocladene D ring. It was proposed to use a cyanide addition reaction at this point, under conditions which had been reported to convert the initially formed nitrile to the amide. Hydrolysis and ester formation could be followed by a Reformatsky reaction to obtain the ester-lactone, LXXX. After reduction of the lactone, the diester, LXXXI, could be converted to the ketone, LXXXII, through a Dieckman ring closure followed by decarboxylation. Ethyl formate would convert the ketone, LXXXII, to the corresponding α,β-keto aldehyde. It is known that this type system can be readily converted, through the acetal, to an α,β-unsaturated aldehyde, LXXXIII. Briggs and co-workers have shown that this type aldehyde can be converted to the exocyclic olefin, LXXXIV, through a normal Wolff-Kishner reaction. Then, upon oxidation and heating, the desired BCD ring system, LXXXV, should be obtained. After reduction and methylation, the addition of ring A could be accomplished by the procedure of Wenkert in which either an α,β-unsaturated ester or ketone is condensed to form ring A. Methyl
FIGURE 24 continued:

\[
\begin{align*}
&\text{LXXXIV} \\
&\xrightarrow{\text{NH}_2\text{NH}_2} \xrightarrow{\text{CrO}_3} \xrightarrow{\Delta} \text{LXXXVI} \\
&\xrightarrow{1) \text{Zn}} \xrightarrow{2) \text{CH}_3\text{I}} \text{LXXXV} \\
&\text{or} \\
&\xrightarrow{1) \text{Zn}} \xrightarrow{2) \text{CH}_3\text{I}} \text{or} \\
&\xrightarrow{1) \text{CH}_3\text{I}} \xrightarrow{2) \text{Zn}, \text{HCl}} \text{XI}
\end{align*}
\]
acrylylacetate would be particularly useful at this point if it were desirable to extend the diterpene into some derivative such as cafestol. If ring A were formed by a condensation with methyl vinyl ketone, methylation would yield phyllocladene, XI.

An attempt was made to carry out the cyclization reaction on the dione, LIV, using the Robinson annelation procedure.²¹ An intractable oil was obtained from this reaction. By subsequent investigations, it was shown to be a combination of polymerization products and products from a retro-Diels-Alder reaction of the dione. The retro reaction proved to be much more facile than had been expected. In fact, when the dione was refluxed in benzene with the mild base, pyrrolidine, in an attempt to form the enamine, the only discernable products were those which would arise from the retrogression. Hydroquinone was the major product. It had been felt that the enamine would offer a suitable method for a cleaner, more direct cyclization reaction of the dione because it is well known that enamines tend to form to the least hindered side of unsymmetrical ketones.⁵⁰

In order to prevent this reverse reaction from taking place too soon in the reaction scheme, two alternatives were available. The double bond could be blocked by some species which could be readily removed at the desired time. Tying up the pi electrons of the double bond in this manner would prevent the retro-Diels-Alder reaction. The other choice would involve the reduction of one carbonyl group in order to change the oxidation state of the ring and prevent the formation of hydroquinone.
Since such a reaction appeared to be difficult to carry out, bromination of the double bond was the logical choice.

Bromination of the dione, LIV, resulted in a mono-bromo derivative of unknown structure. When this compound was treated with one equivalent of pyridine in refluxing ethanol, a trace amount of a crystalline material was obtained. Because of the melting point (73-74°) and thin-layer chromatography comparison, it was tentatively identified as the original Diels-Alder adduct, LIII. This information, coupled with spectral and analytical data, prompted the suggestion of 10-bromo-endo-tetracyclo[6.2.1.0^2.7.0^5.9]-undeca-3,6-dione, LXXXVII, as the structure of this compound. (See Figure 25.) This structure was proposed despite the fact that the
carbon-hydrogen analysis fit closer for the formula $C_{11}H_{13}O_3Br$ than for the required $C_{11}H_{11}O_2Br$. Since the difference in these two formulas is the elements of water, the discrepancy was not too surprising. It was suspected that caged compounds of this type might trap solvent molecules within the framework of the molecule. Precedence for this structure was found in the work reported by Cookson in 1964 concerning photochemical reactions of LIII. By uv irradiation of this Diels-Alder adduct, either in solution or in the crystalline state, he obtained the cage-like isomer.

Further work which involved detailed nmr spectral analyses to be described later indicated discrepancies in the suggested structure. It became apparent from the nmr work that the compound contained a hydroxyl group. When treated with sodium ethoxide under carefully controlled conditions of temperature and atmosphere, the bromo compound yielded two products, an epoxide, LVIII, and a compound in which ethoxide had apparently replaced the bromide. Further investigations revealed that it was this same product which had been obtained in the reaction with pyridine in ethanol rather than LIII. When treated with zinc dust in an ethanol solution, the compound underwent dehalogenation to yield the starting dione, LIV. The new evidence, together with the discrepancy of the proposed compound, LXXXVII, and the carbon-hydrogen analysis, made some other structure more probable. All evidence now accumulated suggests the structure of 10-bromo-6,9-epoxy-6-hydroxy-endo-tricyclo[6.2.1.0^2,7]undecan-3-one, LVII.
Figure 26 gives summary of the chemical evidence for this structure.

The ether linkage described for this compound is well known. Henbest and Nicholls have described the formation of such ethers from various unsaturated bicycloheptane systems.\textsuperscript{52} The structure of the bromo derivative being thus established, it seemed evident
that some other means would have to be used in order to continue the proposed synthetic scheme.

It now became necessary to attempt the second approach to block the retro-Diels-Alder reaction. The first attempt made to prepare the system with one carbonyl reduced was through a selective reduction. In order to reduce only one carbonyl, the dione was treated with exactly an equivalent of sodium borohydride. Most of the dione was recovered unreacted, along with a trace of completely reduced material. With the idea that perhaps the oxidation could be controlled, and therefore be more selective, the dione was reduced to the diol, LIX. This diol was treated with exactly one equivalent of chromium trioxide. The reaction mixture was kept very cold in an effort to control the reaction. However, the results were similar to those previously described. A part of the material was unreacted and a part was oxidized to the dione.

Since neither of the "selective" reactions appeared to be suitable for obtaining the desired ketol, it was decided to attempt its preparation through an indirect route. The diol, LIX, was brominated under the same conditions which had been used in the bromination of the dione, LIV. Again the product was a monobromo derivative. It was identified as 10-bromo-6,9-epoxy-endo-tricyclo[6.2.1.02,7]undecan-3-ol, LX, through spectral analysis, elemental analysis, and chemical evidence. Treatment with zinc dust in ethanol yielded the diol. Under the conditions of the Jones oxidation, this alcohol was easily converted to the
corresponding ketone, 10-bromo-6,9-epoxy-endo-tricyclo[6.2.1.0²⁷]undecan-5-one, LXI, and readily dehalogenated by treatment with zinc dust in ethanol to yield the desired unsaturated ketone, 6-hydroxy-endo-tricyclo[6.2.1.0²⁷]undec-9-en-3-one, LXIII. Attempts to carry out the Robinson annelation reaction with this compound met with little more success than the original reaction. Again a dark oil was obtained. This time it was purified to the extent that small amounts of the starting material were recovered.

Since it had been demonstrated that the bromine could be readily removed from the ketone, LXI, to regenerate the unsaturated system required for the retro Diels-Alder reaction, the idea of using this compound in the synthetic scheme was developed. Since the ketone was easily obtained in reasonable quantities, the cyclization reaction was attempted once more. This time a cyclization did take place; however, the product did not contain bromine. Apparently, after cyclization, a Darzen reaction had occurred instead of dehydration. (See Figure 27.) All available evidence indicates that the product is 3,14:10,13-diepoxytetracyclo[10.2.1.0³⁸ 0²⁷]pentadecan-5-one, LXIV. Attempts were made to isomerize this diepoxide to the α,β-unsaturated ketone and to insert an angular functional group. These reactions have not been successful.

Attempts were then made to obtain a more useful system as the basic BC ring structure through modifications of the cyclization reaction described above. Attempts to prepare a methiodide
salt from the bromo ketone LXI, and to react this with methyl vinyl ketone were unsuccessful. Use of the enamine of the bromo-ketone, LXI, to increase the yield of the cyclization reaction resulted in only trace amounts of the previously described cyclization product, LXIV. No method which was attempted gave more promise of a successful addition of the C ring than the straightforward Robinson annelation of LXI.

It appeared at this point that a thorough investigation of the chemistry and structure of the dione, LIV, and its derivatives was in order. This compound was unexpectedly reactive, making it difficult to control reactions and obtain desired products. Products of unexpected structural complexity were obtained in some cases. The idea from which its use in the synthesis of the terpene systems originated has great potential; however, if
the system is to be useful in synthetic work, much must be learned about the nature of these compounds.

By using deuterium labeling, it was demonstrated that the dione did not enolize significantly in a neutral solution. However, under mild catalytic conditions, enolization occurred to both sides. There was complete exchange of all hydrogens alpha to the carbonyl with deuterium after a trace of trichloroacetic acid was added to a stirred solution of the dione in D$_2$O.

In order to study the conformation of the carbonyl containing ring of LIV, temperature studies of its nmr spectrum were conducted. The results of these studies are shown in Figure 29. The 1,4-cyclohexanodione ring is generally reported to be in a boat or skewed-boat form and non-equilibrating. If the boat form of the cyclohexandione ring is correct for this tricyclo compound, whether the methylene groups are syn or anti to the double bond, or in equilibrium between the two positions, the four methylene hydrogens will be required to be eclipsed at all times. This confirmation should have much higher energy requirements than that of a skewed confirmation in which the hydrogens would be eclipsed only in the transition state between the two conformers. When the Diels-Alder adduct, LIII, is reduced to LIV, the sharp singlet in the nmr spectrum for the ethylenic hydrogens at C-4 and C-5 changes to an A$_2$B$_2$ type pattern between 1.66 and 3.08 ppm for the four methylene protons. This splitting would be expected for either conformer of the boat conformation,
or for the time average of a rapid equilibrium between the two skewed conformers. The temperature studies were conducted on this part of the nmr spectrum. An equilibrium is definitely indicated by a comparison of spectra at high and low temperatures. There is a definite change in the pattern, a broadening of the signals, as the temperature is lowered. This indicates that the time average $A_2B_2$ system that exists is different at the different temperatures. Figure 29 indicates this change down to $-40^\circ \mathrm{C}$. Work at lower temperatures, to a minimum of $-80^\circ \mathrm{C}$, shows a continuation of the same pattern change. This change in the pattern is evidence for an equilibrating system. The most likely form of
Figure 29

Chemical structures and spectra at different temperatures in CH$_2$Cl$_2$. Temperatures: +110, +100, +80, +60, +40, 0, -20, -40°C.
this equilibrium should be from one skewed form to another since this conformation should have lower energy requirements than the boat form.

In order to learn more about the structure of the halogenated derivatives of the dione, a detailed nmr spectral study of LVII, LX, and LXI was conducted. The most striking feature of the spectra of all three of these compounds was the presence of two sets of broad apparent doublets in approximately the same downfield region. This portion of the spectrum of each of these compounds is illustrated in Figure 30. In each case, the signals shown are the most downfield signals for the compound described. The most downfield signal is in relatively the same position for each compound, while the second doublet shifts upfield by over 0.5 ppm when the carbonyl group is introduced at the C₃ carbon atom. These data indicate that the hydrogen responsible for this signal is in close proximity to the functional group at C-3 and is shifted by the π cloud of the carbonyl. The nmr spectrum of the oxime of LXI revealed that the signal for the C₁₀ proton was shifted downfield, indicating deshielding. A multiplet which appears at 4.0 ppm (2H) in LX and at 4.18 ppm (1H) in LXI is absent in the spectrum of LVII. This signal does not shift in relation to the most downfield doublet on going from the alcohol to the ketone. By use of deuterium labeling, it was shown that this signal is due to the hydrogens on C-3 and C-6. When the ketone, LXI, was brominated at C-4, the nmr signal for the remaining C-4
hydrogen was shifted downfield. This made the upfield region of
the spectrum much less complex and enabled assignment of the sig-
nals due to the C\textsubscript{4} hydrogens.

Decoupling experiments were performed on compounds LVII
and LXI, the two ketones. The coupling constant data obtained
from this work (listed in Table II) together with the other avail-
able evidence enabled the assignment of proton chemical shifts for
these compounds. This information is given in detail in Table I.
The most downfield signal is due, in all cases, to the exo hydrogen
at C-9. The second broad doublet is assigned to the endo hydrogen
at C-10, which is geminal to the bromine. When the corresponding
iodo compounds were prepared, it was shown that the C\textsubscript{9} hydrogen
(vicinal to the halogen) was affected to a greater extent by the
change than the hydrogen geminal to the substituent. The down-
field shift of the hydrogen vicinal to the iodo substituent (see
NMR-3) is in agreement with observations made for simpler systems.\textsuperscript{54}

Although all the evidence for the structures assigned to
these bromo compounds was in good agreement, a literature survey
presented a reason for serious doubt as to the validity of these
structures. It was discovered that a much simpler compound, 5-
iodo-2,6-bicyclo[2.2.1]heptanecarbolactone, LXV, has an nmr spec-
trum which shows an amazing similarity to the compounds just dis-
cussed.\textsuperscript{55} (See NMR-10.) The same two downfield apparent doublets
occur in relatively the same positions. Decoupling experiments
revealed the same type coupling between corresponding signals here
and in the previous series of compounds. All this would indicate similar environments for the hydrogens involved. Studies of models did not reveal the required similarity, particularly regarding any shielding of the C₅ hydrogen of the lactone by the carbonyl group.

In order to further investigate apparent similarities between the structures of the two systems, the unsubstituted lactone, 2,6-bicyclo[2.2.1]heptanecarbolactone, LXXV, was prepared according to the procedure of Alder and Stein.⁴⁰ Since the structure of the iodo lactone, LXV, had been assigned on the basis of the γ lactone structure which Alder and Stein had originally assigned to the unsubstituted lactone, that structure would be significant in this investigation. The significant feature of the nmr spectrum of LXXV was a broad triplet at 4.95 ppm. (See NMR-9.) This signal is assigned to the hydrogen at C-6. The two broad doublets found in all the halogenated compounds are, of course, not present. The corresponding unsubstituted compounds in the tricyclo[6.2.1.0²⁷]undecane series, LXIX and LXX, were prepared. Both of these compounds exhibit the same type broad triplet downfield, at 4.40 and 4.30 ppm, respectively. The nmr spectral analyses of these unsubstituted compounds again indicated that the exo C₉ hydrogen and endo C₁₀ hydrogen on the tricyclo compounds are in an environment which is the same as that for the hydrogens at C-5 and C-6 of the bicyclo lactones.

In order for this similarity of environment for the above mentioned hydrogens to exist, models indicate that the
structures assigned to the compounds in one or the other of the series must be altered. However, if the ether linkage in the tricyclo compounds was to C-10 rather than C-9, models do not reflect any way in which the hydrogen geminal to the halogen could be influenced by the change from hydroxyl to carbonyl at C-3. On the other hand, if the lactone structure was that of a six-membered ring, or δ, lactone, the C₆ hydrogen (now geminal to the halogen) would be in a direct alignment with the carbonyl. (See Figure 32.)

While studying the problem of these structures, it was noted that this was not the only time the lactone structure had been questioned. In 1964, Crundwell, et al., reported that the hydroxy lactone corresponding to the iodo lactone, LXV, was unexpectedly resistant to oxidation under conditions by which the hydroxy diester was readily oxidized.⁵⁶ (See Figure 31.) They offered no explanation for this unusual resistance of the lactone to oxidation other than to suggest that the structure assigned to the lactone may be incorrect. However, no attempt was made to suggest a suitable structure.

Apparently, when Alder and Stein assigned the γ lactone structure to the system, no consideration was given to the possibility of the δ lactone isomer being formed. Studies of this system since that time refer to this original work. If the lactone is indeed the δ lactone, both the nmr spectral observations and the resistance of the hydroxy lactone to oxidation can be readily explained. As was mentioned, the C₆ hydrogen is in close
proximity to the carbonyl in this structure, analogous to the effect in the tricyclo series. The resistance to oxidation by the lactone in which X is hydroxyl can be understood from this structure also. As the C₆ carbon is rehybridized from sp³ to sp², the two carbonyl groups would be forced into exact alignment in this boat conformation. This is an arrangement which would have very high energy requirements and is therefore undesirable. Another consideration is the steric requirement for the oxidation reaction. Crundwell attempted the oxidation using chromium trioxide as an oxidizing agent. In the mechanism of the reaction, this bulky reagent would be required to crowd into a limited space underneath
the molecule in the $\delta$ lactone. The spatial restriction for the reagent would not be so great in the $\gamma$ lactone.

Of course, the possibility exists for the formation of either the $\gamma$ or $\delta$ lactone from addition reactions to the olefin. In the next higher series, the bicyclo[2.2.2]octanecarbolactones,
both possible isomers have been reported. The assignment of structures corresponding to the \( \gamma \) and \( \delta \) lactones in this series was based upon the carbonyl stretching frequencies in the infrared. In an infrared spectrum, it is well known that, other things being equal, these frequencies are a function of the size of the lactone ring. The important point to be noted, then, in this work is the actual carbonyl stretching frequencies which were observed. As expected, that reported for the \( \delta \) lactone is at a longer wavelength (5.68 \( \mu \)) than that observed for the \( \gamma \) lactone (5.60 \( \mu \)). In all the lactones investigated in the bicyclo[2.2.1]heptane series (iodo, LXV; bromo, LXXIV; and unsubstituted, LXXV) the carbonyl stretching frequency is at 5.62-5.63 \( \mu \). It is reasonable to assume that in the more highly strained heptane series, lactones of the same ring size as in the octane series would have carbonyl absorptions at shorter wavelengths. Following this reasoning, the absorptions at 5.63 \( \mu \) should represent the \( \delta \) lactone. If this is the \( \gamma \) lactone, as reported in the literature, it would be in the unlikely situation of exhibiting a longer wavelength than the corresponding lactone in the less strained octane series. Reports have been made of similar observations of the carbonyl stretching frequencies of lactones in other highly strained bi- and tricyclo systems. Wilder has reported a study of the carbonyl stretching frequencies of lactones derived from exo-cis-7-isopropylidenebicyclo[2.2.1]heptane-2,3-dicarboxylic acid anhydride. In his work, he reports a \( \delta \) lactone which has
maximum absorption at 5.64 μ in carbon tetrachloride and one γ lactone which absorbs at 5.58 μ in a nujol mull while another shows absorption at 5.53 μ in carbon tetrachloride.

It was felt that if both lactone isomers in the heptane series could be obtained, the assignment of structures could be easily made on the basis of the infrared spectra. The preparation of the two isomers was attempted according to the scheme summarized in Figure 33. The idea was to prepare a mixture of the two possible alcohols which could be oxidized to the corresponding two ketones and then reduced to the two desired lactones. Separation of the lactones could be accomplished by column chromatography. When these procedures were carried out, only one lactone was obtained. It was identical in every respect to the compound described.
previously in this work and in literature references.* When this process failed to produce the two desired isomers, the method used to obtain the two isomers in the octane series was employed. Since, in that case, the δ lactone was produced by an extension of the reaction time, it was necessary to go the other way in the heptane series in attempts to obtain the γ lactone. Reaction conditions were altered from 0° C in the dark for only the length of time required for addition of the reagent to three days at room temperature in the light. In every case, the original lactone was the product.

*More recent work in these laboratories indicates that probably both lactones were formed in this reaction scheme, but that the γ lactone spontaneously decomposes. Because only one lactone had been isolated by the reaction scheme described above, an attempt was made to develop another method whereby both isomers could be obtained. The work of Iles and Worrall was noted in which the bromo lactone, LXXIV, was reported to be converted to the ketone, 6-oxobicyclo[2.2.1]heptane-2-carboxylic acid, by treatment with sodium hydroxide. On the assumption that this reaction involves an epoxide intermediate, the use of this reaction to produce a mixture of the two desired lactone isomers seemed promising. When the iodo lactone, LXV, was treated with two equivalents of sodium ethoxide, two products were actually obtained, a lactone and an unsaturated acid. The acid was converted into an amide for analysis. The analysis suggested C₁₀H₁₅O₂N, and the structure of LXXXVIIIb has been proposed. It has been suggested that this compound resulted from the decomposition of the highly strained γ lactone according to the scheme outlined in Figure 34. From the neutral fraction of this reaction, the ethoxy lactone corresponding to the original iodo lactone was obtained. This compound was isolated and, when an attempt was made to purify it by distillation, decomposition occurred. The decomposition product appeared to be a salt which, when acidified, was soluble in ether. It is suggested that this compound is the isomeric ethoxy acid, LXXIX.
FIGURE 34
Since it had not been possible to obtain the second iso-
mer of the lactone in the heptane series, it was necessary to de-
grade the lactone in order to make a final assignment of the
structure. Since the structures of the halogenated lactones had
been assigned on the basis of the structure of the unsubstituted
lactone, LXXV, the two needed to be compared to ascertain that the
structures were indeed the same. When the iodine was catalytically
removed from LXXV, the same unsubstituted lactone was obtained.
In order to be sure that no rearrangement via unsaturated acid
had occurred during the reduction, the unsaturated acid was re-
duced under identical conditions. There was no evidence of lac-
tone formation in this reaction. Having thus established the same
ring structure for the halogenated and unsubstituted lactones, it
was the unsubstituted lactone which would be degraded.

The degradation and identification procedure to be fol-
lowed is outlined in Figure 35. It was hoped that by following
the procedures indicated here, one of the two diketones, XCa or
XCb, could be obtained. Since the 2,5-isomer is now known, identifica-
tion should be easy. The oxidation of LXXVII to LXXIX
took place readily; however, the ketol was resistant to dehydra-
tion. Attempts to dehydrate by standard procedures such as re-
fluxing in acetic acid or treatment with 50% sulfuric acid for
twenty four hours always resulted in recovery of the starting
ketol unchanged. It was also recovered unchanged from trifluoro-
acetic acid. During these dehydration attempts, the reaction
mixture always turned a dark brown, but the white crystals of starting material were recovered. The reason for this resistance to dehydration is not understood. It is possible that under the dehydration conditions an equilibrium is established between the starting ketol and the hemi-ketal. This could easily be the case
if the hydroxyl group is properly aligned beneath the carbonyl group. Ring closure could occur rapidly in the presence of acid.

![Chemical Structures](image)

Figure 36

This seems reasonable in view of the fact that a very stable ether, LXXVIII, is formed when the diol, LXXVII, is refluxed in acetic acid. When the ketol, LXXIX, is refluxed in benzene in the presence of p-toluenesulfonic acid catalyst in a Dean-Stark apparatus, some type of reaction does occur. A dark oil is formed. Spectral evidence indicates the presence of a new compound, but attempts to obtain it in a form pure enough for identification have not been successful.

Another possibility was considered in light of the resistance of the oxidation product to dehydration. Initially, it
was suggested that the ketone, LXXIX, does not actually have the structure which is assigned here. A fused ring system, IXC, could be formed during the oxidation reaction in the manner shown in Figure 37. This compound would be expected to be resistant to dehydration; however, this possibility was deleted by converting LXXIX into the corresponding ether, LXXVII.

Meinwald has suggested the fragmentation of the ring structure of bicyclo[2.2.1]heptane epoxy compounds under conditions of acid hydrolysis. It is possible that this type reaction is taking place in the system under consideration; however, this was not considered to be the probable reaction, since the crystalline product was recovered from every attempted reaction. It was resistant to ozonolysis. Any fragmentation product should contain double bonds which would be reactive under these conditions.

In summary, the use of endo-tricyclo[6.2.1.0^2,7]undeca-9-en-3,6-dione, LIV, as a precursor to tetracyclic diterpenes of the phyllocladene family has been attempted. This compound has potential use in synthetic work; however, it is an unusual system and its chemistry must be carefully studied. The structures which have been assigned to the bromo derivatives of this system because of the accumulated evidence are reasonable. The indications are that the bromine must be on the C_{16} position in order for the observed interactions with the functional group at C-3 to occur. If this is true, then either the structural assignment of the
FIGURE 37
2,6-bicyclo[2.2.1]heptanecarbolactones must be incorrect or an anomalous system exists for which there are no ready explanations for the observed phenomenon.
REFERENCES TO THE LITERATURE

1. O. Wallach, Ann. Chem., 238, 78 (1887); 239, 49 (1887).
3. L. Ruzicka, Experientia, 9, 357 (1953).


SELECTED BIBLIOGRAPHY


L. Ruzicka, Experientia, 9, 357 (1953).


VITA

Linda Ledbetter Green was born in Ruston, Louisiana, and attended public school there. She obtained the B.S. degree in chemistry from Louisiana Polytechnic Institute in 1962. During the academic year 1963-1964, she served as acting Instructor in chemistry at Louisiana Polytechnic Institute. In 1965 she received the M.S. degree in organic chemistry from that institution. In September, 1965, she entered graduate school at Louisiana State University as a Graduate Teaching Assistant. During the fall semester of 1968, she was appointed half-time Instructor in chemistry at Louisiana State University. She is currently a candidate for the Doctor of Philosophy degree with a major in organic chemistry and a minor in analytical chemistry.
EXAMINATION AND THESIS REPORT

Candidate: Linda Ledbetter Green

Major Field: Chemistry


Approved:

[Signatures]

Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

[Signatures]

Date of Examination:

May 12, 1969