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THE RICE INSTITUTE

The Structure of Cassaic Acid

by

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A THESIS
SUBMITTED TO THE FACULTY
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
Doctor of Philosophy

Houston, Texas
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To my wife Joanne,

and the memory of my father.
ACKNOWLEDGMENT

I wish to express great appreciation to Dr. R. B. Turner who directed this research and guided my graduate career.

The contributions of the faculty of the Rice Institute and of numerous graduate students and post-doctoral fellows to my graduate training are also gratefully acknowledged. Finally I am deeply indebted to the Monsanto Chemical Company, Texas City, for a fellowship during the years 1956-58.
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I. INTRODUCTION
I. INTRODUCTION

The toxic properties of preparations derived from trees of the genus Erythrophleum have long been recognized by the natives of tropical Africa. Erythrophleum extracts have served as the chief ordeal poison for tribes in most of this region and have been widely employed in the manufacture of arrow poisons.\(^1\) The use of powdered Erythrophleum bark as a cardiac stimulant in primitive medical practice has also been reported.\(^2\) Investigations of the physiological properties of crude infusions of the drug were undertaken in Europe as early as the middle of the 19th century, but only within the last 25 years have pure crystalline alkaloids been isolated and subjected to extensive chemical and pharmacological study. Work leading to the establishment of complete chemical structures for three of these substances is reported in this thesis.

The Erythrophleum genus is classified in the legume family. Erythrophleum guineense G. Don, the most thoroughly studied and probably the most common species, is native to the western and central parts of equatorial Africa, and includes several subspecies which are difficult to differentiate botanically.\(^2\) All parts of the tree are very poisonous. Although the bark represents the most common source of alkaloids, its alkaloid content is subject to wide variations. Of four samples of bark employed in the present study only two from the Sierra Leone region contained the alkaloid cassaine, whereas two samples from the vicinity of Stanleyville in the
Belgian Congo were devoid of this substance. One of the latter specimens, in fact, yielded only insignificant amounts of material in the total alkaloid fraction. This experience is contrary to that of Engel and Tondeur\(^3\) who regard plant material from the province of Stanleyville as superior to that from other regions.

The second most important species is E. couminga from Madagascar and the Seychelles Islands.\(^4\) Other varieties such as E. fordii from Indochina, E. densiflorum from the Philippine Islands and E. chlorostachys from Australia have not been examined in any great detail, although they appear to be less toxic than either E. guineense or E. couminga.\(^2\)

**Cassaine.** The first crystalline, well-characterized alkaloid from Erythrophleum bark (guineense) was isolated by Dalma\(^5\) in 1935, and named cassaine after the native designation (Cassa) for the tree. The compound is readily obtained from its crystalline bisulfate salt which is precipitated from an acetone solution of the amorphous total alkaloids by addition of sulfuric acid. Analyses of the free base and of various salts including the bisulfate established the empirical formula \(\text{C}_{24} \text{H}_{39} \text{O}_4 \text{N}\). Cassaine forms a monoacetate and a monoxime and hence contains one hydroxyl group and one ketonic function.\(^2\) The remaining two oxygen atoms are present in an ester linkage, since on hydrolysis with dilute hydrochloric acid cassaine furnishes \(\beta\)-dimethylaminoethanol and cassaic acid, \(\text{C}_{20} \text{H}_{30} \text{O}_4\).\(^2\)
from which cassaine can be regenerated by treatment of the sodium salt with $\beta$-dimethylaminoethyl chloride. The fact that the free hydroxyl group of cassaine is secondary has been demonstrated by mild chromic acid oxidation of cassaic acid to a diketone (dehydrocassaic acid) which shows a negative response in aldehyde tests.²

The ultraviolet absorption spectra of cassaine ($\lambda_{\text{max}}$ 223 mp, log $\epsilon$ 4.26), of cassaic acid ($\lambda_{\text{max}}$ 215 mp, log $\epsilon$ 4.3), and of dehydrocassaic acid methyl ester ($\lambda_{\text{max}}$ 223 mp, log $\epsilon$ 4.2) indicate that all three substances are $\alpha,\beta$-unsaturated carboxyl derivatives.⁷ This conclusion is confirmed by the fact that both cassaine and cassaic acid on catalytic hydrogenation furnish dihydro compounds which retain the keto group, but which show no discrete absorption in the ultraviolet.⁶,⁷ Whereas acid catalyzed hydrolysis of cassaine furnishes cassaic acid without double bond migration, strong treatment with base is reported to yield an isomeric substance, allocassaic acid, for which a $\beta,\gamma$-unsaturated structure has been proposed in view of the lack of characteristic ultraviolet absorption.⁷ Allocassaic acid and cassaic acid are further stated to yield the same dihydro derivative.⁶,⁸

* The conditions necessary to obtain the allo acid are obscure. Several conflicting statements regarding this preparation appear in the literature (see references 4, 6, 88), and in this laboratory the hydrolysis of cassaine bisulfate under basic conditions did not provide allocassaic acid.
In order to obtain information on the carbon skeleton of cassaic acid, which is inferred to be tricyclic from the data given above, dihydrocassaic acid was reduced with sodium and alcohol to a saturated dihydroxy acid which was then dehydrogenated with selenium. The product was identified as 1,2,8-trimethylphenanthrene, and 17 of the 20 carbon atoms of cassaic acid are thus accounted for. The isolation of 1,2,8-trimethylphenanthrene suggested that cassaic acid is a terpene derivative, and partial structure (1), which obeys the isoprene rule, was provisionally advanced by Ruzicka and Dalma on the basis of an assumed analogy to other terpenoid substances. The dehydrogenation reaction was hence interpreted as involving decarboxylation, retropinacol rearrangement in ring A, and loss of the two angular methyl groups.

As a test of this hypothesis dihydrocassaic acid was oxidized to the corresponding diketone which was then reduced by the Wolff-Kishner method to cassanic acid, tentatively formulated as (2). Selenium dehydrogenation of cassanic acid afforded not the expected 1,8-dimethylphenanthrene but

* The nomenclature that has been generally adopted in this series is based on the name cassanic acid for the fully saturated but unsubstituted acid, C_{20}H_{34}O_{2}. Dehydrocassaic acid may thus be designated as diketocassanic acid and cassaic acid as hydroxyketocassanic acid, although the terms cassaic acid and allocassaic acid have been retained as trivial names.

** In addition a small amount of an isomeric substance, isocassanic acid, was obtained. Clemmensen reduction of the diketo acid results in removal of only one of the two keto groups. (See reference 6).
instead 1,2,8-trimethylphenanthrene. \textsuperscript{9} It seemed clear then that the methyl group at carbon atom 2 in the dehydrogenation product is not derived by retropinacol rearrangement, and the cassaic acid formulation was accordingly modified as indicated in expression (3) to account for this result. \textsuperscript{10}

\begin{align*}
(1) & \quad (2) & \quad (3)
\end{align*}

The next phase of the investigation centered on efforts to establish the positions of the various functional groups through the technique of labelling the groups involved by reaction with the Grignard reagent. \textsuperscript{10} Thus hydroxycassanic acid, obtained by Wolff-Kishner reduction of dihydrocassaic acid, was converted into the methyl ester and oxidized to the corresponding amorphous ketocassanic acid methyl ester which was in turn treated with excess methylmagnesium bromide. The product, after dehydration with acetic anhydride, was dehydrogenated over palladium-charcoal. Chromatography of the yellow oil obtained in this way yielded a small crystalline fraction characterized as the trinitrobenzoate, m.p. 153-154°, which gave analyses corresponding to those calculated for the
trinitrobenzoate of a tetramethylisopropylphenanthrene. Four possible structures (4, 5, 6, and 7) were considered for the dehydrogenation product, the isopropyl group being derived by Grignard attack on the ester function and the starred methyl group representing the point of attachment of the original hydroxyl group of cassaine. Ring C was excluded as a possible location for the latter function, since (a) the hydroxyl group in question is secondary, (b) cassaic acid is not the enol derivative of a \( \beta \)-keto acid, and (c) the diketone, dehydro-cassaic acid, does not possess the chromophore \( \text{O}=\text{C}-\text{C}=\text{C}-\text{COOH} \).

An attempt was made to synthesize 1,2,3,10-tetramethyl-7-isopropylphenanthrene (4) for comparison with material derived from natural sources, but the lengthy synthesis was ultimately abandoned. \(^{10}\)

While this investigation was in progress it was also noted that in an appropriate case the starred methyl groups in the phenanthrene structures given above could alternatively be regarded as marking possible positions for the keto group in cassaic acid. In an abortive attempt to develop this idea acetoxyketocassanic acid methyl ester was treated with methyl-magnesium bromide, and the resulting material was subjected to purification by distillation and chromatography. Two crystalline compounds were obtained which proved to be the expected triol and an unsaturated diol. Both derivatives were subjected to dehydrogenation over palladium-charcoal, but in both cases
CHART I

(4)

(5)

(6)

(7)
brown oils were obtained which failed to yield crystalline material on treatment with trinitrobenzene.\textsuperscript{10}

The Swiss group\textsuperscript{10, 11} finally hoped to establish at least the position of the carboxyl group of cassaic acid by the dehydrogenation method. Cassanic acid methyl ester was accordingly treated with methylmagnesium bromide, and the product was successively dehydrated and dehydrogenated with selenium to a crystalline hydrocarbon, $\text{C}_{20}\text{H}_{22}$, which was assigned structure (8). A compound of this structure was subsequently obtained by synthesis, and since it proved to be not identical with the hydrocarbon from cassaic acid, structure (3) for the latter substance was of necessity abandoned.

In 1949 the results of a comparative study of the ultraviolet absorption spectra of various synthetic trisubstituted and tetrasubstituted phenanthrenes were reported from the Zürich laboratories.\textsuperscript{12} The data strongly indicated that the $\text{C}_{20}\text{H}_{22}$ product was a trisubstituted phenanthrene and not a tetrasubstituted derivative as had previously been supposed. This development opened the way for new interpretations, of which one advanced by Humber and Taylor\textsuperscript{13} in 1955 involved relocation of the carboxyl group as indicated in skeletal structure (9). Although this formulation does not obey the isoprene rule it could plausibly be derived from (10), a biogenetic precursor for diterpene acids suggested by Ruzicka,\textsuperscript{14, 15}
by cyclization and methyl migration. The formation of 1,2,8-trimethylphenanthrene as a dehydrogenation product could now

be interpreted as involving decarboxylation and the loss of two methyl groups from quaternary centers, the methyl groups at C. 1 and C. 2 in the phenanthrene derivative being supplied by ring C substituents and not by carbon atoms attached to ring A. It was further noted that acceptance of structure (9) requires the assignment of structure (13) to the \( C_{20}H_{22} \) hydrocarbon obtained from cassanic acid by the Grignard-dehydrogenation sequence. Synthesis of (13) from 1,8-dimethyl-9,10-dihydrophenanthrene (11) by the steps indicated below, furnished material identical in all respects with the \( C_{20}H_{22} \) degradation product, and the ring C arrangement in cassaine was thereby established. On the basis of analogy, and in consideration of factors discussed more fully in a subsequent section, structures (14) and (15) were then advanced as tentative formulations for cassaic acid and for cassaine, respectively. In this connection reference was made by Humber and Taylor to a private communication.
received from Dr. B. G. Engel describing experiments carried out by him in the E. T. H. laboratories in Zürich. This work, which has only recently been published,\textsuperscript{16} involved ozonization of the diketo derivative, dehydrocassaic acid, which furnishes oxalic acid in 70% yield and a triketone in which the carbonyl groups are isolated and hence presumably in different rings.

**Cassaidine.** From the mother liquors obtained from the total alkaloids of *E. guineense* after removal of cassaine, Dalma isolated a second crystalline alkaloid to which he gave the name cassaidine.\textsuperscript{5} The formula $C_{24}H_{14}O_{4}N$ was established for this base, which gives only amorphous acyl derivatives, but which contains two hydroxyl groups as indicated by the results of the Zerewitinoff analysis.\textsuperscript{17} Like cassaine, cassaidine affords $\beta$-dimethylaminoethanol on hydrolysis. The acidic product formed in this reaction, cassaidic acid, possesses the formula $C_{20}H_{32}O_{4}$ and exhibits ultraviolet absorption characteristic of an $\alpha,\beta$-unsaturated acid. Basic hydrolysis of cassaidine yields an allo acid devoid of discrete absorption in the ultraviolet.\textsuperscript{17} No further information is available concerning this substance, which is presumably a $\beta,\gamma$-unsaturated product analogous to allocassaic acid.

The relationship of cassaidine to cassaine has been shown by chromic acid oxidation of cassaidic acid to dehydrocassaic acid. Moreover, cassaidine can be reduced to a dihydro derivative hydrolyzable by base to a product identical with
dihydroxycassanic acid, prepared by sodium-alcohol reduction of dihydrocassaic acid.\textsuperscript{17}

**Erythrophtalamine.** This alkaloid from *E. guineense*\textsuperscript{18} was designated as alkaloid "A" by Tondeur in his doctoral dissertation\textsuperscript{19} and has been shown to be identical with a substance isolated earlier by Ruzicka, Plattner and Engel\textsuperscript{20} from *E. couminga*. The analytical results are consistent with the formula \( C_{25}H_{39}O_6N \) and the compound possesses one methoxyl group and the usual \( \alpha,\beta \)-unsaturated carboxyl function esterified with \( \beta \)-dimethylaminoethanol. The parent acid,\textsuperscript{21} erythrophtalaminic acid, \( C_{21}H_{30}O_6 \), yields a methyl ester from which a monoacetate and a monoxime have been obtained. It follows that of the six oxygen atoms of erythrophtalamine, two are present in an ester linkage, one is accounted for by a methoxyl group, one by a hydroxyl group, and one by a ketonic function. The nature of the sixth oxygen atom has not been established.

**Cassamine.** Also isolated from *E. guineense* by Tondeur,\textsuperscript{3,18,19} cassamine possesses the formula \( C_{25}H_{39}O_5N \) and contains one methoxyl group and one keto group. Hydrolysis\textsuperscript{21} with dilute acid affords \( \beta \)-dimethylaminoethanol and an \( \alpha,\beta \)-unsaturated acid, cassaminic acid, for which the formula \( C_{21}H_{30}O_5 \) has been established. The fifth oxygen atom is unassigned. Both cassamine and erythrophtalamine are in all probability closely related to cassaine, but this point has not thus far been demonstrated.
Coumingine and Coumingidine. These two alkaloids have been obtained from Erythrophleum couminga, which has also furnished cassaine, cassaidine and erythrophlamine (see above). One of these, coumingine, was isolated by Dalma in 1938 and was subsequently obtained in somewhat purer form by Ruzicka, Dalma and Scott. The empirical formula was ultimately established as \( C_{29}H_{47}O_6N \), and the alkaloid furnishes a monoxime, but is unaffected by mild treatment with acetylat ing agents. Coumingine is hydrolyzed by dilute mineral acid to coumingic acid, \( C_{25}H_{38}O_6 \), and \( \beta \)-dimethylaminoethanol. Basic hydrolysis on the other hand affords cassaic acid, \( \beta \)-dimethylaminoethanol, and a steam volatile, low molecular weight acid. The same two acids are likewise obtained in the base-catalyzed hydrolysis of coumingic acid. The results provide strong evidence for the fact that coumingine is a derivative of cassaine in which the hydroxyl group is esterified by a low molecular weight acid. After the expenditure of considerable effort in following a false lead, the latter acid was finally identified as \( \beta \)-hydroxyisovaleric acid by direct comparison of the hydrazide with an authentic sample. In terms of the Humber-Taylor proposal for cassaine, coumingine should therefore be formulated as indicated in structure (16).

Coumingidine was isolated in crystalline form by Schlittler in 1938. A decision between the formulas
C_{28}H_{45}O_{6}N and C_{27}H_{43}O_{6}N could not be made on the basis of the analytical results, but Schlittler favored the C. 28 formulation. In contrast to coumingine, coumingidine yields a neutral N-acetyl derivative upon acetylation, and can be purified through the crystalline N-nitroso derivative, from which the free base can be regenerated by treatment with cuprous chloride and concentrated hydrochloric acid. Coumingidine absorbs one mole of hydrogen on catalytic hydrogenation and hence presumably contains an ethylenic double bond. Since no ultraviolet data were reported, the alkaloid cannot definitely be assigned the \( \alpha, \beta \)-unsaturated ester structure common to the other Erythrophleum bases.

Hydrolysis of coumingidine affords \( \beta \)-methylamino-ethanol, an observation that is consistent with the formation of the N-acetyl and N-nitroso derivatives noted in the preceding paragraph. When the hydrolysis is carried out with 6% aqueous oxalic acid under reflux, an acid, C_{25}H_{36}O_{5},
is obtained which possesses two double bonds and which hence presumably suffers dehydration under the conditions of hydrolysis. It is noteworthy that cassaic acid has been isolated from the mother liquors. Small amounts of cassaic acid are also obtained on alkaline hydrolysis of coumingidine. Treatment of N-acetylcoumingidine with potassium carbonate and cold methanol results in transesterification and the formation of a methyl ester, which on further reaction with alkali furnishes an acid, 
\[ \text{C}_2\text{O}_3\text{H}_2\text{O}_4 \], that is not identical with either cassaic acid or allocassac acid. The possibility that this substance is related to isocassanic acid (footnote, page 4) is not excluded.

**Erythrophleine.** The first chemical investigation of the Erythrophleum alkaloids was undertaken in 1875 by Gallois and Hardy\(^{25}\) on an impure mixture of amorphous bases of uncertain botanical origin which was designated as "erythrophleine." The early results are reviewed in "The Plant Alkaloids" by Henry\(^{26}\) and will not be discussed here. The problem was subsequently taken up for reinvestigation in 1940 by Blount, Openshaw and Todd\(^{27}\) who obtained an amorphous alkaloid from a drug preparation supplied by E. Merck and Co. of Darmstadt which they named erythrophleine. The product yielded an amorphous sulfate, but was cleaved on hydrolysis to \(\beta\)-methylaminoethanol and a
crystalline acid (erythropheic acid), $C_{21}H_{30}O_5$. The latter substance showed a typical ultraviolet absorption maximum at 221 mp. (log ε 4.2), and the presence of one methoxyl group, one keto group, and one hydroxyl function was established by conventional methods. Dehydrogenation afforded 1,2,8-trimethylphenanthrene. A close relationship to cassaine was noted by the British investigators, but no further work on erythropheine has been reported since the 1940 publication.

Pharmacology. The pharmacological properties of the Erythropheum alkaloids have been extensively investigated by K. K. Chen of the Eli Lilly laboratories, and several reviews covering this subject are available in the literature. 26, 28, 29 The bases as a group show a remarkable combination of local anaesthetic properties and digitalis-like activity on the heart, but vary individually with respect to intensity of action. Several of the alkaloids also possess emetic and diuretic properties. The high toxicity of these substances limits their usefulness as therapeutic agents. The diterpene acids produced on hydrolysis of the alkaloids are physiologically inactive.
### TABLE I. CRYSTALLINE ERYTHROPHLEUM ALKALOIDS

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>m.p.</th>
<th>$[\alpha]_D$</th>
<th>Empirical Formula</th>
<th>Derivatives and Melting Points</th>
<th>Hydrolytic Acid</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>cassaine</td>
<td>142.5°</td>
<td>-118&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$C_{24}H_{39}O_4N$</td>
<td>HCl, 220° f HV&lt;sup&gt;d&lt;/sup&gt; HBr, 221-225° HV HClO&lt;sub&gt;4&lt;/sub&gt;, 202-204°d HV oxalate, 210-212°d HV acetate, 123-124° acetate-HClO&lt;sub&gt;4&lt;/sub&gt;, 160-163° oxime, 123-125°</td>
<td>cassaic acid, 223-224° e HV methyl ester, 189-190° allocassaic acidβ 222-224° HV</td>
<td>2, 3, 4</td>
</tr>
<tr>
<td></td>
<td>-101&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-103&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cassaidine</td>
<td>139.5°</td>
<td>-98&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$C_{24}H_{41}O_4N$</td>
<td>HCl, 251° HV HSO&lt;sub&gt;4&lt;/sub&gt;, 228° HV oxalate, 198-201° HV</td>
<td>cassaidic acid, 275-277° HV methyl ester, 162-163° allocassaidic acid</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>-104&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Compound</td>
<td>Melting Point</td>
<td>Boiling Point</td>
<td>Molecular Formula</td>
<td>Reactions</td>
<td>Refs</td>
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<td></td>
</tr>
<tr>
<td>Coumingine</td>
<td>142° J</td>
<td>-70°</td>
<td>C_{29}H_{47}O_{6}N</td>
<td>HCl, 195° k HV oxime, 165°</td>
<td>Coumingic acid, f 200° HV methyl ester, 217-218° HV</td>
<td></td>
</tr>
<tr>
<td>Coumingidine</td>
<td>160-161°</td>
<td></td>
<td>C_{27}H_{43}O_{6}N</td>
<td>HCl, 217-219° N-acetyl, 155° N-nitroso, 174° phenylthiourea, 146°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrophlamine</td>
<td>149-151°</td>
<td>-62.5°</td>
<td>C_{25}H_{39}O_{6}N</td>
<td>Picrate, 184-187° HV HCl 1 HSO_4 1 HClO_4 1 Acetate, 100°</td>
<td>Erythrophilaminic acid, 218-220° HV methyl ester, 175°</td>
<td></td>
</tr>
<tr>
<td>Cassamino acid</td>
<td>86-87°</td>
<td>-56a</td>
<td>C_{25}H_{39}O_{5}N</td>
<td>HC1O_{4}, 189-192° HV</td>
<td>217-219° HV methyl ester</td>
<td>cassaminic acid, f</td>
</tr>
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<td>---------------</td>
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| a in 95% ethanol | b in .1 NHCl | c in absolute ethanol | d in evacuated sealed tube | e originally reported 203° | f obtained by acid hydrolysis | g obtained by basic hydrolysis | h originally reported 212-213° | i not characterized | j 147° first reported | k originally reported 205° | l amorphous |
II. DISCUSSION
II. DISCUSSION

At the time when the present investigation was undertaken, the portion of the cassaic acid structure that could be regarded as firmly established was that indicated in formula (17). The further expansion of this expression to structure (14) suggested by Humber and Taylor, while consistent with the known facts, relied entirely on analogy for placement of the additional methyl groups at C. 1 and C. 12 and for location of the secondary hydroxyl group at C. 2. These assumptions, if valid, restrict the carbonyl group to position 9 or 10, for cassaic acid is not an α- or a β-hydroxyketone, does not possess the properties of a vinylogous β-keto ester, and does not exhibit conjugated ketonic absorption in the ultraviolet. These arguments receive additional support from the observation of Engel that ozonization of dehydrocassaic acid affords a triketone which is not an α- or a β-dicarbonyl derivative. Of the two positions C. 9 is preferred on the grounds that the presence of axial methyl groups at C. 1 and C. 12 should
greatly hinder the attack of carbonyl reagents on a C. 10 ketone. Cassaic acid and its derivatives show no unusual lack of reactivity with respect to the formation of ketonic derivatives.

The work now to be described provides an unequivocal demonstration of the correctness of structure (14) for cassaic acid and in addition supplies evidence for the details of stereochemistry. The discussion is divided into four general sections: (A) Operations in the Ring A System, (B) Location of the Ketonic Function, (C) Proof of Structure by Synthesis, and (D) Elucidation of Stereochemistry. Since the work was seriously handicapped, particularly in the early stages, by the small available supplies of cassaine, several interesting lines of attack were terminated short of full development as a necessary conservation measure. During the course of the investigation several crystalline compounds were isolated from bark extracts which, for lack of time, could not be fully characterized. It is hoped that these substances can be examined more thoroughly in the future.

A. Operations in the Ring A System

A well-known reaction in terpene chemistry, which establishes the presence of a 6-membered ring containing a geminal dimethyl grouping and an adjacent equatorial hydroxyl group (18), is the retropinacol rearrangement. This
reaction, which is brought about by the action of phosphorus pentachloride or other similar reagents, results in dehydration with ring contraction and the formation of a product (19) that can be cleaved to acetone and a 5-membered

\[
\text{HO} \quad \text{→} \quad \text{ } 
\]

ring ketone. The success of such a reaction sequence in the cessaic acid series would, of course, establish the details of the ring A structure to a reasonable degree of certainty. The method offers the further advantage that, if the keto group of cassaine is located at C. 9 or C. 10, the 5-ring ketone obtained would be a 1,4- or 1,3-diketone (see Chart III). In the latter case the compound would be readily identifiable by routine methods, and in the former introduction of a double bond in conjugation would afford an enedione (cf. structure 25) possessing characteristic absorption in the ultraviolet. The initial attack on the problem therefore was made at this point.

In preliminary work carried out by Dr. D. Buckley in this laboratory, a sample of dihydrocassaic acid methyl ester (20) melting at about 90° was treated with phosphorus
CHART III

(20) \[ \text{HO} \rightarrow \text{CH}_2\text{COOMe} \]
(21) \[ \text{CH}_2\text{COOMe} \]
(22) \[ \text{CH}_2\text{COOMe} \]

\[ \text{TsO} \rightarrow \text{CH}_2\text{COOMe} \]
(23) \[ \text{CH}_2\text{COOMe} \]
(24) \[ \text{CH}_2\text{COOMe} \]
(25) \[ \text{CH}_2\text{COOMe} \]

(26) \[ \text{Cl} \]
(27) \[ \text{CH}_2\text{COOMe} \]
(28) \[ \text{CH}_2\text{COOMe} \]
pentachloride in petroleum ether under a wide variety of conditions, but no well-defined products were obtained. In some experiments starting material was recovered, and in some cases chlorine-containing substances were produced. A poorly crystalline sample of a chloride was ultimately isolated which was thought to be (26), but the chlorine content (8.29%) was lower than that required (9.67%) for a compound of this structure, and the halogen was not eliminated under the influence of methanolic potassium hydroxide. In further experiments treatment of (20) with phosphorus pentachloride yielded olefinic material (positive tetranitromethane test) convertible with methanolic hydrogen chloride into an amorphous product (or products) showing an ultraviolet absorption maximum at 243 mλ, ε 7,000, and possibly containing some of compound (27). As an alternative procedure solvolysis of the tosylate of (20) in weakly basic medium was also investigated, but the results of this work were likewise unproductive.

In the further examination of the retropinacol rearrangement which was carried out as part of the present research program, attention was first directed towards application of the method to a readily derived model compound (32), the synthesis of which is outlined in Chart IV. 4,4-Dimethylcholesteryl acetate (29)31 was oxidized with chromium trioxide in acetic acid,35 and the resulting α,β-unsaturated
CHART IV

1. Pt/H₂
2. CrO₃-Py

(29) → (31) → (32)
ketone (30) was hydrogenated over platinum and reoxidized to the saturated acetoxy ketone (31). Saponification of the latter product furnished the corresponding hydroxy ketone (32), which possesses the structural elements suggested by Humber and Taylor, without stereochemical implications, for the A and B rings of cassisic acid.

Treatment of (32) with excess PCl₅ in petroleum ether (see Chart V) afforded a compound, m.p. 136.5-137.5°, λCS₂ max 5.86 μ, which gave a positive Beilstein test, but no color with tetranitromethane. On the basis of analytical values, which correspond to the formula C₂₉H₄₈OCl₂, structure (38) is tentatively suggested for this compound.* When the amount of phosphorus pentachloride was reduced and the reaction conducted at 0° in either petroleum ether or methylene chloride-petroleum ether, a product (33), C₂₉H₄₈O, m.p. 147.5-148.5°, λCS₂ max 5.86 μ, was obtained, which gave a negative Beilstein test and a dark yellow color with the tetranitromethane reagent. Treatment of this compound with osmium tetroxide and cleavage of the resulting glycol with lead tetraacetate furnished acetone, identified as the 2,4-dinitrophenylhydrazone, and the diketone (34) which showed characteristic 5-ring ketone absorption in the infrared at 5.73 μ in addition to a 6-ring ketone band

* The halogenation of ketones by phosphorus pentahalides has been previously observed (reference 36).
CHART V

(32) \[\rightarrow\] (33) \[\rightarrow\] (34)

(35) \[\downarrow\] (36) \[\rightarrow\] (37)

(38)
at 5.83 μ. The retropinacol product (33) gave tars with hydrochloric acid in acetic acid, but with p-toluenesulfonic acid in benzene yielded a crystalline, α,β-unsaturated ketone, $\lambda_{\text{EtOH}}^{\text{max}} = 242.5 \text{ m\mu}$, ε = 12,300, provisionally formulated as (37).

Conversion of (32) into the corresponding tosylate (35) followed by solvolysis in acetic acid containing sodium acetate gave an olefin isomeric with (33), which showed a pale yellow color in the tetranitromethane test. A band at 13.75 μ in the infrared spectrum of this product, not found in other compounds of this series, occurs in the region that has been assigned to the C-H out-of-plane deformation in cis-disubstituted olefins. The compound does not yield an α,β-unsaturated ketone under conditions employed for the preparation of (37). The structure of this olefin has not been investigated further, but formula (36) would appear to represent a reasonable possibility. The fact that no retropinacol rearrangement product could be isolated from the solvolysis of (35) is somewhat surprising in view of the very recent report that the p-toluenesulfonyl derivative of lanosterol with potassium acetate in acetic acid gave predominantly the rearranged isopropylidene derivative. The reaction of terpene alcohols with phosphorus oxychloride, however, has occasionally led to the formation of unarranged olefins.
With conditions established for successful rearrangement of 4,4-dimethyl-7-ketocholestanol (32), the work with dihydrocassaic acid methyl ester (20) was then resumed. In the earlier experiments dihydro methyl ester melting at 90° had served as starting material. However, melting points of 92°, 9 108°, 6 111°, 8 and 121° 9 are reported for this substance in the literature, and Ruzicka, Dalma and Scott 9 have observed that the highest melting point is reached only after repeated crystallizations. The possibility that the observed scattering of melting points may be due to the production of diastereomeric dihydro compounds in the hydrogenation reaction has been noted. 9 The purity of the cassaic acid derivatives employed in the various hydrogenation experiments is also not beyond question.

Several recrystallizations of the 90° ester afforded material melting at 102-103°, and attempts to effect purification through the acetyl derivative, while affording a nicely crystalline sample of acetate methyl ester melting at 183-184°, failed in its objective since saponification and remethylation of the latter product gave back low melting ester. However, when a very pure sample of cassaic acid was subjected to hydrogenation, a dihydro acid melting at 245-248° was obtained, which afforded a methyl ester, m.p. 118-119°. Further recrystallization of this compound gave a product melting at 121-122°, which showed infrared absorption differing slightly in the 8-10 μ region from
that exhibited by the low melting (90°) dihydro ester. Only material melting above 117° was employed in the subsequent experiments.*

Although failure of the earlier attempts to effect retropinacol rearrangement of dihydrocassaic acid methyl ester might be attributed to impurity of the starting material, the question of the configuration of the hydroxyl group constitutes a problem of somewhat greater importance. Terpenes derivatives in which the hydroxyl group in question is axial rather than equatorial as in (18), while not of common occurrence, undergo dehydration without rearrangement.40 In order to establish the configuration of the hydroxyl group in cassaic acid and its derivatives, the dihydro acid (39) was oxidized to the corresponding diketone (40), which in turn was reduced with sodium and alcohol and esterified with diazomethane to give the dihydroxy ester (41). Compound (41) was also obtained directly from (39) by successive treatment with sodium-alcohol and diazomethane. These correlations establish that in compounds of this series the original hydroxyl group possesses the thermodynamically more stable equatorial configuration,41 which is 3 if

* It should be noted that isolation and purification of the dihydro acid is essential if high melting dihydro ester is to be obtained. In those cases where this step was omitted (including the experiments of Buckley) the resulting ester was unsatisfactory.
CHART VI

(39) \[ \text{CH}_2\text{COOH} \rightarrow \text{CrO}_3 \rightarrow \text{HOAc} \rightarrow (40) \[ \text{CH}_2\text{COOH} \]

1. Na, alc.
2. CH\textsubscript{2}N\textsubscript{2}

(41) \[ \text{CH}_2\text{COOMe} \]

1. Na, alc.
2. CH\textsubscript{2}N\textsubscript{2}
cassaic acid possesses a C. 2 hydroxyl group and the A/B trans ring fusion uniformly observed in the naturally occurring terpenes.

With this point of stereochemistry secured, pure di-hydrocassaic acid methyl ester (20) was dissolved in a mixture of methylene chloride and petroleum ether and was treated with phosphorus pentachloride at 0°. The crude product, which gave a dark yellow color with tetrinitromethane and showed no discrete absorption in the ultraviolet, was chromatographed on alumina and on silicic acid yielding some unreacted starting material, a poorly crystalline chlorine-containing fraction, and an oil with an ultraviolet maximum at 245 μ, ε 9,000 and infrared absorption at 5.76, 5.90, and 6.03 μ. The appearance of α,β-unsaturated ketonic material after chromatography is contrary to observations made in the 4,4-dimethyl-7-ketocholestanol series (see Chart V, page 27), where the rearrangement product (33) was recovered unchanged after chromatography. Rearrangement over alumina has, however, been observed in other cases.39 Although these results can be interpreted as indicating that rearrangement of (20) into (21) (see Chart III, page 23) does, in fact, occur accompanied by extensive isomerization of the latter compound to the endocyclic isomer (24), other explanations--in particular rearrangement into product (28)--are not
excluded (cf. rearrangements in the lupeol series). Since pursuance of this line of investigation appeared to require the commitment of larger amounts of cassaic acid than could reasonably be justified in terms of the promise of the method, work in this area was discontinued at this stage. Alternate schemes for establishing the structural features of the ring A system are described later in this discussion, and final proof is given in Section C.

B. Location of the Ketonic Function

In considering methods which might be utilized to establish the location of the keto group in cassaic acid, preference was initially given to procedures that could be carried out on small scale. In this connection the fact that cassaic acid possesses an unsaturated center in ring C offered the possibility that partial aromatization might yield a product identifiable as an $\alpha$- or $\beta$-tetralone. With an appropriate choice of starting materials the presence or absence of a keto (or hydroxyl) group at either C. 9 or C. 10 might therefore be established. Small samples (1 to 10 mg.) of cassaic acid acetate methyl ester were treated accordingly under a variety of conditions with various dehydrogenation catalysts, and the crude products were scanned in the ultraviolet. In those cases where dehydrogenation was conducted in $\alpha$-methylnaphthalene at 260° with a palladium-charcoal catalyst, oily material was obtained
that showed ultraviolet absorption reminiscent of that exhibited by \( \alpha \)-tetralone. The infrared absorption of this material showed a very weak band at 5.95 \( \mu \), and in no case was any crystalline conversion product encountered. Milder dehydrogenation procedures involving the use of palladium and \( p \)-benzoquinone,\(^{43}\) chloranil in boiling xylene,\(^{43}\) and mercuric acetate in dioxane-acetic acid\(^{44}\) were without effect. Cassaic acid acetate methyl ester was also treated successively with \( N \)-bromosuccinimide and collidine in the hope that introduction of a second double bond might facilitate dehydrogenation. The results of this work were likewise unproductive.

In contrast to the behavior of the cassaic acid derivative, bromination and dehydrobromination of dihydrocassaic acid acetate methyl ester (42) afforded in good yield a beautifully crystalline \( \alpha, \beta \)-unsaturated ketone with an ultraviolet absorption maximum at 247.5 \( \mu \mu \), \( \epsilon 8,700, (\lambda_{\text{CS2}} \text{max} 5.78, 6.02 \mu) \). The position of the absorption band is that predicted for an \( \alpha, \beta, \beta \)-trisubstituted \( \alpha, \beta \)-unsaturated ketone without an exocyclic double bond,\(^{45}\) and, if it is assumed that cassaic acid possesses a geminal dimethyl grouping at C. 1 and an angular methyl group at C. 12, the only structure that can be written for the conjugated ketone is that indicated in formula (43).* The spectral

* A ring C position for the keto group is excluded by evidence discussed previously (see page 20).
characteristics of (43) are in good agreement with those reported for the abietic acid derivative (46), $\lambda_{\text{max}}$ 249 μμ, € 6,400, and it follows, subject to reservations regarding the positions of methyl groups, that the keto group of cossaic acid is located at C. 9. In order to provide further confirmation for the C. 9 assignment, (43) was converted into the corresponding enol-acetate, which showed ultraviolet absorption, $\lambda_{\text{max}}$ 242 μμ, € 17,500, entirely consistent with structure (44). Oxidation of the latter substance by established methods afforded a small amount of a crystalline product, the ultraviolet spectrum of which showed a maximum at 261 μμ, € 8,000, characteristic of the enedione structure indicated in formula (45). At about this time the possibility of providing an entirely rigorous demonstration of the position of the keto group in cossaic acid was presented by developments in an alternate degradation scheme, and full characterization of the enedione was not completed.

Before proceeding to a discussion of the definitive experiments, mention should be made of the fact that in the model series, 4,4-dimethyl-7-ketocholestanyl acetate (compound 31 of Chart IV, page 25) undergoes bromination and dehydrobromination to yield amorphous material showing ultraviolet absorption at 237.5 μμ, € 4,000. Although concerted efforts to isolate a pure, crystalline compound in this case failed, there seems little reason to doubt
that the major absorbing component is product (30), $\lambda_{\text{max}}$
237.5 mp, $\epsilon$ 13,000. The reasons for the difference in beha-
vor observed in reaction of (31) on the one hand and of
(42) on the other are not entirely clear. The relative
stabilities of the various enols are probably involved,
since small structural modifications can exert a marked
influence on the direction of bromination as in the cases
of cholestan-3-one and coprostan-3-one.28, 49 A further
contributing factor is perhaps the fact that a single $\beta$
axial methyl group (at C. 12) hinders axial bromination50
at C. 14, whereas two such groups (at C. 1 and C. 12)
restrict axial attack at position 10. In 4,4-dimethyl-7-
ketocolesterol acetate (31) the C. 6 and C. 8 positions
both suffer two 1,3-interactions with axial methyl groups.
It should be noted, however, that the bromine atom in an
$\alpha$-bromoketone does not always occupy the position of ini-
tial attack, and that the position of a double bond in an
$\alpha,\beta$-unsaturated ketone does not necessarily serve to
locate the bromine atom in the $\alpha$-bromoketone from which it
is derived. The facile rearrangement of 5-bromo-6-keto-
cholesterolyl acetate into the corresponding 7-bromo deri-
vative,51 and the formation of 21% of cholest-4-en-3-one
in the pyridine dehydrobromination of 2-bromocholestan-3-
one52 provide well-known examples of isomerization in
systems of this type.
CHART VII

(42) → (43) → (44)

AcO

CH₂COOME

AcO

CH₂COOME

0Ac

(45) → (46) → (47)

AcO

CH₂COOR

(48) → (49)

AcO

H
Mention should finally be made of the fact that the phenomenon of conformational transmission has been shown to produce rather large changes in rates of reaction at distant centers.\textsuperscript{53} Evidence for the operation of environmental effects at the B/C ring fusion in constitutionally related tri- and tetracyclic derivatives can be drawn from the observation that the conjugated carbonyl system in (46) absorbs at 249 µ whereas the same chromophore in (47) shows a maximum at 255 µ.\textsuperscript{54} An additional example relates to the peracid epoxidation of dienes (48) and (49). The former compound furnishes a $\Delta^7$-9,11-oxide, while (49) is attacked in ring B with formation of the $\Delta^9(11)$-7,8-oxide.\textsuperscript{55}

Since the point of attachment of the $\alpha,\beta$-unsaturated acid side chain in cassaic acid is well established,\textsuperscript{13} the possibility of relating the position of this group to that of the keto group was considered at an early stage in the investigation. When it became evident that the keto group is in all probability located at C. 9 (i.e., two carbon atoms removed from the double bond), the attractiveness of this approach was considerably increased. A direct attack upon the correlation problem was therefore undertaken.

Ozonization of cassaic acid acetate methyl ester (50) in a mixture of ethyl acetate and acetic acid,\textsuperscript{56} afforded an acetoxydiketone (51), m.p. 169-170°, in 55% yield.
CHART VIII

(50) $\xrightarrow{\text{CHCOOMe}}$ (51)

(52) $\Leftrightarrow$ (53)
Treatment of this substance with sodium methoxide followed by reacetylation afforded an epimer, m.p. 150.5-151.5°, the infrared absorption characteristics of which differed from those of compound (51). The epimerization product is assigned structure (52).*

The relationship of the two carbonyl groups in these products was easily established. Reaction of (52) with bromine and acetic acid followed by dehydrobromination of the resulting product with collidine yielded a compound (53), m.p. 186.5-187.5°, which showed the typical ultraviolet absorption spectrum, $\lambda_{\text{max}} 266.5$ μ, ε 10,800, of an enedione. Treatment of (53) with zinc dust and acetic acid resulted in smooth regeneration of the stable, saturated diketone (52). Facile reduction of the double bond is, of course, a characteristic property of the enedione system.57, 58 The formation of (53) provides unequivocal proof for assignment of the keto group to C. 9 in cassaic acid.

Bromination and dehydrobromination of the unstable diketone (51) afforded a poorly crystalline product showing enedione absorption, $\lambda_{\text{max}} 266$ μ, ε 6,000. The material proved exceedingly difficult to purify, and chromatography followed by several recrystallizations

* The arguments on which the stereochemical assignments are based are discussed in Section D.
yielded a sample melting at 170-178\(^\circ\). The matter was not investigated further.

C. Proof of Structure by Synthesis

With the structural aspects of the B and C rings fully established there remained only the question of the constitution of ring A. Various approaches to the solution of this problem were considered at one time or another, but all were ultimately rejected in favor of proof of structure by total synthesis. However, since certain of these approaches possess features of considerable chemical interest, and since a few experiments of a very tentative nature were carried out in this connection, a brief description of three of these projected schemes may be appropriate.

It will be noted first that conversion of the diketone (52) into the enedione (53) (see Chart VIII, page 39) by the bromination-dehydrobromination sequence, while not unexpected, was by no means assured. The possibility that the unsaturated diketone (54) might be the major isolable product was regarded as an entirely reasonable alternative, and plans were made for utilization of this material should it be formed (see Chart IX).† Oxidation of a compound of structure (54) to the diacid derivative (55) is a reaction

* Examination of the ultraviolet spectra of residues from mother liquors of (53) gave some indication of the presence of small amounts of compound (54). However, the latter substance was not obtained in pure form.
CHART IX

(54) \rightarrow (55)

(56) \rightarrow (57)

(58) \rightarrow (59)
for which there is ample analogy, and introduction of unsaturation in (55) to give (56) should present no unusual difficulties. The endocyclic position for the double bond in (56) is deemed more likely than the alternate exocyclic position (dotted line), but it is clear that in either case further oxidation should yield the acetoxydicarboxylic acid (57). The latter product might also be obtained by ozonization of the enol-acetate (44) (Chart VII, page 37) since an analogous degradation has been successfully accomplished in the case of α-onocein. It should be noted, however, that in some instances ozonization of diene systems of this type has proved exceedingly difficult.

At the time when these experiments were contemplated the diacid (57) was unknown, and a preparative scheme was devised based upon utilization of the lactone (58) which was prepared for this purpose by a peracid oxidation of 4,4-dimethyl-7-ketocholestanoyl acetate (31) (Chart IV, page 25). However, the homologous diacid (59) has been reported very recently by Barton, and diacid (57) is now available in both optically active modifications through work of Woodward.

A second approach to the ring A problem was based upon the supposition that an α,β-unsaturated ketone of structure (27) (see Chart X) might ultimately be isolated from the products of PCl₅ treatment of dihydrocassaic acid methyl ester. Degradation of this substance following
CHART X

(27) $\xrightarrow{\text{---}}$ (60)

(61) + (62)
procedures developed by Cornforth\textsuperscript{65} for the strictly ana-
logous degradation of cholest-5-en-7-one should lead by a
reverse Michael reaction in the keto-aldehyde (60) to
2-isopropyl-5-methylcyclopentanone (61) and the ring C
fragment (62). Isolation of (61) would, of course, cons-
titute proof of the ring A structure in cossaic acid.

A final scheme, also based on the reverse Michael re-
aaction, is outlined in Chart XI. Preparation of the un-
saturated diketone (63) from the easily obtainable 2-acetoxy
derivative (43) (Chart VII, page 37) presents no foresee-
able difficulties. Should it prove possible to establish
equilibrium between this substance and the enolate anions
(64) and (65), fragmentation to isopropyl vinyl ketone and
the phenol (67) might well ensue, with aromatization serv-
ing as the driving force for the forward reaction. In the
event that strong alkali should be required, conversion of
the vinyl ketone into methyl isopropyl ketone by reverse
aldol cleavage might be anticipated in view of the experi-
ence of Eschenmoser, Heusser and their collaborators.\textsuperscript{66}

As a preliminary step towards testing this hypothesis
lanost-8-ene-3,7-dione (68)\textsuperscript{67} was prepared since this sub-
stance constitutes a readily available model compound for
the proposed transformation. Unfortunately, due to the
pressure of other work, it has not been possible to pur-
sue this idea further. It is hoped that the matter can
be taken up at a future date.
After careful consideration of the merits of the procedures outlined in the preceding paragraphs, and of several other methods as well, the decision was made to attempt establishment of the missing details of structure by total synthesis. The first synthetic efforts were devoted to the approach indicated in Chart XII. Hagemann's ester (69), 68 which is known to undergo alkylation at the position adjacent to the keto group, 69 was allowed to react with 1-chloropentanone-3 in the presence of triethylamine. The product (70), which was purified by distillation, afforded a crystalline bis-semicarbazone, m.p. 207-208.5° (dec.). Cyclization of the diketone (70) could be accomplished with sodium hydride, or alternatively with boron trifluoride-etherate, 70 and the bicyclic product (71) was obtained as an oil, b.p. 131-132°/0.03 mm., λ max 295 μ, ε 19,000. The semicarbazone which was prepared as a derivative melted at 184°. Addition of the third ring was carried out with sodium hydride and 1-chloropentanone-3, followed by sodium hydride catalyzed cyclization. The crude product showed ultraviolet absorption at 245 μ, ε 8,000, and 300 μ, ε 9,500, λ CS max 5.85, 6.04 μ. Distillation was accompanied by extensive decomposition, and no characterizable carbonyl derivatives could be isolated. No crystalline fractions were obtained after chromatography, and all attempts to convert the material into a crystalline derivative by hydrogenation, partial dehydrogenation, treatment with acid,
CHART XII

(69) \[ \rightarrow \] (70)

(71) \[ \rightarrow \] (72)
etc. were to no avail. The material was finally reduced with lithium aluminum hydride and submitted to selenium dehydrogenation. In this case 15% of 1,2,8-trimethylphenanthrene, identified by direct comparison with an authentic sample,* was obtained. On the basis of the yield of trimethylphenanthrene, it is estimated that the crude material derived from (71) may have contained up to 50% of the desired product (72), or double bond isomers thereof. Thus, although the method may be potentially capable of yielding in three simple steps a tricyclic compound containing all but two of the carbon atoms of cossaic acid, failure of attempts to isolate the key intermediate (72) in pure form precluded any useful application in the present investigation.

The synthetic procedure that ultimately proved successful followed the more conventional lines set forth in Chart XIII. The 2,6-dimethoxynaphthalene (73) that served as starting material was prepared by alkali fusion of Schaeffer's acid followed by methylation of the resulting 2,6-dihydroxynaphthalene. Reduction of (73) with sodium and isoamyl alcohol according to Robinson's procedure gave the enol-ether (74), m.p. 75-78°, which on hydrolysis afforded the β-tetralone (75), semicarbazone,  

* Kindly supplied by Drs. O. Jeger and M. Perelman, E. T. H., Zürich.
CHART XIII

(73) \[\rightarrow\] (74) \[\rightarrow\] (75)

(76) \[\rightarrow\] (77)

(78) \[\rightarrow\] (79)
CHART XIII (Con't)

(80) \[ \rightarrow \]

(81a, \( R = H \))
(81b, \( R = Ac \))

(82a, \( R = H \))
(82b, \( R = Ac \))

(83)

(84) \[ \rightarrow \] (85)
m.p. 162-163°. Since this tetralone is somewhat sensitive to air oxidation, it was methylated directly without distillation or other purification. The methylation procedure involved conversion of the tetralone into the corresponding pyrrolidine enamine, which, without isolation, was treated with methyl iodide. Hydrolysis afforded 6-methoxy-1-methyl-2-tetralone (76), b.p. 110-112°/0.05 mm. This substance is also unstable, but if distilled it can be stored under nitrogen in the cold for a period of weeks. The semicarbazone, m.p. 202-204° (dec.), shows no appreciable tendency towards deterioration, and the tetralone can be regenerated from this derivative in 80% yield by exchange to pyruvic acid.

6-Methoxy-1-methyl-2-tetralone has also been prepared in a somewhat different manner (Chart XIV) by Howell and Taylor. The Howell-Taylor synthesis was not considered suitable for the purposes of the present investigation due to the evident hazards associated with conducting the per-acid oxidation step on large scale. It should be noted, however, that by substituting monoperphthalic acid for the perbenzoic acid employed in the original procedure, Stork has recently been successful in applying the method to bulk preparations.

Condensation of tetralone (76) with dimethylaminobutanone methiodide was carried out according to the published
CHART XIV

\[ \text{CHO}_2 \text{COOH} \quad \text{H}^+ \Rightarrow \text{CHO}_2 \text{COOH} \]

(76)

(77)
procedure of Howell and Taylor. The yield of tricyclic ketone (77) (50%) was considerably greater than that (25%) reported by the British investigators. The ultraviolet absorption spectrum of (77), \( \lambda_{\text{max}} 231 \text{ mp}, \epsilon 25,000 \),* is anomalous in that the Woodward rules* predict an absorption maximum at about 240 mp for a substance of this constitution. Similar shifts have been observed in the closely related product (86), and in numerous compounds of types (87) and (88) containing nitrogen and sulfur as hetero atoms. No entirely satisfactory electronic interpretation of this phenomenon has been advanced, and the possibility that conformational factors may be involved cannot be dismissed.

![Chemical Structures](image)

(86) (87) (88)

The tricyclic ketone (77) was methylated by the Woodward procedure (potassium t-butoxide and methyl iodide), and

---

* Subtraction of the spectrum of (80) from that of (77) gives \( \lambda_{\text{max}} 232 \text{ mp}, \epsilon 20,700 \) for the contribution of the conjugated carbonyl system to the absorption of the latter compound.
the resulting product (78) was reduced successively with lithium aluminum hydride and platinum and hydrogen. Isolation of the lithium aluminum hydride reduction product (79) was frequently omitted when these reactions were carried out on a preparative scale. It should be noted that both (78) and (79) show a pronounced tendency to develop coloration on standing and that it was found desirable to hold material in the unmethylated form (77) until it could be carried through to (80) without interruption.

At this stage in the synthesis the anisole ring was reduced with lithium and ammonia, and the enol-ether (81a) was obtained in nicely crystalline form. This compound afforded an acetyl derivative (81b), and both substances were smoothly cleaved to the corresponding \( \beta, \gamma \)-unsaturated ketones (82a and 82b, respectively) by the action of aqueous oxalic acid. The 2-hydroxy and 2-acetoxy \( \alpha,\beta \)-unsaturated ketones (89a, \( \lambda \) max 241 \( \mu \), 15,500, and 89b, \( \lambda \) max 240 \( \mu \), \( \alpha \) 16,000) could be obtained by the use of mineral acid. The latter transformations were carried out on small scale, and the question of yield was not carefully examined. However, in an analogous case (90), Barltrop and Rogers obtained roughly equal amounts of \( \alpha,\beta \)- and \( \beta,\gamma \)-unsaturated ketones by treatment of the enol-ether with strong hydrochloric acid. In view of this fact, and since the \( \alpha,\beta \)- and \( \beta,\gamma \)-unsaturated ketones, which furnish the same enolate ion with base, can be used interchangeably in
the next step of the synthesis, isolation and purification
at the β,γ-unsaturated stage was adopted as the preferred
procedure.

\[ \text{(89a, } R = H) \]
\[ \text{(89b, } R = \text{Ac}) \]

Attention was next directed towards the problem of
introducing a methyl group at C. 8 of the tricyclic nucleus.
Although controlled methylation of conjugated ketones with
potassium t-butoxide and methyl iodide has been reported in
a single communication to furnish monomethylation products in
yields of 50-70\%, other investigators have been unable to
duplicate these results, and yields of only 5-10\% have been
a common experience.\(^6\)\(^4\), 83 Despite the generally adverse
indications of the literature, the β,γ-unsaturated ketones
(82a) and (82b) were treated in the presence of potassium
t-butoxide with approximately one equivalent of methyl iodide.
Although the hydroxy ketone (82a) gave a dark oil that showed
an infrared maximum at 2.80\(\mu\), but no maximum in the 5-6\(\mu\)
region, the corresponding acetate (82b) yielded material that
after reacetylation and chromatography afforded a monomethylated, \(\alpha, \beta\)-unsaturated ketone (83), \(\lambda_{\text{max}} 249 \text{ nm}, E 17,500\), in about 30\% yield. The reasons for success in the one experiment and failure in the other are unknown and have not been investigated further. As a matter of expediency additional material that was brought up was processed through the acetoxyketone (82b).

The next and final objective involved introduction of a C. 9 keto function into (83). This operation, if successful, would provide a product (84), in optically inactive form for comparison with the optically active compound (53, Chart VIII, page 39) derived from natural sources. The plan originally devised for accomplishing this transformation involved conversion of (83) into the enol-acetate (91) followed by treatment with peracid, hydrolysis, and oxidation according to the method that has proved successful in various other instances. Compound (83) was therefore allowed to react with acetic anhydride in the presence of acetyl chloride, and the resulting oily product was examined in the ultraviolet.
No high intensity absorption attributable to the diene system in (91) was observed. Failure to obtain the required enol-acetate in this reaction prompted consideration of other approaches, of which one involved direct bromination of (83) with N-bromosuccinimide. Attempts along these lines were likewise unsuccessful in bringing about the desired result. The acetoxyketone (83) was finally treated with chromic acid in acetic acid at 60° in the hope that direct introduction of the C. 9 keto group might be effected. The goal was at last achieved. The crude oxidation product deposited crystalline, though grossly impure material, which on repeated recrystallization afforded a pure sample of the desired enedione (84), m.p. 165-165.5°, λ max 266 mp, ε 11,000. The infrared spectrum of the synthetic substance and that of the optically active degradation product from cassaic acid, when measured in chloroform solution, were identical. In order to provide a further point of correlation compound (84) was reduced with zinc and acetic acid. The reduction product (85) melted at 157.5-159.5° and showed infrared absorption in chloroform solution identical with that exhibited by the optically active saturated diketone (52) (Chart VIII, page 39). Thus, although resolution of the synthetic products (84 and 85) has not yet been accomplished, there can be no doubt as to the structural identity of these substances with the corresponding products derived from cassaic acid. Structure (14) (page 20) for cassaic acid is thereby established.
Shortly after this work had been completed, a paper by King, King and Uprichard appeared in which a correlation was established between cassanic acid and the diterpene acids, vouacapenic acid (92) and vinhaticoic acid (94) (Chart XV). The latter two substances are C. 1 epimers, since they yield the same dimethyl derivative (93) by lithium aluminum hydride reduction to the primary alcohols, CrO$_3$-pyridine oxidation to the aldehydes, and Wolff-Kishner reduction. Treatment of (93) with monoperphthalic acid furnishes the hydroxy lactone (95), convertible by reduction with zinc and acetic acid into keto acid (96). The latter product yields a thiketal with ethanedithiol which is readily reduced by Raney nickel to cassanic acid (97). Vinhaticoic acid has finally been converted into the known triacid (98), and the presence of the geminal dimethyl grouping (C. 1) and an angular methyl group at C. 12 in cassaic acid is thereby confirmed.

More recently Gensler has obtained evidence (Chart XVI) which permits assignment of the hydroxyl and keto groups of cassaic acid to carbon atoms 2 and 9, respectively. Decarboxylation of cassaic acid affords the methylene ketone (99), which as the 2-acetate reacts with

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* The results of the synthetic investigation were presented in a lecture delivered by R. B. Turner at the Quartermaster Research and Engineering Center, Natick, Massachusetts, November 6, 1958.
CHART XV

(92) → (93) → (94)

(95) → (96) → (97)

(98)
CHART XVI

(99) \[ \rightarrow \]

(101)

(100) \[ \rightarrow \]

(102)

(103)

(104)
methyllithium to give diol (101). Selenium dehydrogenation of (101) at 300° gave 1,7,8,9-tetramethylphenanthrene (103) which proved identical with an authentic sample synthesized for purposes of comparison. 39

A similar reaction sequence was applied to the diketone (100) obtained by decarboxylation of dehydrocassaic acid. Treatment of this material with methylmagnesium iodide under mild conditions gave an amorphous product, presumably (102), which on lithium aluminum hydride reduction followed by selenium dehydrogenation was converted into a hydrocarbon (104), identified as 1,2,7,8-tetramethylphenanthrene by direct comparison with authentic material supplied by Dr. B. G. Engel. Although the keto group in cassaic acid and various of its derivatives fails to react with the Grignard reagent under mild conditions, the fact that this reaction succeeds under forcing conditions (refluxing toluene) has already been mentioned (page 6).

D. Elucidation of Stereochemistry

Relative Configurations

The structure that has now been established for cassaic acid possesses six centers of asymmetry represented by carbon atoms 2, 8, 11, 12, 13 and 14. On the basis of evidence now to be discussed the configurations indicated in formula (105) may be assigned to these centers with reasonable certainty. The arguments are as follows.
The equatorial orientation of the C. 2 hydroxyl group is demonstrated by the results of sodium-alcohol reduction of dihydrocassaic acid (39) and of the corresponding diketone (40) discussed earlier (page 30). Supporting evidence is derived from the fact that in the synthetic series the hydroxyl group in question is generated by lithium aluminum hydride reduction of the corresponding ketone, a reaction that in comparable cases affords the equatorial alcohol. The configuration (α or β) of an equatorial substituent at C. 2 is determined by the nature (cis or trans) of the A/B ring fusion and will be β if the ring fusion is of the trans type. That this is indeed the case is suggested by the close analogy between the catalytic hydrogenation of (79) to (80) and the similar reduction step involved in the synthesis of dehydroabiestic acid which leads unambiguously to a trans-fused product. Further evidence on this point is provided by the correlation of
cassanic acid with vinhaticoic acid and conversion of the latter compound into the triacid (98) (Chart XV, page 60) under conditions where epimerization at C. 11 is unlikely. Triacid (98) has also been obtained by oxidation of abietic acid, and its stereochemistry is fully established.\textsuperscript{86}

The configurations at the B/C fusion are less well defined. That this fusion represents a thermodynamically stable arrangement seems reasonably well established by the numerous instances in which cassaic acid derivatives have been subjected to the action of base without inversion at the epimerizable center C. 14. For example, cassaic acid is obtained from coumingic acid after a 1\textfrac{1}{2} hour reflux period with 0.4 N aqueous-alcoholic potassium hydroxide;\textsuperscript{4} the base-stability of dihydrocassaic acid has also been demonstrated.\textsuperscript{7, 9} Moreover, the regeneration of cassaine from cassaic acid\textsuperscript{6} establishes the important point that no inversion is involved in the hydrolytic cleavage of the parent alkaloid. These arguments, coupled with the demonstration of \textit{trans} stereochemistry at the A/B fusion, limit the possible sets of configurations at C. 13 and C. 14 to two, indicated for the corresponding 9-ketoperhydrophenanthrenes by structures (107) and (108) (Chart XVII). The greater stability of the \textit{trans-anti-trans} structure (107) as compared to the \textit{trans-anti-cis} arrangement (106) is well-known,\textsuperscript{91} and the failure of the \textit{trans-syn-cis} compound
CHART XVII

(106) \[\xrightarrow{\text{base}}\] (107)

(108) \[\xrightarrow{\times}\] (109)
(108) to undergo isomerization to the corresponding \textit{trans-syn-trans} product (109), noted by Linstead and Whetstone,\textsuperscript{92} is satisfactorily explained by Johnson's observation\textsuperscript{93} that the configuration indicated in (109) requires a "boat" conformation in the central ring.

Differentiation between the stable \textit{cis-} and \textit{trans-} structures (cf. 108 and 107) for cassaic acid requires information concerning the configuration of the C. 13 hydrogen atom. The conclusion that this atom is \textit{\alpha-} oriented in the great majority of diterpenoid substances has been drawn by Klyne from a study of molecular rotation differences.\textsuperscript{94} In the present instance the best available argument appears to rest on the observation that the synthetic ketone (83) is formed under conditions (strong base) that ensure equilibration of configuration at C. 13. The C. 13 hydrogen atom in this compound, and presumably also in the enedione (84), is therefore almost certainly \textit{\alpha-} oriented, since only this arrangement permits the C. 5 - C. 13 bond to assume the favored equatorial conformation with respect to ring B. Conversion of (84) into the base stable diketone (85) by the action of zinc and acetic acid has already been noted (Chart XIII, page 50). The \textit{trans-anti-trans} structure indicated in Chart XVIII is hence proposed for this substance. Since (85) is obtained in optically active form (52 of Chart VIII, page 39) from cassaic acid by reactions which do not involve the center of asymmetry at C. 13, it follows
CHART XVIII

(83) → (84) → (85)

(110) → (111) → (51)

(112) → (113)
that, to a very high degree of probability, the trans-anti-
trans formulation (105) for cassaic acid is correct. The
configuration of the C. 8 methyl group may now be considered.

As noted previously (page 38) cassaic acid acetate
methyl ester affords on ozonization an acetoxydiketone (51)
(see Chart XVIII) convertible into (52) by the action of
sodium methoxide in methanol followed by reacetylation.
Isomerization also occurred when (51) was chromatographed
on a sample of alumina previously treated with ethyl acetate
in order to remove the alkali. However, the corresponding
C. 2 hydroxy derivative was recovered unchanged after pas-
sage through commercial (Woelm) "neutral" alumina. On the
basis of the assumption that the B/C ring fusion is not in-
volved (see above), the isomerization can be explained only
by a change in configuration of the methyl group which must
be from axial (α) to equatorial (β). In an attempt to ob-
tain further information on this point cassaic acid acetate
methyl ester was reduced with sodium borohydride to the
hydroxy derivative (110) and this was in turn ozonized to
the acetoxyhydroxyketone (111) which now possesses only one
epimerizable center. On oxidation with chromium trioxide
and acetic acid (or with the chromium trioxide-pyridine
complex) at room temperature (111) afforded the unstable
diketone (51). Compound (111) was hydrolyzed to the cor-
responding dihydroxyketone by vigorous treatment with base,
and the latter substance was then oxidized with chromium trioxide and acetic acid. The triketone (112), m.p. 185-187°, also obtainable from casacic acid by ozonization and subsequent oxidation, inverted on treatment with base to yield a triketone (113), m.p. 200-201.5°, identical with that obtained from (51) by hydrolysis and oxidation. In this connection it is interesting to note that Engel\textsuperscript{16} has reported that ozonization of dehydrocasacic acid methyl ester affords a crude product melting at 180°, which furnishes a pure triketone, m.p. 198.5-200°, on chromatography. The latter substance is stable to base and is clearly identical with compound (113). However, the fact that isomerization occurs during chromatography was overlooked by Engel.

The fact that (111) is resistant to base-catalyzed epimerization, whereas the derived ketones (51) and (112) suffer this reaction with extreme ease, implies that either (a) the B/C ring fusion is, in fact, involved, or (b) special circumstances favor an axial orientation for the C. 8 methyl group in (111), but an equatorial configuration in (52) and in (113). In the face of evidence presented earlier in this section (page 64), the latter view is regarded as the more acceptable. The following arguments can be advanced in support of this contention.

Catalytic hydrogenation of the borohydride reduction product (110), saponification, and remethylation with diazomethane furnishes a substance identical with compound (41)
(Chart VI, page 31), obtained by treating dihydrocassaic acid with sodium and alcohol and diazomethane. The C. 9 hydroxyl group in (110), and also in (111), therefore occupies the thermodynamically preferred orientation, which is normally expected to be equatorial. Now an equatorial configuration for the hydroxyl group in (111), (see diagram in Chart XIX) has the interesting consequence that epimerization (axial to equatorial) of the C. 8 methyl group must afford a product (114) in which the methyl and hydroxyl groups are eclipsed. The geometry of the system is, in fact, that found for 1:3-diaxial substituents in the cyclohexane ring. Since the 1:3-diaxial interaction is severe, it is reasonable to suppose that the methyl group in (111) will prefer the α-configuration indicated. Oxidation of the C. 9 hydroxyl group effectively removes hindrance of the C. 8 equatorial position, and epimerization in the 9-keto derivatives occurs as expected. An effect similar to that discussed here has been observed recently by Barton and his associates in connection with work in the santonin series.

As final proof for the conclusion that epimerization of the ketones (51) and (112) involves only the center at C. 8, the hydroxyketone (111) was converted into the corresponding ketal (115). The latter compound was obtained as an oil and was contaminated by a small amount of unsaturated material that could be removed by chromatography.
Oxidation of (115) with chromium trioxide in acetic acid under conditions where isomerization can be excluded, furnished an acetooxyketoketal (116), m.p. 172.5-173°, that was recovered unchanged after vigorous treatment with base and subsequent reacetylation.

Product (116) proved to be identical with a compound obtained from the stable diketone (52) by conversion of the latter substance into the bis-ketal (117) followed by partial exchange in the presence of acetone and p-toluene-sulfonic acid. It differs from a second monoketal, tentatively assigned structure (118), which was prepared by direct partial exchange dioxolanation of diketone (52). Since (116) is obtainable by two routes starting from compounds that possess different configurations at C. 8, it follows that inversion must occur in one or the other reaction series. In view of the stability exhibited by (111) under enolizing conditions there is little justification for supposing that epimerization takes place in the conversion of this substance into the corresponding ketal, although mechanisms for such a change are clearly available (cf. (119)→(120)). In the case of the transformation (52)→(116), however, epimerization might well occur. Although the arrangement of substituents in ring C of (116) (cf. 121) is one for which Barton would predict an equatorially stable methyl group at C. 8, it will be
observed that the 2-carbon bridge between the ketal oxygen atoms serves to fill the gap between these substituents and hence destabilizes the C. 8 equatorial position. The same effect is presumably operative in (117) as well.

Reduction of (116) with sodium borohydride yields amorphous material showing an infrared absorption spectrum identical with that of (115). Cleavage of the borohydride product with acetone and p-toluenesulfonic acid affords the acetoxyhydroxyketone (111). A method is therefore available for conversion of the synthetic diketone (85) into a product possessing the appropriate configuration at C. 8.

Although time has not permitted full exploitation of these results, it is clear that application of the Reformatsky or Wittig\textsuperscript{98} procedures to (111), coupled with resolution at a suitable stage, should complete the total synthesis of cassaic acid. In this connection it should be noted that differentiation between the C. 2 and C. 9 oxygen functions (cf. 111) need not be maintained, since Engel has successfully converted cassaidine into cassaine, and dehydrocassaic acid into cassaic acid.\textsuperscript{99}

As a result of this investigation structure (105) for cassaic acid is established beyond any reasonable doubt, and formulas (122) and (123) may be assigned to cassaine and to coumingine, respectively. Cassaidine, which can now be correlated with (110) through identity of
dihydrocassaidic acid with the sodium-alcohol reduction product of dihydrocassaic acid, possesses structure (124).

**Absolute Configuration**

Although no experiments have as yet been carried out which would permit assignment of absolute configuration to any of the Erythrophleum alkaloids, it is clear that successful degradation of cassaic acid to the diacid (57) (Chart IX, see discussion page 43) would furnish this information. In the absence of such evidence the only argument that can be presented at this time relates to the molecular rotation data of Table II. It will be observed that in every case where a direct comparison is possible among molecular rotation differences for compounds of the cassaic series and derivatives of known absolute configuration, the sign of $\Delta \kappa_D$ is the same. The suggestion can, therefore, be made that the alkaloids of the Erythrophleum group belong to the same stereochemical series already established for the steroids and terpenes.$^{100}$ Structures (122), (123), and (124) are hence tentatively regarded as indicated true structures for the compounds in question in the absolute sense.
### TABLE II. MOLECULAR ROTATION DIFFERENCES

<table>
<thead>
<tr>
<th>Compound</th>
<th>$M_D$</th>
<th>$M_D^{\text{deriv.}} - M_D^{\text{cpd.}}$</th>
<th>$\Delta \text{Ac}$</th>
<th>$\Delta \text{Ketone}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cassaic acid methyl ester</td>
<td>-432</td>
<td>+77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrocassaic acid methyl ester (20)</td>
<td>+25</td>
<td>+26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cassaic acid (105)</td>
<td>-409</td>
<td>-135</td>
<td>-135</td>
<td></td>
</tr>
<tr>
<td>Dihydrocassaic acid (39)</td>
<td>0</td>
<td>-130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$2\beta$-Hydroxy-8$\alpha$-methyldapocarpane-7,9-dione</td>
<td>-105</td>
<td>+52</td>
<td>-105</td>
<td></td>
</tr>
<tr>
<td>$2\beta$-Hydroxy-8$\beta$-methyldapocarpane-7,9-dione</td>
<td>-158</td>
<td>+71</td>
<td>-19</td>
<td></td>
</tr>
<tr>
<td>4,4-Dimethylcholestan-3$\beta$-ol-7-one (32)</td>
<td>-125</td>
<td>+45</td>
<td>-35</td>
<td></td>
</tr>
<tr>
<td>Lanostan-3$\beta$-ol-7-one*</td>
<td>+123</td>
<td>+46</td>
<td>-101</td>
<td></td>
</tr>
</tbody>
</table>

* Values taken from reference 58.
III. EXPERIMENTAL
III. EXPERIMENTAL

Preparation of 4,4-Dimethylcholest-5-en-3β-ol-7-one Acetate (30). To a solution of 5.0 g. of 4,4-dimethylcholesteryl acetate (prepared from cholestenone by the published procedure) in 150 ml. of glacial acetic acid (purified by distillation from chromic acid) at 55° 4.5 g. of chromium trioxide was added over a 2 hour period with mechanical stirring. After further stirring for 2 hours the solution was concentrated, and the product crystallized after dilution with water. After filtration the material was dissolved in ether. The ethereal solution was washed successively with dilute sodium hydroxide, water, and a saturated solution of sodium chloride and was dried over anhydrous sodium sulfate. The residue from evaporation of the solvent was recrystallized from methanol, yielding 2.9 g. of (30), m.p. 143-146°. A sample was further recrystallized several times from ether-methanol to furnish the analytical sample, m.p. 156.5-157°, \( \lambda_{\text{max}}^{\text{EtOH}} \) 237.5 mp, \( \epsilon \) 13,000, \( \lambda_{\text{max}}^{\text{CS}_2} \) 5.76, 6.00, 8.10 \( \mu \), \( \left[ \alpha \right]_D^{25} \) -89° (c .98 ethanol).

Anal. Calcd. for \( C_{31}H_{50}O_3 \): C, 79.09; H, 10.70.

Found: C, 79.21; H, 10.83.

Preparation of 4,4-Dimethylcholestan-3β-ol-7-one Acetate (31). The material from the above experiment (2.9 g.) in 100 ml. of glacial acetic acid was hydrogenated over 470 mg. of Adams catalyst. The hydrogen absorption ceased after the uptake of two equivalents of the gas. The solvent
was removed in vacuo, and the residue was dissolved in ether. After the solution was washed with dilute base, water, and saturated sodium chloride solution and dried over sodium sulfate, the solvent was removed yielding 2.9 g. of a poorly crystalline solid. The infrared spectrum of this material in carbon disulfide showed a strong hydroxyl band and one carbonyl band at 5.78 μ. Without further purification, this substance was dissolved in 25 ml. of pyridine and was added to 30 g. of chromium trioxide in 30 ml. of cold pyridine. After remaining at room temperature for 4 hours, the brown mixture was diluted with 1 N sodium hydroxide, and the product was extracted with ether. The organic layer was washed with dilute hydrochloric acid, water, and saturated sodium chloride and was dried over sodium sulfate. The product from evaporation of the solvent was recrystallized from methanol to yield 2.36 g. of 4,4-dimethylcholestan-3β-ol-7-one acetate (31), m.p. 172-174°. The analytical sample was prepared by chromatography on alumina followed by several recrystallizations from ether-methanol, m.p. 182-183°, λ^CS2 5.78, 5.84, 8.08 μ, [α]D -17° (c 1.20 ethanol). An initial small fraction from the chromatogram showed a very weak band at 5.84 μ in addition to the strong band at 5.78 μ; it follows that a small amount of hydrogenolysis may have occurred during the catalytic reduction.
Anal. Calcd. for C_{31}H_{52}O_{3}: C, 78.76; H, 11.09; O, 10.15.

Found: C, 78.87; H, 11.24; O, 10.01.

Attempts to reduce the double bond in (30) without reduction of the keto group using platinum in ethyl acetate failed, although this is a satisfactory procedure of reduction of 7-ketocholesteryl acetate to cholestan-3β-ol-7-one acetate. 101 Bromination of compound (31) with either bromine in acetic acid or N-bromosuccinimide followed by dehydrobromination with collidine afforded an oil with an ultraviolet absorption maximum at 237.5 μ, ε 4,000. Pure α,β-unsaturated ketone could not be isolated by recrystallization or by chromatography.

Saponification of (31) to 4,4-Dimethylcholestan-3β-ol-7-one (32). A solution of 1.1 g. of the acetoxyketone (31) in 60 ml. of 90% methanol containing 50 mg. of potassium hydroxide was refluxed under nitrogen for 4 hours. The solution on concentration and cooling yielded 940 mg. of crystalline product (32), m.p. 182-183°. A sample was prepared for analysis by chromatography and recrystallization from ether-methanol, m.p. 188-189°, λ_{max}^{CS2} 2.76, 5.85 μ, [α]_{D}^{29°} -29° (c .925 ethanol).

Anal. Calcd. for C_{29}H_{50}O_{2}: C, 80.87; H, 11.70.

Found: C, 80.54; H, 11.46.

Oxidation of (32) to 4,4-Dimethylcholestan-3,7-dione.

Sixty-six milligrams of hydroxyketone (32) in 1 ml. of
pyridine was added to 63 mg. of chromium trioxide in 0.5 ml. of cold pyridine. After 4 hours at room temperature dilute sodium hydroxide solution was added, and the product was extracted with ether. After the usual washing and drying procedure the solvent was removed, and the residue was recrystallized from ether-methanol providing 42 mg. of the diketone, m.p. 142-143°. The analytical sample melted at 143-144.5°, \( \lambda_{\text{max}}^{\text{CS}_2} 5.85 \mu, [\alpha]_D^{10} -37^\circ \) (c .879 ethanol).

**Anal.** Calcd. for \( C_{29}H_{48}O_2 \): C, 81.25; H, 11.29.

**Found:** C, 81.32; H, 11.44.

**Treatment of (32) with Phosphorus Pentachloride.** A mixture of 390 mg. of phosphorus pentachloride and 155 mg. of hydroxyketone (32) in 10 ml. of petroleum ether was stirred at room temperature for 2 hours. Ice was added to the reaction mixture, which was then diluted with ether. The organic layer yielded 166 mg. of a yellow oil which was chromatographed on alumina. Elution with petroleum ether gave 70 mg. of a product which, after recrystallization from ether-methanol, melted at 115-121°. Several recrystallizations from ether-methanol gave the analytical sample, m.p. 136.5-137.5°, \( \lambda_{\text{max}}^{\text{CS}_2} 5.86 \mu, [\alpha]_D^{10} -37^\circ \) (c .60 chloroform). This substance showed no color with tetranitromethane and gave a positive Beilstein test.

**Anal.** Calcd. for \( C_{29}H_{48}OCl_2 \): C, 72.02; H, 10.00.

**Found:** C, 72.20; H, 9.88.
Treatment of 500 mg. of (32) with 340 mg. of phosphorus pentachloride in 20 ml. of petroleum ether at 0° for 1 hour afforded, after the usual work-up procedure, 275 mg. of (33), m.p. 145-149°, recrystallized once from ether-methanol. Several recrystallizations from the same solvent provided the analytical sample, m.p. 147.5-148.5°, $\lambda_{\text{CS}_2}^{\text{max}}$ 5.86 μ, $[\alpha]_D^{12}$° (c .94 chloroform). This compound gave a yellow-brown color with tetranitromethane and a negative Beilstein test.

**Anal.** Calcd. for C$_{29}$H$_{48}$O: C, 84.40; H, 11.72.

*Found:* C, 84.52; H, 11.61.

The substitution of a 50:50 mixture of methylene chloride-petroleum ether for petroleum ether alone did not alter the course of the above reaction.

Ten milligrams of (33) in petroleum ether solution was placed on a column of freshly activated, ethyl acetate-washed alumina. After 6 hours the column was stripped with ether, and evaporation of the solvent and recrystallization of the residue afforded 8.4 mg. of material, m.p. 145-149°, which was identical with the material placed on the column.

**Cleavage of the Retropinacol Product (33).** Two hundred milligrams of the olefin (33) and 150 mg. of osmium tetroxide were dissolved in a mixture of 3 ml. of pyridine and 7 ml. of ether, and the brown solution was allowed to remain in a well-stoppered vessel at room temperature for 4 days. After
removal of the solvent in vacuo 25 ml. of benzene, 6 ml. of water, 12 ml. of ethanol, 0.8 g. of mannitol and 0.8 g. of potassium hydroxide were added, and the mixture was refluxed for 4 hours with stirring. On cooling the organic layer was washed with dilute base, dilute acid, and water and was dried over sodium sulfate. Evaporation of the solvent yielded 211 mg. of poorly crystalline glycol. A solution of the crude product in 15 ml. of acetic acid which contained 0.55 mmole of lead tetraacetate was allowed to stand at room temperature for 24 hours. After the addition of 5 ml. of water, approximately half of the solvent was distilled from the mixture. The distillate was processed as indicated below. Water was added to the residual solution, and the product was extracted with ether. The extracts were washed and dried as usual and yielded, on evaporation of the solvent, 160 mg. of crystalline material, which showed no hydroxyl band in the infrared and carbonyl bands at 5.75 and 5.85 μ. Two recrystallizations from ether-methanol afforded 54 mg. of the diketone (34), m.p. 144.5-149.5°. The basic washings from the cleavage reaction were acidified and gave 9 mg. of an oil which showed no discrete absorption in the ultraviolet. The analytical sample of (34) melted at 150.5-152°, λCS2 max 5.73, 5.83 μ, [α]D +62° (c 1.45 chloroform).
Anal. Calcd. for $C_{26}H_{42}O_2$: C, 80.77; H, 10.95.

Found: C, 80.67; H, 10.83.

The distillate obtained above yielded 42 mg. of a 2,4-dinitrophenylhydrazone, m.p. 126.5-128°, which did not depress the melting point of an authentic sample of acetone 2,4-dinitrophenylhydrazone.

Two attempts were made to introduce a double bond between the keto groups in compound (34) with selenium dioxide. The first, conducted in refluxing ethanol with excess reagent, afforded only starting material, and the second, which was carried out in boiling acetic acid, gave a small amount of amorphous material, $\lambda_{\text{EtOH}}^{\text{max}}$ 250 μm, ε 9,000.

Acid-catalyzed Rearrangement of (33) into the α,β-Unsaturated Ketone (37). A solution of 110 mg. of the retropinacol product (33) and 50 mg. of p-toluenesulfonic acid in 10 ml. of benzene was refluxed under nitrogen for 3 hours. After dilution with ether, the solution was washed with dilute base, water and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed and the residue was recrystallized several times from ether-methanol. The yield of (37), m.p. 94-97°, was 40 mg. Further recrystallization provided the analytical sample, m.p. 101-102.5°, $\lambda_{\text{CS}_2}^{\text{max}}$ 6.00 μ, $\lambda_{\text{EtOH}}^{\text{max}}$ 242.5 μm, ε 12,300, $[\alpha]_D^{\text{max}}$ -59° (c .58 chloroform).

Anal. Calcd. for $C_{27}H_{48}O$: C, 81.40; H, 11.72.

Found: C, 81.51; H, 11.55.
Preparation of the Tosylate of the Model Compound (32).
A solution of 500 mg. of (32) and 230 mg. of p-toluenesulfonyl chloride in 10 ml. of dry pyridine was allowed to stand for 4 days at room temperature. After the addition of ice the product was extracted with ether, and the extracts were washed in the usual manner and dried over sodium sulfate. Three hundred milligrams of tosylate (35), m.p. 161-164°, was obtained by evaporation of the solvent and two recrystallizations of the residue from ether-methanol. The analytical sample melted at 171.5-173.5°, λ_{CS2}^{max} 5.85 μ, [α]_{D}^{14°} (c .93 chloroform).

Anal. Calcd. for C_{36}H_{56}O_{4}S: C, 73.92; H, 9.65.
Found: C, 73.87; H, 9.80.

Solvolyis of the Tosylate of 4,4-Dimethylcholestan-3β-ol-7-one (32). One hundred and seventeen milligrams of the tosylate (35) was dissolved in 5 ml. of glacial acetic acid containing 100 mg. of anhydrous sodium acetate, and the mixture was refluxed under a slow stream of nitrogen for 1 hour. After removal of a portion of the solvent the solution was diluted with ether and washed with dilute base, dilute acid, water, and a concentrated solution of sodium chloride. After drying over sodium sulfate, the solvent was removed in vacuo furnishing 84 mg. of poorly crystalline material that was chromatographed on alumina. Elution with 90:10 petroleum ether-benzene afforded a fraction which,
after one recrystallization from ether-methanol, gave 31 mg. of an olefin, m.p. 95.5-97°, that gave a pale yellow color with tetranitromethane. The analytical sample was obtained by further recrystallization, m.p. 99-100°,

\[ \lambda_{\text{max}}^{\text{CS}_2} \ 5.85, \ 13.75 \mu, [\alpha]_D^{+2} \ (c \ .55 \ \text{chloroform}). \]

Anal. Calcd. for C_{29}H_{48}O: C, 84.40; H, 11.72.

Found: C, 84.32; H, 11.63.

Treatment of the above olefin with p-toluenesulfonic acid in refluxing benzene under conditions employed for (33) provided material which showed no absorption maximum in the ultraviolet spectrum.

Examination of the crude solvolysis product in the infrared indicated that no acetate was formed in the reaction, a result that is surprising in view of the fact that the tosylate of 3β-hydroxy tsttallocholanic acid methyl ester afforded a 50% yield of the 3α-acetate under the conditions employed above. The 4,4-dimethylcholestan-3α-ol-7-one acetate was desired for a study of molecular rotation differences.

**Peracid Oxidation of (31).** To a solution of 70 mg. of the acetoxyketone (31) in 1 ml. of benzene, there was added 0.4 ml. of a 0.38 M solution of perbenzoic acid in benzene; the mixture was allowed to stand in the dark at room temperature (35°) for 6 days. After dilution with ether and subsequent washing, the solution was dried over sodium sulfate and evaporated. Recrystallization of
the resulting product from methanol afforded 50 mg. of the acetoxy lactone (58), m.p. 197-200°. The analytical sample melted at 209-210°, $\lambda_{\text{max}}^{CS_2} 5.76$, $8.10 \mu, [\alpha]_{D}^{o} -4^o$ (c .60 chloroform).

**Anal.** Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.73.

**Found:** C, 75.95; H, 10.77.

Attempts to open the lactone and oxidize the resulting hydroxyl group without cleavage of the C. 3 acetate group failed. With chromium trioxide in acetic acid containing a small amount of concentrated sulfuric acid, the acetate was cleaved, and with chromium trioxide in pyridine the starting lactone was recovered.

**Preparation of Dihydrocassaic Acid (39) and its Methyl Ester (20).** Cassaine bisulfate was hydrolyzed under conditions reported in the literature for the acid-catalyzed hydrolysis of cassaine. The bisulfate, prepared from total Erythrophleum bases (kindly supplied by Eli Lilly and Co.), gave, in approximately 60% yield, cassaic acid which possessed a melting point above 210° (evacuated capillary). The cassaine salt (a commercial sample from Labatec, Geneva) provided the same acid in slightly higher yield. The material from both sources furnished a methyl ester with diazomethane which, after several recrystallizations, melted at the literature value of 189-190°. This material afforded the acetate methyl
ester (50), m.p. 149-151°, on treatment with acetic anhydride-pyridine.$^{2, 4}$

The hydrogenation of cassaic acid over palladium-charcoal in ethanol solution afforded approximately 40% of dihydrocassaic acid (39) which melted at 245-248° (evacuated capillary) after one recrystallization from acetone. The melting point could be raised to 253-254° by further recrystallization from ethyl acetate.$^{7}$ Treatment of the acid with diazomethane afforded the methyl ester (20), m.p. 121-122° (from aqueous methanol).$^{9}$ The reduction of pure cassaic acid methyl ester under similar conditions afforded a dihydro ester, m.p. 83-110°. This substance on saponification, recrystallization of the resulting acid, and remethylation with diazomethane furnished a methyl ester, m.p. 117-118°, identical with that obtained above. The acetyl derivative of the dihydro ester (42) melted at 188-189° (literature value, m.p. 189°).$^{9}$

Examination of the Low Melting Dihydro Ester (20).

The dihydrocassaic acid methyl ester, m.p. 90°, obtained from Dr. D. Buckley, showed infrared absorption differing slightly in the 8-10 μ region from that exhibited by the sample, m.p. 122°. Recrystallization of the former substance raised the melting point to 102-103°. Treatment of this material with acetic anhydride-pyridine gave an acetyl derivative, m.p. 183-184°. Saponification gave a poorly
crystalline hydroxy acid. Chromatography of the acid, methyl ester, or of the methyl ester acetate did not afford satisfactory products.

Sodium and Alcohol Reductions of Dihydrocassaic Acid (39) and of Diketocassenic Acid (40). Reduction of dihydrocassaic acid according to the published procedure\textsuperscript{7, 9} and esterification of the product with diazomethane gave dihydroxycassanic acid methyl ester, m.p. 174.5-176°.

Dihydrocassaic acid was oxidized with chromium trioxide in acetic acid to give the known diketocassenic acid, m.p. 214-215°.\textsuperscript{6, 9} Small pieces of sodium were added over a 3 hour period to 23 mg. of this acid dissolved in 2 ml. of ethanol. After addition of water the solution was acidified with hydrochloric acid, and the product was extracted with methylene chloride. The extract was washed with a saturated sodium chloride solution and was dried over sodium sulfate. After evaporation of the solvent the residue was treated with excess diazomethane and 17 mg. of crude ester was obtained. Partition chromatography of this substance over silica gel afforded, after recrystallization, 5 mg. of a compound, m.p. 172.5-174°. This ester did not depress the melting point of the compound prepared directly from dihydrocassaic acid, and the infrared absorption spectra of the two products were identical.
Treatment of Dihydrocassaic Acid Methyl Ester (20) with Phosphorus Pentachloride. A mixture of 160 mg. of phosphorus pentachloride and 200 mg. of dihydrocassaic acid methyl ester, (m.p. 117-118°), in 20 ml. of 50:50 petroleum ether-methylene chloride was stirred at 0° for 1 hour. Ice was added to the solution, and the mixture was extracted with ether. The extracts yielded 200 mg. of product which provided 36 mg. of starting material on recrystallization from ether-petroleum ether. The amorphous material from the mother liquor, which gave a yellow-brown color with tetranitromethane, was chromatographed on alumina. Twenty milligrams of starting material, 10 mg. of a poorly crystalline chloride (positive Beilstein test), and 100 mg. of an oil which showed a positive tetranitromethane test were obtained. Rechromatography of the latter substance on alumina afforded amorphous material, $\lambda_{\text{max}} 245$ μ, ε 9,000, $\lambda_{\text{max}}^{\text{CS}} 5.76$, 5.90, 6.03 μ. The crude product before chromatography showed no discrete absorption in the ultraviolet.

Attempted Partial Dehydrogenation of Cassaic Acid Acetate Methyl Ester (50). In a typical experiment 2.0 mg. of cassaic acid acetate methyl ester (50), 1.6 mg. of palladium-black, and 3 drops of α-methylnaphthalene were sealed in an evacuated glass tube and heated for 7 hours at 260°. The mixture was chromatographed on alumina. Elution with petroleum ether removed the solvent, α-methylnaphthalene, and elution with ether afforded an oily product,
1.7 mg., which showed a maximum in the ultraviolet absorption spectrum at 254 μ, ε 6,000, with a shoulder at 300 μ. The combined material from several experiments possessed a strong infrared absorption band at 5.78 μ and a weak band at 5.95 μ.

**Treatment of Cassiaic Acid Acetate Methyl Ester with N-Bromosuccinimide.** A mixture of 55 mg. of N-bromosuccinimide (1 equivalent) and 120 mg. of (50) in 5 ml. of carbon tetrachloride was refluxed over a 60 watt Mazda light bulb for 20 minutes. After filtration of the succinimide and evaporation of the solvent, the residue was dissolved in 5 ml. of collidine, and the solution was refluxed under nitrogen for 30 minutes. After addition of ether the mixture was washed with dilute acid, dilute base, water, and a saturated solution of sodium chloride and was dried over sodium sulfate. The residue from evaporation of the solvent was chromatographed on alumina yielding 50 mg. of starting material and 20 mg. of an oil, λ<sub>max</sub><sub>EtOH</sub> 257 μ, ε 8,000, λ<sub>max</sub><sub>CS2</sub> 5.79, 5.85, 6.00 μ. This material was unaffected by treatment with p-toluenesulfonic acid in refluxing benzene or with palladium-charcoal in refluxing xylene.

**Preparation of the α,β-Unsaturated Ketone (43) from (42).** A mixture of 47 mg. (1 equivalent) of N-bromosuccinimide and 104 mg. of dihydrocassiaic acid acetate methyl
ester (42) in 5 ml. of carbon tetrachloride was refluxed over a light bulb for 20 minutes. After filtration and evaporation of the solvent, the residue was dissolved in 4 ml. of collidine, and the solution was refluxed under nitrogen for 30 minutes. After addition of ether the solution was washed and dried by the usual procedure. Evaporation of the solvent and recrystallization of the residue from ether-petroleum ether afforded 91 mg. of (43), m.p. 141-142°. Several further recrystallizations furnished the analytical sample, m.p. 145-146.5°, λ<sub>EtOH</sub> max 247.5 μ, ε 8,700, λ<sub>CS<sub>2</sub></sub> max 5.78, 6.02 μ, [α]<sub>D</sub> -39° (c. 86 ethanol).

**Anal.** Calcd. for C<sub>23</sub>H<sub>34</sub>O: C, 70.74; H, 8.78.

**Found:**
C, 70.97; H, 8.85.

Bromination of (43) with N-bromosuccinimide, followed by treatment with collidine, afforded an amorphous product with an ultraviolet absorption λ<sub>EtOH</sub> max 250 μ, ε 8,000, 305 μ, ε 1,800, similar to α-tetralone. Since the infrared spectrum of this material is very similar to that of (43), this substance probably is the starting α,β-unsaturated ketone, contaminated with a compound in which a double bond has been introduced in conjugation with the chromophore.

**Preparation of the Enol-acetate (44) from (43).** A solution of 49 mg. of (43) in 3 ml. of acetic anhydride and 1 ml. of acetyl chloride was refluxed under a slow
stream of nitrogen for 4 hours. On dilution with ether, the solution was washed with dilute base, water and saturated sodium chloride and was dried over sodium sulfate. The residue on evaporation of the solvent was recrystallized from ether-petroleum ether affording 38 mg. of the enol-acetate (44), m.p. 160.5-163°. The analytical sample melted at 165-166°, \( \lambda_{\text{max}}^{\text{EtOH}} \) 242 mp, \( \epsilon \) 17,500, \( \lambda_{\text{max}}^{\text{CS}_2} \) 5.75 μ, \( [\alpha]_D^{\text{-155}} \) (c 0.68 ethanol).

**Anal.** Calcd. for C\(_{25}\)H\(_{36}\)O\(_6\): C, 69.41; H, 8.39.

**Found:** C, 69.41; H, 8.22.

**Attempted Preparation of the Enedione (45) from (44).**

A solution of 50 mg. of (44) in 2.5 ml. of benzene which contained 0.15 mmole of perbenzoic acid\(^{103} \) was allowed to stand in the dark at room temperature for 48 hours. After the usual work-up procedure the oily residue (50 mg.) was dissolved in 5 ml. of methanol and 0.1 ml. of glacial acetic acid, and the solution was refluxed under nitrogen for 1 hour. The product of this treatment was oxidized with the chromium trioxide-pyridine complex, and 15 mg. of a crystalline acid was obtained, \( \lambda_{\text{max}}^{\text{EtOH}} \) 261 mp, \( \epsilon \) 8,000.

**Ozonization of (50) to 2\( \beta \)-Acetoxy-8\( \alpha \)-methylpodo-carpane-7,9-dione (51).** A solution of 134 mg. of cassaic acid acetate methyl ester (50) in 5 ml. of ethyl acetate and 5 ml. of glacial acetic acid was cooled in a salt-ice-bath. Four molar equivalents of ozone were passed into
the solution, and the mixture was allowed to stand at the reduced temperature for 1 hour. After the addition of 300 mg. of zinc dust and 0.2 ml. of water, the solution was stirred for \(\frac{1}{2}\) hour. The product was recrystallized twice from ether-petroleum ether, affording 65 mg. of (51), m.p. 163-168°. The analytical sample melted at 169-170°, \(\lambda_{\text{max}}^{\text{CS}_2} 5.78, 5.88, 8.10 \mu, [\alpha]_D^{160} (c .95 \text{ ethanol})

**Anal.** Calcd. for \(\text{C}_{20}\text{H}_{30}\text{O}_4\): C, 71.82; H, 9.04.

**Found:** C, 72.03; H, 8.74.

**Isomerization of (51) into 2β-Acetoxy-8β-methylpodocarpane-7,9-dione (52).** A solution of 20 mg. of (51) in 2 ml. of methanol which contained 0.2 mmole of sodium methoxide was refluxed under a stream of nitrogen for 2 hours. Water was added to the cooled solution, and the product was extracted with ether. The ethereal extracts yielded 15 mg. of the hydroxydiketone which was acetylated in the usual manner with acetic anhydride-pyridine. The crude acetate was recrystallized from ether-petroleum ether and yielded 13 mg. of (52), m.p. 144-146°. The melting point of this substance on admixture with (51) was depressed to 135°. The infrared spectra of the two compounds differed. An analytical sample was prepared, m.p. 150.5-151.5°, \(\lambda_{\text{max}}^{\text{CS}_2} 5.76, 5.83, 8.06 \mu, [\alpha]_D^{260} (c .93 \text{ ethanol})

**Anal.** Calcd. for \(\text{C}_{20}\text{H}_{30}\text{O}_4\): C, 71.82; H, 9.04.

**Found:** C, 71.86; H, 9.23.
The above isomerization could also be affected by base at room temperature and by passage of 151 through a column of ethyl acetate-washed alumina.

**Preparation of 2\-Acetoxy-8-methylpodocarp-8(14)-ene-7,9-dione (53).** To a solution of 72 mg. of the stable acetoxydiketone (52) in 2 ml. of acetic acid 4.5 ml. of a 0.05 M solution of bromine in acetic acid was added drop-wise. After the addition of the bromine solution, the mixture was allowed to stand for 15 minutes before it was diluted with ether. The solution was washed with dilute base, dilute acid, water, and saturated sodium chloride and was dried over sodium sulfate. Evaporation of the solvent yielded 84 mg. of a crystalline bromide which without further purification was dissolved in 3 ml. of collidine. The solution was refluxed under nitrogen for 30 minutes, and the product was then isolated in the usual manner. Several recrystallizations from ether-petroleum ether gave 20 mg., m.p. 183-185°, of the yellow enedione (53). A second crop, 8 mg., m.p. 177-180°, was obtained from the mother liquor. The analytical sample melted at 186.5-187.5°, λ<sub>max</sub> <sub>EtOH</sub> 266.5 μ, ε 10,800, λ<sub>max</sub> <sub>CHCl<sub>3</sub></sub> 5.82, 5.96 μ, [α]<sub>D</sub> -7° (c .82 ethanol).

**Anal.** Calcd. for C<sub>20</sub>H<sub>28</sub>O<sub>4</sub>: C, 72.26; H, 8.49.

**Found:** C, 71.97; H, 8.54.
The amorphous material from the mother liquor of the above experiment showed in the ultraviolet absorption spectrum maxima at 224 m\(\mu\), \(\varepsilon 5,000\), and 255 m\(\mu\), \(\varepsilon 3,000\). In a separate experiment the crude product from the bromination and dehydrobromination was chromatographed on alumina. Besides a small amount of the enedione, an amorphous product, \(\lambda_{\text{max}} 243\ m\(\mu\), \(\varepsilon 6,000\), was obtained. In still another experiment the bromo compound was recrystallized, m.p. 153-165° (dec.), before treatment with collidine, but the overall yield of (53) from (52) was unsatisfactory.

One hundred and ten milligrams of unstable acetooxidiketone was brominated and dehydrobrominated under similar conditions, and the product was chromatographed on alumina. Thirty milligrams of material, \(\lambda_{\text{EtOH max}} 266\ m\(\mu\), \(\varepsilon 6,000\), was obtained which after several recrystallizations from ether-petroleum ether afforded 4.5 mg. of a substance, m.p. 170-178°, \(\lambda_{\text{CS₂ max}} 5.78, 5.85, 6.02\ m\(\mu\). Further elution gave 25 mg. of oily material, \(\lambda_{\text{EtOH max}} 245\ m\(\mu\), \(\varepsilon 4,000\).

**Zinc and Acetic Acid Reduction of (53) to (52).** A mixture of 100 mg. of zinc dust and 12 mg. of enedione (53) in 2 ml. of acetic acid was refluxed under nitrogen for 2 hours. The solution was concentrated in vacuo and was diluted with ether. The ethereal solution after the usual work-up procedure and several recrystallizations of the product from ether-petroleum ether yielded 4.4 mg. of
material, m.p. 149-150.5°, which did not depress the melting point of an authentic sample of (52).

Preparation of (70) from Hagemann's Ester. Ninety grams of 1 chloropentane-3 was added over a 4 hour period to a refluxing solution of 68 g. of Hagemann's ester 68 in 150 ml. of triethylamine. After refluxing for a further 16 hours the solution was concentrated in vacuo, and water and ether were added. Dilute sulfuric acid was added until the aqueous layer was acidic to Congo Red. After the separation of the two layers, the aqueous portion was washed with ether. The combined ethereal extracts were washed with dilute acid, water, and a saturated solution of sodium chloride and were dried over sodium sulfate. After removal of the solvent two distillations afforded the product (70), 72 g., b.p. 143-148/0.03 mm., n25° 1.4927, d25° 1.081, λ Cs2 5.83, 6.02 μ.

Found: C, 67.31; H, 8.23.

The bis-semicarbazone of (70) was prepared, m.p. 207-208.5° (dec.), λ Nujol 5.93 μ.

Found: C, 53.23; H, 7.80; N, 22.04.

Cyclization of (70) to the Bicyclic Keto Ester (71).

Treatment of (70) in benzene with sodium hydride afforded
(71) in a poor yield. Several distillations of the product afforded the analytical sample, b.p. 131-132°/0.03 mm., n^25_0 1.5483, \( \lambda_{max}^{EtOH} = 295 \text{ mp}, \epsilon = 19,000, \lambda_{max}^{CS_2} = 5.82, 6.05 \mu. \)

**Anal.** Calcd. for \( C_{15}H_{20}O_3 \): C, 72.55; H, 8.12.

Found: C, 72.26; H, 8.21.

This material provided a semicarbazone, m.p. 184°.

**Anal.** Calcd. for \( C_{16}H_{23}O_3N_3 \): C, 63.00; H, 7.54; N, 13.78.

Found: C, 62.95; H, 7.74; N, 13.88.

**Preparation of 2,6-Dihydroxydihydropyran.** Five hundred grams of reagent potassium hydroxide was heated to 290° in a 3-liter stainless steel beaker with two Fisher burners. One hundred and sixty grams of technical Schaeffer's salt (obtained from Eastman Kodak Company) was added over a short period of time with stirring. The light brown, viscous liquid began to spit as stirring and heating was continued. At 320° the reaction subsided and at 340-360° the melt became thin. The mixture was allowed to stand at this temperature for 10 minutes with occasional stirring. The hot, brown liquid was poured into a mixture of 900 ml. of concentrated hydrochloric acid and 5 liters of ice. The greenish-brown precipitate was collected by filtration, dissolved in hot water, and treated with charcoal. After filtration the product crystallized in greenish-brown plates, m.p. 200-212° (dec.); yield, 20-30%. The diacetate melted at 173-175° (literature m.p. 175°).
Preparation of 2,6-Dimethoxy-1,4-dihydronaphthalene (74).

2,6-Dihydroxynaphthalene was converted into the dimethyl ester (73) with dimethyl sulfate and methanolic sodium hydroxide in 80% yield, m.p. 150-153°C (literature m.p. 150°C). This compound was reduced according to Robinson's procedure to give the dihydronaphthalene (74), m.p. 75-78°C, in 75% yield (literature m.p. 83-84°C).

Preparation of 6-Methoxy-1-methyl-2-tetralone (76).

Fifty grams of the enol ether (74) was hydrolysed to 6-methoxy-2-tetralone (75). A sample of this ketone gave a semicarbazone melting at 162-163°C (literature m.p. 159°C). The undistilled tetralone was dissolved in 500 ml. of benzene, and the solution was flushed with nitrogen for 10 minutes. Then 100 ml. of pyrrolidine was added, and the mixture was refluxed for 1½ hours under a slow stream of nitrogen. Five milliliters of water was collected in a water separator during this period. The solution was cooled and evaporated in vacuo at room temperature on a Rinco rotary evaporator. The resulting liquid occasionally crystallized, but no attempt was made to purify the enamine since the compound is very sensitive to air oxidation. The enamine was immediately dissolved in 500 ml. of methanol, and 25 ml. of methyl iodide was added. After the red solution was refluxed for ½ hour under a stream of nitrogen, an additional 50 ml. of methyl iodide was added and refluxing was continued for
1 hour. Excess methyl iodide was removed by distillation, and 50 ml. of glacial acetic acid and 50 g. of sodium acetate in 100 ml. of water were added to the methanolic solution. After 45 minutes of refluxing the mixture was concentrated in vacuo, and water was added. The product was extracted into ether and the resulting solution was washed with acid, base, water, and saturated sodium chloride. After the solution was dried over sodium sulfate and evaporated, the residue was distilled, giving 30 g. of methyltetralone (76) (b.p. 110-112°/0.05 mm.).

In separate experiments the enamine was converted directly into the semicarbazone of (76) by the addition of 50 g. of semicarbazide hydrochloride and 50 g. of sodium acetate in 150 ml. of water to the methanolic solution after the excess methyl iodide had been removed. The mixture was cooled and filtered, giving 50 g. of the semicarbazone of (76), m.p. 202-204° (dec.). This compound did not depress the melting point of a specimen prepared by an alternate procedure, 75, 77 and the infrared spectra of the two samples were identical. The semicarbazone could be cleaved by a steam distillation in the presence of phthalic anhydride to the methyltetralone (76) but the recovery was poor.

The methyltetralone (76) before distillation deposited small amounts of ether insoluble, colorless needles, m.p. 138-140°. The infrared spectrum in Nujol showed no hydroxyl
band and one carbonyl band at 5.95 μ. The ultraviolet absorption spectrum in ethanol showed a maximum at 275 μ, ε 1,700. A crystalline semicarbazone could not be obtained.

Preparation of 2,3,4,9,10,12-Hexahydro-7-methoxy-12-methyl-2-oxophenanthrene (77). 6-Methoxy-1-methyl-2-tetralone was converted into (77) by the procedure of Howell and Taylor in 50% yield, m.p. 105-107.5° (from ether-light petroleum ether), \( \lambda_{\text{max}}^\text{EtOH} = 231 \) μ, ε 25,000. An unstable crystalline modification with m.p. 62-63° was obtained in the early experiments. The semicarbazone, m.p. 215-220° (literature m.p. 233-236°), was identical (mixed melting point and infrared) with the same derivative prepared by the British procedure. 75, 77

Catalytic Hydrogenation of the \( \alpha,\beta \)-Unsaturated Ketone (77). Two hundred and forty-three milligrams of (77) was hydrogenated over 600 mg. of 10% palladium-charcoal in 10 ml. of glacial acetic acid. After the hydrogen uptake ceased, the mixture was filtered and diluted with ether. The ether solution was washed with dilute sodium hydroxide, dilute hydrochloric acid, water, and saturated sodium chloride, was dried over sodium sulfate, and was evaporated to give 220 mg. of oil which crystallized on standing in the refrigerator. Recrystallization from ether-petroleum ether afforded 164 mg. of cis-1,2,3,4,9,10,11,12-octahydro-7-methoxy-12-methyl-2-oxophenanthrene, m.p. 62-64°. An
analytical sample was prepared by further recrystallization, m.p. 68-69°, λ CS \textsubscript{2} 5.82 μ.

Anal. Calcd. for C\textsubscript{16}H\textsubscript{20}O\textsubscript{2}: C, 78.65; H, 8.25.

Found: C, 78.51; H, 8.13.

Preparation of (78). A solution of 1.99 g. (50 mmole) of potassium in 50 ml. of dry t-butanol was added to 4.00 g. (17 mmole) of compound (77) in 100 ml. of t-butanol after the system had been thoroughly flushed with nitrogen. After the addition of 6.5 ml. (100 mmole) of methyl iodide in 10 ml. of t-butanol, the mixture was stirred for 1½ hours at 30° and then 10 minutes at reflux temperature. Dilute hydrochloric acid was added to the cooled suspension, and the mixture was extracted with ether. The ether layer was washed with dilute sodium hydroxide, water, and saturated sodium chloride and was dried over sodium sulfate. After the solvent was removed in vacuo, the resulting oil was dissolved in petroleum ether-benzene (80:20) and filtered through a short column of alumina (Woelm activity II-III). The material from the petroleum ether-benzene washings was recrystallized from methanol-water and furnished 1.70 g. of 1,2,3,4,9,12-hexahydro-7-methoxy-1,1,12-trimethyl-2-oxcphenanthrene (78) in colorless prisms, m.p. 78-80°. The mother liquors yielded a slightly yellow second crop, 400 mg., m.p. 75-77°. The ketone slowly became red in color on standing in contact with air. A freshly prepared sample was recrystallized four times
from ether-petroleum ether for analysis, m.p. 80-81\(^\circ\),
\[ \lambda_{\text{max}}^{\text{EtOH}} 277, 284 \text{ m} \mu, \varepsilon 1,800, 1,700, \lambda_{\text{max}}^{\text{CS}_2} 5.83 \mu. \]

**Anal.** Calcd. for C\(_{18}\)H\(_{22}\)O\(_2\): C, 79.96; H, 8.20.

Found: C, 79.92; H, 8.20.

Careful chromatography of the crude product on alumina afforded, besides the above product, small amounts of impure starting material (77) and a substance which crystallized from ether in colorless plates, m.p. 175.5-176\(^\circ\), \[ \lambda_{\text{max}}^{\text{EtOH}} 224, 262, 325 \text{ m} \mu, \varepsilon 22,000, 12,000, 3,000, \lambda_{\text{max}}^{\text{CS}_2} 5.88, 6.05 \mu. \]
The latter substance has not been investigated further.

**Lithium Aluminum Hydride Reduction of (78).** A solution of 1.70 g. of (78) in 50 ml. of dry ether was added dropwise over an hour period to 700 mg. of LiAlH\(_4\) in 100 ml. of ether under gentle reflux. After further stirring for 1 hour, the excess reagent was destroyed with methanol, and dilute hydrochloric acid was added. The ether layer was washed with dilute sodium hydroxide, water, and saturated sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent and recrystallization of the residue from ether-petroleum ether afforded 1.31 g. of 1,2,3,4,9,12-hexahydro-7-methoxy-1,1,12-trimethyl-2-hydroxyphenanthrene (79), m.p. 126-127\(^\circ\). The mother liquor gave a second crop, 255 mg., m.p. 121-123\(^\circ\). A sample was recrystallized several times from ether-petroleum ether for analysis, m.p. 127-128\(^\circ\),
\[ \lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2} 2.82 \mu. \]
Found: C, 79.35; H, 8.64.

Preparation of trans-1,2,3,4,9,10,11,12-Octahydro-7-methoxy-1,1,12-trimethyl-2-hydroxyphenanthrene (80) by Catalytic Reduction of (79). Two hundred and seventy-seven milligrams of (79) was dissolved in 5 ml. of glacial acetic acid and hydrogenated over 190 mg. of 10% palladium-charcoal. After filtration through Celite and dilution with ether, the solution was washed with dilute sodium hydroxide, dilute hydrochloric acid, and water and was dried over sodium sulfate. Evaporation of the solvent and subsequent recrystallization of the residual material from ether-petroleum ether yielded 210 mg. of (80), m.p. 139-140°. A second crop, 26 mg., m.p. 138-139°, was obtained. A sample was recrystallized three times from ether-petroleum ether for analysis, m.p. 140-141°, $\lambda_{\text{max}}^\text{CS2} 2.78 \mu$.

Found: C, 78.84; H, 9.60.

The acetate of the above compound (80) was prepared as a derivative. The analytical sample melted at 103-103.5°, $\lambda_{\text{max}}^\text{CS2} 5.78, 8.08 \mu$.

Anal. Calcd. for $\text{C}_{20}\text{H}_{28}\text{O}_3$: C, 75.91; H, 8.92.
Found: C, 75.74; H, 9.10.
Birch Reduction of (80) to (81a). Three hundred and ninety milligrams of lithium wire in small pieces was added to a solution of 100 mg. of (80) in 50 ml. of liquid ammonia, 20 ml. of ether, and 2 ml. of ethanol over a 45 minute period with mechanical stirring. After 30 minutes the blue color disappeared. After the addition of water and ether the organic layer was washed with cold dilute hydrochloric acid, water, and saturated sodium chloride and was dried over sodium sulfate. On evaporation and recrystallization of the residue from ether-petroleum ether, 81 mg. of trans-1,2,3, 4,5,8,9,10,11,12-decahydro-7-methoxy-1,1,12-trimethyl-2-hydroxyphenanthrene (81a) was obtained, m.p. 129-131°. Further recrystallization provided the analytical sample, m.p. 139-139.5°, \( \lambda_{\text{max}}^{\text{CS}_2} 2.78 \mu \).

**Anal.** Calcd. for \( \text{C}_{18}\text{H}_{28}\text{O}_2 \): C, 78.21; H, 10.21.

*Found:* C, 77.98; H, 10.21.

The acetate (81b), prepared by the acetic anhydride-pyridine method and recrystallized from ether-petroleum ether, melted at 107.5-108.5°, \( \lambda_{\text{max}}^{\text{CS}_2} 5.79, 8.04 \mu \).

**Anal.** Calcd. for \( \text{C}_{20}\text{H}_{30}\text{O}_3 \): C, 75.43; H, 9.50.

*Found:* C, 75.08; H, 9.38.

Cleavage of the Enol-ether (81a) to 2β-Hydroxypodocarp-13(14)-en-7-one (82a) and 2β-Hydroxypodocarp-8(14)-en-7-one (89a). Twenty-five milligrams of (81a) and 67 mg. of oxalic acid were dissolved in 2 ml. of ethanol and 0.1 ml. of water. After 1½ hours at room temperature the
solution was poured into water, and the product was extracted
with ether. The ether extract was washed with dilute base
and water and was finally dried. The residue from evaporation
of the solvent was recrystallized from ether-petroleum ether
to give 17 mg. of (82a), m.p. 152-158°. The analytical sample
melted at 150-152°, λ\textsubscript{max}^\text{CH}_2\text{Cl}_2 2.79, 5.88 µ.

**Anal.** Calcd. for C\textsubscript{17}H\textsubscript{26}O\textsubscript{2}: C, 77.81; H, 9.99.

**Found:**
C, 77.70; H, 10.09.

Four hundred milligrams of (80) provided 235 mg. of (82a),
m.p. 152-158°, without purification of the intermediate (81a).
The material from the mother liquor of this reaction showed
a maximum in the ultraviolet absorption spectrum at 239 µ, ϵ 1,800, but no absorption attributable to an anisole group-
ing. This residue (152 mg.) was dissolved in 10 ml. of
methanol and 10 ml. of 1 N HCl. The mixture was heated to
60-70° under nitrogen for 1 hour. The crude product, 135
mg., gave 34 mg. of 2β-hydroxypodocarp-β(4)-en-7-one (89a),
m.p. 148-150°, after two recrystallizations from ether-petroleum ether. The analytical sample melted at 151-152°, λ\textsubscript{max}^\text{EtOH}
241 µ, ϵ 15,500, λ\textsubscript{max}^\text{CH}_2\text{Cl}_2 2.79, 6.03 µ.

**Anal.** Calcd. for C\textsubscript{17}H\textsubscript{26}O\textsubscript{3}: C, 77.81; H, 9.99.

**Found:**
C, 77.43; H, 9.85.

**Preparation of 2β-Acetoxypodocarp-β(4)-en-7-one (82b).**
One hundred and ninety-seven milligrams of enol-ether acetate
(81b) and 647 mg. of oxalic acid were dissolved in 20 ml. of
ethanol and 1 ml. of water. After an hour at room temperature the reaction was worked up in the usual way, and the product was recrystallized from ether-petroleum ether to give 160 mg. of (82b), m.p. 101-102.5°. The sample for analysis melted at 103.5-104.5°, \( \lambda_{\text{max}}^{\text{CS}_2} \) 5.82 μ.

**Anal.** Calcd. for C₁₉H₂₈O₃: C, 74.96; H, 9.27.

**Found:**
C, 75.06; H, 9.01.

Treatment of (82a) with acetic anhydride-pyridine afforded an oil which failed to crystallize.

Five hundred and fifty-four milligrams of residue from the mother liquors of enol-ether acetate (81b) was cleaved with oxalic acid in ethanol and water. The oily product, 482 mg., was chromatographed over alumina (Woelm activity II-III). The main fraction (250 mg.), eluted with petroleum ether-benzene (80:20), was the acetate of compound (80). Elution with petroleum ether-benzene (60:40) gave 34 mg. of material which on recrystallization from ether-petroleum ether furnished 12 mg. of (89b), m.p. 112-113°, \( \lambda_{\text{max}}^{\text{EtOH}} \) 240 μm, ε = 16,000, \( \lambda_{\text{max}}^{\text{CS}_2} \) 5.78, 6.00, 8.10 μ. Further recrystallization did not improve the melting point.

**Anal.** Calcd. for C₁₉H₂₈O₃: C, 74.96; H, 9.27.

**Found:**
C, 74.74; H, 9.13.

Eighty-five milligrams of material from the mother liquor of (82b) was dissolved in 2 ml. of t-butanol which contained 20 mg. of dissolved potassium. After 1 hour at room temperature the reaction was worked up to give 75 mg. of an oil, \( \lambda_{\text{max}}^{\text{EtOH}} \) 235 μm, ε = 6,000, with a shoulder at 280 μm.
Preparation of $2\beta$-Acetoxy-3-methylpodocarp-8(14)-en-7-one (83). Six hundred and seventy-seven milligrams of (82b) was dissolved in 25 ml. of t-butanol, and 7.3 ml. of a potassium t-butoxide solution, prepared by dissolving 176 mg. of potassium in 10.0 ml. of t-butanol, was added after the system was flushed with nitrogen. The solution was heated to reflux, and then 0.14 ml. of methyl iodide in 60 ml. of t-butanol was added dropwise from a funnel over a 2 hour period under a nitrogen atmosphere. After a further $\frac{1}{2}$ hour period of refluxing the reaction mixture was diluted with ether and dilute hydrochloric acid. The organic layer was washed with dilute base and water and was dried over sodium sulfate. The residue from evaporation of the solvent was acetylated with acetic anhydride-pyridine. The product (618 mg.) was chromatographed over alumina (Woelm activity II-III). The fraction (315 mg.) eluted with petroleum ether-benzene (90:10) was recrystallized from ether-petroleum ether to give 208 mg. of (83), m.p. 126-128°. Further recrystallization from this solvent pair gave the analytical sample, m.p. 136-137°.

$\lambda_{\text{max}}^\text{EtOH}$ 249 mp, $\epsilon$ 17,500, $\lambda_{\text{max}}^{\text{CS}_2}$ 5.78, 6.02 μ.

Anal. Calcd. for C$_{20}$H$_{30}$O$_3$: C, 75.43; H, 9.50.

Found: C, 75.25; H, 9.46.

Forty-six milligrams of (82b), treated as above except that the reaction solution was not refluxed, yielded 34 mg. of an oil with phenol-type absorption in the ultraviolet.
Eighty-seven milligrams of the hydroxy-β,γ-unsaturated ketone (82a) on monomethylation (with refluxing) gave 83 mg. of a dark colored oil that possessed a band at 2.80 μ and none in the 5-6 μ region in the infrared.

**Chromic Acid Oxidation of (83) to 2β-Acetoxy-8-methylpodocarp-8(14)-ene-7,9-dione (84)**. To a solution of 155 mg. of ketone (83) in 8 ml. of glacial acetic acid there was added 150 mg. of chromium trioxide in 6 ml. of 90% acetic acid. The solution was stirred at 60° for 2 hours and after cooling was poured on ice, and the product was extracted with ether. The ether extract was washed and dried as usual and yielded on evaporation 94 mg. of a crystalline material. After three recrystallizations from ether-petroleum ether 17 mg. of (84) was obtained with a m.p. 158-161°. Further recrystallization furnished the analytical sample, m.p. 165-165.5°, λmaxEtOH 266 μ, ε 11,000, λmaxCHCl3 5.82, 5.96 μ. The infrared spectrum of this synthetic product was identical with that of the optically active compound (53).

**Anal. Calcd. for C20H28O4**: C, 72.26; H, 8.49.
**Found**: C, 71.97; H, 8.38.

The mother liquors from the purification of (84) yielded 4.7 mg. of needles, m.p. 178-180°, λmaxEtOH 242 μ, ε 1,400.

Oxidation of 28 mg. of (83) with chromium trioxide in acetic acid at 40° afforded not (84) but 2.8 mg. of the needles, m.p. 178-181°.
Zinc and Acetic Acid Reduction of (84) to 2β-Acetoxy-8β-methylpodocarpene-7,9-dione (85). A mixture of 100 mg. of zinc dust and 7.5 mg. of enedione (84) (synthetic material) was refluxed in 4 ml. of glacial acetic acid for 2 hours. After addition of ether the solution was washed with dilute base, dilute acid and saturated sodium chloride and was dried over sodium sulfate. The solvent was removed, and the residue was recrystallized four times from ether-petroleum ether to give 3 mg. of (85), m.p. 157.5-159.5°. The analytical sample melted at 158-160°. The infrared absorption spectra (in chloroform) of this material and of the natural acetoxydiketone (52) were identical.

**Anal. Calcd. for C_{20}H_{30}O_4:** C, 71.82; H, 9.04.

**Found:** C, 71.90; H, 8.83.

Oxidation of (80) to trans-1,2,3,4,9,10,11,12-Octahydro-7-methoxy-1,1,12-trimethyl-2-oxophenanthrene. An effort was made to obtain trans-1,2,3,4,9,10,11,12-octahydro-7-methoxy-1,1,12-trimethylphenanthrene, an intermediate in the synthesis of totarol, from compound (80) in order to correlate the two synthetic series. Since this phenanthrene has been shown to be trans, such a correlation would provide further evidence for the trans fusion of rings A and B in cassaic acid. The attempted preparation involved the oxidation of (80) to a ketone, conversion of the ketone to the ethylenethioketal, and removal of this function by treatment with Raney nickel.
Sixty-seven milligrams of (80) in 2 ml. of pyridine was added to a mixture of 66 mg. of chromium trioxide and 0.5 ml. of pyridine, and the solution was allowed to stand at room temperature for 5 hours. The mixture was poured into a dilute solution of sodium hydroxide, and the product was extracted with ether. The organic layer was washed with dilute hydrochloric acid and water and was dried over sodium sulfate. Evaporation of the solvent and recrystallization of the residue from ether-petroleum ether yielded 46 mg. of the desired ketone, m.p. 70-71°. Several recrystallizations afforded the analytical sample, m.p. 73-73.5°, λ<sub>max</sub> 5.85 μ.

**Anal.** Calcd. for C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>: C, 79.37; H, 8.88.

**Found:** C, 79.52; H, 8.86.

Four hundred and fourteen milligrams of the unsaturated ketone (78) in 5 ml. of glacial acetic acid was hydrogenated over 600 mg. of 10% palladium-charcoal. When the hydrogen uptake ceased, the mixture was filtered through Celite and diluted with ether. The ether solution yielded 230 mg. of a substance, m.p. 62-65° (from ether-petroleum ether), identical with the material prepared in the previous experiment.

One milliliter of ethanedithiol was added to a cooled solution of 180 mg. of the ketone in 4 ml. of alcohol-free chloroform which had been saturated with hydrogen chloride. After 24 hours at 0° the solution was diluted with ether,
washed with dilute sodium hydroxide, water, and saturated sodium chloride and dried over sodium sulfate. After evaporation of the solvent the residue was recrystallized twice from ether-petroleum ether to give 84 mg. of material melting at 127-130°. An analytical sample was prepared, m.p. 132-134°.

**Anal.** Calcd. for C_{20}H_{28}O_{2}S: C, 68.91; H, 8.10.
C_{20}H_{28}O_{2}S: C, 72.24; H, 8.49.

**Found:** C, 71.82; H, 8.75.

A mixture of 43 mg. of the above compound and W-2 Raney nickel in 10 ml. of dioxane was refluxed under nitrogen for 5 hours. By the usual work-up procedure an oil was obtained that gave an infrared spectrum similar to compound (80). A 5.85 μ band of low intensity was also present in the spectrum.

The analytical values and the results of the Raney nickel treatment indicate that the 132-134° melting compound was not the dithioketal but the corresponding hemithioketal. This latter compound could arise from impure ethanedithiol reagent.

**Ozonization of Cassaïc Acid to 2/3-Hydroxy-8α-methylpodocarpane-7,9-dione.** Forty-four milligrams of cassaic acid in 5 ml. of ethyl acetate and 5 ml. of methanol was treated with ozone under the conditions employed for ozonization of cassaic acid acetate methyl ester. One hundred milligrams of zinc dust and 1 ml. of 75% acetic
acid were added to the cold mixture, which was then stirred for 1/2 hour. Recrystallization of the crude product afforded 33 mg. of the hydroxydiketone. Further recrystallization provided the analytical sample, m.p. 176-180°, \( \lambda_{\text{max}} \text{CH}_2\text{Cl}_2 \) 3.00, 5.86 \( \mu \), \( \alpha_d \) -36° (c 1.02 ethanol). The melting point of this substance was variable and not sharp. The compound may undergo thermal rearrangement into the stable 8\( \beta \)-isomer on melting.

**Anal.** Calcd. for C\(_{18}\)H\(_{28}\)O\(_3\): C, 73.93; H, 9.65.

**Found:** C, 74.25; H, 9.49.

**Hydrolysis of (51) to 2\( \beta \)-Hydroxy-8\( \beta \)-methylpodocarpane-7,9-dione.** A solution of 190 milligrams of acetoxydiketone (51) derived from mother liquors, in 15 ml. of methanol and 5 ml. of 1 N sodium hydroxide solution was refluxed for 1.5 hours. On cooling the solution was diluted with ether and yielded 180 mg. of an oil. Chromatography of this crude product on alumina afforded 55 mg. of the 8\( \beta \)-methylhydroxydiketone. Recrystallization from ether-petroleum ether provided the analytical sample, m.p. 173-174°, \( \lambda_{\text{max}} \text{CH}_2\text{Cl}_2 \) 3.00, 5.86 \( \mu \), \( \alpha_d \) -54° (c 0.75 ethanol). The melting point of this material, mixed with the product of the previous experiment, was sharply depressed, and the infrared spectra of the two compounds were different in the 8-10 \( \mu \) region.

**Anal.** Calcd. for C\(_{18}\)H\(_{28}\)O\(_3\): C, 73.93; H, 9.65.

**Found:** C, 73.83; H, 9.71.
2β-Hydroxy-8β-methylpodocarpene-7,9-dione was also obtained by refluxing the 8α-methyl isomer in a sodium methoxide solution. However, the 8α-methyl compound was recovered unchanged from a passage through a column of Woelm alumina (activity II-III).

Preparation of 8α-Methylpodocarpene-2,7,9-trione (112) and the 8β-Isomer (113). A solution of 14 mg. of chromium trioxide in 1 ml. of 90% acetic acid was added to 50 mg. of 2β-hydroxy-8α-methylpodocarpene-7,9-dione in 0.5 ml. of acetic acid, and the mixture was allowed to stand at room temperature for 2½ hours. After the addition of methylene chloride and ether the solution was washed with dilute base, water and a saturated solution of sodium chloride. After drying and evaporation of the solvent the residue was recrystallized from methylene chloride-petroleum ether yielding 15 mg. of (112). As in the case of the 8α-methyl-hydroxydiketone the melting point was variable and not sharp; the highest melting point observed was 185-187° with sintering at 180°. Several recrystallizations afforded the analytical sample, \( \lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2} \) 5.86 μ, \([\alpha]_D^{73°} \) (c 0.93 ethanol).

**Anal.** Calcd. for \( \text{C}_{18}\text{H}_{26}\text{O}_3 \): C, 74.44; H, 9.03.

**Found:**

C, 74.40; H, 9.04.

Oxidation of 50 mg. of 2β-hydroxy-8β-methylpodocarpene-7,9-dione under the same conditions as in the previous experiment afforded 17 mg. of (113), m.p. 198-200.5° (from
methylene chloride-petroleum ether). A second crop was obtained, 9.5 mg., m.p. 197-199°. The infrared spectrum of this product was different in the 8-10 μ region from that of (112). The analytical sample melted at 200-201.5°, λ\text{max}^\text{CH}_2\text{Cl}_2 5.86 μ, [α]_D^\text{max} -61° (c .77 ethanol).

\textbf{Anal.} Calcd. for C\text{18}H\text{26}O\text{3}: C, 77.44; H, 9.03.

Found:

C, 74.52; H, 8.96.

Compound (113) was also prepared by the treatment of (112) with a sodium methoxide solution at room temperature.

\textbf{Sodium Borohydride Reduction of (50) to (110).} A solution of 820 mg. of cassaic acid acetate methyl ester (50) and 310 mg. of sodium borohydride in 25 ml. of methanol was allowed to stand at room temperature for 6 hours. After neutralization with acetic acid the mixture was concentrated in \textit{vacuo} and then diluted with ether. The ether solution yielded 625 mg. of (110), m.p. 140-142° (from ether-petroleum ether). Several recrystallizations provided the analytical sample, m.p. 145.5-146°, λ\text{max}^\text{EtOH} 222.5 μ, ε 18,000, λ\text{max}^\text{CS}_2 2.80, 5.80, 5.88, 6.01, 8.08 μ, [α]_D^\text{max} -90° (c .92 ethanol).

\textbf{Anal.} Calcd. for C\text{23}H\text{36}O\text{5}: C, 70.37; H, 9.24.

Found:

C, 70.20; H, 9.02.

The Conversion of (110) into (41). Twenty milligrams of (110) in 2 ml. of ethanol was hydrogenated over 20 mg. of palladium-charcoal. The residue from filtration and evaporation of the solvent was dissolved in 5 ml. of methanol and
5 ml. of 1 N sodium hydroxide solution, and the mixture was refluxed for 1½ hours. The saponification product after treatment with diazomethane gave 13 mg. of ester, m.p. 168-171° (from ether-petroleum ether). Recrystallization afforded material, m.p. 173-174.5°, which did not depress the melting point of (41). The infrared absorption spectra of the two samples in methylene chloride were identical.

**Ozonization of** (110) **to 2β-Acetoxy-9β-hydroxy-8α-methylpodocarpan-7-one** (111). Six hundred and three milligrams of (110) in 10 ml. of methanol and 10 ml. of ethyl acetate was treated successively with ozone and zinc and acetic acid under the conditions employed for cassaic acid. The crude product was recrystallized from ether-petroleum ether and afforded 323 mg. of (111), m.p. 132-133°. A second crop was obtained, 55 mg., m.p. 130-131°. The analytical sample melted at 135-136°, \( \lambda_{\text{CS}_2}^{\text{max}} 2.76, 5.76, 5.84, 4.10 \mu \), \([\alpha]_D^{-5°}\) (c .70 ethanol).

**Anal.** Calcd. for \( C_{20}H_{32}O_4 \): C, 71.39; H, 9.59.

**Found:** C, 71.57; H, 9.56.

A sample of (111) was recovered unchanged on passage through a column of ethyl acetate-washed alumina, a procedure which converts (51) into (52).

**Oxidation of** (111) **to** (51). A solution of 15 mg. of (111) and 2.5 mg. of chromium trioxide in 1.5 ml. of glacial
acetic acid was allowed to stand at 25° for 5 hours. Water and ether were then added to the mixture. After the usual washing and drying the solvent was evaporated, and the residue was recrystallized from ether-petroleum ether affording 11 mg. of product, m.p. 165-166.5°. Further recrystallization gave material, m.p. 169-170°, which did not depress the melting point of an authentic sample of (51). The infrared absorption spectra of the two substances were identical.

Treatment of (111) with Base and the Oxidation of the Product to (112). A solution of 55 mg. of (111) in 4 ml. of methanol and 1 ml. of 1 N sodium hydroxide was heated under reflux in a stream of nitrogen for 1 hour. On cooling the product was extracted with methylene chloride-ether. The organic layer yielded 33 mg. of a dihydroxyketone, m.p. 181-182.5° (from methylene chloride-petroleum ether). Oxidation of this substance with 20 mg. of chromium trioxide in acetic acid at room temperature provided 16 mg. of a triketone, m.p. 181-185°, which did not depress the melting point of a sample of (112) and which showed an infrared absorption spectrum identical with that of (112). A mixed melting point determination with a sample of (113) was depressed to 157-165°.

Attempted Removal of the C. 9 Oxygen Function in Cassaic Acid. In order to demonstrate the isomerization of the
8-methyl group in the conversion of (51) into (52), an attempt was made to remove the 9-keto group in cassaic acid before ozonization. Although this approach would provide information on the configuration of the 8-methyl group, it would furnish no evidence for the stereochemistry of the B/C ring fusion.

Three milliliters of ethanedithiol was added to a solution of 370 mg. of cassaic acid methyl ester in 10 ml. of cold chloroform (alcohol-free), which had been saturated with hydrogen chloride. After 24 hours at 0°C, the mixture was diluted with ether, and the solution was washed with dilute base, water, and saturated sodium chloride. The residue on drying and evaporation of the solvent was recrystallized from chloroform-petroleum ether and gave 350 mg. of thioketal, m.p. 243-246°C. The analytical sample melted at 246.5-247.5°C, \( \lambda_{\text{EtOH}}^{\text{max}} \) 221 mp, \( \epsilon \) 17,000, \( \lambda_{\text{CHCl}_3}^{\text{max}} \) 2.76, 5.86, 6.08 μ.

**Anal.** Calcd. for \( C_{23}H_{36}O_3S_2 \): C, 65.05; H, 8.55.

**Found:** C, 64.76; H, 8.54.

Treatment of this thioketal with Raney nickel (W-2) in refluxing dioxane afforded a poorly crystalline material that showed an infrared absorption spectrum, \( \lambda_{\text{max}}^{\text{CS}_2} \) 2.78, 5.78 μ, indicating that reduction of the double bond had occurred. When the reaction was carried out in acetone cassaic acid methyl ester was obtained. In dioxane with Raney nickel which had been pre-treated with
acetone, a poorly crystalline substance that probably is the desired 9-desoxocassaic acid methyl ester was obtained after chromatography. This approach was abandoned since the desired information was obtained from the experiments now to be described.

**Formation of the Ethylene Ketal (115) from (111).** One hundred and fifty-milligrams of (111) and 12 mg. of 2-toluenesulfonic acid were dissolved in 6 ml. of 2-methyl-2-ethyl-1,3-dioxolane. The solvent (b.p. 117°/760 mm.) was slowly distilled from the mixture; the volume of the solution was reduced by 1/2 in 10 hours. After addition of ether the solution was washed with base, acid, water, and saturated sodium chloride and was dried over sodium sulfate. Evaporation of the solvent afforded an oil which was chromatographed on alumina (Woelm activity II-III). The initial, oily fraction, 30 mg., showed in the infrared absorption spectrum no hydroxyl peak and a carbonyl band at 5.78 μ. Further elution gave 150 mg. of amorphous material, (115), λ<sub>max</sub> <sub>CS</sub> 2 2.78, 5.76, 8.05 μ.

**Oxidation of (115) to (116).** A solution of 150 mg. of (115) and 40 mg. of chromium trioxide in 3.5 ml. of glacial acetic acid was allowed to stand at room temperature for 2½ hours. Ether was added, and the solution was washed and dried according to the usual procedure. The product from evaporation of the solvent was recrystallized twice from
ether-petroleum ether affording 73 mg. of (116), m.p. 169-
171°. The analytical sample melted at 172.5-173°, \( \lambda_{\text{CS2}} \) max
5.75, 5.86, 8.05 \( \mu \), \([\alpha]_D^0 +5^\circ \) (c 1.20 ethanol).

**Anal.** Calcd. for C\(_{22}\)H\(_{34}\)O: C, 69.81; H, 9.05.

**Found:**
C, 69.93; H, 9.05.

A solution of 19 mg. of (116) in 4 ml. of 0.1 N sodium
methoxide in methanol was allowed to stand at room tempera-
ture for 20 hours. The crystalline product on acetylation
and recrystallization from ether-petroleum ether afforded
12 mg. of material, m.p. 173-174.5°, identical with (115)
(by mixed melting point and infrared).

**Preparation of the bis-Ketal (117) from (52).** A solu-
tion of 150 mg. of (52) and 42 mg. of \( p \)-toluenesulfonic acid
in 10 ml. of 2-methyl-2-ethyl-1,3-dioxolane was refluxed
for 51/2 hours. On cooling ether was added and the solution
was washed and dried. Evaporation of the solvent and two
recrystallizations of the residue afforded 50 mg. of (117),
m.p. 198-200°. The analytical sample melted at 206.5-
207.5°, \( \lambda_{\text{CS2}} \) max 5.78, 8.05 \( \mu \), \([\alpha]_D^0 -25^\circ \) (c .98 ethanol).

**Anal.** Calcd. for C\(_{24}\)H\(_{38}\)O\(_6\): C, 68.22; H, 9.06.

**Found:**
C, 68.23; H, 9.06.

**Isolation of (116) from Cleavage of the bis-Ketal (117).**
A solution of 220 mg. of (117) and 20 mg. of \( p \)-toluenesul-
fonic acid in 10 ml. of acetone was refluxed for 3 hours and
then was diluted with ether. The product after washing, drying, and evaporation was recrystallized giving 115 mg. of (52). The oily material from the mother liquor was chromatographed on alumina (Woelm activity II-III) and afforded 40 mg. of impure (52) and 9 mg. of a substance, m.p. 173-174° (from ether-petroleum ether), identical with (116) (by mixed melting point, infrared, and rotation).

Preparation of the Monoketal (118) from (52). A solution of 150 mg. of (52) and 22 mg. of \( p \)-toluenesulfonic acid in 10 ml. of 2-methyl-2-ethyl-1,3-dioxolane was refluxed for 1 hour. On cooling ether was added, and the solution was washed and dried. Evaporation of the solvent and two recrystallizations of the residue afforded 75 mg. of (118), m.p. 156-159°. The infrared spectra of (113) and (116) differed in the finger print region. The material prepared for analysis melted at 163-164°, \( \lambda_{\text{max}} \) 5.76, 5.85, 8.06 \( \mu \), \([\alpha]_D +38° \) (c 1.09 ethanol).

**Anal.** Calcd. for \( \text{C}_{22}\text{H}_{34}\text{O}_4 \): C, 69.81; H, 9.05.

**Found:** C, 69.80; H, 8.72.

Reduction of 20 mg. of (118) with 20 mg. of sodium borohydride in 2 ml. of methanol afforded 17 mg. of an acetoxyhydroxyketal, m.p. 197-200° (from ether-petroleum ether), different from (115) (by infrared). Cleavage of this material with acetone and \( p \)-toluenesulfonic acid gave 10 mg. of an
acetoxyhydroxyketone, m.p. 142-144° (from ether-petroleum ether), not identical with (111) (by mixed melting point and infrared).

Preparation of (111) from (116) by Reduction and Ketal Cleavage. Reduction of 33 mg. of (116) with 14 mg. of sodium borohydride in 1.5 ml. of methanol afforded 30 mg. of oil which exhibited an infrared absorption spectrum identical with that of (115). Cleavage of this material with 2.4 mg. of p-toluenesulfonic acid in 3 ml. of refluxing acetone (1 hour) provided 26 mg. of oil. This material on chromatography on alumina and two recrystallizations from ether-petroleum ether gave 6.3 mg. of product, m.p. 135-135.5°, identical with (111) (by mixed melting point and infrared).

Treatment of (111) with Acid. In a preliminary experiment 10 mg. of (111) was treated with 6 mg. of p-toluene sulfonic acid in refluxing toluene for 8 hours. The oily product (8 mg.) showed infrared absorption bands at 5.78, 5.82 (weak), 6.00, and 8.05 μ. The 6.00 μ band indicates the probable presence of (83) in the product of this reaction.

Isolation of (83) from natural sources would provide a more convenient relay point in the synthesis of cassaic acid.
IV. SUMMARY
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The research which has been described unequivocally establishes the structure of the diterpene, cassaic acid. In addition, the configurations at the six asymmetric centers present in cassaic acid have been assigned.

A degradative compound, which has also been obtained by synthesis, has been converted into a substance which on treatment with a Reformatsky or Wittig reagent, followed by mild oxidation, should provide cassaic acid acetate methyl ester. Resolution at a suitable stage would then complete the total synthesis of cassaic acid and cassaine, the β-dimethylaminoethanol ester of cassaic acid.

Cassaine is a member of the pharmacologically important Erythrophleum alkaloids. These alkaloids, all of which are presumably related to cassaine, possess typical digitallis-like heart action, a property very unusual for this class of compounds.
V. REFERENCES
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