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Stereochemical Equilibria Involving 1-Methyl-trans-decalone-2 and Its Derivatives

by

Jeen-lee Lin

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Thesis Director's signature:

Houston, Texas

June, 1967
To my parents.
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I wish to express my appreciation to Prof. Richard B. Turner, who directed this research, for his advice, assistance and criticism.

I want to thank my parents for their moral support and their financial support of my undergraduate work. My thanks to my colleagues for their help.

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INTRODUCTION

Some years ago a study of the structure and total synthesis of cassaic acid (1) was undertaken in this laboratory. In the course of this investigation it was observed that ozonolysis of cassaic acid acetate methyl ester affords an acetoxy diketone (2) which is transformed into an epimer (3) by chromatography on certain types of alumina or by treatment with base and subsequent re-acetylation.\textsuperscript{1,2}

\begin{center}
\begin{tikzpicture}
\node (1) [label=below:A.] {1};
\end{tikzpicture}
\end{center}

Although epimerization at the B/C ring fusion was considered as a possible alternative to methyl inversion, this interpretation was rejected in view of the general stability of cassaic acid derivatives toward mild basic reagents\textsuperscript{3,4} and on the grounds that dihydro-cassiac acid (4) survives treatment with strong base.
The original assignment of axial orientation to the methyl group in (2) and the corresponding equatorial arrangement in (3) was based on (a) the general preference for the equatorial over the axial configuration for substituents in 6-membered rings,⁵ and (b) to the further preference for non-polar substituents to lie in the nodal plane of the carbonyl group,⁶,⁷ in this case in the equatorial position.

In the further examination of this point of stereochemistry, it was noted that reduction of cassaic acid acetate methyl ester with sodium borohydride furnished a hydroxy derivative, which was converted into the acetoxy hydroxy ketone (5) by ozonolysis. The diacetate, diol, and triketone derivatives of this substance were prepared and it was demonstrated by appropriate interconversions that on treatment with base compound (5) does not undergo any stereochemical change. Since oxidation of (5) with chromium trioxide in acetic acid yields the thermodynamically unstable acetoxy diketone (2), the configuration of the methyl groups in the two substances must be the same. The facts of the case are readily
accommodated by the assumption that the hydroxyl group introduced by borohydride reduction is equatorial. In this event epimerization of the methyl group would give a product (6) in which, although both substituents in question are equatorial, they possess the geometrical relationship of energetically unfavorable 1,3-diaxial substituents. An equatorial hydroxyl group would thus tend to enforce an axial orientation for the methyl group three carbon atoms removed. Although this point could not be directly tested since compound (6) was unavailable, it is reasonable to assume that one is dealing with a simple equilibrium in which compound (5) very largely predominates.

Reaction of the acetoxy hydroxy ketone (5) with 2-butanone ethylene ketal in the presence of p-toluenesulfonic acid yielded a monoketal (7), which could be reconverted into (5) by exchange with acetone and which yields an acetoxy keto ketal (8) on oxidation with chromic acid. Borohydride reduction of (8) leads to regeneration of the starting alcohol (7).
Partial dioxanolation of the stable diketone (3) furnishes an acetoxy keto ketal differing from (8) to which structure (9) was assigned. It is a matter of considerable interest that treatment of either (8) or (9) with p-toluenesulfonic acid in refluxing benzene affords an equilibrium mixture containing approximately equal quantities of the two isomers, which is easily resolved by chromatography on alumina. Of the three equilibria thus far described, that involving the acetoxy diketones (A) furnishes the equatorial epimer exclusively, that involving the acetoxy hydroxy ketones (B) furnishes the axial methyl derivative exclusively,
whereas by contrast equilibrium (C) gives equal amounts of both epimers. In rationalizing this behavior it was noted\(^2\) that in terms of classical steric effects an equatorial methyl group should suffer steric interaction with the methylene groups of an adjacent ethyleneketal function (cf. 9a) whereas an axial methyl group should be unaffected (8a). The net result is some destabilization of the equatorial position.

\[
\begin{align*}
\text{(9a)} & \quad \begin{array}{c}
\text{O} \\
\text{C}_2 \text{H}_{5} \\
\end{array} \\
\text{(8a)} & \quad \begin{array}{c}
\text{O} \\
\text{C}_2 \text{H}_{5} \\
\end{array}
\end{align*}
\]

Two important points arise from this work. First, by operating with the ketal instead of with the ketone it should be possible to effect the introduction of axial substituents in the \(\alpha\)-position. Secondly, such configuration can be maintained by incorporation of a suitably oriented function in the \(\gamma\)-position. The utility of these procedures is illustrated in the accompanying diagram which outlines the method employed for converting the thermodynamically stable acetoxy diketone (3) into the thermodynamically unstable isomer (2), and which embodies the key elements in the total synthesis of cassaic acid,\(^2\) obtained from (3) by way of (5) by procedures that will not be discussed.
Although the thermodynamic character of compounds in this series is well defined by experiment, as is the fact that cessaic acid and substance (2) possess the same arrangement of the methyl group, the matter of stereochemical assignment—axial (∞) or equatorial (β)—is clearly open to question. The arguments that have been advanced are logically consistent, but they are not rigorous, and it is possible that a tenable position could be constructed in which all of the assignments made above are reversed. For example the stability relationships among the various derivatives might be determined, not by simple steric interactions as is suggested, but by more complex factors involving bond hybridization differences. Thus,
Dauben\textsuperscript{9} has shown that whereas diketone (10) is the more stable member of the B-norsteroid pair (10) and (11), conversion of the trigonal carbon atom (C.3) to tetrahedral hybridization as in (12) and (14) results in systems that are now thermodynamically unstable with respect to isomers that are assigned structures (13) and (15), respectively.

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node (a) at (0,0) {\includegraphics[width=1cm]{10}};
\node (b) at (1.5,0) {\includegraphics[width=1cm]{11}};
\node (c) at (0,-2) {\includegraphics[width=1cm]{12}};
\node (d) at (1.5,-2) {\includegraphics[width=1cm]{13}};
\node (e) at (0,-4) {\includegraphics[width=1cm]{14}};
\node (f) at (1.5,-4) {\includegraphics[width=1cm]{15}};
\end{scope}
\end{tikzpicture}
\end{center}

In 1963 a paper by Mathieson and his associates\textsuperscript{10} appeared in which the stereochemistry of cassamic acid (16) was discussed. Epimerization of the C.8 methyl group in keto derivative (19) was observed, but the investigators interpreted this result as an equatorial to axial change. Since cassamic acid has been chemically correlated with cassaic acid by unambiguous methods,\textsuperscript{11} the
Implication of the British work was that the configurations assigned above to the C.8 methyl group of cassaic acid and its degradation products were incorrect. The arguments of the Mathieson group are outlined in the accompanying chart, in which the various compounds are given the British stereochemical designations.

Sodium borohydride reduction of cassamic acid (see 16a) affords the hydroxy acid (17), reconvertible into the starting material by oxidation with chromium trioxide in pyridine. Ozonolysis of (17) gives hydroxy ketone (18), which is stated to be configurationally stable although experimental evidence is not supplied. This substance is converted by chromium-trioxide pyridine oxidation into a diketone (19), which is readily transformed into the more stable epimer (20) by chromatography on alumina or by treatment with hydrochloric or oxalic acids. Since (20) is obtained directly by ozonolysis of cassamic acid, it follows that epimerization must occur either during the course of the ozonization reaction or in the process of work up. Finally, removal of the carbonyl group of
CHART I

(16a) → NaBH₄ → (17) → CrO₃-Py → (16a)

Cassamic acid

(18) → CrO₃-Py → (19) → H⁺ or Al₂O₃ → (20)

Non-epimerizable → Stable form

(21) → O₃ → (22)

Non-epimerizable
cassamic acid by Clemmensen reduction furnishes a deoxo derivative (21), further convertible into monoketone (22) by ozonization.

Ultimate assignment of configuration to the centers pertinent to these transformations is based upon the following considerations. Monoketone (22) resists attempts at epimerization, and shows a positive Cotton effect in the optical rotatory dispersion curve, from which the Octant Rule\textsuperscript{12} predicts a $\beta$-orientation (equatorial) for the C.8 methyl group. The shape of the rotatory dispersion curve and its amplitude are stated to be almost identical with that of 4-$\alpha$-methylcholestan-3-one. The $\beta$-configuration assigned to the hydroxyl group of (17) and (18) is deduced from a comparison of suitable molecular rotation differences with those of appropriate model systems.

Several difficulties arise in connection with the Mathieson scheme. No explanation is provided for the failure of (18) to epimerize and thereby relieve the 1,3-interaction of the hydroxyl and methyl groups. Acceptance of the idea that diketone (19) undergoes epimerization from equatorial ($\beta$) to axial ($\alpha$), whereas monoketo (22) retains the equatorial ($\beta$) configuration of the methyl
group, is required. Although this possibility cannot be summarily rejected in view of the Dauben results referred to above, the interpretation that is offered is unconvincing. Thus it is stated that in diketone (19) the equatorial methyl group "is subject to considerable interaction with both (ketonic) oxygen atoms." However, a careful examination of molecular models reveals that an 8 β-methyl group lies very nearly in the nodal plane\(^6\text{,}^7\) of the C.7 carbonyl group, and that the dispositions of the C.9 keto function with respect to either an 8 α- or 8 β-methyl group are essentially equivalent. In accounting for the failure of monoketone (22) to epimerize in a manner analogous to (19), the suggestion is made that for conformational reasons the keto group in this molecule enolizes in one direction only and that this is on the side opposite the methyl group. Since enolization is an equilibrium process, this view necessitates a very large energy difference between the two enols or an exceptionally large difference in activation energy for enolization in the two directions or both. In any event it is difficult to see why epimerization should not occur if given sufficient time.

In support of this contention a study of the behavior of 4 α- and 4 β-methylcholestan-3-one by Jones and his collaborators\(^13\) is cited. In summary, the Jones work indicates that 4 β-methylcholestan-3-one is not isomerized by weak base, while under more vigorous conditions only resinous products are obtained. This point would appear to warrant further investigation.

The most serious objection that can be raised to Mathieson's stereochemical assignments relates to the fact that they ultimately
depend upon maintenance of stereochemical integrity in the transformation of cassamic acid into (21) and thence into monoketone (22). In both steps possibilities for epimerization are present. In the Clemmensen reduction stage epimerization could be accomplished by simple acid-catalyzed equilibration of the \( \alpha, \beta \)-double bond with the available \( \beta, \gamma \) positions. As far as the ozonization reaction is concerned, it is remarkable that in the face of the epimerization known to occur in the direct ozonolysis of cassamic acid to diketone (20), a similar possibility was not considered for the ozonolysis of (21). It is clear that should epimerization be involved in either of these steps then all the structures with the exception of (22), and possibly (21), would require revision.

The situation has been clarified by subsequent events which support the earlier stereochemical assignments, and clearly indicate that the Mathieson structures are in error. A detailed NMR examination of cassaic acid methyl ester and comparison of the results with simple model substances defines the orientation of the C.8 methyl group as axial (\( \alpha \)) in the naturally derived substance.\(^{14}\) A rigorous chemical demonstration coupled with further NMR work has recently been published by Clarke, Daum, Shaw, and Kullnig.\(^{15}\) Treatment of acetoxy hydroxy ketone (5) with trimethylphosphonoacetate yields a mixture of two \( \alpha, \beta \)-unsaturated esters (24) and (25), absorbing at \( \lambda_{\text{max}} \text{ m} \mu (\varepsilon 17,900) \) and at \( \lambda_{\text{max}} \text{ m} \mu (\varepsilon 16,500) \), respectively. The fact that the substances are isomeric at the double bond was indicated by catalytic hydrogenation to a common dihydro derivative. Structures were assigned to these substances on the basis of deshielding of the C.8 hydrogen by the carbomethoxyl
group in (25), and one of the compounds, (24), proved to be identical with the product obtained by sodium borohydride reduction of cassaic acid acetate methyl ester. Similar Wittig treatment of the stable acetoxy diketone (3) afforded a mixture from which a single pure unsaturated ester (26) could be isolated ($\lambda_{\text{max}}$ 223 m$\mu$, $\varepsilon$ 15,900). The double bond stereochemistry was implied by the fact that the alternate arrangement should result in non-planarity in the chromophore owing to steric interaction between the methyl and carbomethoxyl groups, which in turn should give rise to a perturbed ultraviolet spectrum. The position of the double bond is clearly established by the transformations (26) $\rightarrow$ (27) $\rightarrow$ (28) $\rightarrow$ (5), and it therefore follows that (26) is C.8 methyl epimer of cassaic acid acetate methyl ester. Sodium borohydride reduction of (26) yields a mixture of epimeric alcohols of which one (27) affords on ozonolysis an acetoxy hydroxy ketone (28) convertible by base into the known dihydroxy ketone (29) alternately prepared by hydrolysis of (5). The anticipated epimerization, (28) $\rightarrow$ (29), therefore does in fact occur.
Finally, mention should be made of work by Mori and Matsui\textsuperscript{16} which establishes that the flaw in the British investigation discussed above resided in failure to recognize epimerization in the ozonolysis of (21) to (22).
DISCUSSION

Shortly after work on the total synthesis of cassaic acid had been completed, and before any discussion of stereochemistry had appeared in the literature, a project was undertaken in this laboratory with the following objectives in mind. Since the orientation of the C-8 methyl group in cassaic acid was open to question, information on this point was desired. In this connection the problem of equilibria in systems that differed with respect to the presence of trigonal and tetrahedral carbon atoms was to be investigated. Finally, and most important, the generality of ketal equilibrium (8 $\leftrightarrow$ 9) as a procedure for the incorporation of an axial methyl group adjacent to a carbonyl function, and maintenance of such configuration by inclusion of an appropriately oriented hydroxyl group (as in 5), were to be tested.

The 1-methyl-trans-decalin system was chosen for study, and both mono and dioxygenated derivatives based on this nuclear arrangement were subjected to detailed examination. The dioxygenated substances were investigated by R.B. Miller, while results in the monooxygenated series constitute the subject of this thesis.

The choice of the 1-methyl-trans-decalin system was dictated by two major considerations. It constitutes an appropriate model for that portion of the cassaic acid molecule that was of interest, and it offered a skeletal arrangement in which the stereochemical relationships could be rigorously established.
The two decahydro-1-naphthoic acids, (30) and (33), as well as the corresponding cis-fused isomers, are known. \(^{18,19}\) The stereochemistry of these substances is well established. \(^{17,18,19}\) Lithium aluminum hydride reduction affords respectively the alcohols (31) and (34), from which the parent acids can be regenerated by chromic acid oxidation. \(^{17}\) It follows that no stereochemical change accompanies the reduction process. The alcohols thus produced afford p-toluene-sulfoxoxy derivatives, which on subsequent reduction with lithium aluminum hydride furnish the hydrocarbons (32) and (35), respectively. These products show only minor differences in the infrared and NMR spectra, but are readily differentiated by vapor chromatography and by their mass spectral fragmentation patterns. The samples obtained
in this way were employed as reference compounds in the subsequent investigation.

For the preparation of 1-methyl-trans-decalone-2, 1-methyl-\(\Delta^1\)-octalene-2 (39) served as starting material and was prepared by the general Stork procedure.\(^{20}\) Cyclohexanone pyrrolidine enamine (36) was condensed with ethylvinyketone and furnished, after hydrolysis, a mixture containing about 44% of monocyclic diketone (37) and bicyclic ketol (38). The structure assigned to the latter substance is based on the appearance of a methyl doublet in the NMR. The alternate bridged structure is expected to show a methyl triplet. The mixture was not ordinarily separated but was treated directly with base to give the desired conjugated ketone (39).

\[
\begin{align*}
\text{(36)} & \quad + \quad \text{CH}_3\text{CH}_2\text{C}^=\text{CH}_2 & \quad \rightarrow & \quad \text{(37)} \\
\text{(38)} & \quad + \quad \text{(38a)} & \quad \rightarrow & \quad \text{(39)}
\end{align*}
\]
Palladium-catalyzed hydrogenation of (39) was then attempted in the hope that cis addition of hydrogen might lead in part to the formation of the syn-trans ketone (40), which might then be equili-brated with the epimeric anti-trans product (41). Hydrogenation gave two ketones which were separable by vapor chromatography. One of these substances proved to be identical with the thermodynamically stable trans-fused epimer (41) discussed below, and it follows that epimerization occurred either during the hydrogenation reaction or less probably during the work-up procedure. The second substance could not be converted into (41) by treatment with base, and it is tentatively assigned structure (42).

Since catalytic hydrogenation did not afford a thermodynamically unstable methyl ketone (presumed to be 40) and since it represented an inefficient procedure for the preparation of (41), reduction of the conjugated ketone (39) with sodium in liquid ammonia and alcohol was next explored. In this way a crystalline alcohol to which structure (43) is assigned was obtained as the only isolated product. The stereochemistry of this substance at the centers C.1, C.9, and C.10 was established as follows. Treatment with p-toluenesulfonyl chloride in pyridine yielded the corresponding p-toluenesulfoxy derivative (44), which was then reduced with lithium aluminum hydride.
In addition to some 30% of recovered alcohol derived by hydride attack on sulfur, there was obtained (40% yield) a chromatographically homogeneous hydrocarbon that proved identical in all respects with reference compound (31).

Oxidation of alcohol (43) with chromium trioxide in acetic acid under conditions which should not result in epimerization of the product, afforded ketone (41). Reduction of this substance with lithium aluminum hydride furnished a mixture of the two epimeric alcohols (43) and (45) in a ratio of about 3:1. Compounds (43) and (45) were also obtained by catalytic hydrogenation of (41) in the presence of platinum oxide and acetic acid, but in a ratio of 1:4. This correlation of (43) and (41) provides clear evidence for the configuration of the methyl group (\(\Delta\)) in ketone (41). Since (45)
is converted into (41) by chromium trioxide-acetic acid oxidation, it follows that it must differ from (43) only in the configuration of the hydroxyl group.

When ketone (41) was allowed to react with sodium methoxide in methanol, it was recovered from the reaction mixture unchanged. Material before and after exposure to base showed identical NMR and infrared spectra, and identical retention time on vapor chromatography. Dinitrophenylhydrazones derived from the two samples likewise proved to be identical. Although this evidence strongly suggests that (45) represents the thermodynamically more stable of the two methyl epimers, the argument is not conclusive since failure of (41) to enolize in a direction appropriate for methyl epimerization (see above) would prevent the establishment of equilibrium. In order to test this point compound (41) was treated with sodium methoxide in CH$_3$OD under conditions identical with those of the unlabeled experiment. Material processed in this way was then examined in the mass spectrograph which revealed parent peaks at mass-to-charge ratios of 169 and 168 corresponding to about 82% of the former and 18% of the latter species. Since undeuterated (41) shows no peaks of significant intensity above m/e 166, * it is clear that deuterium exchange of all three $\alpha$-protons in (41) is a major process in the base-catalyzed reaction. Thus enolization towards C.1 does occur and the possibility for stereoechemical equilibrium is

* The appearance of M + 1 peaks of very low intensity in the mass spectra of carbonyl compounds, owing to hydrogen atom capture by the parent molecule ion, has been noted (ref 24).
not precluded. Further comments on this matter will be found in a later section.

The question of the effect of trigonal versus tetrahedral carbon atoms on stereochemical equilibria has been referred to above (p 7). It was, therefore, of interest to examine the behavior of the alcohols (43) and (45) as contrasted with that of ketone (41) with respect to the favored orientation of the methyl group. Base-catalyzed equilibration of alcohols, for example cholestanol (46) and epicholestanol (47), is a well-known process, and it has been shown by Doering and Aschner that the reaction proceeds by hydride transfer with ketone as the intermediate. This being the case,

[Diagram of molecules (46) and (47)]

equilibration of (43) and (45) should allow a change in configuration of methyl as well as of the hydroxyl group, and the major product should therefore be that possessing favored stereochemistry at both centers.

The two alcohols, (43) and (45), were accordingly treated at 165-170° in sealed tubes with sodium n-butoxide in n-butanol containing a small amount of benzophenone. Equilibrium was established
slowly, but was essentially complete after 144 hours. From (43) there was obtained an alcohol mixture which, after vapor chromatographic separation, yielded 73% of (43) and 27% of (46). The mixture obtained when (45) was employed as starting material contained 70% of (43) and 30% of (45). In neither case was the presence of a third component detected, although the combined yield of the two alcohols after column chromatographic separation was only 73%. Since both alcohols possess an equatorially (\( \alpha \)) oriented methyl group, it follows that in both the alcohol and ketone cases the equatorial methyl group is thermodynamically favored over the alternate axial arrangement.

Attention was next directed towards the preparation and examination of the equilibrium behavior of the ethylene ketal derived from ketone (41). This substance (48) was readily obtained by treatment of the ketone with ethylene glycol in refluxing benzene for six hours in the presence of catalytic amounts of p-toluenesulfonic acid. When a purified sample of (48) was heated in refluxing benzene with

\[
\begin{align*}
\text{(48)} & \quad \text{H} \quad \text{H} \\
\quad \text{O} & \quad \text{O} \\
\quad \text{C} & \quad \text{H}_3 \\
\end{align*}
\]

\[
\begin{align*}
\quad \text{O} & \quad \text{O} \\
\quad \text{C} & \quad \text{H}_3 \\
\end{align*}
\]

larger amounts of p-toluenesulfonic acid for 24 hours, equilibrium with a second ketal (49) was established. Vapor chromatographic analysis of the reaction mixture indicated the presence of 73% of
(48) and 22% of (49). The remaining material was accounted for by 5% of ketone (41) which is presumed to arise by hydrolysis promoted by traces of water. Isolation of compound (49) by preparative vapor chromatography gave material which was also subjected to acid-catalyzed equilibration. The product distribution in this case was the same as that obtained when ketal (48) was employed as starting material. Since equilibria involving ketone (41) and the alcohols (43) and (45) give products in which the methyl group is essentially exclusively equatorially oriented, it is evident that the equatorial position is destabilized to some extent by the presence of an adjacent ethylene ketal function. The simplest explanation for this phenomenon is one in which non-bonded repulsion between the equatorially oriented methyl group and methylene groups of the ketal bridge is invoked as indicated in structures (48a). Such interactions are,

![Structures](image)

of course, absent in the axial isomer (49a).

Of special interest is the fact that cleavage of a chromatographically homogeneous sample of ketal (49) by exchange with acetone in the presence of p-toluenesulfonic acid, affords 82% of a mixture of ketones (41) and (40) in a ratio of about 3:7. Thus it is possible to effect ketal cleavage and isolation of the thermodynamically
unstable ketone product (40) without complete isomerization to the stable epimer (41). As expected ketone (40) is readily converted

\[ \text{(40)} \]

into (41) by the action of sodium methoxide in methanol, and it affords on lithium aluminum hydride reduction a mixture of two alcohols which differ in retention time from alcohols (43) and (45). Unfortunately, the amount of reduced material was insufficient for characterization of the separated products.

The fact that ketal (48) in cleavage furnishes exclusively the thermodynamically stable ketone (41), whereas cleavage of (49) yields ketone (40) as the major product serves to establish the stereochemistry of the ketal derivatives. It is of interest to note that the transformation (49) → (40) also implies that enol (50) is not an important intermediate in the cleavage reaction, since preferred

\[ \text{(50)} \]

axial protonation should furnish ketone (41) instead of (40). Moreover, if (50) were a common intermediate in the cleavages of both ketalts, the same product or product mixture should be obtained in each case, an observation that is contrary to the facts.
The results of equilibration of ketals (48) and (49) suggested that examination of the behavior of the corresponding thio ketals might prove profitable. Ketone (41) was accordingly treated with ethanedithiol in benzene solution in the presence of p-toluenesulfonic acid. The product was identified as a thio ketal by infrared and NMR analysis and showed a single peak on vapor chromatography. Prolonged treatment of the material with p-toluenesulfonic acid in refluxing benzene, however, produced no detectable change. In order to investigate the point further, the "equilibrated" thio ketal was subjected to Mozingo reduction,28 and the hydrocarbon fraction thus produced was analyzed by vapor chromatography. Both methyl decalins (32) and (35) were obtained, with the equatorial epimer (32) predominating by a factor of about seven. Although involvement of the methyl group in the desulfurization reaction is a possibility, it seems more likely that the thio ketal starting material was in fact a mixture which was not resolved in the vapor chromatographic procedure employed.

Brief mention has been made in an earlier section of work by E.R.H. Jones and his associates,13 which is interpreted as demonstrating that 4β-methylcholestanone-3 (51) is not subject to epimerization into the 4α-methyl isomer (52). This matter must now be considered in greater detail.
For the preparation of compounds (51) and (52), cholestanone served as starting material. This substance was condensed with ethyl formate to yield the hydroxymethylene ketone (53) which was in turn allowed to react with trimethylene ditoluene-$p$-thiosulfonate and potassium acetate according to the procedure of Woodward and his collaborators. The product obtained in this way was the thieketal (54). Methylation of this substance with methyl iodide and potassium t-butoxide furnished a mixture of monomethylated derivatives (55) and (56) together with some dimethylated material, which could be separated by chromatography. The product (55), to which a $\beta$-configuration for the methyl group was subsequently assigned, was isomerized to the 4$\alpha$-isomer (56) by the action of potassium t-butoxide in benzene, and from the relative amounts of (55) and (56)
obtained under varying methylation conditions, it appeared that (55) was the product of kinetic control. Raney nickel reduction of the two thioketals yielded 4β-methylcholestanone-3 and 4α-methylcholestanone-3, respectively. Although characterization of the 4β-epimer (51) was scanty there is little basis for the supposition that the structure may have been incorrectly assigned.

In attempting to effect isomerization of (51) into (52) the following experiments were carried out by the Jones group.

(a) Compound (51) in ether solution was shaken for 15 minutes with aqueous potassium carbonate.

(b) The ketone was heated under reflux with 2.5% sodium methoxide in methanol for 1 hour.

(c) The ketone was allowed to stand in benzene solution on an alumina column for 28 hours.

Under all of these conditions it is reported that starting material was recovered unchanged. Subjection of (51) to the action of potassium t-butoxide in refluxing t-butanol for 1 hour and to 10% potassium hydroxide in ethylene glycol at 170° for 2 hours led to destruction of the sample, and only yellow resin could be recovered from these reactions.

In view of the results obtained in the present investigation with a simple model system, the Jones observations are puzzling. In particular it should be noted that the driving force for epimerization should be larger in the case of (51), owing to the presence of a 1,3-diaxial interaction between methyl groups, than in the case of (40) in which one of the methyl groups is replaced by hydrogen. It appeared, therefore that a re-examination of this question was
in order. To this end an alternate synthesis of 4β-methylcholestanone-3 (51) was undertaken.

Cholestenone (57) was reduced by the Wolff-Kishner method, which proceeded with double bond migration to yield the $\Delta^{3,4}$-olefin (58). Epoxidation of this product with monoperphthalic acid then furnished the known 3α, 4α-epoxide (59). Opening of the epoxide with methyl lithium proved difficult, but was ultimately accomplished by treatment of (57) with methyl lithium in refluxing ether for a period of 3 days. The product was isolated by chromatography and is assigned structure (60) on the basis of the general rule that oxides undergo opening in the trans diaxial sense. Methyl lithium was employed in this case instead of the Grignard reagent in order to avoid the possibility of rearrangements which commonly occur in the Grignard reaction of epoxides. Chromium trioxide oxidation of the alcohol (60) proceeded smoothly and afforded a ketone melting at 132-136°. The Jones ketones (51) and (52) melt respectively at 125-127° and at 122-122.5°. Treatment of the ketone mp 132-136°, to which we assign structure (51) with 2.5% sodium methoxide in
methanol for 8 hrs at room temperature gave material which was chromatographed on basic alumina. The product (52) after recrystal-
лизация from ether-petroleum ether melted at 121-123°. It follows, therefore, that ketone (51) is epimerizable with base as predicted on the basis of work presented in this thesis, and the assumption of unidirectional enolization is, therefore, invalid.

It is not possible to point directly to the discrepancy in the Jones work. It is not unlikely that the ketone sample employed by him in the epimerization studies was in fact not (51) but rather cholestanone (mp 129°). Such a product could be reasonably isolated from the preparative procedure that was followed.
EXPERIMENTAL

Preparation of 1-Methyl-\(\Delta^{1,9}\)-octalone-2 (39)\(\textsuperscript{20}\)-To a solution of 18 g of the pyrrolidine enamine of cyclohexanone (prepared by the usual procedure)\(\textsuperscript{20}\) in 100 ml of anhydrous dioxane, 10 g of freshly distilled ethyl vinyl ketone was added. The reaction mixture became warm and was allowed to stand at room temperature for 4 hrs. At the end of this time 12 ml of acetic acid, 25 ml of water, and 6.2 g of sodium acetate were added, and the resulting solution was heated on the steam bath for 1 hr. The mixture was then cooled, diluted with water, and extracted with ether. The resulting ethereal solution was then washed successively with water, dilute sodium hydroxide solution, and a saturated solution of sodium chloride. After filtration through anhydrous magnesium sulfate, the solvent was removed under reduced pressure yielding 16.4 g of crude amorphous product.

* A. Melting points were taken on a Fisher-Johns melting point block and are uncorrected.

B. All analyses were carried out by commercial analytical laboratories.

C. Infrared spectra were taken on either a Beckmann IR-5 or on a Perkin-Elmer Model 21 spectrophotometer.

D. Nuclear magnetic resonance spectra were taken on an A-60 Varian spectrometer.

E. Qualitative gas chromatographs were taken on a Perkin-Elmer Model 21 flame-ionization gas chromatograph with Ucon column unless otherwise indicated.
The material was taken up in petroleum ether and filtered through an alumina column. From the combined filtrate and petroleum ether washings there was obtained 9.6 g of diketone (37), which was purified by distillation under reduced pressure: bp 162-167°/4 mm, \( \lambda_{\text{max}}^{CS_2} = 5.85 \mu \).

Elution of the alumina column with ether furnished 4.4 g of bicyclic ketol (38), mp 109-111° (from ethanol), \( \lambda_{\text{max}}^{CS_2} = 2.9 \mu \) (broad). The NMR spectrum taken in CCl₃CN showed a methyl doublet centered at \( \delta = 0.9 \).

**Anal.** Calc. for C₁₁H₁₈O₂: C, 72.48; H, 9.95.

Found: C, 72.52; H, 9.89.

Both (37) and (38) were cyclized by the method of Shunk and Wilds to give a total of 11.3 g of 1-methyl-\( \Delta^1,9 \)-octalone-2 (39). The procedure as applied to diketone (37) was as follows.

To 1 liter of methanol, through which a slow stream of nitrogen was passed, there was added 40 g of potassium hydroxide, 80 ml of water and 10.4 g of compound (37). After standing at room temperature for 2-1/4 hrs the slightly yellow reaction mixture was poured into 2 l of saturated sodium chloride solution, and the product was extracted with four portions of ether. The combined ether extracts were then thoroughly washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation of the residue furnished 7.0 g of 1-methyl-\( \Delta^1,9 \)-octalone-2 (39), bp 143-146°/17.5 mm, \( \lambda_{\text{max}}^{CS_2} = 6.0 \mu \), EtOH \( \text{max} = 248 \mu \) (\( \epsilon = 10,000 \)) (lit). EtOH \( \text{max} = 249 \mu \).

The dinitrophenylhydrazone prepared as a derivative melted at 181-182° (lit mp 177.5-178.5°).
Catalytic Hydrogenation of Unsaturated Ketone (39).—A solution of 525 mg of ketone (39) in 6 ml of ethanol was stirred with 66 mg of 10% palladium-on-charcoal in an atmosphere of hydrogen until hydrogen uptake had ceased (1 hr). The catalyst was removed by filtration, and the filtrate was evaporated to dryness. The residue was subjected to vpc analysis. Two peaks were observed of which one showed a retention time identical with that of ketone (41). The second peak differed in retention time from ketones (41) and (40). Chromatographic analysis of the reduction mixture after treatment with base to effect equilibration revealed no changes in composition.

Preparation of 2β-Hydroxy-1α-methyl-trans-decalin (43).—1-Methyl-1,9-octalone-2 (7.09 g) was dissolved in 140 ml of ethanol in a 1 liter, 3-necked flask, and the mixture was cooled in an acetone-Dry Ice bath. Liquid ammonia (200 ml) was then condensed in the reaction vessel and sodium metal was added slowly in small pieces to maintain a blue color. The reaction mixture was stirred for 4-1/2 hrs, at the end of which time the cooling bath was removed, and the ammonia was allowed to evaporate. Dilution with water and extraction with ether furnished an organic phase, which was washed successively with 0.1 N sulfuric acid, water, 0.1 N sodium bicarbonate, and saturated sodium-chloride solution. After drying over anhydrous magnesium sulfate, the solvent was removed by evaporation, and 4.96 g of crude product was obtained. Sublimation at 60° and water pump pressure furnished 4.42 g (62%) of nicely crystalline material, mp 55-57°, $\lambda_{\text{max}}$ 2.78, 9.50, 9.68, 9.78 μ. The NMR signal for the methyl group appeared as an unresolved singlet.
Anal. Calc. for $C_{11}H_{20}O$: C, 78.51; H, 11.97.
    Found: C, 78.53; H, 11.88.

The 3,5-dinitrobenzoate prepared as a derivative melted at 162-164° (from methanol)

Anal. Calc. for $C_{18}H_{22}N_{2}O_6$: C, 59.66; H, 6.12; N, 7.73.
    Found: C, 59.32; H, 6.10; N, 7.56.

Preparation of the p-Toluenesulfonyl Derivative (44) of Alcohol (43).--To a solution of 345 mg of the alcohol (43) in 15 ml of anhydrous pyridine, 644 mg of p-toluenesulfonyl chloride was added. The resulting solution was allowed to stand at room temperature for 5 days. At the end of this time, the mixture was poured onto ice, and ether and cold dilute sodium hydroxide solution (0.1 N) were added. The ether layer was separated, washed with water and saturated sodium chloride solution, and finally dried over anhydrous magnesium sulfate. Removal of the solvent furnished 494 mg of crude tosylate, which was twice recrystallized from ligroin, mp 100-100.5°, $\lambda_{\text{max}}^{CS_2}$ 7.33, 8.41, 8.49 μ.

Anal. Calc. for $C_{18}H_{26}O_8$: C, 67.04; H, 8.12; S, 9.94.
    Found: C, 67.00; H, 8.16; S, 9.94.

Preparation of 1β-Methyl-trans-decalin (31) from Tosylate (44).--Lithium aluminum hydride, 242 mg, was suspended in 9 ml of anhydrous ether, and 347 mg of tosylate (44) was added. The mixture was stirred at room temperature for 40 hrs, at the end of which time the excess lithium aluminum hydride was destroyed by careful addition of ethanol. The resulting mixture was diluted with 0.1 N sulfuric acid and extracted with ether. The ether extracts were
washed successively with dilute sulfuric acid, water, dilute sodium hydroxide, water, and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was removed, and the residue was taken up in petroleum ether and filtered through a column of alumina. In this way 66 mg of hydrocarbon was obtained which proved to be identical in all respects (IR, NMR, vpc retention time) with an authentic sample of 1α-methyl-trans-decalin prepared by R.B. Miller.17

Elution of the alumina column with ether yielded 45 mg of alcohol (43).22,23

**Chromium Trioxide-Acetic Acid Oxidation of Alcohol (43).** -- Alcohol (43), 3.42 g, was dissolved in 30 ml of acetic acid, and a solution of 2.18 g of chromium trioxide in 1 ml of water was added. The mixture was stirred for 30 min at 10° and then for 3 hrs at room temperature. At the end of this time, the bulk of the acetic acid was removed under reduced pressure, water was added, and the mixture was extracted with ether. The ether solution was then washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide, and saturated sodium chloride solution. Filtration through anhydrous magnesium sulfate and removal of the solvent afforded 2.80 g of ketone (41), $\text{CS}_2$ 5.83 $\mu\lambda$, methyl doublet centered at $\delta = 0.9$ in the NMR, which showed a single symmetrical peak on vapor chromatography.

The dinitrophenylhydrazone was prepared as a derivative by the following procedure. The liquid ketone (41), 48 mg, was added to a solution of 70 mg of 2,4-dinitrophenylhydrazine in 45 ml of
chloroform and 45 ml of acetic acid which had been purged with nitrogen and cooled to 0°. After standing at 0° for 1-1/2 hrs, the reaction mixture was diluted with 90 ml of water. The chloroform layer was then separated and washed rapidly with dilute sulfuric acid, dilute sodium bicarbonate and water. After filtration through anhydrous magnesium sulfate, the solution was concentrated to a volume of about 2 ml and 25 ml of absolute ether was added. Cooling in a Dry Ice-acetone bath afforded 73 mg of yellow, crystalline product, which was twice recrystallized from ethyl acetate; mp 187.5-189°.

Anal. Calc. for C_{17}H_{22}N_{4}O_{4}: C, 58.94; H, 6.40; N, 16.17.

Found: C, 58.72; H, 6.43; N, 16.25.

Base-catalyzed Equilibration and Deuterium Exchange of Ketone (41).--(a) To a solution of 68 mg of ketone (41) in 5 ml of methanol, 108 mg of sodium methoxide was added. The mixture was allowed to stand at room temperature for 22 hrs, at the end of which time water was added and the product was extracted with ether. The ether layer was washed thoroughly with water and saturated sodium chloride solution. Filtration through anhydrous magnesium sulfate followed by evaporation of the solvent furnished 60 mg of material that proved to be identical (IR, NMR, vpc) with ketone (41).

(b) A 70 mg sample of ketone (41) was treated with sodium methoxide as described in the previous experiment except that deuteromethanol (CH_{3}OD) was substituted for the methanol solvent. The product (59 mg) was isolated as before; \( \chi_{\text{max}} \) 4.7 (weak), 5.83 μ. The material showed a broad singlet at \( \delta = 0.95 \) in the NMR. The
mass spectrum indicated the presence of 82% of a species M + 3 (m.w. 169) and 18% of a species M + 2 (m.w. 168).

Lithium Aluminum Hydride Reduction of Ketone (41).--An excess of lithium aluminum hydride was added to a solution of 208 mg of ketone (41) in 15 ml of ether, and the resulting mixture was stirred at room temperature for 27 hrs. The excess reagent was then destroyed by cautious addition of ethanol and water, and the product was isolated by ether extraction of the acidified mixture. The ether layer was washed successively with dilute hydrochloric acid, water, dilute sodium hydroxide, water, and saturated sodium chloride solution. Filtration through anhydrous magnesium sulfate and removal of the solvent afforded 161 mg of crude material which showed two peaks in a ratio of 1:3 on vapor chromatography.

Column chromatography on alumina (activity II-III) furnished by elution with petroleum ether-benzene (8:2) 30 mg of an amorphous alcohol (45), \( \lambda_{\text{max}}^\text{CS} = 2.78, 10.03, 10.45, 10.68 \mu \). The 3,5-dinitrobenzoate prepared as a derivative melted at 123-125°.

Anal. Calc. for \( \text{C}_{18}\text{H}_{22}\text{N}_{2}\text{O}_6 \): C, 59.66; H, 6.12; N, 7.73.

Found: C, 59.58; H, 6.15; N, 7.96.

Elution of the column with 50-50 petroleum ether benzene gave 95 mg of crystalline material identical in all respects with alcohol (43).

Catalytic Hydrogenation of Ketone (41).--Platinum oxide (80 mg) was added to a solution of 320 mg of ketone (41) in 20 ml of acetic acid. The reaction vessel was connected to a buret system and was stirred magnetically in an atmosphere of hydrogen until hydrogen
uptake ceased (1 hr). The catalyst was removed by filtration, and
the bulk of the acetic acid was distilled off under reduced pressure.
Dilution with water and extraction with ether followed by the usual
washing and drying procedures, yielded 298 mg of crude product which
was separated by chromatography on alumina, as described in the
previous experiment. In this way 207 mg of compound (45) and 51 mg
of alcohol (43) were obtained.

**Chromium Trioxide Oxidation of Alcohol (45).**—A solution of
80 mg of alcohol (45) in acetic acid was oxidized in the presence
of excess chromium trioxide according to the procedure outlined for
the corresponding oxidation of epimer (43). Removal of the bulk of
the solvent by evaporation, dilution with water, and extraction with
ether yielded an organic phase which was washed and dried by the
standard procedure. Evaporation of the ether finally furnished
60 mg of material which was indistinguishable from ketone (41) by
infrared, NMR, and vpc analysis.

**Sodium n-Butoxide Catalyzed Equilibration of Alcohols (43) and
(45).**—(a) A solution of 90 mg of alcohol (43) in 3 ml of dry
n-butanol was added to a solution prepared by dissolving 310 mg of
sodium metal in 4 ml of dry n-butanol. Benzophenone (9 mg) was then
added and the mixture was sealed under vacuum in a small glass tube,
which was immersed in a metal bath at 165-170° for 144 hrs. At the
time this time the reaction tube was cooled, and the contents were
diluted with water and extracted with ether. The ether solution was
thoroughly washed with water and with saturated sodium chloride
solution. After drying over anhydrous magnesium sulfate, the solvent
was removed, and the residue was analyzed by vapor chromatography. Two major peaks showing retention times identical with those of alcohols (43) and (45) were obtained in a ratio of 73 to 27. Chromatography on alumina afforded 19 mg of (45), 46 mg of (43), and 8 mg of unidentified material.

(b) When 60 mg of alcohol (45) was treated in the same manner, 31 mg of (43) and 13 mg of (45) were obtained.

Preparation of Ketal (48).--A solution of 2.40 g of ketone (41) in 40 ml of anhydrous benzene containing 3 ml of ethylene glycol was treated with 180 mg of p-toluenesulfonic acid. The mixture was heated to reflux under a water separator until collection of water had ceased (about 6 hrs). The solution was then cooled, diluted with ether, and washed with dilute sodium hydroxide, water, and saturated sodium chloride solution. Filtration through anhydrous magnesium sulfate and removal of the solvent by evaporation afforded 2.62 g of ketal (48) showing no carbonyl absorption in the infrared. The NMR spectrum contained a methyl doublet centered at δ = 0.9 and a multiplet at δ = 3.9 assigned to the ketal methylene groups. Vpc analysis showed that the sample was substantially pure, but did reveal the presence of traces of ketal (49).

Equilibration of Ketals (48) and (49).--(a). Ketal (48). A 2.53 g sample of ketal (48) was dissolved in 45 ml of dry benzene, and 120 mg of p-toluenesulfonic acid was added. The resulting solution was heated under reflux for 24 hrs at the end of which time the mixture was cooled and diluted with ether. Washing with dilute sodium chloride was followed by filtration through anhydrous
magnesium sulfate. Removal of the solvent furnished 2.43 g of residual material. The NMR spectrum of the crude product revealed two methyl doublets centered at $\delta = 0.9$ and at $\delta = 1.0$, respectively. Vpc analysis showed two major peaks together with about 5% of ketone (41). The main fractions represented ketal (48) and (49) in a ratio of 73 to 22. Preparative separation was accomplished on a Carbowax 20 M column under the following conditions: column temperature, 198º; injector temperature, 250º; collector temperature, 250º; carrier gas flow, 200 ml/min. The retention times were: ketai (48), 32 min, and ketal (49), 34 min, 40 sec. In this way 930 mg of pure ketal (48) was obtained and 280 mg of pure ketal (49). The infrared spectra of the two ketais showed marked differences.

(b). Ketal (49). Equilibration of 25 mg of ketal (49) in 4 ml of dry benzene containing 1 mg of p-toluenesulfonic acid, was carried out by the procedure described in the previous experiment. The products and product ratios were the same as those indicated above.

**Cleavage of Ketal (49).**--A sample ketal (49), 245 mg, was dissolved in 6 ml of acetone, and 15 mg of p-toluenesulfonic acid was added. The mixture was then stirred at room temperature for 10 hrs. The bulk of the solvent was removed on a stream of nitrogen without external heating, and the residue was taken up in ether and washed thoroughly with water and with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the ether was removed at low temperature. The residue consisted of 170 mg of crude ketone, $\lambda_{max}^{CS_2} 5.83 \mu$. Vpc analysis of the cleavage product showed two peaks (ratio 70:30) of which that representing the minor component was
identified as corresponding to the thermodynamically stable ketone (41).

Preparative separation was accomplished on an FFAP column: column temperature, 150°; injector temperature, 200°; collector temperature, 200°; carrier gas flow, 200 ml/min; retention times, ketone (41), 15 min, and ketone (40), 17 min, 30 sec. The NMR spectrum of ketone (40) showed a methyl doublet centered at $\delta = 1.0$.

**Base-catalyzed Equilibration of Ketone (40).**--A 6 mg sample of ketone (40) was dissolved in 2 ml of methanol, and 22 mg of sodium methoxide was added. The reaction mixture was allowed to stand at room temperature for 20 hrs, at the end of which time it was diluted with water and extracted with ether. The ether solution was washed, dried and evaporated yielding a residue which was identified as ketone (41) by infrared and vpc analysis.

**Lithium Aluminum Hydride Reduction of Ketone (40).**--Ketone (40), 42 mg, was dissolved in 10 ml of anhydrous ether to which an excess of lithium aluminum hydride was added. The resulting mixture was stirred at room temperature for 21 hrs. At the end of this time, the excess reducing agent was decomposed by addition of ethanol and water. The product, 38 mg, was isolated by ether extraction followed by the usual washing and drying procedure. Vpc analysis of the crude material ($\lambda_{\text{max}}^\text{CS}_2 = 2.78 \mu\lambda$) indicated the presence of two alcohols which were well differentiated in retention time from alcohols (43) and (45). Reoxidation of the alcohol mixture with chromium trioxide-acetic acid afforded 3 mg of material that proved identical in all respects with ketone (40). No further work was
carried out on the reduction product owing to lack of time and material.

**Preparation of Thioketal from Ketone (41).**—A 290 mg sample of ketone (41) was dissolved in 15 ml of dry benzene to which 3 ml of ethanedithiol and 30 mg of p-toluenesulfonic acid were added. The reaction mixture was then heated at reflux temperature under a water separator until the distillation of water ceased (about 7 hrs). The resulting solution was cooled, diluted with ether, and washed with water, dilute sodium hydroxide, and saturated sodium chloride. After drying over anhydrous sodium sulfate the solvents were removed by evaporation and the residue was thoroughly dried under oil pump vacuum. The amorphous product showed no carbonyl absorption in the infrared, and exhibited a methyl doublet centered at $\delta = 1.15$ in the NMR. A signal attributed to the methylene groups of the thioketal function appeared at $\delta = 3.2$. The sample gave a single peak on vapor chromatography.

**Attempted Equilibration of the Thioketal.**—The thioketal obtained in the preceding experiment (342 mg) was dissolved in 25 ml of benzene. p-Toluenesulfonic acid (30 mg) was added, and the mixture was heated under reflux for 30 hrs. The product was isolated as described above. Examination of the material by infrared, NMR, and vpc showed no substantial change as compared with the starting thioketal.
Desulfurization of the "Equilibrated" Thioletal.--A 68 mg sample of thioletal recovered from the previous experiment was dissolved in 40 ml of ethanol and treated with freshly prepared Raney nickel obtained from 4.0 g of Raney alloy. The mixture was heated to reflux temperature for 8 hrs, at the end of which time the catalyst was removed by filtration, and the filtrate was concentrated to small volume. The product (18 mg) was isolated by water dilution and ether extraction, followed by the usual washing and drying procedures. Vapor chromatographic analysis showed two peaks with retention times identical with those of compounds (32) and (35). Integration indicated the presence of 88% of (32) and 12% of (35).

Preparation of Cholest-3-ene$^{30}$ $\Delta^4$-Cholest-3-one (8.0 g) was dissolved in 100 ml of diethylene glycol to which 5 ml of 85% hydrazine hydrate and 3.5 g of potassium hydroxide were added. The mixture was heated under reflux for 1 hr at the end of which time the reflux condenser was removed and the reaction temperature was raised to 190°. Reaction was continued at the higher temperature for an additional 4 hrs. The mixture was then cooled, acidified, and extracted with 300 ml of petroleum ether. The resulting organic phase was washed with water, dilute sodium carbonate solution, and saturated sodium chloride. Drying over anhydrous magnesium sulfate and evaporation of the solvent furnished 6.5 g of crude yellow oil, which was chromatographed on 350 g of alumina. Elution with petroleum ether furnished 450 mg of crystalline material. A pure sample, 205 mg, mp 73-74°, $\lambda_{max}^{CCl_4} 6.2 \mu$, was obtained after four recrystallizations from ether-methanol.
Preparation of 3α,4α-Epoxysterolone.**-To 203 mg of cholest-3-ene there was added 3 ml of a solution of monoperphthalic acid in ether (0.4 mmols of peracid per ml). The mixture was stirred in the dark for 100 hrs and was then diluted with ether and washed with dilute sodium hydroxide and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the ether was removed under reduced pressure to give 106 mg of crude product, mp 106°. The melting point was raised to 116-117° by two recrystallizations from methanol (lit.** mp 117-118°). The infrared spectrum was identical with that given in the literature.**

Preparation of Ketone (51).--The epoxide prepared above (193 mg) was treated with 20 ml (excess) of an ethereal solution of methyl lithium obtained from the Foote Chemical Co. After heating under reflux for a period of 3 days, the excess reagent was destroyed by the addition of wet ether. The ethereal solution was then washed with water, and after drying and evaporation of the solvent 109 mg of crude product was obtained, which showed hydroxyl absorption in the infrared. Chromatography on alumina furnished 70 mg of starting epoxide and 70 mg of an alcohol, mp 138-141°.

The alcohol (46 mg) was dissolved in 2 ml of acetic acid and 14 mg of CrO₃ in 2 drops of water was added. The mixture was allowed to stand at room temperature for 4 hrs. At the end of this time, water was added and the product was extracted with ether. The ether phase was thoroughly washed with water, and was dried over anhydrous magnesium sulfate. Removal of the solvent furnished 37 mg of ketone which melted at 130-135° after crystallization from
acetic acid, $\lambda_{\text{max}}^{\text{CS}_2}$ 5.83 $\mu$. Recrystallization from ether-petroleum ether gave a sample melting at 132-136°. A mixed melting point with cholestan-3-one was depressed to 104-122°.

**Epimerization of Ketone (51).**--Ketone (51), 34 mg, was dissolved in 2 ml of methanol and 50 mg of sodium methoxide was added. The reaction mixture was allowed to stand at room temperature for 8 hrs, at the end of which time water was added, and the product was extracted with ether. The ethereal solution was washed, dried, and evaporated, and the residual material was finally chromatographed on basic alumina. There was obtained 26 mg of a fraction, mp 114-120°, which on recrystallization from ether-petroleum ether afforded a pure sample of $\alpha'$-methylcholestan-3-one (52), mp 121-123° (lit. $^{13}$ mp 122-122.5°). Mixed melting point determinations with ketone (51) and with cholestan-3-one were depressed to 102-116° and 114-123°, respectively.
REFERENCES


