CHAPTER II
LONG RANGE SHIELDING BY AN ALKYL GROUP
INTRODUCTION

It has been known since long\textsuperscript{1,2} that axial protons in cyclohexane ring resonate at higher field than the equatorial protons. It was generally believed\textsuperscript{1,2} that this shielding or deshielding is due to the $C_2-C_3$ bond which shields the axial proton and deshields the equatorial proton (Fig. 1).

![Fig. 1](image)

Long range shielding in cyclohexane

Bhacca and Williams\textsuperscript{3} have summarised the shielding and deshielding of ring protons of cyclohexane by replacement of one axial or equatorial hydrogen by different functional groups such as hydroxyl, acetoxy, thiol etc. Since then several studies of this type have been made.

Studies involving shielding and deshielding by alkyl substituents is comparatively more recent.
In a detailed study of the anisotropy of the C-C single bond, Zürcher\(^2\) supplied a possible explanation for such shielding and deshielding.

However, by a very careful analysis of the effects of alkyl substituents on ring protons in different cyclohexanols Elieel et al\(^4\) demonstrated that shielding is not the contribution of the anisotropy of C-C single bond alone; the major contribution to such shielding is due to the syn-axial hydrogens which implies a contribution by the anisotropy of the C-H bond. This suggestion is in direct contrast to an opinion\(^1\) that the C-H anisotropy would not have any significant contribution.

The results obtained by Elieel et al and corroborated by other workers\(^5,6\) are briefly summarized below.

An equatorial methyl group causes a shielding of the equatorial hydrogens on the adjacent carbon by +17 cps (+ = shielding); and on C\(_3\)-equatorial hydrogen it has a negligible effect. (−1 cps). This methyl group causes a shielding of axial hydrogen at C\(_2\) by 28 cps, whereas there is a small deshielding effect (≈2 cps) on C\(_3\) axial hydrogen. Fig. 2 summarises these results.
Effect of equatorial methyl on protons of a cyclohexane ring.

A very significant finding was the observation that the shielding is not uniform for different alkyl groups. Thus an equatorial alkyl substituent has different shielding effects on the adjacent axial proton, the shielding being 28, 21, 11 and 2 cps when the alkyl group is a methyl, ethyl, isopropyl and t-butyl respectively.

Similar values have been observed in cyclohexylamines\(^7\) and phthalimido cyclohexanes\(^7\).

The different effects observed for alkyl substituents is even more dramatic when one considers the effect of the equatorial methyl on the vicinal equatorial proton. Two series in which this has been well established are the 2 alkyl cyclohexyl amines\(^7\) and the nea-menthols\(^8\) which suggests that the magnitude of shielding is in the order: methyl + 24 cps >> ethyl, n-propyl, n-butyl (+12 cps) > isopropyl, cyclohexyl (0.4) > t-butyl (-12 cps). In this series therefore t-butyl causes an appreciable deshielding.

An axial methyl group causes a large shielding (+24 cps) of the adjacent equatorial proton whereas it deshields both the C\(_2\)-axial hydrogen (-12 cps) and the C\(_3\)-axial
hydrogen (-11 cps). In quinalizidines the deshielding of the C₃-axial proton has been found to be 15 cps. The axial methyl also deshields (~ 5 cps) the C₃-equatorial proton. Fig. 3 summarises these results.

Fig. 3
Effect of axial methyl on remaining cyclohexyl protons

Such effects have been used by Booth to explain several very interesting results in disubstituted cyclohexanes and some cis-decalin derivatives.

In order to ensure that their systems did not have conformational mobility Bliel et al. had chosen examples wherein one of the substituents was large enough (isopropyl or t-butyl) to prevent ring flip; as this substituent preferred to exist in the equatorial geometry, the orientation of other substituents was also fixed.
To have some examples in rigid skeletons wherein these effects would be more useful in assigning the geometry to a methyl group in an unknown structure, the present investigations chose examples from steroid and santonin field in which the configurations have been rigorously established.

Present Work

The work described in this chapter can be considered in two sections. In the first of these, preparation of suitable compounds having a rigid skeleton is described. In the second the spectral shifts observed through long range shielding by alkyl groups is discussed.

Preparation of suitable compounds

Cholestanol, its acetate and methyl ether were prepared by known procedures37 starting from cholesterol.

Lupeol was obtained in a pure state through chromatography of a mixture rich in lupeol*. The lupeol thus isolated was characterised by its physical constants and spectral data. Its hydrogenation over Adam's

* We are indebted to Mr. C. Quasim of this laboratory for this sample.
catalyst as described by Heilbron et al\textsuperscript{3} afforded lupanol (XIV, $R = OH$).

![Chemical Structure](image)

Lupanol acetate (XIV, $R = OAc$) was prepared by the usual method while the methyl ether (XIV, $R = OMe$) was prepared by a method modified by Narayanan and Iyer\textsuperscript{10}.

The santonin alcohol represented by (V, $R = OH$) has been prepared earlier\textsuperscript{11} by hydrogenation of $\alpha$-santonin using platinum oxide and acetic acid\textsuperscript{*}. However in this method the formation of another compound is also reported\textsuperscript{11}. The purification of the desired alcohol being achieved through its acetate. In our hands this method gave, as reported, the alcohol (IV) in about 10% yield as an ether insoluble residue. Its NMR clearly demonstrated this structure, as the $C_6$ proton appears as a quartet.

\textsuperscript{*} This major alcohol (M.P. 110-111\textdegree) obtained in this reduction was characterised by Cocker and McMurry\textsuperscript{11} as 3\textalpha-hydroxy 4,5 $\alpha$(H) 6,11 $\beta$(H)-eudesman 6-13-olide, but recently\textsuperscript{12} it has been established beyond doubt by NMR studies of the acetate and alcohol that the $C_6$ proton is axial. Rotational changes\textsuperscript{11} from alcohol to acetate and steric considerations\textsuperscript{11} also support this finding.
centered at 264 cps ($J = 10$ and 4 cps). The C$_6$ axial hydrogen has a vicinal C$_7$-axial proton which would account for the 10 cps coupling while the small (4 cps) coupling should be due to coupling with the C$_6$ equatorial proton. The C$_3$ proton appeared as a narrow signal ($WH = 7$ cps) at 225 cps. Its position and nature indicates that this proton is equatorial.

Crystallisation of the ether soluble portion gave the desired alcohol ($V, R = OH$) in comparatively low yield (55%). Besides, the melting point (low by $3,4^\circ$) suggested that this sample was not very pure.

An alternate method, involving hydrogenation of santonin to tetrahydrosantonin (II) using 2% Pd/SrCO$_3$, and reduction of the tetrahydrosantonin on platinum oxide in acetic acid, exclusively furnished the required alcohol $V$ ($R = OH$) of high purity. This gave the reported physical constants. When the hydrogenation of tetrahydrosantonin (II) was carried out, with the same solvent and catalyst, under pressure (60 psi) the corresponding acetate ($V, R = OAc$) could directly be obtained in 79% yield.

Reduction of tetrahydrosantonin to corresponding alcohol ($V, R = OH$) could also be achieved by sodium borohydride$^{13}$ (Chart 1).
**Chart 1.**

1. **Reaction 1:**
   - **Product:** IV
   - **Reagents:** PtO₂/AcOH
   - **Condition:** Ether insoluble

2. **Reaction 2:**
   - **Product:** V (R=OH)
   - **Reagents:** PtO₂/AcOH, NaBH₄

3. **Reaction 3:**
   - **Product:** V (R=OMe)
   - **Reagents:** K/Mel, benzene, Ac₂O/pyridine

4. **Product V:**
   - **Structure:**
   - **Reagents:**
     - PtO₂/AcOH (60 psi)
     - PtO₂/MeCO (R=OAc)
     - PtO₂/MeCO (R=OMe)
The methyl ether of this alcohol was prepared by treatment with potassium and methyl iodide as reported earlier.\textsuperscript{10} It may be pointed out that alkali formed in destroying excess of potassium with methanol opens the lactone ring, to the hydroxy acid, to some extent. It is therefore necessary to acidify and warm the mixture after destroying potassium. The yield of methyl ether is low. This methyl ether was characterised by its infrared spectrum which had no hydroxyl absorption but displayed characteristic absorption for an aliphatic ether (1108 cm\textsuperscript{-1}) and a \ce{\gamma}-lactone (1770 cm\textsuperscript{-1}). The NMR spectrum (Fig. 4) showed the $C_3$-proton as a broad signal at 195 cps (axial proton). The NMR spectrum also revealed the methoxy methyl at 200 cps as a sharp singlet. The $C_6$ proton appeared as a triplet ($J = 10$ cps). These couplings represent axial-axial couplings with $C_5$ and $C_7$ hydrogens. This not only shows the intact lactone but also established that no change has taken place in the stereochemistry of the lactone. The $C_{10}$ methyl appeared at 63.5 cps while $C_4$ and $C_{11}$ secondary methyls appeared as doublets centered at 73 and 53.5 cps respectively ($J = 7$ cps each). This and the elemental analysis clearly established that this is the desired methyl ether ($V$, $R = \text{OMe}$).
FIG. 4. NMR SPECTRUM OF 3β-METHOXY-4,5α(H), 6-11β(H)-EUDESMAN-6-13-OLIDE

FIG. 5. NMR SPECTRUM OF 3β-METHOXY-5α(H), 4, 6, 11β(H)-EUDESMAN-6-13-OLIDE
In order to obtain the hydroxy lactone with a 4α methyl group (VI, R = OH), tetrahydro santonin (II) was converted to tetrahydro santonin (III) by acid catalysed epimerisation\(^\text{14}\) at C\(_4\). Reduction\(^\text{11}\) of this ketone (III) with sodium borohydride gave the 3β-alcohol (VI, R = OH) as the major product (81%). Inverted dry column chromatography\(^\text{16}\) of mother liquors afforded the C\(_3\) epimer (VII, R = OH) in low yield (15%). Catalytic reduction of the above ketone however furnished the C\(_3\)-α epimer in 42% yield. (Chart 2)\(^2\)

Acetylation of VI (R = OH) was comparatively easy whereas that of VII (R = OH), because of its axial geometry, required more drastic conditions.

The methyl ether (VI, R = OMe) was prepared from the corresponding alcohol by the usual method. Its yield was poor; though appreciable starting material was recovered. This compound was characterised by its I.R. spectrum which displayed ether absorption at 1096 cm\(^{-1}\) and absence of any hydroxyl band. The band at 1770 cm\(^{-1}\) could be assigned to the intact γ lactone. The NMR data (Fig. 5) given in Table 1 also confirms its structure.

In the case of VII (R = OMe) solvolysis of the mesylate\(^\text{16}\) (VI, R = OMeS) provided a convenient route for the preparation of this compound.

This solvolysis afforded a mixture of two products besides the unreacted mesylate. Separation by column chromatography over silica gel provided in earlier benzene
CHART - 2

II \[ \xrightarrow{\text{PTS acid/\text{AcOH} or HClO}_4/\text{ethanol}} \] III

\[
\begin{align*}
\text{PtO}_2 & \quad \text{AcOH} \\
\text{NaBH}_4 & \\
15\% & \quad 81\%
\end{align*}
\]

\[ \text{Ac}_2\text{O/Pyridine} \]

VII, \( R=\text{OAc} \)

VI, \( R=\text{OMeS} \)

VI, \( R=\text{OMe} \)

VI, \( R=\text{OAc} \)

\[ \xrightarrow{\text{CH}_2\text{SO}_2\text{Cl/Pyridine}} \]

\[ \xrightarrow{K/\text{Me}_2\text{N/Pyridine}} \]

\[ \xrightarrow{\text{Ac}_2\text{O/Pyridine}} \]

dry methanol 88 hrs.

VII, \( R=\text{OMe} \)

VIII
fractions a crystalline solid m.p. 146-47°, $[\alpha]_D + 21^\circ$ whose I.R. spectrum indicated an intact lactone (1775 cm$^{-1}$) and olefinic absorption (1660 cm$^{-1}$) which must be cis disubstituted (690 cm$^{-1}$). The NMR spectrum (Fig. 6) provided incisively that this olefin is the $\Delta^2$ olefin (VIII) as it showed a very characteristic AB quartet centered at 330 cps ($J = 11$ cps, AB 11.5 cps). Apart from this quartet one quaternary methyl (singlet at 57 cps), one doublet (6H, centered at 72 cps, $J = 7$ cps) and a proton on carbon carrying oxygen (triplet at 228.5 cps $J = 10$ cps) could be detected.

The later benzene fractions gave the methyl ether (VII, R = OMe). Its IR spectrum displayed bands at 1770 cm$^{-1}$ (lactone) and 1097 (OCH$_3$). The detailed analysis of the NMR spectrum (Fig. 7) shown in Table 1 established its structure.

**Table 1**

Analysis of the NMR spectra of the methyl ether VI (R = OMe) and VII (R = OMe)

<table>
<thead>
<tr>
<th>Line position</th>
<th>Nature</th>
<th>No. of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>205 in VI, 200 in VII</td>
<td>Singlet</td>
<td>3H</td>
<td>Methoxyl methyl</td>
</tr>
<tr>
<td>230 in VI, 229 in VII</td>
<td>Triplet (J=10 cps)</td>
<td>1H</td>
<td>$C_6$-H</td>
</tr>
<tr>
<td>158 in VI, 190 in VII</td>
<td>Broad in VI Narrow in VII</td>
<td>1H</td>
<td>$C_3$-H</td>
</tr>
<tr>
<td>61 in VI, 59 in VII</td>
<td>Singlet</td>
<td>3H</td>
<td>$C_{10}-CH_3$</td>
</tr>
<tr>
<td>72, 74 in VI, 69, 71 in VII</td>
<td>Doublets (J=7 cps)</td>
<td>3H each</td>
<td>$C_{11}^-$ and $C_4$-CH$_3$</td>
</tr>
</tbody>
</table>
FIG. 6 NMR SPECTRUM OF 5α(H) 4,6,11β(H)-EUDESMAN-2-en-

6-13 OLIDE (VIII)
FIG. 7. NMR SPECTRUM OF 3α-METHOXY 5α(H), 4, 6, 11β(H)-
EUDESMAN-6-13 OLIDE
The best known method\textsuperscript{17} for preparing epicholesterol is the hydrogenation of cholestan-3-one in acid medium. Though yields up to 70\% have been reported by this method, in the present investigation the yield of epicholesterol was rather poor (\textunderscore 17\%). The only change that was made being the replacement of dibutyl ether by di-isopropyl ether as a solvent.

In view of this an alternate method starting from cholestanyl tosylate was preferred. In this reaction cholestanyl tosylate (IX, $R = OTs$) was subjected to formolysis with dimethyl formamide. It has been reported\textsuperscript{18} that the ratio of epi-cholestanyl formate (X, $R = OCHO$) to the $\Delta^2$ olefin (XI) is 3:1. We were however able to get the formate in 60\% yield. Hydrolysis of the formate (characterised by its physical constants and spectral data) afforded epi-cholestanol (X, $R = OH$) in quantitative yield.

In view of the known difficulty to acetylate epicholesterol\textsuperscript{19}, epicholesterol acetate (X, $R = OAc$) was directly prepared by the action of a mixture of $\text{BF}_3$ etherate and acetic anhydride on cholestanyl methyl ether\textsuperscript{13} (IX, $R = OMe$) at $0^\circ$ for fifteen hours. From the resulting mixture of products (Chart 3) the required acetate (X, $R = OAc$) was isolated in (27\%) by Inverted dry column chromatography\textsuperscript{15}, along with the epimeric acetate (IX) and $\Delta^2$ olefin (XI).
CHOLESTAN-3 ONE

\[ \text{CHOLESTAN-3 ONE} \xrightarrow{\text{H}_2/\text{Pt}, \text{HBr}} \text{Di-iso propyl ether} \]

\[ \begin{align*}
  &\text{R} + \text{R} \\
  &\text{17%} + \text{80%}
\end{align*} \]

\[ \text{X, R=OH} \quad \text{IX, R=OH} \]

\[ \begin{align*}
  &\text{IX, R=OTs} \\
  &\text{DMF, 78°, 24 hrs.}
\end{align*} \]

\[ \begin{align*}
  &\text{R} + \text{R} \\
  &\text{60%} + \text{X}
\end{align*} \]

\[ \text{X, R=OCHO} \quad \text{XI} \]

\[ \begin{align*}
  &\text{R} + \text{R} \\
  &\text{X, R=OMe} \\
  &\text{X, R=OH}
\end{align*} \]

\[ \begin{align*}
  &\text{IX, R=OMe} \\
  &\text{BF}_3 \text{Etherate/} \text{Ac}_2\text{O} \\
  &0°, 15 hrs.
\end{align*} \]

\[ \begin{align*}
  &\text{R} + \text{R} + \text{R} \\
  &\text{X, R=OAc} \quad \text{IX, R=OAc} \quad \text{XI}
\end{align*} \]
When cholestanyl tosylate (IX, R = OTs) was subjected to methanolysis under the conditions reported by Nace\(^1\), the major product (73\% (Chart 3) is the desired methyl ether (X, R=OMe) characterised by its physical constants.

In applying the above reactions to get 3\(\alpha\) epimers in 4\(\beta\) methyl santoinin derivatives, the mesylate (V, R = OMeS) was refluxed with methanol to get the methyl ether formed through inversion at C\(_2\). However in practice it was observed that the product of the above reaction contained apart from a large amount of unchanged mesylate two other compounds (TLC). Separation of this mixture by chromatography over silica gel gave all three compounds in pure form.

The fastest moving of these (XIII) had infrared vibration corresponding to \(\gamma\) lactone (1775 cm\(^{-1}\)) and a tri-substituted olefin (1650, 790, 860 cm\(^{-1}\)). The NMR spectrum (Fig. 8) of this had signals ascribable to a quaternary methyl (singlet 55.5 cps) a secondary methyl (doublet at 72 cps; \(J = 7\) cps), a vinylic methyl (broad singlet at 110 cps), a proton on a carbon carrying oxygen (multiplet at 233 cps) and an olefinic proton (multiplet at 325 cps). The presence of slight traces of \(\Delta^2\) olefin in this compound could be established by the minor signals at 62.5 and 335 cps*.

---

* An authentic specimen of \(\Delta^2\) olefin has important signals at this position.
FIG. 8. NMR SPECTRUM OF 5α(H) 6,11β(H)-EUDESM 3-en-

6-13-Olide (XIII)
The latter fractions after crystallisation showed IR vibration for γ lactone (1780 cm\(^{-1}\)) and an exomethylene group (1660, 830 cm\(^{-1}\)).

The NMR spectrum (Table 2, Fig. 9) analysed well for a \(\Delta^4\) (14) olefin (XII, Chart 4).

### Table 2

<table>
<thead>
<tr>
<th>Line position</th>
<th>Nature of the signal</th>
<th>No. of protons</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>51.5 cps</td>
<td>Singlet</td>
<td>3</td>
<td>(\text{C}_{10})-CH(_3)</td>
</tr>
<tr>
<td>72.5 cps</td>
<td>Doublet ((J = 7))</td>
<td>3</td>
<td>(\text{C}_{11})-CH(_3)</td>
</tr>
<tr>
<td>238 cps</td>
<td>Triplet ((J = 10) cps)</td>
<td>1</td>
<td>(\text{C}_6)-H</td>
</tr>
<tr>
<td>286</td>
<td>Broad signals</td>
<td>1</td>
<td>Exomethylene protons</td>
</tr>
<tr>
<td>296</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Methanalysis of tosylate (\(V, R = \text{OTs}\)) or formolysis of mesylate (\(V, R = \text{OMeS}\)) afforded mixtures, NMR analysis of which suggested once again the same mixture of olefins without any formation of the desired methyl ether or formate respectively.

It is conceivable that in order to have suitable trans-anti geometry these compounds may pass into a conformation in which the A ring is a boat. Formation of a boat (A, Chart 5) in the transition state would be aided by the energy release arising from a relief of
FIG. 9 NMR SPECTRUM OF 5α(H) 6.11β(H) EUDESM-4(14)-en-6-13 OLIDE (XII)
CHART - 4

$CH_3SO_2Cl$ / Pyridine

$V, R = OH$

$\text{Methanol} / 90 \text{ hrs.}$

$DMF, 78^\circ$

$V, R = OMeS$

$R = oT$
CHART - 5
1:3 dixial methyl-methyl interactions (B). If such a boat transition state (A) can be invoked then those molecules which acquire sufficient energy to reach the transition state can easily undergo trans elimination to afford the $\Delta^3$ or the isomeric $\Delta^4$ olefin. This transition state would explain the almost total absence of $\Delta^2$ olefin in this reaction. It may be relevant to point out that the corresponding 4-methyl derivative (C) gave only the $\Delta^2$ olefin as the elimination product. A boat intermediate (D) in this later case would not have any steric relief as there is no relief of dixial interaction as in the present case and instead the $C_4$-methyl now has 1:3 interaction with 2-methyl hydrogen in the boat conformation (Chart 5). This therefore will undergo more solvolysis and less elimination.

Epilupanol acetate (XV, R = OAc) was obtained by hydrogenation of epilupeol acetate*. Prolonged hydrolysis of the acetate furnished epilupanol (XV, R = OH) in good yields. Attempted methylation of the small sample available did not afford the desired methyl ether and starting alcohol was recovered even under drastic conditions.

Attempts at preparing 3-methyl ether of lupanol by methanolysis$^{21,22}$ of the 33 tosylate were unsuccessful.

* We are grateful to Prof. T. R. Govindachari of Ciba Research Centre, Bombay for the sample of this compound.
(NMR of crude product obtained did not show any peak for OCH₃).

\[ \text{R} = \text{OTs} \quad \text{XIV} \]

\[ \text{R} = \text{OMe} \quad \text{XV} \]

It may be mentioned in summing up that of the series of compounds whose preparation was undertaken no derivatives corresponding to \(3-\alpha R, 4,8-\alpha(H) 6,11 \beta(H)\) eudesman 6-13 oxide \( (R = \text{OH, OAc or OMe}) \) could be obtained. Epilupanol methyl ether also could not be obtained.

**Spectral Shifts**

The NMR spectrum of cholestanol \((\text{IX, } R = \text{OH})\) shows the C₃ hydrogen signal as a broad multiplet centred at 215.5 cps, whereas in lupanol \((\text{XIV, } R = \text{OH})\). This proton signal appears as quartet centred at 191 cps (Table 3). Overall, there is therefore, a shielding of 24.5 cps by introduction of the gem-dimethyl group at C₄. It is obvious that other differences in the structure of lupanol and cholestanol would not have any effect on the signal of the C₃ hydrogen because these changes are very far removed from the centre, at present, under consideration.
### TABLE 3

**SHIFT OF C₃-AXIAL PROTON BY ADJACENT METHYL GROUP**

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Chemical shift in Alcohol</th>
<th>Acetate</th>
<th>Methyl ether</th>
</tr>
</thead>
<tbody>
<tr>
<td>IX</td>
<td><img src="image" alt="Compound IX" /></td>
<td>215.5</td>
<td>281</td>
<td>187</td>
</tr>
<tr>
<td>V</td>
<td><img src="image" alt="Compound V" /></td>
<td>225</td>
<td>287</td>
<td>196</td>
</tr>
<tr>
<td>VI</td>
<td><img src="image" alt="Compound VI" /></td>
<td>186</td>
<td>261</td>
<td>158.5</td>
</tr>
<tr>
<td>XIV</td>
<td><img src="image" alt="Compound XIV" /></td>
<td><strong>Observed values</strong></td>
<td><strong>Calculated values</strong></td>
<td><strong>Difference</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>191</td>
<td>264</td>
<td>158.5</td>
</tr>
</tbody>
</table>
To determine the contributions of each of these methyls the spectrum of santonin derivative (VII, R = OH) having C₃-equatorial hydroxyl and C₄-β-methyl (axial) was examined. In the spectrum of this compound the C₃ hydrogen resonates at 225 cps (broad multiplet). Thus the introduction of β-methyl at C₄ causes deshielding of 9.5 cps on C₃-axial hydrogen. The C₄-enimer of this compound (VII, R = OH) displayed (Fig. 10) its C₃ hydrogen as a broad multiplet centered at 186 cps, thus causing a shielding of the C₃-axial hydrogen by 29.5 cps+ as compared to cholestanol. These values are in good agreement with the reported values (axial methyl deshields the axial proton on adjacent carbon atom by ~12 cps and equatorial methyl shields it by ~28 cps) of such effects in cyclohexane derivatives. This agreement suggests that a comparison of cholestanol and santonin derivatives is justified.

If one assumes that these values are additive then the C₃-proton signal in lupanol (XIV, R = OH) would be expected to be shielded by 20 cps as compared to cholestanol (i.e. is at 196 cps). Using earlier values this shielding would be expected to be 16 cps (i.e. the resonance should be

+ It would be obvious that more accurate comparison can be made if 4α-methyl and 4β-methyl cholestanol are examined but the more readily available santonin derivatives were used because in these ring A has essentially the same features as cholestanol. Ring B substituents are too far from the C₃-hydrogen to have any significant effect.
FIG. 10. NATURE OF C₃–H IN EQUATORIAL ALCOHOLS

R=OH

(a) in IX (b) in V (c) in VI
at 199 cps). The slight deviation between expected and observed values may indicate that additivity is not necessarily first order.

Similar comparisons of the acetates (Fig. 11) and methyl ethers of these derivatives (Table 3) would require the C₃-H in corresponding lupanol derivatives to resonate at 267 and 166.5 cps respectively; the observed resonances are at 264 and 158.5 cps respectively.

An examination of the differences between calculated and the observed values for lupanol derivatives brings out the fact that in all cases the observed values are at slightly higher field than the calculated ones. Another interesting observation is that shifts in the acetates are of lesser magnitude than the alcohols and methyl ethers.

With a view to observe similar effects on equatorial protons, derivatives epimeric at C₃ were examined (Table 4).

Epicholestanol (X, R = OH) has the resonance of its C₃-hydrogen at 243 cps as a narrow signal indicating its equatorial nature. The corresponding 4α-methyl santonin derivative (VII, R = OH) had its C₃-H resonance (Fig. 12) as a narrow signal at 228.5 cps. This corresponds to a shielding of the vicinal equatorial proton by an equatorial methyl by 14.5 cps. The previously reported value for such a shielding is 17 cps. The corresponding 4β-methyl santonin derivative could not be prepared though several attempts (see experimental section) in this direction had been made.
FIG. 11. NATURE OF C₃-H IN EQUATORIAL ACETATES R = OAc

(a) in IX  (b) in V  (c) in VI
FIG. 12. NATURE OF C$_3$-H IN AXIAL ALCOHOLS R=OH

(a) in X (b) in XV (c) in VII
If one uses the literature value of +24 for such a shielding (equatorial hydrogen by adjacent axial methyl) the calculated value for C₃-proton of epilupanol (XV, R = OH) would be 208 cps. The observed signal for C₃-H at 203 cps in epilupanol is therefore in good agreement. The analogous shift value for the acetate is also presented in Table 4.

Using these ideas the calculated value for C₃-H of epilupanol methyl ether (XV, R = OMe) would be 166 cps. Though several attempts to prepare this compound were made, these were not successful. It can however be anticipated that in epilupanol methyl ether the C₃-hydrogen should resonate at ~166 cps.

If one looks at the C₆-hydrogen in different santonin derivatives, then it would be anticipated that though this hydrogen is in a different ring as compared with the C₄-methyl, its spatial relationship with C₄ is exactly identical with the spatial relationship of the C₂ axial hydrogen with the C₄-methyl, if the methyl at C₄ is β oriented. It can therefore be expected that this C-6 hydrogen would feel a similar long range effect of the 4β-methyl as the C₂-axial hydrogen. Eliel et al.⁴ have shown that an axial methyl deshields the axial hydrogen, which is in a cis 1:3 relation with it, by 11 cps. It can therefore be argued that the C₆-hydrogen of santonin derivatives having a 4β-methyl group would be deshielded by ~11 cps in comparison with santonin compounds having no methyl at this position.
### TABLE 4

**SHIFT OF C₃ EQUATORIAL PROTON BY ADJACENT METHYL GROUP**

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Chemical shift in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td>X</td>
<td><img src="image" alt="Compound X" /></td>
<td>243</td>
</tr>
<tr>
<td>VII</td>
<td><img src="image" alt="Compound VII" /></td>
<td>228.5</td>
</tr>
<tr>
<td></td>
<td>Shift caused by C-4 equatorial methyl</td>
<td>+14.5</td>
</tr>
<tr>
<td></td>
<td>Literature shift by axial methyl on adjacent equatorial proton</td>
<td>24</td>
</tr>
<tr>
<td>XV</td>
<td><img src="image" alt="Compound XV" /></td>
<td>Observed values: 203, 278</td>
</tr>
<tr>
<td></td>
<td>Calculated values: 204.5, 274, 166.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diff.: +1.5, -4</td>
<td></td>
</tr>
</tbody>
</table>
FIG. 13. NATURE OF $C_3$-$H$ IN AXIAL ACETATES  R =OAc

(a) in X  (b) in XV  (c) in VII
The position regarding the C₄-equatorial methyl and this hydrogen is not the same in comparison with the C₂-axial hydrogen and C₄-equatorial methyl group. This distance in the former is only $3.2^0_A$ whereas in the latter it is $4.0^0_A$. As the relative geometries are however the same the difference between the effects on these two hydrogens should be essentially one of magnitude. Eliel et al have shown⁴ that in such a situation there is a deshielding of 2 cps. It can therefore be expected the C₆-hydrogen should also feel deshielding due to equatorial C₄-methyl which may perhaps be slightly larger (~ 3 cps).

From this rationalisation it can be expected that in those santoin derivatives (V,XVII) having an axial C₄-methyl, the C₆-hydrogen should be at ~ 8 cps lower field than the corresponding santoin derivatives having a C₄-equatorial methyl. Table 5 demonstrates the validity of this argument and elegantly shows how an understanding of these effects could help in establishing stereochemical assignments for unknown compounds.
### TABLE 5

**SHIFT OF C₆-AXIAL PROTON**

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Chemical shift in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td>V</td>
<td><img src="image0" alt="Structure V" /></td>
<td>240</td>
</tr>
<tr>
<td>VI</td>
<td><img src="image1" alt="Structure VI" /></td>
<td>231</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>9</td>
</tr>
<tr>
<td>XVI</td>
<td><img src="image2" alt="Structure XVI" /></td>
<td>R = 0: 232</td>
</tr>
<tr>
<td>XVII</td>
<td><img src="image3" alt="Structure XVII" /></td>
<td>238</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>6</td>
</tr>
</tbody>
</table>
Reasons for different shifts:

Elie! et al\(^4\) had suggested on the basis of very large differences in shielding of proton by adjacent methyl, ethyl, isopropyl and t-butyl that the carbon-carbon bond anisotropy is not the only factors and that a very important role in shielding, is played by syn-axial hydrogens. They even considered that each syn-axial hydrogen causes a shielding of ~ 20 cps. However they were unable to explain how an equatorial methyl has different shielding effects on adjacent equatorial and axial hydrogens.

If one carefully examines this particular example one can see the presence of one syn-axial hydrogen in both the cases (XVIII and XIX) in the preferred conformation wherein

(XVIII) \hspace{2cm} (XIX)
the methyl group is staggered in relation to the carbon carrying it. In both XVIII and XIX the two other hydrogens of the methyl group are placed at a dihedral angle of $120^\circ$ with the concerned axial and equatorial protons respectively. The new carbon-carbon bond is placed at an angle of $60^\circ$ with respect to the axial and equatorial hydrogens of the adjacent carbon. It is therefore very difficult to rationalise how the shieldings by this methyl on adjacent axial and equatorial hydrogens are 28 and 17 cps respectively even if one considers the anisotropy of both carbon-carbon and carbon-hydrogen single bonds.

In agreement with this qualitative reasoning very recently Apsimon et al.\textsuperscript{23} calculated the shifts caused in these two compounds and obtained values of +19.5 and 19.8 respectively, using a modified McConnell equation\textsuperscript{25} and anisotropies based on the values of suitable alkyl cyclohexanols measured by Elie1 et al.\textsuperscript{4} and Musher\textsuperscript{5}.

Using different anisotropy values, obtained from the chemical shifts of axial and equatorial protons of cyclohexane and equation derivatived by Zürcher\textsuperscript{2} and Buckingham, Prechard and Whiffen\textsuperscript{24}, they obtained a second set of shift values which are 13.4 and 13.7 respectively.

\* This work of Ap-Simon et al appeared after most of our results had been completed and attempts to explain in a mathematical manner, the shifts observed through long range effects of methyl group and does not affect the qualitative arguments that are presented by us.
It is thus clear that no suitable explanation for the different shifts caused by an equatorial methyl on adjacent axial (XVIII) and equatorial (XIX) protons can be, as yet advanced.

If we consider the shielding caused by an axial methyl group on the adjacent protons, then examination of models show that the equatorial proton (XX) has a syn-axial relationship with one of the hydrogens of the methyl group in the preferred conformation of this molecule (methyl group staggered with respect to the carbon holding it). Furthermore the other two hydrogens of this methyl make dihedral angles of $120^\circ$ with this hydrogen and the new carbon-carbon bond is at an angle of $60^\circ$ with the equatorial hydrogen under consideration.
All these factors necessitate a shielding similar to that observed in the earlier two cases wherein the geometry was exactly identical. The reported value for this shielding in cycloalkanols is +24 cps.

The shift values calculated by Apsimon et al are +21.4 and +14.4 cps depending upon which anisotropy value is used. In keeping with our qualitative resonating these values are quite close to those obtained, for shielding by equatorial methyl on adjacent axial (+19.5 and +13.4 cps) and equatorial protons (+19.8 and +13.7 cps).

The effect of an axial methyl on the adjacent axial proton is a deshielding of 12 cps. In the preferred conformation of this molecule (XXI) the three hydrogens of the methyl all make a dihedral angle of 120° with the concerned axial hydrogen and the carbon-carbon bond is at an angle of 180° with this carbon-hydrogen bond. This situation is therefore vastly different from the considered earlier but is in a way similar to the situation in XXII where one considers the effect of axial methyl on the axial hydrogen placed in a cis 1-3 relation with it. This similarity is reflected in an almost identical deshielding (11 cps).

The values calculated by Apsimon et al are -4.4 and +1.3 cps for the effect of axial methyl on adjacent axial proton using different anisotropy values whereas the corresponding values for XXII are -0.3 and -5.4 cps. These calculated values therefore suggest
larger differences in these situation than are actually observed.

Conformations of aliphatic alcohols

From the above consideration (in highly simplified form) these arguments can be extended to come to an understanding of the conformation of simple aliphatic alcohols.

The NMR spectrum of ethanol had its -\(\text{CH}_2\) protons as a quartet centered at 223.5 cps. If the spectrum of n-propanol is examined these protons (-\(\text{CH}_2\text{OH}\)) now resonate at 216 cps.

Table VI
Chemical shift of hydroxy methyl protons in simple alcohols

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3\text{CH}_2\text{OH})</td>
<td>223.5 (q)</td>
</tr>
<tr>
<td>(\text{CH}_3\text{CH}_2\text{CH}_2\text{OH})</td>
<td>215  (t)</td>
</tr>
<tr>
<td>(\text{CH}_3\text{C}--\text{OH})</td>
<td>240  (m)</td>
</tr>
<tr>
<td>(\text{CH}_3\text{H})</td>
<td>205  (d)</td>
</tr>
<tr>
<td>(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH})</td>
<td>216  (t)</td>
</tr>
</tbody>
</table>

d-doublet, t-triplet, q-quartet, m-multiplet.
If one considers the different conformations of isopropanol it can be seen that in the anti conformation (A, Chart 6) there are two hydrogens in a syn-axial relationship with these hydroxy methyl protons, hence shielding of these protons is anticipated in this conformation. On the other hand if one looks at the gauche conformation (B) or (C) one finds that there is now only one hydrogen which is feeling a syn-axial effect in each of these conformers whereas the other hydrogen has the three hydrogens of the new methyl group at 120° with regard to it. Such a relationship can be regarded (D, Chart 6) as corresponding to an effect of axial methyl on the adjacent axial hydrogen (H₁) and should therefore result in deshielding of that proton by 12 cps. The syn-axial relationship in this gauche conformation can also be regarded as similar to a shielding by axial methyl on adjacent equatorial hydrogen* and should correspond to shielding of 24 cps of H₂ (D). This gauche conformation should therefore feel a net shielding of ~12 cps (24-12).

In the anti-conformation each of the hydrogens of the hydroxy-methyl group has one hydrogen syn-axially placed to the hydrogen of the methyl and this hydrogen makes an angle of 120° with remaining two methyl hydrogens. Overall therefore both these hydrogens should behave as though they are equatorial hydrogens feeling the effect of

* It can also be regarded (E, Chart 6) as an equatorial methyl on the adjacent axial proton (H₁). This should cause a shielding of 28 cps giving a net shielding of 16 cps (28-12).
Dotted lines in these figures do not imply bonds, but merely show the similarity to a cyclohexane chair.
axial methyl (F) and this effect should be around 24 cps. As the observed value is much closer to the gauche conformation, it seems from the present evidence that the methyl group has a gauche conformation with regard to the hydroxyl function.

Though this may appear to be in conflict with stability requirement, it is in fact not so. It has been demonstrated by several methods that in the case of n-propyl chloride and even n-propyl bromide the gauche form is lower in internal energy than the anti-form by values ranging between 0.1 to 0.6 Kcal/mol. In the case of n-propyl chloride this value has been arrived at by consideration of infrared, electron diffraction and microwave studies.

Different reasons have been proposed to explain these factors and the accepted explanation suggests that a methyl group and the chlorine atom in the gauche conformation fall either in or very close to the attractive part of the Van-der-Waal's curve. It may incidentally be pointed out that in the case of n-propyl bromide such a reasoning would anticipate strong predominance of anti-form contrary to experiment. Whatever the explanation it is clear that in these molecules the anti-isomer may be less stable than the gauche. If the same reasoning that holds good for the halo compounds applies to alcohols as well the explanation of the NMR results given above would satisfy
the stability requirements also.

A sort of confirmation for these ideas can be made by examining the spectrum of isobutyl alcohol which displays the resonance of hydroxymethyl protons at 205 cps. This indicates a shielding of 10 cps in comparison with n-propyl alcohol. As this shielding is almost the same as observed on passing from ethyl alcohol to n-propyl alcohol, it would seem that the new methyl group must have an almost identical relation with regard to methylene protons of the hydroxymethyl group. This location is only possible if the methyl group in n-propyl alcohol is gauche placed in respect to the hydroxyl group and if the new methyl group of isobutyl alcohol is also gauche placed with respect to the hydroxyl group. This reasoning requires isobutyl alcohol to have conformation (G, R = OH) in preference to an alternate conformation (H, R = OH). If isobutyl had conformation (H, R = OH) it is very difficult to visualise how both methyl groups would cause an identical shift.

* It can be mentioned that in n-propyl mercaptan despite the high polarisability of sulphur the antiform is more stable than the gauche form by 0.4 Kcal/mol30. However this may be due to the larger size of the sulphur atom.
In isobutyl alcohol however the stability position is more difficult to explain as isobutyl chloride has been shown to exist to the extent of 80% in gauche-anti conformation ($H, R = Cl$) rather than in the gauche-gauche conformation. ($G, R = Cl$). In view of the earlier observation of n-propyl chloride this finding is difficult to rationalise though Pauli, Momany and Bonham have suggested that for a favourable interaction between the gauche methyl and the chlorine the dihedral angle should be larger than the normal 60° angle. As this cannot occur in conformation ($G, R = Cl$) the molecule prefers to exist in the conformation ($H, R = Cl$). A sort of confirmation for this comes from the observation that the Cl-methyl angle in isobutyl chloride is 60°.

If n-propyl alcohol has a gauche conformation then in n-butyl alcohol similarly the ethyl group and the hydroxyl function must also be gauche with respect to one another. Substitution of methyl in n-propyl alcohol can occur at either of the three hydrogens of the methyl group. Its occurrence at the hydrogen eclipsing the hydroxyl (I, Chart 7) can be ruled out because of the extreme closeness of the new methyl to the hydroxyl group (the distance between oxygen and methyl hydrogen is 1.2\(\AA\)). In the second gauche location (J, Chart 7), the methyl group should remove one of the possible factors for deshielding of hydroxy-methyl protons in isopropyl alcohol and the NMR spectrum should have the hydroxy methyl protons at the same location as in ethyl alcohol. As this is not the case this
possibility can also be ruled out. It seems fairly reasonable to presume that the new methyl group is antiplaced with respect to $C_1-C_2$ bond. In this conformation ($K$, Chart 7) the hydroxymethyl protons in n-butyl alcohol would have the same chemical shift as in isopropyl alcohol.

The NMR spectrum therefore establishes the conformation ($K$) for n-butyl alcohol and this conformation would agree with that expected from stability considerations, provided n-propyl alcohol exists in the gauche conformation.

In this connection it is of interest to note that 1-bromobutane on the basis of electron diffraction data exists in the all anti (zigzag) conformation ($L$, Chart 7), in contrast, in n-butyl chloride the conformation ($K$) in which chlorine is gauche to ethyl abounds and it appears that whereas the antiform is preferred about the $C_3-C_2$ bond by about 0.4 Kcal/mol, the gauche form predominates about the $C_1-C_2$ bond by 0.3 Kcal/mol. A very significant finding that the gauche-gauche* form ($I$), in which methyl and chlorine approach most closely, contributes as much as 24% and suggests some special stability, possibly London attraction between methyl and chlorine.

In isopropyl alcohol in the preferred, staggered conformation the carbinyl proton has an anti-relationship with one of the hydrogens of the new methyl group (as

---

* Our NMR findings cannot rule out this conformation.
compared to ethyl alcohol). Such locations are known to cause deshielding of a proton. The other two hydrogens of this methyl group are placed at 60° with the carbinyl hydrogen and should not therefore exert any marked influence. On the whole therefore carbinyl proton of isopropyl alcohol should be deshielded in comparison with the corresponding protons of ethyl alcohol. The observed finding (a deshielding of 16.5 cps*) suggests the importance of conformational factors.

* This explanation provides a reason for the lower frequency of methine proton apart from the usual explanation based on the increased inductive effect.
EXPERIMENTAL

For general procedures see Chapter 1.

Preparation of compounds XVI and XVII \((R = H_2)\) is described in Chapter 1.

**Cholesterol-3β-ol** (IX, \(R = \text{OH}\))

Hydrogenation of cholesterol in ethyl acetate using platinum oxide as catalyst and few drops perchloric acid furnished cholestanol in high yield.

**M.P. 140°**

**Cholesterol-3β-acetate** (IX, \(R = \text{OAc}\))

Acetylation of cholesterol-3β-ol using pyridine/acetic anhydride gave the acetate in quantitative yield.

**M.P. 110°**

**Cholesterol-3β-ol methyl ether** (IX, \(R = \text{OMe}\))

Cholesterol-3β-ol was methylated as reported by Narayanan and Iyer\(^{19}\). The product crystallised from methanol.

**M.P. 81.5-82.5°**
**Lit. 83°**
**\([\alpha]_D\) +21.5**
**Lit. +29°**
Lupeol* was hydrogenated in ethyl acetate over Adam's catalyst at atmospheric pressure. Lupanol was obtained in quantitative yield.

M.P. 199-201°  Lit. 201-202°

**Lupan-3β-ol-acetate** (XIV, \( R = \text{OAc} \))

Acetylation of lupanol under normal conditions furnished the acetate from acetone-methanol.

M.P. 246°  Lit.\(^9\) 245-246°

[\( \alpha \)]\( _D \) -2°  Lit.\(^9\) -1.8°

**Lupan-3β-ol-methyl ether**\(^{10}\) (XIV, \( R = \text{OMe} \))

This was prepared by the same method as cholestan-3β-ol methyl ether except that instead of refluxing with potassium for one hour, it was refluxed for three hours. The yield of methyl ether was 82%.

M.P. 227-228°  Lit.\(^{10}\) 227-228°

[\( \alpha \)]\( _D \) +4°  Lit.\(^{10}\) +2.33°

**3β-Hydroxy-4,6α(R) 6,11β(R)-eudesman-6-13-olide** (V, \( R = \text{OH} \))

3-Oxo-4,5α(R), 6,11 β(R)-eudesman-6-13-olide

(II, 2 g) in acetic acid (60 ml) was stirred in an atmosphere

---

* Lupeol purified by chromatography (From the mixture rich in lupeol kindly supplied by C. Quasim of this laboratory) had M.P. 215° and [\( \alpha \)]\( _D \) +26°.
of hydrogen in presence of pre-reduced Adam's catalyst. Absorption of hydrogen ceased after uptake of two moles (six hours). The catalyst was filtered off and most of the acetic acid was removed under vacuo. The concentrate was diluted with water and the precipitate was taken up in ether.

The substance obtained gave on crystallisation from ether-pet ether exclusively the pure β alcohol (1.78 g).

M.P. 110-111°  Lit.11  108-110°
[α]_D^{28} +38°  Lit.11  36°
I.R. 3350 cm\(^{-1}\) (OH) 1780 cm\(^{-1}\) (γ-lactone)

\(3\beta\)-Acetoxy-4,5 α(H) 6,11 β(H) eudesmane 6-13 olide (V, R = OAc)\(^{11}\)

Hydrogenation of the keto-lactone (II, 500 mg) under pressure (60 psi) using the same catalyst and solvent furnished the acetate (V, R = OAc 460 mg) directly.

M.P. 200°  Lit.11  199-200°
[α]_D^{28} +17°  Lit.11  +15.4°
IR 1775 cm\(^{-1}\) (γ-lactone) 1726, 1251 cm\(^{-1}\) (acetate)

NMR:
1 H broad signal at 287 cps (C_3\(\alpha\)-H)
3 H sharp singlet at 123 cps (O-\(\alpha\))

The product did not depress the melting point of the acetate prepared from the alcohol by the usual pyridine/acetic anhydride method.
3β-Methoxy 4,5 α(Δ) 6,11 β(Δ) eudesman 6-13 olide (V, R = OMe)

The alcohol (V, R = OH, 500 mg) in dry benzene (30 ml) was refluxed with potassium metal (500 mg) for three hours in an atmosphere of nitrogen with frequent vigorous shaking to disperse the molten potassium. Methyl iodide (10 ml) was added to the cooled reaction mixture and refluxing continued further for five hours. Excess of potassium was destroyed and the alkaline reaction mixture was acidified and warmed. It was then extracted with ether. Ether layer was washed with water and dried. Removal of solvent gave a residue (430 mg) which showed two spots on TLC, the lower one corresponding to the starting alcohol. The residue was therefore chromatographed on silica gel (15 g). 5% Ether in benzene eluted a homogenous (TLC) material (138 mg) which was crystallised from pet. ether and was characterised as the expected 3β methyl ether.

M.P. 164-166°

$\left[\alpha\right]_D^{28} +17.2°$

IR 1770 cm$^{-1}$ (γ-lactone) 1190, 1108 cm$^{-1}$ (ether)

NMR:
3 H sharp singlet at 200 cps (3β-OCH$_3$)
1 H broad signal at 195 cps (3α-H)

Analysis:

Found: C, 72.40; H, 10.07%

C$_{16}$H$_{26}$O$_3$ required: C, 72.14; H, 9.84%.

Elution of the column with ether gave the starting alcohol (340 mg)

M.P. and mixture m.p. 110°.
3β-Hydroxy-5α(H) 4,6,11 β(H)-eudesman 6-13 olide \(^{11}\) (VI, \(R = \text{OH}\))

3-0x0-5α(H) 4,6,11 β(H)-eudesman 6-13 olide

(III, 1 g) in methanol (20 ml) was added slowly with stirring to sodium borohydride (200 mg) in water (2 ml). After allowing to stand overnight at room temperature the reaction mixture was acidified with dil. HCl and was diluted with water. Precipitated material was taken up in ethyl acetate. Ethyl acetate extract was washed with water and dried over anhydrous sodium sulphate. The residue obtained on removal of solvent crystallised from ether-pet. ether and furnished the required alcohol (600 mg, single spot in TLC).

\[
\begin{align*}
\text{M.P.} & \quad 171-172^\circ \\
\left[\alpha\right]_D^{28} & \quad 46^\circ \\
\text{I.R.} & \quad 3500 \text{ cm}^{-1} (\text{OH}), 1780 \text{ cm}^{-1} (\gamma\text{-lactone})
\end{align*}
\]

Mother liquors (320 mg) which showed no carbonyl absorption in U.V. had two close spots in TLC. Inverted dry column chromatography\(^{15}\) of this material afforded both the compounds in pure form. The slow moving (150 mg) was the 3β alcohol while the faster moving (150 mg) was identified as the C3 ketone. Thus on the whole the yield of 3β epimer is 81% while that of α is 15%.
3β-Acetoxy-5α(H) 4,6,11 β(H) eudesman 6:13-olide (VI, R = OAc)

The hydroxy-lactone (VI, R = OH, 250 mg) was allowed to stand for twentyfour hours in pyridine (5 ml) and acetic anhydride (5 ml) under anhydrous conditions. It is then poured into crushed ice and allowed to stand for two-three hours to decompose acetic anhydride. Usual work up followed by crystallisation from ether-pet. ether afforded the acetate (240 mg).

M.P. 141°  
Lit. 
11 143°  
[α]_D^{28} +68°  
Lit. 
11 +63.1°  
I.R. 1780 cm⁻¹ (γ-lactone) 1750, 1260 cm⁻¹ (acetate)

3β-Methoxy-5α(H) 4,6,11β(H)-eudesman-6:13-olide (VI, R = OMe)

To the hydroxy-lactone (VI, R = OH, 250 mg, dried well by boiling with dry benzene and keeping in vacuo for three hours) in dry benzene (30 ml), potassium metal (250 mg) was added and the mixture was refluxed in an atmosphere of nitrogen for three hours with vigorous shaking at intervals to disperse the molten potassium metal into small globules. Methyl iodide (5 ml) was added and refluxing continued further for five hours when potassium iodide gradually separated out.

Reaction mixture was cooled and excess of potassium was destroyed by methanol. Work up as in the earlier case afforded a material which showed two spots in TLC, the lower one corresponding to the starting alcohol.
The residue was therefore chromatographed over silica gel column. Elution with 5% ether in benzene gave a white material (90 mg) which crystallised from pet. ether and was identified as 3β methoxy-5α(H)-4,6,11β(H) eudesman-6-13-olide (VI, R = OMe).

M.P. 109-110°

\([\alpha]_D^{28} +58.12°\)

I.R. 1776 cm\(^{-1}\) (γ-lactone), 1196, 1095 cm\(^{-1}\) (ether)

NMR: 3H singlet at 205 cps (0 CH\(_3\))

\(1H\) broad signal at 153 cps (CH\(_3\)-H)

**Analysis:**

Found: C, 72.04; H, 10.07%

C\(_{16}H_{26}O_{3}\) requires: C, 72.14; H, 9.84%

Elution with 10% ether in benzene afforded the starting alcohol.

M.P. and mixture m.p. 170°.

3\(\alpha\)-Hydroxy-6\(\alpha\)(H)-4,6,11\(\beta\)(H)-eudesman-6-13-olide (VII, R = OH)

The keto lactone (III, 2 g) in glacial acetic acid (60 ml) was hydrogenated in presence of platinum oxide catalyst (400 mg). Absorption of hydrogen ceased in six hours, after 2 moles of hydrogen were absorbed. The catalyst was filtered off and most of the solvent was removed under reduced pressure. The concentrate was taken up in ether, diluted with water and the precipitate was washed free of acetic acid and dried over sodium sulphate. Removal of solvent yielded a colourless residue which showed two very close spots in TLC neither of which corresponds to starting ketone. (I.R. showed absence of ketone)
Inverted dry column chromatography\textsuperscript{15} employing ethyl acetate:benzene (3:7) solvent system furnished both the compounds in pure form.

The faster moving (650 mg) was characterised as 3\(\alpha\) hydroxy 5\(\alpha\)(H) 4,6,11 \(\beta\)(H) eudesman 6-13 olide (VII, \(R = \text{OH}\)).

\begin{center}
\begin{tabular}{ll}
M.P. & 143\(^\circ\)C \\
[\(\alpha\)]\textsubscript{D}\textsuperscript{28} & +13.5 \\
I.R. & 3500 cm\textsuperscript{-1}(OH), 1770 (\(\gamma\)-lactone)
\end{tabular}
\end{center}

NMR:
1 H narrow signal at 228 cps (C\(3\beta\)-H)
1 H broad signal at 230 cps (C\(6\)-H)

The slow moving (320 mg) was the C\(3\beta\) epimer

Besides these, an unresolved mixture (400 mg) of these two epimers was also obtained. Assuming (from the intensity on TLC) that this mixture contains equal percentage of both epimers the yield of \(\alpha\) epimer is \(\sim 42\%\) while that of \(\beta\) is \(\sim 51\%\).

3\(\alpha\)-Acetoxy 5\(\alpha\)(H) 4,6,11 \(\beta\)(H) eudesman 6:13 olide (VII, \(R = 0\text{Ac}\))

The above alcohol (250 mg) in pyridine (5 ml) and acetic anhydride (5 ml) was warmed on steam bath for two hours and kept aside at room temperature for twentyfour hours.

Usual work up gave a material which crystallised from ether-pet. ether mixture to afford the acetate (225 mg) as rhombs.

\begin{center}
\begin{tabular}{ll}
M.P. & 153\(^\circ\)C \\
[\(\alpha\)]\textsubscript{D}\textsuperscript{28} & -30 \\
I.R. & 153-154\(^\circ\)
\end{tabular}
\end{center}
I.R. 1770 cm\(^{-1}\) (\(\gamma\)-lactone) 1780, 1260 cm\(^{-1}\) (acetate)

NMR:
1 H narrow signal at 298 cps (C\(_{3}\beta\)-H)
3 H sharp singlet at 124 cps (COCH\(_3\))
1 H broad signal at 230 cps (C\(_6\)-H)

3\(_{\beta}\)-Hydroxy 5\(\alpha\)(H) 4,6,11 \(\beta\)(H) enodesman 6-13 olide 3-mesylate
(VI, R = \(\text{OCS}\))

The alcohol (VI, R = OH, 1 g) in pyridine (10 ml) was cooled to 0\(^\circ\)C and to it was added precooled methane sulphonyl chloride (1 ml). Reaction mixture was kept at 15\(^\circ\)C for sixtyfour hours. It was then poured in cold water and extracted with ethyl acetate. Ethyl acetate extract was washed free of pyridine, methane sulphonic acid and dried over sodium sulphate. Residue obtained on solvent removal, crystallised from ethanol to furnish the mesylate (960 mg; TLC single spot).

M.P. 156\(^\circ\)
[\(\alpha\)]\(D\)\(^{28}\) +61.3\(^\circ\)

I.R. 1770 cm\(^{-1}\) (\(\gamma\)-lactone) 1183, 885 cm\(^{-1}\)

NMR:
1 H broad signal at 257 cps (C\(_{3}\alpha\)-H)
1 H triplet at 231 cps (C\(_6\)-H)
(J = 10 cps)
3 H singlet at 180.5 cps (CH\(_3\) SO\(_2\)\(^{-}\))
6 H doublets centered at 71 cps (J = 7 cps)
(C\(_4\) and C\(_{11}\) -CH\(_3\))
3 H singlet at 60 cps (C\(_{10}\)-CH\(_3\))

Analysis:

Found: C, 57.97; H, 7.69%

C\(_{16}\)H\(_{26}\)O\(_{5}\)S requires: C, 58.17; H, 7.93%.
Solvolyis of 3β-hydroxy-5α(H) 4,6,11β(H) eudesmane 3-olide-3 mesylate

The mesylate (VI, R = OMe; 660 mg) was refluxed with super-dry methanol (50 ml) for ninety hours. Reaction mixture was then poured into water (200 ml) and the precipitated material was taken up in ether. Ether extract was washed with bicarbonate solution, water and dried over sodium sulphate. Removal of solvent left a colourless gummy residue (493 mg) which showed three spots on TLC the lower to one corresponding to the starting mesylate. It was therefore chromatographed on a silica gel column. First three benzene fractions gave a material (90 mg) which was crystallised from pet. ether and was characterised as Δ² olefin VIII (Chart 2).

M.P. 146-147°

[α]D +21°

Later benzene fractions gave a pure 3α methoxy derivative (VII, R = OMe 317 mg).

M.P. 111-112°

[α]D +28°

I.R. 1770 cm⁻¹ (Y-lactone) 1195, 1198 cm⁻¹ (ether)

NMR: 3 H singlet at 200 cps (OCH₃)

1 H narrow signal at 190 cps (C₃β-H)

Analysis:

Found: C, 72.31; H, 9.85%

C₁₆H₂₆O₃ requires: C, 72.14; H, 9.84%

Fraction D (57 mg) was unreacted starting mesylate.
**Cholestan-3β-ol tosylate** (IX, R = OTs)

To a cooled solution of cholestan-3β-ol (2.5 g) in dry pyridine (15 ml) was added a cold solution of p-toluene sulphonyl chloride (5.6 g) in pyridine (20 ml). The resultant mixture was allowed to stand at room temperature for twenty-four hours, after which it was poured in crushed ice. The solid was taken up in ether, washed with water, 2N HCl and again with water. The ethereal solution was dried (Na₂SO₄), filtered and evaporated to dryness. The residue crystallised from ethanol to furnish the tosylate (2.4 g).

M.P. 132-133°
[α]_D^-39.8°
I.R. 1693, 1190, 1175 and 1095 cm⁻¹.

**Formolysis of cholestan-3β-ol tosylate**

The above tosylate (1 g) in dimethyl formamide (40 ml) was heated at 78° for twenty-four hours. The reaction mixture was then diluted with excess of water and the precipitate was taken up in ether. Ether extract was washed with water, dried (Na₂SO₄) and ether was evaporated. Semisolid obtained was chromatographed over silica gel. Pet. ether eluted a substance (536 mg) which was identified as 3α-formate (X, R = OCHO).

M.P. 111-113°
I.R. 1720 (C=O)

Ether elution afforded the starting tosylate (103 mg).
Cholestan-3\(\alpha\)-ol \(X, R = \text{OH}\)

The above formate (206 mg) was kept in 5% methanolic potassium hydroxide (20 ml) for twentyfour hours. Cholestan-3\(\alpha\)-ol obtained (180 mg) was crystallised from methanol.

\[
\begin{array}{ll}
\text{M.P.} & 182^\circ \\
\langle\alpha\rangle_D & +24^\circ \\
\text{Lit.} & 182^\circ \\
\text{Lit.} & +26^\circ \\
\end{array}
\]

Cholestan-3\(\alpha\)-ol acetate \(X, R = \text{OAc}\)

Reaction of BF\(_3\)-etherate/acetic anhydride on cholestan-3\(\beta\)-ol methyl ether\(^{10}\).

Cholestan-3\(\beta\)-ol methyl ether (1 g) in acetic anhydride (40 ml) and dry ether (2-3 ml) to dissolve the compound) was cooled to 0\(^\circ\). Freshly distilled BF\(_3\)-etherate (7 ml, cooled to 0\(^\circ\)) was added and the mixture kept at 0\(^\circ\) for fifteen hours. It was then poured into crushed ice and extracted with ether after few hours. Ether extract was washed with bicarbonate and water and dried (Na\(_2\)SO\(_4\)). The residual pale yellow oil (980 mg) was resolved into three pure compounds by Inverted dry column chromatography.\(^{15}\) The fastest moving one (200 mg) was identified as \(\Delta^2\) cholestone XI. Next to that was cholestan-3\(\alpha\)-ol acetate (210 mg).

\[
\begin{array}{ll}
\text{M.P.} & 94^\circ \\
\text{Lit.} & 95^\circ \\
\text{I.R.} & 1725, 1250 \text{ cm}^{-1} \\
\end{array}
\]

The most polar compound (450 mg) was cholestan-3\(\beta\)-ol acetate. An unresolved mixture (105 mg) of \(\alpha\)- and \(\beta\)-acetates was also obtained.
3β-Hydroxy 4,5α(H) 6,11β(H) eudesman 6-13-olide
3 mesylate (V, R = OMeS)

To the cooled solution of hydroxy lactone
(V, R = OH, 1.7 g) in pyridine (15 ml) pre-cooled methane
sulphonyl chloride (2 ml) was added and the mixture was
allowed to stand at 15° for sixtyfive hours. It was
then poured in water and worked up. Crystallisation from
ethanol gave the mesylate (1.8 g).

M.P. 151°
[α]D +12°
I.R. 1770 cm⁻¹ (γ-lactone)

NMR:
1 H broad signal centered at 283 cps (C₃-H)
1 H triplet centered at 238 cps (C₆-H) J = 10 cps
3 H sharp singlet at 180 cps (CH₃ SO₂)
3 H doublet centered at 64, J = 7 (C₁₁-CH₃)
3 H doublet centered at 72.5, J = 7 (C₄=CH₃)
3 H singlet at 64.5 (C₁₀-CH₃)

Analysis:
Found: C, 58.03; H, 7.67%

C₁₆H₂₆O₅S requires: C, 58.17; H, 7.93%.

Solvolyze of 3β-hydroxy 4,5α(H) 6,11β(H) eudesman 6-13
olide-3 mesylate (V, R = OMeS)

Mesylate (800 mg) was refluxed with methanol (50 ml)
for ninety hours. Usual work up gave a colourless gum
(620 mg) which showed three spots on TLC (benzene), one
(Rf 0.02) corresponding to starting mesylate. Other two
had Rfs 0.25 and 0.35. It was chromatographed on silica gel.
Chromatogram shows the results.
<table>
<thead>
<tr>
<th>Fr. No.</th>
<th>Solvent</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Pet. ether (4x25 ml)</td>
<td>negligible material</td>
</tr>
<tr>
<td>b</td>
<td>Pet. ether:benzene (3:1) (4x25 ml)</td>
<td>negligible material</td>
</tr>
<tr>
<td>c</td>
<td>Pet. ether:benzene (1:1)</td>
<td>single spot ($R_f$ 0.35)</td>
</tr>
<tr>
<td>d</td>
<td>Pet. ether:benzene (1:1)</td>
<td>single spot ($R_f$ 0.35)</td>
</tr>
<tr>
<td>e</td>
<td>Pet. ether:benzene (1:1)</td>
<td>two spots ($R_f$ 0.35, 0.25)</td>
</tr>
<tr>
<td>f</td>
<td>Pet. ether: benzene (1:1)</td>
<td>single spot ($R_f$ 0.25)</td>
</tr>
<tr>
<td>g</td>
<td>Pet. ether:benzene (1:1) 3x25 ml</td>
<td>single spot ($R_f$ 0.25)</td>
</tr>
<tr>
<td>h</td>
<td>Ether (4x25 ml)</td>
<td>starting mesylate</td>
</tr>
</tbody>
</table>
Fractions c and d, together (174 mg) crystallised from pet. ether and gave the following constants.

M.P. 116-122°

\([\alpha]_D^o + 114.6°\)

NMR and I.R. analysis indicate that it is a \(\Delta^3\) olefin (XIII)\(^{13}\) with little \(\Delta^2\) olefin.

Fractions f and g were combined (80 mg), crystallised from pet. ether and was identified as \(5\alpha(III) 6,11(II) \Delta^4(14)\) eudesmen-6-13-olide (XII).

M.P. 125-137°  Lit.\(^{34}\) 140°

\([\alpha]_D^o +151.6°\)  Lit.\(^{34}\) 140°

NMR analysis Table 2 and I.R. bands at 1660 and 890 cm\(^{-1}\) also suggest the above structure.

**Formolysis of the mesylate \((V = OMe)\)**

The mesylate (250 mg) in dimethyl formamide (once distilled, 10 ml) was heated at 78°. Reaction was monitored by TLC and mesylate was found to be completely reacted in twentyfour hours. Reaction mixture was cooled and poured in cold water. Material separated on cooling was collected and crystallised from methanol to give plates (153 mg).

M.P. 106-107°

I.R. 1760 cm\(^{-1}\) (lactone), 1640, 980, 880 cm\(^{-1}\) (olefin)

NMR revealed no formate proton, rather it showed that it is a mixture of the same olefins XII and XIII.
3β-Hydroxy 5α(H) 4,6,11β(H) endesman 6-13 olide
3-tosylate (VI, R = OTs)

To the cooled solution of the hydroxylactone (VI, R = OH, 500 mg) in pyridine (15 ml) was added p-toluene sulphonyl chloride (2 g) in pyridine (20 ml) and the mixture was allowed to stand at room temperature for twenty-four hours. It was then poured in water and extracted with ether. Total ether extracts were washed with 2N HCl, bicarbonate solution and finally with distilled water. Residue obtained on evaporation of the solvents and crystallised from alcohol to furnish the tosylate (VI, R = OTs, 650 mg).

M.P. 166-168°  Lit.13 168-169°

$[\alpha]_D^{23} +24^0$  Lit.13 $+20^0$

I.R. 1776 cm$^{-1}$ (lactone) 1608, 996, 946, 849 (aromatic)

Methanalysis of 3β-hydroxy 5α(H) 4,6,11β(H) endesman 6-13 olide, 3 tosylate

Tosylate (500 mg) was refluxed with dry methanol (50 ml) for 102 hours.

Reaction mixture was then concentrated at reduced pressure and diluted with water. Precipitated material was extracted with ether. Ether extracts were washed with sodium bicarbonate solution and distilled water. Removal of solvent afforded the residue which showed three spots in TLC, one corresponding to the starting tosylate.

NMR of the total material revealed no peak around 200 cps (no methyl ether formation) and showed a mixture of the same two olefins (XII and XIII) as in the case of mesylate.
Epi-lunanol acetate (XV, R = OAc)

Epilupeol acetate* (250 mg) was hydrogenated in ethyl acetate (20 ml) in the presence of pre-reduced Adam's catalyst (25 mg) as described by Heilbron et al.\(^9\).

After usual work up the product was crystallised from ethanol when epilupanol acetate (220 mg) was obtained.

- M.P. 164\(^\circ\) C
- \([\alpha]_D^0\) 44\(^\circ\) C
- I.R. 1750, 1260 cm\(^{-1}\) (acetate) no band at 890 cm\(^{-1}\)

Epi-lupanol (XV, R = OH)

Epilupanol acetate (180 mg) was kept at room temperature for forty-eight hours with methanol (20 ml) containing potassium hydroxide (1 g).

The solution was diluted with water and extracted with ether. Processing of ether extract afforded epilupanol in quantitative yield. It is crystallised from acetonitrile.

- M.P. 161\(^\circ\) C
- \([\alpha]_D^0\) 2\(^\circ\) C
- I.R. 3450 cm\(^{-1}\) (OH)

---

* We are indebted to Prof. T. R. Govindachari for this sample.
REFERENCES


13. H. Ogura,

14. J. B. Hendrickson and T. L. Bogard,

15. V. K. Bhalla, U. R. Nayak and Sukh Dev,
   J. Chromatog, 26, 64 (1967).

16. H. R. Nace,

17. E. F. Fieser and M. Fieser,
    "Natural Products related to phenanthrene"

18. 

19. K. N. Iyer,
    "Studies in steroids and related compounds", Ph.D. Thesis,
    Bombay University, 1965.

20. E. Siscovic,

21. J. F. Bielmann and G. Ourison,

22. C. W. Shoppee and G. A. R. Johnson,

    L. Saunders and W. B. Whally,

24. A. D. Buckingham, W. H. Prigchard and D. H. Whiffen,
25. H. M. McConnell,

26. N. Sheppard,

27. Y. Horino and K. Kuchitsu

28. T. N. Sarachman,

29. M. R. Kreevoy and E. A. Mason,

30. R. E. Pennigton, D. W. Scott, H. L. Finke, J. P. McCullough,
    J. F. Messerly, I. A. Hossenlop and G. Waddington,

31. G. H. Pauli, F. A. Momany and R. A. Bonham,

32. F. A. Momany, R. A. Bonham and W. H. McCoy,

33. T. Ukaji and R. A. Bonham,

34. A. M. Shaligram, A. S. Rao and S. C. Bhattacharyya,
    Tetrahedron, 18, 969 (1962).

35. A. K. Ganguly, T. R. Govindachari, P. A. Mohamed,
    A. D. Rahimtulla and N. Viswanathan,

36. B. Tursch and E. Tursch,

37. J. R. Lewis and C. W. Shoppee,