Chapter I

SYNTHESES

OF

ELEMOL, EUDESMOL, DIHYDROEUDESMOL DIHYDROCARISSONE AND, EUDESM 3-EN-12-OL
12-Step synthesis of \( \alpha \)-eudesmol, starting from \((-\)\( \alpha \)-santonin has been effected. A convenient route has been developed for the preparation of (1), a key intermediate in the above synthesis. This involves hydrogenation of 6-epi-santonin and subsequent esterification of the resulting acid (9). Catalytic hydrogenation of (1) in acetic acid- HCl in the presence of Pt catalyst furnishes (6). The ester (2), a key intermediate in eudesmol synthesis, has been prepared by two different routes. The first approach involves the action of a strong base on the tosylhydrazone of (1); the second approach which is more convenient involves dehydration of (7) in the presence of POCl₃-pyridine. Oxidative decarboxylation of (3) furnishes the ester (4) which has been transformed to \( \alpha \)-eudesmol (5) through the following sequence of reactions: (a) saponification (b) oxidation with Jones reagent (c) treatment with MeMgI. A similar sequence of reactions has been employed in synthesising dihydroeudesmol (9) from which is prepared through hydrogenation. (4) (2)

Elemene-2,3,11-triol synthesised from santonin has been transformed to elemol through the following sequence of reactions (4) tosylation (b) transformation of the resulting ditosylate (12) to diiodocompound (13) with NaI in acetone (C) dehydrohalogenation with potassium tertiary butoxide in dimethylsulphoxide. The preparation of the diketone (11) from (10) is also described.
Terpenes\textsuperscript{1,2,3} have been classically identified through the recognition of an isoprene pattern in their carbon skeleton. It is the number of these significant C\textsubscript{5} units in a compound that has given rise to a simple primary classification system. The organisation of isoprenyl carbon skeleton within each primary class then gives rise to various secondary classes. This arbitrary classification based on carbon number and selected carbon skeleton are recognisable in a number of naturally occurring compounds.

Elemol (I) is a monocyclic sesquiterpene alcohol with elemene skeleton (Ia).

Eudesmol (II) dihydroeudesmol (III) and dihydrcarissone (IV) have dihydroeudesmane (IIa) skeleton.

A synthesis of the above mentioned sesquiterpenes (I, II, III, IV) have been carried out in this laboratory.

We confine our discussion only to elemanic and eudesmanic compounds.

A brief survey of some of the naturally occurring terpenes (1) elemene skeleton (Chart II) and (2) eudesmane skeleton (Chart III, IV) is presented in this Chapter. The details of source can be had from the references cited.
ELEMOL
I

α-EUDESMOL
II

DIHYDROEUDESMOL
III

DIHYDROCARISSONE
IV

ELEMANE
Ia

EUDESMANE
IIa

CHART I
NATURALLY OCCURRING ELEMANIC COMPOUNDS

α-ELEMENE
β-ELEMENE
δ-ELEMENE

ELEMENAL
β-ELEMENONE
epi-SHYBUNONE

GEIJERENE
GEJERONE
ELEMENOL

ISOSERICENINE
CURZERENE

SERCEALACTONE
VERNOLEPIN

CHART II
NATURALLY OCCURRING EUODASMANIC COMPOUNDS

HYDROCARBONS

SELINANE\(^{16}\)  \(\alpha\)-SELinene\(^{17}\)  (+)-\(\beta\)-SElinene

\(\gamma\)-SElinene\(^{21,22,23}\)  Sibirene\(^{24}\)  Bicyclo\([4,4,0]\)-4,9-Dimethyl-6-iso-propenyl decene-4

ALDEHYDES, KETONES AND ACIDS

COSTAL\(^{25}\)  \(\alpha\)-Cyperone\(^{19}\)  Carisstone\(^{26}\)

COSTIC ACID\(^{27,28}\)  ILICIC ACID\(^{29}\)  12-Carboxy-euodesma-3,11(13)-diene\(^{30}\)

CHART III
ALCOHOLS

α-EUDESMOL, δ, €, £, ¶, ¥

β-EUDESMOL, δ, €, £, ¶, ¥

γ-EUDESMOL, δ, €, £, ¶, ¥

NEO-INTERMEDIOL, δ, €, £, ¶, ¥

JUNENOL, δ, €, £, ¶, ¥

COSTOL, δ, €, £, ¶, ¥

AGAROL, δ, €, £, ¶, ¥

CRYPTOMERDIOL, δ, €, £, ¶, ¥

α-β-VERBISINOLS, δ, €, £, ¶, ¥

CYPEROL, δ, €, £, ¶, ¥

ISOCYPEROL, δ, €, £, ¶, ¥

SELIN-11-En-4α-OL, δ, €, £, ¶, ¥

CHART IV
REFERENCES


37. Same as reference No. 36, p. 154.


41. P.D. Gardner, G.J. Park and C.C. Albers,

42. Hikino Heroshi, Aota Keitaro and Takemoto, Tsunematsu,

    1009 (1967).
The crystalline monocyclic sesquiterpene alcohol, elemol (I) C\textsubscript{15}H\textsubscript{26}O was first isolated by Clover\textsuperscript{1} from Manila Elemi oil. Sorm et al.\textsuperscript{2} disapproved the structure proposed by Ruzicka et al.\textsuperscript{3} by synthesising 1-methyl-2,4-diisopropyl benzene (II) and showed it to be identical with the product of dehydrogenation of elemol (I). Therefore the basic skeleton of elemol can be represented by (Ia).

Monocyclic sesquiterpenes undergo fascicle cyclisation\textsuperscript{4} to bicyclic ones as shown by the example of germacrone (III) to selinane (IV) and also by the ten-membered cyclic lactone dihydrocostunolide\textsuperscript{5} (V) which on hydrogenation with Adams catalyst in \textit{HAc} gives santonolide 'c' (VI). The cyclised products are eudesmanic types with C\textsubscript{10} angular methyl and C\textsubscript{7} isopropyl side-chain oriented in the same direction i.e. \( \delta \).

The biogenic approach of Ruzicka\textsuperscript{6} extended by Hendrickson\textsuperscript{7} finds ready analogy in the laboratory (VIII, IX, I). Thus dihydrocostunolide (V) on pyrolysis affords saussurea lactone (VII) in high yields. Synthetic approach elaborated by Halsall et al.\textsuperscript{8} and Bhattacharyya et al.\textsuperscript{9} through different routes shows that elemol has the stereochemistry and absolute configuration represented by (I).

Halsall\textsuperscript{8} had prepared elimsane-2,3,11 triol (Xa) from elemol and from (+)-epi-\( \alpha \)-cyperone of known stereochemistry; (both the samples were found to be identical) Hence the absolute configuration (I).

Bhattacharyya\textsuperscript{9,10} confirmed the absolute configuration of saussurea lactone by the total synthesis of tetrahydrosaussurea
**Chart I**

**I. ELEMOL**

**II.**

**Ia.**

**III. GERMACRONE**

**IV. SELINANE**

**CYCLISATION**

**V. SAUSSUREA LACTONE**

**VI. SANTONOLIDE**

**VII.**

**VIII. EUEDSMOL**

**IX. BIRADICAL INTERMEDIATE**

**IN THE BIOGENESIS**

**CHART I**
lactone (XVIII) of established stereochemistry and absolute configuration. Elemol (I) was converted to (XVIII) by the steps indicated below where reactions do not involve or produce any stereochemical changes at the asymmetric centres (Chart No. 2).

1. Elemol on hydrogenation furnished tetrahydroelemol (XIII).
2. Tetrahydroelemol benzoate (XIV) on pyrolysis furnished tetrahydroelemene (XV).
3. Tetrahydroelemene on hydroboration gave the primary alcohol (XVI).
4. Lead tetraacetate oxidation, followed by chromic acid oxidation afforded the tetrahydro saussurea lactone (XVIII). This unambiguous conversion of elemol (I) to tetrahydrosaussurea lactone (XVIII) convincingly proves that the stereochemistry of elemol is represented by the structure (I).

Natural sources that offer eudesmanic compounds suffer from inconsistency in yields and in purity of the products. Admixed with isomers the individual compounds are difficult to purify. Synthesis to a very large extent annuls the defects. α-Cyperone provides a typical example of an eudesmanic compound save for the synthetic route developed by Pier and Cheng. Striking advantage offered by the synthetic routes is the many intermediates whose stereochemical purity can be checked to ensure stereochemically pure product. A second look at the synthesis of agarofuran helped Marshall et al. to revise the
HYDROBORATION

\[ \text{HYDROBORATION} \]

\[ \text{NUMBER OF STEPS} \]

\[ X = R = H \]

\[ \text{BENZOYLATION} \]

\[ \text{PYROLYSIS} \]

\[ \text{HYDROBORATION} \]

\[ \text{1-KMnO}_4 \]

\[ \text{2 CHROMIC ACID} \]

\[ \text{CHART 2} \]
structure proposed by Bhattacharyya and co-workers.

Here are some of the synthesis of eudesmanic compounds developed by the authors quoted under reference:
α-santonin, β-eudesmol, γ-eudesmol, α-selinene, α-cyperone, α-agarofuran, Juniper camphor, Costol, costic acid etc.

Of these, the first two compounds are discussed below at some length with special emphasis on their synthesis.

**Santonin**

Abe et al. in 1954 synthesised santonin, an outstanding piece of research work. The steps involved are:

1. 3,5-tetra-4,9-dimethyl-1,2,3,7,8,9-hexahydronaphthalene (IX) which was condensed with diethyl malonate (X) to furnish eusantonane (XI) (Chart No. 3).

2. Dehydrogenation of (XI) with selenium dioxide gave the conjugated dienone ester (XII).

3. Alkaline hydrolysis of (XII) and resolution of the acid through brucine salt afforded the enantiomers d-acid (XIII) and l-acid (XIIIa).

4. The l-acid (XIIIa) was decarboxylated by boiling with collidine to yield the optically active (XIV) and its C₁₁-epimer. On treating the decarboxylation product with selenium dioxide in acetic acid an equatorial hydroxy group was introduced at C₆ to produce the hydroxy acids (XV) and (XVⅠ) which immediately lactonised to give (1) α-santonin (XVⅠ)
Abel's synthesis of β-Santonin

CHART 3

XIV

[decarboxylation]

2-SeO₂/Pd-C

α and β-Santonin

synthesis of β-pudesmol

VII

- Oxidation

XIII

[mixture of α and β-Santonin]
and β-santonin. The separation of the isomers was done on the basis of their crystalline forms.

β-Eudesmol

The simplest of the structural types is noteworthy for its role in the structural correlation of terpenes and steroids. This carbon framework of β-eudesmol, including its C4 exocyclic methylene grouping reappears in a number of its closely related species, viz. costol costic acid.

Heathcock and Kelly\(^1\)5 have recently reported the synthesis of (+) β-eudesmol starting from the readily available bicyclic ketone (XVI). This ketone was transformed to the benzoate (XVII).

2. The benzoate on treatment with sodium borohydride and NaOH, gave the homoallylic alcohol (IX).

3. Reaction of (XX) with \(\text{PBr}_3\), followed by treatment Mg, gave the Grignard reagent (XIX).

4. Carbonation of the Grignard reagent furnished the acid. The diazomethane treatment converted the acid to the ester (XXI).

5. The ester (XXI) on reacting with methyl magnesium iodide gave (+) nor-Y-eudesmol (XXII).

6. Hydroboration of (XXII) produced the diol (XXIII) and the oxidation with Jones reagent furnished the ketal (XXIV).

7. Ketals were isomerised with sodium methoxide to yield the single trans fused ketal (XXIV).
8. Action of methylene triphenyl phosphorane in DMSO on (XXIV) furnished the (+) β-eudesmol (XXV).

Marshall\textsuperscript{23} used the same bicyclic ketone as well as Pinder et al\textsuperscript{24}. Huffman and Mole\textsuperscript{25} had used different methods where Robinson-Mannich annelation sequence to construct the bicyclic skeleton was not used.
REFERENCES

6. L. Ruzicka, Experientia, 9, 357 (1953).
21. V. Benesora, V. Herout and F. Sora, 


A search in chemical abstract indices upto the year 1971 reveals about thirty odd sources from which eudesmols have been isolated. Isolation of pure $\alpha$-eudesmol (I) from natural sources is a difficult operation as it is accompanied by $\beta$-eudesmol (II) $\gamma$-eudesmol (III) and a number of other sesquiterpene alcohols. von Rudloff has indicated this difficulty in his work.

The bicyclic sesquiterpene alcohol ($\text{C}_{15}\text{H}_{16}$)$\alpha$-eudesmol (I) (m.p. 32-33°, $(\alpha)_D + 31^\circ$) was first isolated by Baker and Smith. Its structure (I) and absolute configuration is based on its chemical transformation.

Humber and Pinder have synthesised $\alpha$-eudesmol starting from (+)-cerissone of proven structure and configuration (IV). Metalamine reduction of the ketone (IV) furnished trans dihydrocarissone (V). Subsequent condensation with p-toluene sulfonyl hydrazide afforded the hydrazone (VI) which on heating with sodium ethylene glycolate provided $\alpha$-eudesmol (I).

Scarcity of eudesmols and their importance in the synthesis led us to examine several possible approaches for the synthesis of $\alpha$-eudesmol (I) from the readily available starting materials. The results of the investigation are
Several steps

\[ \text{R-NH-NH}_2 / \text{HCl} \to \text{R-NH}_2 \]
presented in this Chapter. Our investigation of synthetic methods for the elaboration of terpenoids resulted in a highly stereo-selective synthesis of α-eudesmol (I), dihydro-carissone (V), elemol (Xa) and related compounds. Hydrogenation of eudesmols furnishes a mixture of dihydroeudesmol (VII) and 4-epi dihydroeudesmol (VIII). The major component of the mixture is dihydroeudesmol. 4-epi dihydroeudesmol (VIII) was synthesised by Kulkarni and Rao through the route shown in the Chart No. 2. The synthesis of dihydroeudesmol (VII) the major hydrogenation product of eudesmols is described in this Chapter. The triol (IX) prepared from (-)-α-santonin (XI) was available to us from the investigations of Kulkarni and Rao. It has now been transformed to the crystalline sesquiterpene alcohol eleaol* (X).

In our present work (-)-α-santonin (XI) was chosen as the starting material for its proven worth in this laboratory and elsewhere to synthesise a large number of eudesmanic and elemanic compounds. Accrued advantages offered by the crystalline sesquiterpene (XI) for the synthesis of α-eudesmol (I), dihydrocarissone (V) and dihydroeudesmol (VII) are, (i) α-eudesmol (I) and santonin (XI) have close structural resemblance. Both have

(a) eudesmane skeleton (Xia)

(b) same absolute configuration at C7 and C10

(2) Stereochemistry of (-)-α-santonin (XI) has been rigorously established both by chemical and X-ray methods of analysis.

Santonin is readily available and its purity can be checked as it has a sharp melting point.

The transformation of (-) α-santonin (XI) to the keto ester (XXI) was studied. The keto ester (XXI) appeared to be an excellent intermediate for the synthesis of α-eudesmol (I) since the keto ester has the required trans fused decalin ring system. The ester has been prepared by Kulkarni and Rao starting from (-) α-santonin (XI). They have followed the method of Bruderer at al. and reduced (-) α-santonin with Li in liquid NH₃ when the conjugated acid (XII) was obtained. Further reduction of the conjugated acid (XII) with Li in liquid NH₃ furnished the keto acid (XIII) which was esterified with diazomethane to furnish the keto ester (XXI). The stereochemistry of (XXI) at the newly introduced asymmetric centres C₄ and C₅ was assigned by them for the following reasons,

a) Keto-ester (XXI) is not epimerised on refluxing with methanolic hydrochloric acid. Therefore C₄-methyl is in a thermodynamically stable configuration.

b) Similar reductions of α,β-unsaturated ketones structurally related to the keto acid (XII) are known to give trans-decalone derivatives. By analogy the stereochemistry of the acid (XIII) and consequently its methyl ester (XXI) are correctly represented as shown (XXI).

c) The optical rotatory dispersion curve of the keto-ester (XXI) is in good agreement with assigned stereochemistry. It exhibits a positive Cotton effect as
CHART - 3.

\[
\begin{align*}
\text{XII} & \xrightarrow{\text{Li/}NH_3} (\cdots) - \alpha' - \text{Santonin} & \xrightarrow{\text{HCl/DMF}} \text{XI} \\
\text{XIII} + \text{XX} & \xrightarrow{\text{H}_2/\text{Pd} - 5\%} \text{XXI} \\
\text{MeOH-HCl} & \xrightarrow{} \text{XXI} \\
\text{XXIa} & \xrightarrow{} \text{XXIb}
\end{align*}
\]
predicted by the Octant rule\textsuperscript{12}. Djerassi and Klyne\textsuperscript{13} have recorded the ORD curves of a number of decalones of the type (XXIa and b) which have \(\beta\)-oriented (axial) angular group and a \(\beta\)-oriented (equatorial) side-chain and a methyl substituent at \(C_4\). Compounds with \(C_4\)-methyl-\(\alpha\)-oriented (equatorial) exhibit a positive Cotton effect curve of large amplitude so also the keto ester (XXI).

We observed that the reduction of (-)-\(\alpha\)-santonin with Li in liquid NH\(_3\) as carried out by Bruderer et al.\textsuperscript{9} often furnished erratic results and it was not always possible to obtain the keto acid (XII) as crystalline solid. Furthermore we considered that the method of Kulkarni and Rao\textsuperscript{4} for the preparation of keto acid (XIII) is not well suited for large scale runs as it involves two separate reductions with Li in liquid NH\(_3\). Hydrogenation of santonin (XI) has been extensively studied\textsuperscript{7}. Though the \(C_6\)-O bond of santonin is allylic to the ethylenic linkage at \(C_4-C_5\), hydrogenolysis does not take place extensively during hydrogenation. This is probably due to the \(C_6\)-O bond in santonin being quasi-equatorial. Dauben et al.\textsuperscript{14} have shown that \(\gamma\)-santonin (XXIb) which has the \(C_6\)-O bond quasi-axial undergoes extensive hydrogenolysis during hydrogenation. Hence santonin (XI) was converted to its 6-epimer (XIX) according to the method of Nakazaki and Naemura\textsuperscript{6,15}. When 6-episantonin (XIX) was hydrogenated in acetone in the presence Pd-C (5\%), as anticipated it underwent hydrogenolysis. The saturated keto

\textsuperscript{*After our work was completed, we have come across a paper by Piers and Cheng\textsuperscript{6} who have noted that the reduction of santonin with Li in liq.NH\(_3\) is not suited for large scale preparation of keto acid (XII).}
acid (XIII) on refluxing with MeOH-HCl furnished the ketoester (XXI). The stereochemistry assigned to (XXI) obtained from hydrogenation of 6-episantonin (XIX) is based on a comparison of its IR and NMR spectra with those of the authentic sample of the keto-ester (XXI) prepared by us according to the literature method. Further confirmation was provided when the ketoester (XXI) prepared from 6-episantonin could be converted to the crystalline 2:4-dinitrophenylhydrazone identified through m.p., IR and NMR spectra.

After successfully developing a convenient route for the preparation of ketoester (XXI) its conversion to unsaturated ester (XXVI) was investigated.

Condensation of a ketone or aldehyde with p-toluene sulfonyl hydrazide (1) in the presence of a mineral acid furnishes the corresponding hydrazone (2). The tosyl hydrazone suffers decomposition when treated with metallic sodium in ethylene glycol to form an olefin (7). The reaction being formally an elimination reaction, accompanied by a shift of hydrogen, is Bamford-Stevens reaction. In the absence of protic solvents the mechanism is carbenoid. The first two steps involve the formation of a diazo compound with compounds containing no β-hydrogen. The diazo compound loses N₂, hydride shift follows to provide the olefin. There are indications that the steps indicated are simultaneous and no free carbene is involved. In Bamford-Stevens reaction sodium methoxide is commonly used as a base. Shapiro and Heath reports a
new synthesis using alkyl lithium. Finder et al. synthesized α-eudesmol from (+) carissone using Bamford-Stevens reaction using sodium ethylene glycolate.

We initially studied the Bamford-Stevens reaction with the readily available α-tetrahydrosantonin (XXII). The ketone (XXII) gave the hydrazone (XXIII) m.p. 183° (decomp.) crystallized from methanol.

The hydrazone (XXIII) on decomposing with sodium ethylene glycolate in N₂ atmosphere followed by acidification furnished the 3-compound (XXIV). IR spectrum shows bands at 12.2μ and 12.9μ (C=C) for the olefin and the NMR spectrum shows signals at 8.19 (at C_4- CH₃); 4.37 (1H, broad, C_3- H olefinic).

Ketoacid (XIII) in methanol-conc. HCl acid mixture (1:8) was refluxed with p-toluene sulfonyl hydrazide for 1.5 hrs. The resulting product was refluxed with sodium ethylene glycolate in N₂ atmosphere for 3 hrs. The yield of the olefinic acid was poor.

The hydrazone of the ketoester (XXI) was prepared by condensing with p-toluene sulfonyl hydrazide (1) in methanol-conc. HCl acid mixture (1:8). The hydrazone was not isolated. The hydrazone on refluxing with sodium ethylene glycolate in N₂ atmosphere furnished the unsaturated acid (XXVIa) as sodium salt; the acid on treatment with methanolic hydrochloric acid furnished the ester (XXVI), purified by chromatography on alumina (Gr. II) (IR showed bands at 12.2μ and 12.9μ
XXII

\[
R = \text{SO}_2 \text{C}_6\text{H}_4\text{CH}_3
\]

XXIII

Bamford - Steven's

XXIV

XXV

R = \text{SO}_2 \text{C}_6\text{H}_4\text{CH}_3

1. Bamford - Steven's
2. MeOH - HCl

XXVI
(C=C). NMR showed signals at 8.47 (C₄-CH₃) 4.57 (1H, broad, C₃-H).

In the ketoester (XXI) the C₄-methyl is equatorial and C₄-H is axial. If the C₃-ketone is reduced in such a fashion that it yields the C₃ α-hydroxy compound (XXVIII; -OH at C₃ is axial) the required unsaturation between C₃ and C₄ can be conveniently introduced since the derivatives of hydroxy ester (XXIX) has the necessary stereochemical arrangement of groups at C₃ and C₄ to undergo facile trans diaxial elimination²¹. Rapid catalytic hydrogenation of cyclohexanones in the presence of mineral acid is known²¹ to furnish predominantly axial alcohols. The keto ester (XXI) in a solution of glacial acid and conc. HCl acid (50:3) on rapid hydrogenation with PtO₂ catalyst furnished the acetate (XXVII) which was purified through chromatography over alumina (Gr. II) (IH spectrum, in liquid film showed bands at 5.7 and 6.8 μ). NMR spectrum shows characteristic bands at 5.17 (1H, half height width 7Hz C₃-H, equatorial proton); 6.37 (3H, singlet, -CO₂CH₃). Saponification of the acetate (XXVII) furnished the hydroxy acid (XXVIII) which was transformed to the hydroxy ester (XXIX) by treatment with methanol-HCl (House et al.²² had used POC₃₅pyridine mixture to dehydrate tertiary alcohols). We found the reagent to give poor yields of (XXX) with hydroxy acid (XXVIII) but the dehydration of the hydroxy ester (XXIX) furnished the unsaturated ester (XXVI) in satisfactory yields.
The dehydration of the ester was successfully carried out under the experimental conditions reported\textsuperscript{22}. This involved treating the ester in pure dry methylene dichloride with POCI\textsubscript{3} pyridine mixture. The product was purified through chromatography to afford the unsaturated ester (XXVI) (IR spectrum shows bands at 12.2 and 12.9\(\mu\) (C = C); NMR signals at 4.65\(\tau\) (1H, broad C\textsubscript{3} - H); 8.4\(\tau\) (3H, singlet, C\textsubscript{4} - \text{CH\textsubscript{3}}).

The hydroxy acid (XXVIII) was converted to the acetoxy compound (XXVIII\textsubscript{a}) by acetylation with NaOAc-HAc. The acetate (XXVIII\textsubscript{a}) on decarboxylation with lead tetracetate, yielded the acetoxy compound (XXVIII\textsubscript{b}) (NMR gave characteristic signals at 8.00\(\tau\)).

As a little extension of our work we wished to use the intermediate, unsaturated ester (XXVI) for the preparation of \(\Delta\textsuperscript{3}\)-alcohol (XXX\textsubscript{a}). Unsaturated ester on LAH reduction in ether furnished the \(\Delta\textsuperscript{3}\)-alcohol (XXX\textsubscript{a}) in high yields (IR spectrum shows bands at 3.9\(\mu\) (for -OH) and at 12.2\(\mu\) (C=C); NMR shows signals at 8.04\(\tau\) (1H, singlet; on D\textsubscript{2}O exchange vanishes); 4.66\(\tau\) (1H, broad, C\textsubscript{3}-H); 8.4\(\tau\) (3H, singlet, C\textsubscript{4} - \text{CH\textsubscript{3}}).
Oxidative decarboxylation of acids with lead tetraacetate in the presence of pyridine affords ester in high yields\textsuperscript{24}. Keto acid (XXX) in benzene and dry pyridine when oxidatively decarboxylated in $\text{N}_2$ atmosphere gave the acetoxy compound (XXXI\textsubscript{a}).

Saponification of the acetate (XXXI\textsubscript{a}) with ethanolic KOH in $\text{N}_2$ atmosphere followed by Jones\textsuperscript{25} oxidation furnished the ketone (XXXII). Methyl magnesium iodide reacted with the ketone (XXXVI) to give (+)-\textit{$\alpha$}-eudesmol (I). The identity of the product synthesised by us was established by comparison of its TLC behaviour with that of the authentic sample.

Dihydrocarissone (V) has been prepared by Humber and Pinder\textsuperscript{26} by the metalamine reduction of (+)-carissone (IV). We have prepared dihydrocarissone (V) as an intermediate for the synthesis of \textit{$\alpha$}-eudesmol from the ketoester (XXI). Oxidative decarboxylation of the ketoacid (XIII) furnished the acetoxy compound (XXXVII) in 69$\%$ yield $\alpha$\textsuperscript{28}\textsuperscript{D} + 32 (C, 1.5 in CHCl\textsubscript{3} and NMR spectrum shows prominent signal at 3.03 (3H, -O-COCH\textsubscript{3}); 5.3 (1H, broad, C\textsubscript{11}-H) saponification of acetoxy compound (XXXVII\textsubscript{a}) followed by Jones\textsuperscript{25} oxidation of the resulting alcohol afforded the diketone (XXXVIII). Conversion of diketone to dihydrocarissone is reported in literature\textsuperscript{28}. 
CHART - 6

\[ \text{Pb (OAc)}_4 \rightarrow \text{Pyridine} \]

\[ \text{H}_2 - \text{Pto}_2 \text{ in EtOH} \]

\[ \text{KOH - MeOH} \]

\[ \text{CH}_3 \text{MgBr} \]

\[ \text{Saponification} \]

\[ \text{Jones oxidation} \]

XXXVIII

XXX VIIa = R = OAc

XXX VIIb = R = -OH

1) Saponification

2) Jones oxidation

XXXVII

XXX IV

XXX III

XXX II

XXX I

XXX VI

XXX VII

XXX VIII

XXX X

XXX XI

XXX XII

XXX XIII

XXX XIV
The ester (XXVI) has been transformed to dihydro-eudesmol (VIII). Hydrogenation of the ester in ethyl alcohol with PtO₂ catalyst furnished the saturated ester (XXXIII) purified by chromatography over alumina (Gr. II) \( \alpha_d + 30^\circ \) (c, 1.6 in CHCl₃); NMR showed characteristic signals at 5.47 (3H, -CO₂CH₂). IR spectrum of ester (XXXIII) was identical with that of the authentic sample of the methyl ester of tetrahydrocostic acid (XXXIII) kindly provided by Drs. Kelkar and Bawdekar of this laboratory. Saponification of the saturated ester (XXXIII) furnished acid (XXXIV) which on oxidative decarboxylation gave the acetoxy compound (XXXVIA). The acetoxy compound afforded the alcohol (XXXVb) on saponification. Jones reagent oxidised the alcohol (XXXVb) to furnish the ketone (XXXVI). The IR spectrum of (XXXVI) obtained by us by the above route was identical with that of the authentic sample of the ketone (XXXVI). Treatment of the ketone (XXXVI) with methyl magnesium iodide furnished dihydroeudesmol (VII) identified by direct comparison (m.p. mixed m.p.; IR and NMR) with authentic sample.

Recently a number of sesquiterpenes having elemene skeleton (Xc) have been isolated from natural sources. Probably many of them are artifacts formed by the thermal rearrangement of corresponding germacrane derivatives. However, it has been shown that Vernolepin (XXXIX) a dilactone is not an artifact. A number of elemene derivatives including saussurea lactone (XL) and elemol (Xa) have been synthesised, starting from suitable 3-oxo eudesmanes.
CHART 7.

(--) α'-Santonin

\[ \text{XII} \]

\[ \text{XI} \rightarrow \text{X} \]

\[ \text{TsCl} - \text{pyr} \]

\[ \text{NoI} \]

\[ \text{KOC(CH}_3\text{)}_3 - \text{DMSO} \]

\[ \text{Xa} = R = H \]

\[ \text{Xb} = R = \text{NO}_2 \text{-C-NO}_2 \]
involving the fission of C₂-C₃ bond.

A sample of triol (IX) synthesised from (-)-α-santonin (XI) was available to us. We have now been able to transform the triol to elemol and thus achieve a new synthesis of elemol. The triol on tosylation furnished the ditosylate (XL). The ditosylate was converted to the diiodo compound (XLII) on treating with NaI in acetone. Dehydrohalogenation of the iodo compound (XLII) with pet.tertbutoxide in DMSO furnished elemol (Xa).

A different approach for the synthesis of dihydro-eudesmol (VIII) and related compounds which could not be carried out till the end is presented below. The lactones (XLIII and XLV) and the corresponding diols (XLIV, XLVI) can be readily prepared from santonin (XI). We attempted the conversion of the diol (XLVII) to the monomethyl ether (XLVIII) by the selective methylation of primary hydroxyl group.

However, the required selective methylation could not be carried out in satisfactory yields (Chart 8).

*The monomethyl ether (XLVIII) appears to be an attractive intermediate for the synthesis of 4-epidihydroeudesmol (VIII) through the following route.
CHART-8

XLIII \rightarrow XLIV

XLIV \rightarrow XLV

CH₂I/K \rightarrow XLVII

XLVII \rightarrow XLVIII

XLVIII \rightarrow XLVI

XLVI \rightarrow XLIX

XLIX \rightarrow L

L \rightarrow VIII

VIII \rightarrow L₀
EXPERIMENTAL

6-Epi-santonin (XIX)

Dry dimethylformamide (475 g) was saturated with dry HCl gas (until the weight of DMF increased by 5% of the weight taken). (-)-α-Santonin (XI) (50 gm) was dissolved in it and the solution heated over a waterbath (80-90°) with a reflux condenser provided with a guard tube for 3 to 4 hrs.; left the contents of the flask overnight. The red orange solution was diluted with water (350 ml) and extracted with chloroform (4 x 50 ml). Chloroform layer was washed successively with saturated brine (2 x 100 ml), sodium bicarbonate solution (5%; 2 x 100 ml) and finally with water (3 x 50 ml). Solvent was removed under suction (so that the temperature inside the flask did not exceed 50°) and residue was chromatographed over alumina (Gr. II; 540 gm). Fraction eluted with benzene afforded a solid which on recrystallisation from ethyl acetate and washing the crystals with ether-m-acetone (1:1) mixture furnished 6-epi-santonin (XIX) m.p. 102-103° (lit. 16 102-104°).

Hydrogenation of (-)-6-epi-santonin

6-episantonin (XIX m.p. 10 gm; 102-103°) and 5% Palladised charcoal (0.5 g) in acetone (150 ml; purified by refluxing with pot.permanaganate) was stirred in hydrogen atmosphere (atmospheric pressure 748 m; 23°). Hydrogenated product was filtered and the solvent removed under suction. The residue in benzene was shaken up with sodium hydroxide solution (2%; 750 ml) and the organic layer washed free of alkali with water (3 x 100 ml) combined aqueous alkaline layer kept separately (B).
Benzene layer was dried and solvent removed. Residue was refluxed with methanol-hydrochloride acid mixture (100 ml of the solution containing 2 ml of 10N HCl) for 3 hrs. Cooled, the mixture diluted with water (100 ml) and extracted with ether (3 x 75 ml). The ether extract was washed with saturated brine (2 x 100 ml), then with water (2 x 50 ml). Ether layer was dried and solvent removed to give a solid, which on recrystallisation from methanol furnished the tetrahydrosantonin (XII) (4 gm) m.p. 164°.

(B) Combined aqueous alkaline layer was acidified with dil. HCl (100 ml of 2N HCl) and extracted with ether (3 x 100 ml). Ether extract was washed with saturated brine (2 x 50 ml) followed by water (2 x 100 ml) dried, solvent removed to furnish 3-oxo-4,11β(H)-5α(H)-eudesman-13-oic acid (XIII). This material was used in subsequent experiments without further purification.

Methyl-3-oxo-4,11β(H), 5α(H)-eudesman-13-oate (XXI)

The moisture free 3-keto acid (XIII) in a solution of methanolic-hydrochloric acid mixture (2 ml of 10N HCl in 100 ml of the solution) was refluxed for 3 hrs. The mixture was cooled diluted with water (100 ml) and extracted with ether (3 x 100 ml). The ether extract was washed free of acid with saturated brine (3 x 50 ml), water (2 x 50 ml), dried and solvent removed. Residue (8.4 gm) was distilled to furnish the methyl ester (XXI) b.p. 170-190° (bath temp.)/3 mm; yield 4.8 gm; (α)D26° + 39° (c, 2.3 in CHCl3). IR spectrum (in liquid film) shows bands at 5.7μ, 5.8μ (scissoring) 6.85, 7.2, 7.4, 7.93, 8.6, 9.2, 9.4, 10, 10.5, 11.2, 11.4, 11.7, 12.7 and 13.1μ. NMR spectrum (in CCl4) shows signals at 9.087 (C12-D4).
J = 7 cps); 8.927 (3H, singlet, angular CH$_3$ on C$_{10}$); 8.897 (1H, doublet, C$_4$- CH$_3$); 6.287 (3H, singlet -CO$_2$CH$_3$).

**2:4-Dinitrophenylhydrazones of methyl ester (XXI)**

The methyl ester (XXI; 0.139 gm) and 2:4-dinitrophenylhydrazine (0.120 gm) in methanol (10 ml) were refluxed for 15 minutes; conc. HCl (0.5 ml; 10N) was added to the above and continued the reflux for 15 more minutes. The solid that separated out was crystallised from methanol m.p. 150-51° (lit. reports 150-51). Mixed m.p. with authentic sample was undepressed.

NMR spectrum shows signals at 8.997 (3H, singlet, angular-CH$_3$ on C$_{10}$); 8.837 and 8.797 (two doublets, J = 7 cps; -CH$_3$ on C$_4$ and C$_{11}$); 6.287 (3H, sharp singlet -CO$_2$.CH$_3$).

**Reduction of ketoester (XXI) with Adams catalyst**

The keto ester (XXI; 2.15 gm) in a mixture (50:3) of glacial acetic acid (50 ml) (purified by refluxing over chromium oxide) and conc. hydrochloric acid (3 ml; 10N, HCl) was stirred with platinum oxide catalyst (0.2 gm) in an atmosphere of hydrogen (30 ml; atmospheric pressure 742 mm; 28°). The solution was filtered free of catalyst and the filtrate was diluted with water (100 ml) and some acetic acid removed under suction. The residual solution was treated with saturated ammonium sulphate solution (100 ml) and extracted with ether (3 x 100 ml). Ether layer was washed with sodium carbonate solution (2 x 50 ml) followed by water (2 x 50 ml). Ether extract was dried and solvent removed to furnish the product (1.8 gm) which was purified through chromatography over alumina.
Pet. ether: benzene mixture (1:1, 100 ml)
eluate on removing the solvent furnished a residue (0.85 gm),
which was distilled at 140-160°(bath temp.)/3 mm to furnish the
pur ester (XXVII) (α) 26° Nl.

**Analysis**

Found: C, 69.64; H, 9.74

C_{18}H_{30}O_{4} requires: C, 69.84; H, 9.68%.

**IR spectrum** (liquid film) shows bands at 5.7, 6.8, 7.2, 8, 8.7,
9, 9.2, 9.8, 10, 10.3, 10.7, 11.8 and 13.1μ.

**NMR spectrum** (in CCl₄) shows signals at: 8.007 (3H, singlet
CH₃-C-O) 6.377 (3H, singlet, -CO₂CH₃) 5.17 (1H, half height width
7 Hz) equatorial proton on C₃-H).

**Conversion of hydroxy acid (XXVIII) to methyl-3-hydroxy-4,

A solution of the hydroxy acid (XXVIII; 1.20 gm) in
methanolic hydrochloric acid (50 ml of the mixture; 2 ml of
10N HCl in 48 ml of methanol) was refluxed for 3 hrs. Refluxed
mixture was diluted with water (50 ml) and the product was
isolated in the usual manner. Removal of the solvent followed
by distillation at 175°-190° (bath. temp.)/2 mm furnished the
methyl ester (XXIX; 1.10 gm).

**Analysis**

Found: C, 71.242; H, 10.44

C_{16}H_{28}O_{3} requires: C, 71.60; H, 10.52%.

**IR spectrum** (in liquid film) showed bands at 2.9, 3.4, 5.7, 6.83,
7.2, 7.9, 9.1, 9.1, 9.5, 9.8, 10, 10.4, 10.5, 11, 11.25, 11.4,
11.8, 12.1 and 13.1μ.
NMR spectrum (showed signals at 6.47 (-CO-CH₃) which overlaps with the signal due to C₃-H.

**Acetate of the hydroxy acid (XXVIII)**

The hydroxy acid (XXVIII; 1.64 gm) in freshly distilled acetic anhydride (3.21 gm) and freshly fused sodium acetate (1.1 gm) was refluxed for 2 hrs. The cooled solution was poured on to ice cold sodium carbonate solution (10% 30 ml). The mixture was stirred overnight and the solution shaken with ether and ether extract rejected. The aqueous layer acidified with dil.HCl (2N, 30 ml) and the product isolated with ether (2 x 50 ml). Ether extract was washed with saturated brine (2 x 50 ml) and removed by water (2 x 50 ml). The ether layer was dried and the residue (1.08 gms; XXVIIIa), on NMR spectrum showed signals at 8.00 (3H, singlet, CH₃-C-O).

(a) **Lead tetraacetate decarboxylation of the acetate (XXVIIIa) to the acetoxy acetate (XXVIIIb)**

(b) **Saponification of the acetoxy acetate**

The acid (XXVIIIa) in a mixture of (0.6 ml) dry pyridine and dry benzene (25 ml) was refluxed with lead tetraacetate (3 gms) for four hours in N₂ atmosphere. Refluxed mixture was cooled and the excess of the lead tetraacetate was destroyed by adding ethylene glycol (2 ml). Diluted the mixture with 10 ml of water and the benzene layer removed. The aqueous layer shaken with benzene (2 x 10 ml) and combined benzene layer was washed with dil.HCl solution (5%, 5 ml). Benzene layer was washed with sodium carbonate solution (2 x 10 ml, 2%), saturated
ammonium sulphate solution (2 x 20 ml) and finally with water (2 x 20 ml). Benzene layer was dried and solvent removed under suction. Residue (XXVIIIb; 0.58 gm) was distilled at 140-160° (bath temp.)/3 mm. NMR spectrum (in CCl₄) showed signals at 9.027 (CH₃ at C₁₀) 8.007 (1H, CH₃-O, single) 5.17 (1H, half height width 7 Hz; equatorial proton at C₃-H).

Saponification of acetoxy compound (XXVII) to 3-hydroxy-4-
11. 8(H). 5(α)H-eudesman-13-oic acid (XXVIII)

A solution of the acetoxy compound (XXVII; 1.8 gm) in 100 ml of methanolic KOH (5 gms of KOH in 100 ml of methanol) was refluxed for 3 hrs. The reaction mixture was cooled and diluted with water (50 ml). Unsaponified matter was removed by shaking with ether (2 x 75 ml) and rejected. Aqueous alkaline layer was acidified with dil. HCl (2N HCl; 150 ml) and the product isolated with ether (3 x 50 ml). The ether extract was worked up, and solvent removed to furnish the hydroxy acid (XXVIII; 1.6 gm) which was taken up for esterification.

Dehydration of the hydroxy ester (XXIX) to Δ³-ester (XXVI)

A solution of hydroxy ester (XXIX 0.268 gm; 1 m mole) in dry pyridine (2.4 ml) and POCl₃ (0.146 ml; 33 m moles) was refluxed for 2.5 hrs. Cooled the contents and poured on to ice-cold dil. HCl acid (50 ml of 2N HCl) and stirred. The Product was isolated with ether and ether layer was washed free of acid.
with saturated ammonium sulphate solution (2 x 50 ml) followed by water. After drying the ether extract, the solvent was removed. The residue (0.12 gm; yield 50%) on distillation at 135°-165° (bath temp.)/3 mm furnished the olefinic ester (XXVI). IR spectrum shows bands at 3.5, 5.8, 6.1, 7, 7.3, 7.5, 7.7, 8, 8.4, 8.7, 9.2, 9.8, 9.9, 10.0, 10.5, 11.8, 12.2, 12.6 and 13.5 μ.

NMR spectrum (in CCl₄) showed signals at 9.057 (C₁₀⁻CH₃) 8.47 (3H, singlet, C₄⁻CH₃) 6.397 (3H, singlet -CO₂-CH₃) 4.657 (1H, broad C₃⁻H olefinic).

**Method II**

To a solution of hydroxy ester (XXIX; 0.70 gm. 3.26 m.mol) in methylene dichloride (17 ml; 470 m.mol) and dry pyridine (3.12 ml; 57 m mol) at 0° was added POCI₃ (0.7 ml; 9.5 m mol) and stirred overnight. The reacted mixture was poured on to ice (about 50 gms) and extracted with chloroform (3 x 50 ml). Chloroform layer was washed with dil. H₂SO₄ (20 ml; 2N), then with sodium carbonate solution (5%; 50 ml) and finally with water (2 x 500 ml), dried and solvent removed. Residue (0.7 gm) was chromatographed over alumina (Gr. II, 20 gm) and successively eluted with pet. ether (100 ml); pet. ether; benzene (1:1) (100 ml) and finally with benzene (100 ml). Fraction eluted with benzene (0.469 gm) on distillation at
165-195° (bath temp.)/3 mm afforded the olefinic ester (0.4 gm, XXVI) IR and NMR spectra were identical with the olefinic ester (XXVI) prepared by alternative methods (see page 45).

**LAH reduction of the unsaturated ester (XXVI)**

A solution of the unsaturated ester (XXVI; 0.3 gm) in dry ether (60 ml) was added to a stirred suspension of LAH (0.3 gm; 6 m mole) in ether (20 ml). The mixture was heated under reflux for 3 hrs. Excess of LAH was destroyed carefully and processed in the usual manner. Removal of the solvent afforded a product (0.23 gm) which on distillation at 140-160°(bath temp.)/3 mm furnished the alcohol (XXXa). [TLC developed with 12% EtoAc in benzene gave Rf value 0.69; (single spot for XXXa).]

**Analysis**

Found: C, 79.98; H, 11.81.

C_{15}H_{26}O requires: C, 81.02; H, 11.81%.

IR spectrum shows the bands at 2.79µ (-OH).

NMR spectrum (page No.64) shows signals at 8.47 (3H, singlet, C_{4} - CH_{3}) 8.047 (1H, singlet, vanished with D_{2}O exchange) 6.57 (2H, multiplet, -CH_{2}OH) 4.657 (1H, broad, C_{3}-H).

**Birch reduction of (−)-α-santonin**

To a solution of (−)-α-santonin (XI) (20 gm) in dry tetrahydrofuran and liquid ammonia (2.5 litres) was added lithium metal pieces (6 gms) over a period of 10 minutes with stirring. After the addition of the metal, the stirring was continued for 15-20 minutes and thereafter solid ammonium
chloride was added (55 gm) in portions over a period of 10 minutes resulting in the discharge of blue colour of the reaction mixture. Ammonia was allowed to evaporate by keeping the flask overnight at room temperature; the residue was diluted with water (500 ml) and acidified with dil. sulphuric acid (2N; 300 ml) till solution was acidic. The acidified mixture was extracted with ether (3 x 250 ml), and worked up in the prescribed manner. The ether solution was dried and solvent removed. Solid that separated was recrystallised from hexane-acetone mixture (1:1; 80 ml) to furnish the crystalline acid (XII; 15 gms) m.p. 123-4° (lit. 4 125-26°). NMR spectrum showed signals at 8.767 (angular CH₃); 8.777 (doublet, J = 7 cps, C₁₁ - CH₃); 8.257 (3H, singlet, C₄-CH₃) and -1.037 (-CO₂H).

Conversion of unsaturated acid (XII) to saturated acid (XIII)

To liquid ammonia (500 ml) was added with stirring Li (200 mg) and an ethereal solution (100 ml) of the unsaturated acid (2 g) under anhydrous conditions. After stirring for 30 minutes ammonium chloride was added gradually till the blue colour was discharged. After keeping overnight the reaction mixture was acidified with cold dil. H₂SO₄ (100 ml) and extracted with ether to furnish a viscous acidic material (1.977 g). The crude acid on esterification with methanolic hydrochloric acid (100 ml; 2 ml of 10N HCl) furnished the keto ester (XXI) (see page No.40). IR and NMR of the acid and
its ester was identical with the one reported earlier (see page No. 40).

**Oxidative decarboxylation of the keto acid (XIII) with lead tetraacetate**

The keto acid (XIII; 2.2 gms; 8.4 m mole) in dry benzene (30 ml) and dry pyridine (1.9 ml) was treated with a suspension of lead tetraacetate (8.4 gm) in benzene and the mixture stirred under reflux in an atmosphere of N₂ for 5 hrs. Cooled and excess of lead tetraacetate was destroyed by ethylene glycol (2 ml). The mixture was taken up in benzene (30 ml) and washed with sodium carbonate solution (50 ml; 5%). Benzene layer was washed free of alkali with saturated brine (2 x 50 ml) followed by water; (2 x 50 ml), dried and solvent removed with a fractionating column. Residue was distilled at 180-200 ° (bath temperature) 3 mm to furnish the keto ester (XXXVII; 0.8 gm (α) D 26° + 32° (c, 1.4, CHCl₃). IR spectrum (in liquid film) showed bands at 3.5, 6.0, 6.9, 7.2, 8, 8.8, 9.5, 9.8 and 10.6 μ.

NMR spectrum (page No. 65) (in CCl₄) showed signals at 8.007 (3H, singlet, -O-COCH₃).

**Saponification of keto-ester (XXXVIIa) to keto alcohol (XXXVIIb)**

Ketoester (XXXVIIa; 1.1 gm) in ethanolic KOH solution (1.5 gm of KOH in 60 ml of ethanol) was saponified under reflux for 3 hrs. The product worked up in the usual manner (ref. page 50) to furnish the keto alcohol (XXXVIIb; 0.95 gm). IR spectrum showed characteristic bands at 2.8 μ and 5.94 μ.
2:4-Dinitrophenyl hydrazone of the keto alcohol (XXXVIIb)

A solution of keto alcohol (XXXVIIb; 0.3 gm) and 2:4-dinitrophenyl hydrazine (0.3 gm) was refluxed for 30 minutes. Conc. HCl (10N, 2 ml) was added to the refluxing solution and continued reflux for 30 more minutes. Cooled the mixture and the product was isolated with chloroform (3 x 25 ml) and worked up in the prescribed manner. After removing the solvent, the residue (0.4 gm) was chromatographed over alumina (Gr. III) and eluted successively with pet.ether (100 ml); pet.ether:benzene (3:1; 100 ml). Solid from the pet.ether:benzene eluate was crystallised from methanol to afford the hydrazone m.p. 121-23°.

Analysis

Found: C, 59.36; H, 7.20

C₂₀H₂₀N₄O₅ requires: C, 59.39; H, 6.98%.

Jones oxidation of ketoalcohol (XXXVIIb) to diketone (XXXVIII)

A solution of ketoalcohol (XXXVIIb; 0.2 gm) in acetone (10 ml) at 0° was stirred with Jones' reagent (8N, 1 ml) and the excess of the oxidant destroyed with ethanol (1 ml). The mixture was diluted with water (10 ml) and isolated the product with ether. Worked up the ether extract in the prescribed manner and solvent was removed, and distilled at 60-180° (bath temp.)/4 mm 0.09 gm to give (XXXVIII). IR spectrum showed bands at 5.8µ.

NMR spectrum agreed with that of the authentic sample.

(a) Preparation of the ketone (XXXII)

Saponification of the unsaturated ester (XXXVI) to the acid (XXX)
(b) Oxidative decarboxylation of the unsaturated acid to the acetate (XXXIa)

(c) Saponification of the acetate to the unsaturated alcohol (XXXIb) and Jones' oxidation of the alcohol to ketone (XXXII)

(a) Saponification of the unsaturated ester (XXVI)

Unsaturated ester (XXVI; 0.29 gm) in methanolic solution of sodium hydroxide (50 ml; 1.75 gm of NaOH in 50 ml of methanol) was refluxed for 3 hrs. Cooled, diluted the refluxed mixture with water (100 ml) and shaken with ether to remove unsaponified matter and rejected. The aqueous alkaline layer was acidified with dil. HCl (75 ml; 2N HCl) and extracted with ether (3 x 50 ml). Ether extract was washed with saturated ammonium sulphate solution (2 x 50 ml), water (2 x 75 ml) dried, and solvent removed. The residue (XXX; 0.285 gm) was taken for decarboxylation without further purification.

(b) Decarboxylation of the acid (XXX)

The acid (XXX, 0.27 gm) in a mixture of dry pyridine (0.5 ml) and dry benzene (20 ml) was refluxed with lead tetraacetate (1 gm) for 4.5 hrs. in N2 atmosphere. The mixture was cooled excess of lead tetraacetate was destroyed by adding ethylene glycol (2 ml). Diluted the solution with water (10 ml) and benzene layer was removed. The aqueous layer was shaken with benzene (2 x 10 ml), combined benzene layer was washed with dil. HCl (2N, 5 ml) then with sodium carbonate solution (2 x 10 ml; 2%) followed by saturated brine (2 x 20 ml) and
and finally with water (2 x 20 ml). Benzene layer after drying and removal of solvent furnished the acetate (XXXIa; 0.35 gm).

(c) The acetate (XXXIa; 0.34 g) in methanolic KOH (0.20 gm of KOH in 25 ml of methanol) was saponified under reflux in N₂ atmosphere. The product worked up in the prescribed manner, furnished the alcohol (XXXIb; 0.196 gm.) TLC developed with 30% ethylacetate in benzene showed the absence of the starting acetoxy compound (XXXIa).

Oxidation of unsaturated alcohol (XXXIb) to the ketone (XXXII)

Unsaturated alcohol (XXXIb; 0.15 gm) in acetone (10 ml) was oxidised with Jones reagent (8N; 2 ml) followed the procedure employed for the oxidation of (XXXVIIb) (page No. 49) to furnish the ketone; (XXXII) (b.p. 170-200° (bath temp.)/2 mm; (Yield 0.1 gm).

Conversion of unsaturated ketone (XXXII) to α-eudesmol (I)

Magnesium turnings (0.25 gm) for Grignard reaction and a crystal of iodine was placed in a flask; methyl iodide (10 ml in 15 ml of ether) in ether was added to the metal turnings and stirred in a N₂ atmosphere. The methyl magnesium iodide solution was treated with the ketone (XXXII) and stirred. The contents were refluxed gently, cooled and transferred to a separatory funnel. Excess of the Grignard reagent was destroyed by adding saturated ammonium chloride solution (20 ml) and extracted with ether (2 x 20 ml). Ether layer was washed with water (2 x 25 ml), dried. The solvent was
removed and residue was distilled at 175-200°C (bath temp.)/5 mm to provide (+)-eudesmol (I) (0.014 gm). On TLC developed with 12% EtoAC in benzene it was compared well with authentic sample (donated by Dr. Shetty of NCL). IR spectrum was superimposable on spectrum of an authentic sample of eudesmol (I).

Preparation of the unsaturated ester (XXVI) by Bamford-Stevens reaction.

To a solution of p-toluenesulfonyl hydrazide (1.38 gm; 7.5 mmol) in a mixture of conc. HCl (1 ml; 1N) and methanol (20 ml) was added ketoester (XXI, 1.32 gm; 5 mmol) and the mixture was refluxed for 1.5 hrs. Poured the reaction mixture on to ice cold saturated ammonium sulphate solution (100 ml) and extracted with ether. The ether extract was washed with brine (2 x 50 ml) followed by water (2 x 50 ml); dried and solvent removed. Residue was purified by chromatography over alumina (Gr. II, 70 g). Fraction with benzene eluate furnished hydrazone (XXV) which was taken up for Bamford-Stevens's reaction directly.

The hydrazone (XXV) in hot ethylene glycol (2 ml) was refluxed with sodium ethylene glycolate (1.25 gm of Na in 40 ml of ethylene glycol) in N_{2} atmosphere at 170°-130° for one hour. Cooled the reaction mixture and poured on to ice cold solution of dil. HCl (2N, 200 ml) and extracted with ether (3 x 50 ml), ether solution worked up to give acid (XXVIa),
The acid without further purification was esterified under the same conditions employed to prepare the ketoester (XXI, see page 40). The residue on distillation at 170-190°C (bath temp.)/1 mm afforded a product (0.1206 gm) which was purified by chromatography over alumina (Gr. II, 6 gm) and the fraction with pet. ether afforded unsaturated ester (XXVI). IR and NMR details were identical with those of the samples prepared by alternate method (ref. page 44).

**Hydrogenation of olefinic ester (XXVI) with Adams catalyst**

A solution of unsaturated ester (XXVI; 0.649 gm) in ethanol (50 ml) was stirred with platinum oxide catalyst (0.1 gm) in hydrogen atmosphere (755 gm; 23°C). At the end of hydrogenation the catalyst was filtered and the filtrate diluted with water (100 ml) and isolated the product with ether (2 x 100 ml). On working up, the residue (0.72 gm) was chromatographed over alumina (Gr. II, 30 gm) and eluted with pet. ether (300 ml). Removal of the solvent followed by distillation at 140-150°C (bath temp.)/7 mm furnished the ester (XXXIII; 0.54 gm); \( [\alpha]_D^{230} + 30^\circ \) (c, 2.4 in CHCl₃).

**Analysis**

Found: C, 76.21; H, 11.34

C₁₆H₂₈O₂ requires: C, 76.14; H, 11.18%.

IR spectrum (in nujol) shows bands at 5.75, 6.9, 7.3, 7.4, 8.34, 9.3, 9.1, 9.2, 9.4, 9.5, 10.2, 10.5, 10.8 and 11.8 μ.

NMR spectrum (in CCl₄) shows signals at 6.66J (3H, singlet, -CO₂-CH₃). No signal near 4.66J (absence of olefinic double
(a) **Saponification of the saturated ester (XXXIII) to the acid (XXXIV)**

The saturated ester (XXXIII; 0.6 g) in ethanolic KOH (1.2 gm of KOH in 25 ml of ethanol) was saponified under reflux for 3 hrs. Cooled and diluted with contents with water (100 ml) and shaken with ether (2 x 50 ml) to remove unsaponified matter. The alkaline aqueous layer, acidified with dil. HCl (50 ml; 2N HCl) and worked up in the prescribed manner to yield a residue (0.36 gm). Without further purification it was taken up for decarboxylation.

(b) **Oxidative decarboxylation of the acid (XXXIV)**

The saturated acid (XXXIV; 0.2 gm) in a solution of benzene (10 ml) and dry pyridine (0.1 ml) was treated with lead tetraacetate (1 gm) and repeated the experiment as described in page No.48. Working up the product in the prescribed manner, the residue (0.18 gm) obtained was saponified directly under the same conditions as described in page No.48 to give the alcohol (XXXVa; 0.19 g) which was taken up for Jones oxidation.

(c) **Decarboxylation of the acid (XXXIV) with lead tetraacetate**

The saturated acid (XXXIV; 0.2 gm) in a solution of benzene (10 ml) and dry pyridine (0.1 ml) was treated with lead tetraacetate (1 gm) and repeated the experiment as described in page No.48. Working up the product in the prescribed manner, the residue (0.18 gm) obtained was saponified directly under the same conditions as described in page No.48 to give the alcohol (XXXVa; 0.19 g) which was taken up for Jones oxidation.

**Jones oxidation of the alcohol (XXXVa) to the ketone (XXXVI)**

The alcohol (XXXVa; 0.19) in acetone (10 ml) was stirred with Jones' reagent (1 ml, added in lots of 0.25 ml) at 0°. The product was isolated and worked up as described in page No.49, Solvent on removal, furnished the ketone (XXXVI 0.01459): IR of the ketone thus prepared was identical
with that of the authentic sample.

(a) **p-Toluene sulfonyl hydrazone of α-tetrahydrosantonin (XXII)**

(b) **Bamford-Stevens reaction on the hydrazone (XXIII) to give 6,13 β(H), 5, 7α(H)-eudesm-3-en-6, 13-olide (XXIV)**

(d) **Preparation of hydrazone (XXIII)**

A solution of α-tetrahydrosantonin (XXIII; 1 gm) and p-toluene sulfonyl hydrazide (0.9 gm) in dry methanol and conc. HCl acid (25:3) was refluxed for one hr. The product was isolated with ether (2 x 5 ml) and worked up to give the hydrazone (XXIII 1.23 gm) m.p. 183°; (α)\(^{23}\)D + 56° (c, 2.5 in CHCl\(_3\)).

**Analysis**

Found: C, 63.05; H, 7.65

\[ C_{22}H_{30}O_4N_2S \] requires: C, 63.14; H, 7.23%.

**IR spectrum** (page No.59) shows bands at 3.2, 3.4, 5.4, 6.1, 6.3, 6.8, 7.1, 7.2, 7.5, 8.1, 8.2, 8.4, 8.5, 9.1, 9.7, 10.1, 10.2, 10.6, 10.9, 11.7 and 12.1 μ.

(b) **Bamford-Stevens's reaction of the hydrazone (XXIII)**

The hydrazone (XXIII; 1.023 gm) in sodium ethylene glycolate (1.3 gm of Na in 40 ml of dry ethylene glycol) was refluxed gently in \( \text{N}_2 \) atmosphere for one hour. The product was treated with ice cold dil. HCl (2N HCl, 150 ml). On working up in the prescribed manner with ether, the residue (XXXIV; 0.76 gm) was recrystallised from methanol to furnish 6,13 β(H), 5, 7α(H)-eudesm-3-en-6,13-olide (XXXIV). NMR and IR spectra of the sample (XXXIV) was in agreement with that of the authentic sample.
Conversion of triol (IX) to ditosylate (XLI)

The triol (IX; 1 gm) in a solution of pyridine (20 ml) and p-toluene sulfonyl chloride (1.6 gm) was kept at 60° for 30 minutes at 40-50° for one hour and at room temperature for 48 hours. The reaction mixture was poured on to ice (40 gms) and the product was isolated with ether. Ether extract was washed with dil. HCl (2N; 50 ml) water (2 x 100 ml), dried and solvent removed to furnish the (XLI; 1.2 gm) (IR bands at 9.0µ and 9.1µ due to tosylate). The compound was used for subsequent transformations.

Conversion of ditosylate (XLI) to diido compound (XLII)

A solution of ditosylate (XLI; 1 gm) and sodium iodide (4 gm) in acetone (20 ml) was refluxed for 6 hrs. The reaction product poured on to ice (30 gms) and isolated with ether. The ether extract was worked up to afford the diiodo compounds (XLII) which was purified by chromatography over alumina (Gr.II). Fraction eluted with pet.ether was taken up for subsequent transformation.

Dehydrohalogenation of diiodide (XLII) to elemol (X)

A mixture of diiodide (XLII; 0.6 gm) potassium-t-butoxide (prepared from 0.4 gm of potassium and t-butanol) and dimethyl sulfoxide (40 ml) was stirred overnight at room temperature. The reaction mixture was poured into ice (50 gm) and extracted with pet.ether (2 x 50 ml). The usual working up furnished (0.3 gm) residue which was purified by chromatography over alumina (Grade II, 40 gm). Fraction eluted with
benzene:ether (100 ml) on distillation furnished elemol (X). IR and NMR spectrum of the sample of elemol thus obtained was identical with that of an authentic sample (X).

VPC: Sample of elemol (X) on VPC agreed with the authentic sample of elemol (X) (A 1.83 m x .006 m column polyester at 180° flow rate of H₂ 1.1 ml/sec.; Chart speed 30°/hr. Griffen and George MK 11).

3:5-Dinitrobenzoate of elemol (X)

Elemol (X, 0.1 gm) in dry pyridine (2 ml) was reacted with 3:5 dinitrobenzyl chloride (0.2 gm) at 20°. The reaction mixture was allowed to stand at room temperature for 18 hrs. Dry benzene was added to the mixture and refluxed for 2 hrs. Cooled and ether added (40 ml) and ether extract washed with sodium carbonate (10%, 40 ml) then water, dried and solvent removed. The product (0.15 gm) recrystallised from ethanol m.p. 111° (lit. 112° mixed melting point undepressed.

Monomethyl ether (XLVI of 5, 6-H), 4:6-8(H), eudesman-6:13 diol (XL)

A solution of diol (XL; 0.49 gm) in dry benzene (25 ml) was treated with K-metal (0.26 gm), in N₂ atmosphere and refluxed for 1 hour. Cooled, added to the contents methyl iodide (10 ml) and refluxed the mixture for 3 hours. Excess of potassium metal was destroyed by adding methanol (5 ml). Contents of the flask diluted with water (50 ml) and extracted
with ether. Ether extract on working up, drying and removal of the solvent furnished a product which on distillation at 160-170° (bath temp.)/1 mm furnished the methyl ether (XLVI; 0.35 gm).

**Analysis**

Found: C, 75.64; H, 11.9; -OCH₃ 14.27%

C₁₆H₃₀O₂ requires: C, 75.33; H, 11.39; -OCH₃ 12.2%.

The higher OCH₃ value obtained points to the presence of some dimethylation.
REFERENCES


19. J.W. Powell and M.C. Whiting, Tetrahedron, 7, 305 (1959);


