HISTORICAL

1. Review of Chemical Compounds in Inuleae

The Inuleae are a universal tribe of the Compositae.
The tribe comprises of 200 genera and 2000 species and is
abundant in South Africa and Australia. While Bentham
divided these plants into nine subtribes as follows
(Harborne, 1977) :-

    a) Tarchonanthinae

    b) Plucheinae

    c) Inulinae

    d) Buphthalminae

    e) Filagininae

    f) Gnaphalinae

    g) Agianthinae

    h) Relhaninae

    i) Athrixinae

Merxmüller *et al.* arranged them into three groups (Harborne,
1977) :-

    a) Inulinae

    b) Gnaphaliinae

    c) Arthrixiinae

Some plants from this tribe have been prized by
man. Three of the best known which were used medicinally
in the past are elecampane, *Inula helenium* L. (for treating

chest diseases), fleabane, *Pulicaria dysenterica* Gaertn. (in herbal remedies) and cat's foot, *Antennaria dioica* Gaertn. (for throat infections). Leaves of *Inula* and *Pulicaria* species have been employed as insecticidal sources (Harborne, 1977).

The chemistry of the tribe has not been extensively explored. The only representative survey seems to be of polyacetylenes. The sesquiterpene lactones have only been identified in relatively few members and little work has been done on flavonoid pigments. Fragmentary information on a range of other constituents is also available (Harborne, 1977).

1.1 Terpenoids

Terpenoids are all based on the isoprene molecule: $CH_2=C(CH_3)-CH=CH_2$ and their carbon skeletons are built up from the union of two or more of these C_5 units linked together in various ways and with different types of ring closures, degrees of unsaturation and functional groups. They are then classified according to whether they contain two (C_{10}), three (C_{15}), four (C_{20}), six (C_{30}) or eight (C_{40}) such units. Chemically, terpenoids are lipid-soluble and are located in the cytoplasm of the plant cell (Harborne, 1973; Robinson, 1980).

1.1.1 Monoterpenoids

Over a hundred monoterpenoids (with 10 carbon atoms) are known. They appear to be built of two isoprene

residues and normally have ten carbon atoms. Both cyclic
and open-chain compounds are known. In fact almost every
possible arrangement of ten carbon atoms seems to occur in
nature. They are characteristically colourless, water-
insoluble, steam distillable liquids having a fragrant
odour. Some are optically active (Robinson, 1980).

Open-chain Monoterpene   Cyclic Monoterpene
    (Myrcene)   (Limonene)

The occurrence of monoterpenoids in Inuleae are
shown below (Harborne, 1977) :-

    Achyrocline satureioides DC.   : Caryophyllene;

                                        p-Cymol; Limonene;

                                        Pinene

    Blumea balsamifera DC.   : Borneol; Camphor

    Sphaeranthus indicus Robyns   : Cadinene;

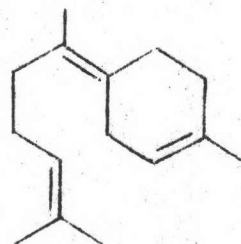   *p*-Hydroxycinnamal-

                                        dehyde; α-Ionone;

                                        Methylchavicol

1.1.2 Sesquiterpenoids

The sesquiterpenoids are C_{15} compounds, usually
regarded as derived from three isoprene residues. They
are found as constituents of steam-distillable essential

oils (Robinson, 1980). Like the monoterpenoids, the
sesquiterpenoids fall chemically into groups according to
the basic carbon skeleton; the common ones are either
acyclic (e.g. farnesol), monocyclic (e.g. γ-bisabolene),
bicyclic (e.g. β-selinene) (Harborne, 1973).
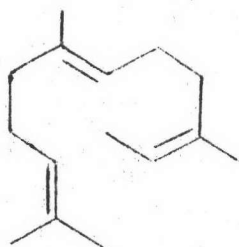
Acyclic Sesquiterpene   Monocyclic Sesquiterpene
    (Farnesol)   (γ-Bisabolene)
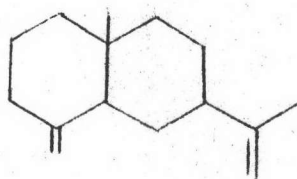
Bicyclic Sesquiterpene
     (β-Selinene)

The occurrence of sesquiterpenoids in Inuleae are
shown as follows :-

Jasonia glutinosa DC.   : α-Epoxy kudtdiol; 5-Epi-

kudtriol; Kudtriol

(Teresa *et al.*, 1980)

Pluchea chingoyo   : Cuauhtemone; Plucheinol

(Chiang *et al.*, 1979)

Pluchea foetida (L.) DC. : **4α**-Acetoxy-3**α**-(2-methyl-

2,3-epoxy-butyloxy)-11-

hydroxy-6,7-dihydroxy-

eudesman-8-one;

Cuauhtemone

(Bohlmann and Mahanta, 1978)

P. rosea Godfrey : Cuauhtemone

(Dominguez *et al.*, 1981)

P. suaveolens Kuntze : 3-σ-Angeloyl-3-epi-

cuauhtemone-4-O-acetate;

3-σ-Angeloyl-3β-ange-

loyloxy-11-hydroxy-6,

7-dehydroeudesman-8-

one; 4α,11-Dehydroxy-

3β-angeloyloxy-6,7-

dehydroeudesman-8-one

(Bohlmann *et al.*, 1980)

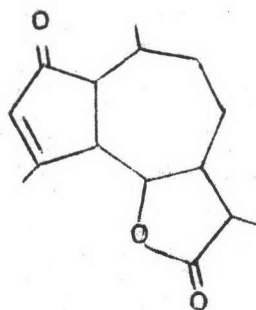### 1.1.3 Sesquiterpene lactones

The sesquiterpene lactones are the combination of sesquiterpene group with lactone ring. Distributional studies reveal that they are rare except in the Compositae. Most characteristic of sesquiterpene lactone compounds in Inuleae tribe are Eudesmanolide, Germacranolide, Guaianolide and Pseudoguaianolide (Harborne, 1977).
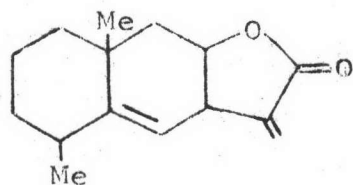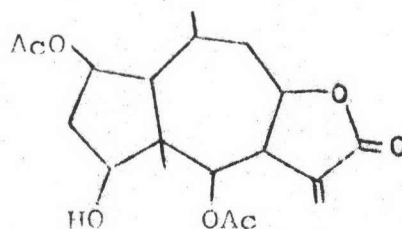
Eudesmanolide
(Alantolactone)
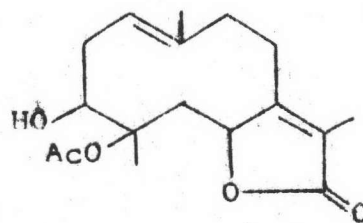
Germacranolide
(Gafranin)

Guaianolide
(Carpesia lactone)

Pseudoguaianolide
(Britannin)

The occurrence of sesquiterpene lactones in Inuleae are shown as follows :-

|	
Carpesium abrotanoides L.	: Carpesia lactone
(Harborne, 1977)	
Codonocephalum grande O.et R. Fedtsch	: Alantolactone; Dihydroalantolactone; Isoalantolactone
(Harborne, 1977)	
Geigeria africana Gries	: Gafranin; Geigerin; Geigerinin; Vermeerin
(Harborne, 1977)	
Inula britanica Bieb.	: Britannin
(Harborne, 1977)	

Inula grandis Shrenk : Carabrone; Granilin;

Ivalin

(Harborne, 1977)

I. graveolens Desf. : Graveolide

(Harborne, 1977)

I. helenium L. : **Alantolactone**; Dihydro-

alantolactone;

Isoalantolactone

(Harborne, 1977)

I. japonica Thunb. : Inulicin

(Harborne, 1977)

I. magnifica Lipsky : Alantolactone; Dihydro-

alantolactone;

Isoalantolactone

(Harborne, 1977)

I. racemosa Hook.f. : Alantolactone; Dihydro-

alantolactone;

Isoalantolactone

(Harborne, 1977)

Pluchea dioscorides DC. : Sesquiterpene lactone

$(C_{20}H_{26}O_6)$

(Bohlmann and Grenz, 1969)

P. rosea Godfrey : 8,9-Dehydroixtlixochilin;

8,9-Dehydroixtlixochilin-

4-O-acetate; 8β-Hydroxy-

ixtlixochilin-4-O-acetate

(Dominguez *et al.*, 1981)

Telekia speciosa (Schreb.)   : Alantolactone;

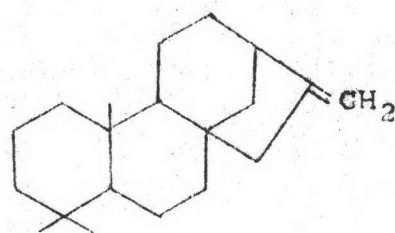Baumg.   Dihydroalantolactone;

Isoalantolactone;

Telekin; Isotelekin

(Harborne, 1977)

1.1.4 Diterpenoids

The diterpenoids are C_{20} compounds which are derived from four isoprenoid residues. Most of them have high boiling points. They are found in resins, gummy exudates and in the resinous high boiling fractions remaining after distillation of essential oils. Owing to their complexity and difficulty of separation, hence only a few complete structures in this group are known. Acyclic diterpenoid (e.g. alcohol phytol) forms a part of the chlorophyll molecule. Many of the cyclic diterpenoids may be regarded as derived from phytol by ring closures (Robinson, 1980).
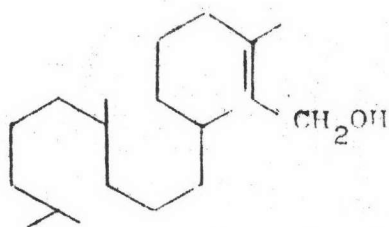
Acyclic Diterpenoid   Cyclic Diterpenoid
(Phytol)   (-)-Kaurene

The occurrence of diterpenoids in Inuleae are shown as follows :-

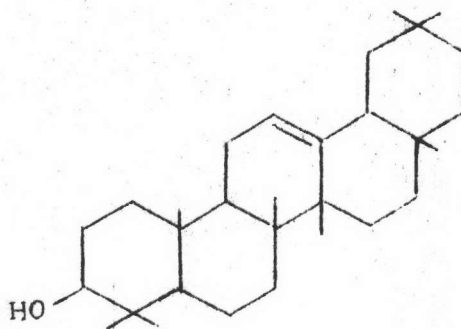*Inula royleana* DC.   : Ferruginol; Inuroyleanol;

Royleanone

(Harborne, 1977)

1.1.5 Triterpenoids

Triterpenoids are widely distributed in plant resins, cork and cutin which their structures are based on six isoprene units. The so-called ricin acids are triterpenoid acids frequently associated with polysaccharide gums in gum resin. Triterpenoid alcohols occur both free and as glycosides. Many of the glycosides are classed as saponins (Robinson, 1980). There are simple triterpenes such as the widely occurring β-amyrin, triterpene lactones such as the bitter limonin of *Citrus* peel, triterpenes based on cholesterol such as diosgenin of *Dioscorea* root (Harborne, 1973). No triterpenoids so far have been found to have monocyclic or dicyclic structures. Tricyclic ones are rare. Several tetracyclic triterpenoids are known. The most important and widely distributed triterpenoids are the pentacyclic compounds (Robinson, 1980).
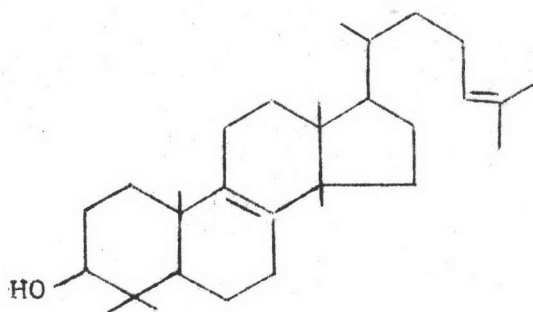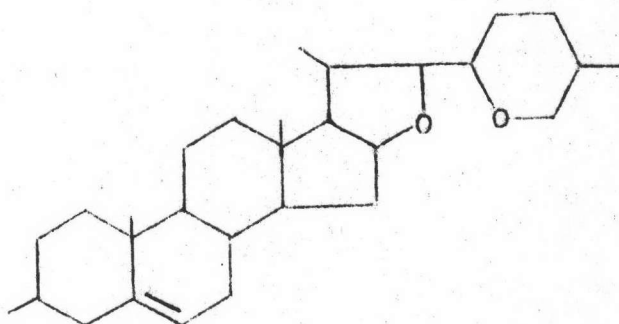
Tetracyclic Triterpenoid   Pentacyclic Triterpenoid

(Lanosterol)   (β-Amyrin)
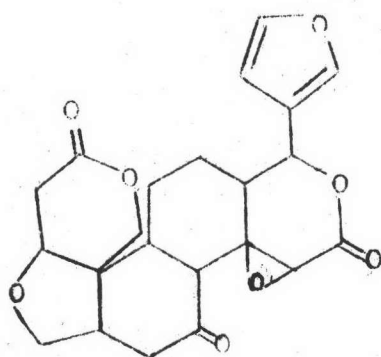
Triterpene Lactone   Triterpene based on cholesterol
(Limonin)   (Diosgenin)

The distribution of triterpenoids in Inuleae are as follows :-

Blumea lacera DC.   : Campesterol

    (Pal *et al.*, 1972)

Helichrysum italicum G.Don : Sitosterol; Ursolic

                                                   acid; Uvaol

    (Manitto and Monti, 1972)

H. steochas (L.) DC.   : Erythrodiol;

                                              Oleanolic acid;

                                              β-Sitosterol;

                                              Stigmasterol;

                                              Ursolic acid; Uvaol

    (Harborne, 1977)

Inula helenium L.   : Dammaradienol;

                                                Friedelin; Stigma-

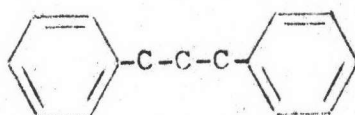   sterol

    (Harborne, 1977)

Pluchea lanceolata L.　　: γ-Sitosterol; Taraxa-

sterol

(Dasgupta, 1967)

P. odcrata Cass.　　　: β-Amyrin acetate;

Campesterol

(Dominguez and Zamudio, 1972)

1.2 Flavonoids

The flavonoid group may be described as a series
of $C_6-C_3-C_6$ compounds. That is, their carbon skeleton
consists of two C_6 groups connected by three carbon
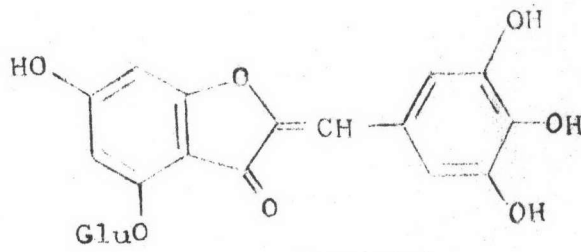aliphatic chain.

Flavonoid skeleton

The different classes within the group are
distinguished by additional oxygen-heterocyclic rings and
by hydroxyl groups distributed in different patterns.
They are all structurally derived from the parent substances
flavone (Robinson, 1980).
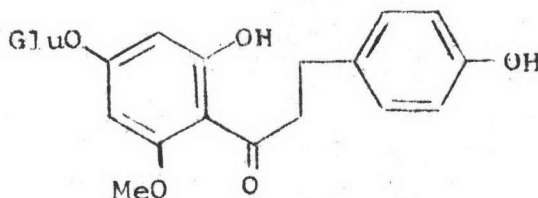
Chalcone

(4,2'-Dihydroxy-4'-glucosyloxy-

6'-methoxychalcone)

Aurone

(Bractein)

Flavonoids identified in Inuleae are as follows :-

Achyrocline satureioides DC. : 3,7-Dimethoxy-5,8-
                                    dihydroflavone

(Harborne, 1977)

Antennaria dioica Gaertn. : Luteolin 7- and 4'
                               glucosides

(Harborne, 1977)

Blumea balsamifera DC. : (2R,3R)-Dihydro-
                            quercetin-4',7-
                            dimethyl ether;
                            (2R,3R)-Dihydro-
                            quercetin-4'-methyl
                            ether

(Ruangrungsi *et al.*, 1981)

B. eriantha DC. : Quercetagetin 3,6
                     7,3',4'-pentamethyl
                     ether

(Harborne, 1977)

Gnaphalium affine Urv. : Luteolin 4'
                            glucoside

(Harborne, 1977)

Gnaphalium multiceps Wall. : 4,2'-Dihydroxy-4'-

glucosyloxy-6'-

methoxy chalcone;

Luteolin 4'-glucoside

(Maruyama *et al.*, 1974)

G. obtusifolium L. : 3,5-Dihydroxy-7,8-

dimethoxy flavone;

5,7-Dihydroxy-8-subst-

flavone; 5-Hydroxy-3,

7,8-trimethoxy flavone;

3,5,7-Trihydroxy-6,8-

dimethoxy flavone

(Harborne, 1977)

Helichrysum affine D.Don : 2',6'-Dihydroxy-4-

glucosyloxy-4'-methoxy

chalcone

(Harborne, 1977)

H. arenarium L. : Galangin; Kaempferol

3-glucoside; Naringenin

(Harborne, 1977)

H. bracteatum Andr. : Bractein; Eriodictyol;

Homoeriodictyol; 3,5-

Dihydroxy-6,7,8-tri-

methoxy flavone; 5,4'-

Dihydroxy-6,7-dimethoxy

flavone; 5,7,4'-Tri-

hydroxy-6,3'-dimethoxy

flavone; 3,4,2',4!,6'-
pentahydroxy chalcone 2'-
glucoside; 3,4,5,2',4',
6'-Hexahydroxy chalcone
3'-glucoside; Kaempferol
3-glucoside; Orientin;
Iso-orientin

(Harborne, 1977)

Helichrysum graveolens : 3,5-Dihydroxy-6,7,8-Tri-
Sweet   methoxy flavone

(Harborne, 1977)

H. italicum G. Don   : 5,7-Dihydroxy-3,8-di-
methoxy flavone

(Harborne, 1977)

H. kraussii Sch. Bip.   : 3,5-Dihydroxy-6,7,8-tri-
methoxy flavone;
Quercetin 3(6-p-coumaryl
glucoside); Quercetin 3-
methyl ether

(Harborne, 1977)

H. polyphyllum Ledeb.   : Naringenin 5-glucoside
(Harborne, 1977)

Inula grandis Shrenk   : 5,6,4'-Trihydroxy-3,7-
dimethoxy flavone

(Harborne, 1977)

Leontopodium alpium Cass. : Luteolin 7 and 4'-

glucosides

(Harborne, 1977)

Pluchea chingoyo DC. : 5,7,4'-Trihydroxy-3,6-

dimethoxy flavone

(Chiang and Silva, 1978)

P. sagittalis (Lam.) : 5,7,3',4'-Tetrahydroxy-

Cabrera   3,6,8-trimethoxy

flavone

(Martino *et al.*, 1976)

Pulicaria dysenterica : 5,6,3'-Trihydroxy-3,

Gaertn.   7,4'-trimethoxy

flavone; Kaempferol

3-glucoside

(Harborne, 1977)

Telekia speciosa (Schreb.) : Luteolin 7-glucoside

Baumg.

(Harborne, 1977)

1.3 Simple Phenolics

The simple phenols are colourless solids when pure,
but usually oxidise and become dark on exposure to air.
Water solubility increases with the number of hydroxy groups
present, but solubility in polar organic solvents is
generally high. Phenols which are only slightly soluble in
water are readily soluble in dilute, aqueous solutions of
sodium hydroxide; but under basic conditions their rate of
oxidation is increased considerably so that any prolonged

treatment with strong alkali should be avoided (Robinson, 1980). The phenolic compounds based on a C_6, C_6-C_2 or C_6-C_3 skeletons have been isolated from individual members of the Inuleae but it is not known whether any of these compounds are at all widespread in the tribe (Harborne, 1977).

MeO─⟨ring⟩ OMe, COMe, OMe
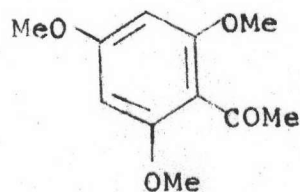
Simple Phenol
(Phloracetophenone trimethyl ether)

The occurrence of phenolic compounds in Inuleae are shown below :-

Blumea balsamifera DC.   : Phloracetophenone tri-
                             methyl ether

(Harborne, 1977)

Helichrysum arenarium L.   : 5,7-Dihydroxyphthalide

(Harborne, 1977)

H. stoechas (L.) DC.   : 2,2-Dimethyl-3-hydroxy-
                             6-acetylchroman

(Quesada et al., 1972)

1.4 Alkaloids

The alkaloids do not represent a chemically homogeneous group, so that any generalisations about them are subject to many exceptions. They all contain nitrogen, frequently in a heterocyclic ring, and many but not all,

are basic as their name indicates. Simple, aliphatic amines are not included here although the distinction is not sharp, ephredrine and mescaline are often placed with the alkaloids although their nitrogens are aliphatic (Robinson, 1980). In Inuleae, alkaloids have been detected in at least eight species but little is known about their chemistry. The only one which has been fully characterised has an aconitine-type structure (Harborne, 1977).

The occurrence of alkaloid in Inuleae is shown below :-

Inula royleana DC. : Diterpene alkaloid

1.5 Polyols and Cyclitols

L-Inositol, unlike the widely distributed D-isomer, has only been so far reported in two families : the Euphorbiaceae and the Compositae. In the Compositae, it occurs in nine of 27 species examined. Among those positive were three Inuleae (Harborne, 1977) :-

Helichrysum arenarium L. : L-Inositol

Inula helenium L. : L-Inositol

Pulicaria dysenterica Gaertn. : L-Inositol

1.6 Lipids

The lipids of the Inuleae seem to be of the usual type. More unusual fatty acid derivatives have occasionally been reported. Thus, β-diketones derived from branched chain organic acids have been found (Harborne, 1977).

The ocurrence of lipid in Inuleae is shown below :-

Helichrysum italicum G. Don   : β -Diketone

1.7 Polyacetylenes

The simple pentayn-ne is universally distributed and two related structures are also widespread. Mono-thiophene acetylenics occur in three groups, while di-thiophene acetylenics are found only in the Buphthalminae. Acetylenics with pyran and furan attachments, some with epoxy and/or chlorine substitution, occur characteristically in the Gnaphalinae. Members of this group contain the most structurally complex polyacetylenes of the Inuleae (Harborne, 1977).

$$CH_3-(C{\equiv}C)_5CH{=}CH_2$$
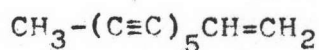
Pentayn-ne

Distribution of polyacetylenes in Inuleae are as follows :-

Calocephalus citreus Less.

Cassinia longifolia R.Br.

Helichrysum apiculatum (Labill.) DC.

Humea elegans Sm.

Ixodia achilleoides R.Br.

Myriocephalus guerinae F.v.M.

Podosperma angustifolia Labill.

(Sørensen, 1977)

2. Chemical Compounds Isolated from *Pluchea* species

Pluchea chingoyo DC. : Cuauhtemone; Plucheinol;

(Chiang *et al.*, 1979)

5,7,4'-Trihydroxy-3,6-

dimethoxy flavone;

(Chiang and Silva, 1978)

5,7,3',4'-Tetrahydroxy-3,

6,8-trimethoxy flavone

(Martino *et al.*, 1976)

P. dioscorides DC.   : Sesquiterpene lactone

$(C_{20}H_{26}O_6)$

(Bohlmann and Grenz, 1969)

P. foetida (L.) DC.   : Cuauhtemone; 4α-Acetoxy-3α

(2-methyl-2,3-epoxy-

butyryloxy)-11-hydroxy-6,7-

dihydroeudesman-8-one

(Bohlmann and Mahanta, 1978)

P. lanceolata L.   : γ-Sitosterol; Taraxasterol;

Plucheine

(Dasgupta, 1967)

P. odorata Cass.   : β-Amyrin acetate;

Campesterol;

(Dominguez and Zamudio, 1972)

Cuauhtemone derivatives

(Bohlmann and Zdero, 1976)

P. rosea Godfrey   : Cuauhtemone; 8,9-Dehydro-

ixtlixochilin;

8,9-Dehydroixtlixochilin-
4-0-acetate; 8β-Hydroxy-
ixtlixochilin-4-0-acetate

(Dominguez *et al.*, 1981)

Pluchea sagittalis   : 5,7,3',4'-Tetrahydroxy-3,
(Lam.) Cabrera   6,8-trimethoxy flavone

(Martino *et al.*, 1976)

P. suaveolens   : 3-σ-Angeloyl-3-epi-
Kuntze   cuauhtemone; 3-σ-Angeloyl-
3-epi-cuauhtemone-4-0-
acetate; 4α-Acetoxy-3β-
angeloyloxy-11-hydroxy-6,7-
dehydroeudesman-8-one; 4α,
11-Dihydroxy-3β-angeloyloxy-
6,7-dehydroeudesman-8-one

(Bohlmann *et al.*, 1980)

P. virgata Less.   : Isochlorogenic acid

(Martino *et al.*, 1979)

3. Biosynthesis of Terpenoids

3.1 Introduction

It has been known for many hundreds of years that
the fragrant odours possessed by many plants are associated
with volatile liquids which can be extractes from the
leaves, fruits, flowers and occasionally other parts of
the plant, and which have come to be known as the essential,
ethereal or volatile oils. Interest in the chemical
constitution of the essential oils became widespread in the

nineteenth century, when they were shown to be complex
mixtures containing acyclic, alicyclic, aromatic and
heterocyclic compounds. Many of the oils were found to
contain, in their more volatile fractions, one or more of
a series of isomeric unsaturated hydrocarbons of formular
$C_{10}H_{16}$, which were judged to be their most characteristic
constituents, and which came to be known as 'terpenes',
from their association with oil of terpentine. The generic
name 'Terpenes' was used to describe all compounds related
to the original 'terpenes'. According to the subsequent
development of this field of chemistry, the term
'terpenoids' is to be preferred since it more appropriately
embraces the wide variety of functional groups, which are
structurally related to the simple terpenes (Templeton,
1966).

Terpenoid compounds may be defined as a group of
natural product whose structure may be divided into
isoprene units. This leads to a rational classification
of the terpenes depending upon the number of such isoprene
units (Hanson, 1972).

Monoterpenes	C_{10}
Sesquiterpenes	C_{15}
Diterpenes	C_{20}
Sesterterpenes	C_{25}
Triterpenes	C_{30}
Tetraterpenes	C_{40}
Polyterpenes	$(C_5)_n$

The monoterpenes and sesquiterpenes are commonly
found as the major components in the volatile oils that
are used as flavouring agents both pharmaceutically and
for culinary purposes. The diterpenes are of little
pharmaceutical value in themselves although certain
diterpene alkaloids do possess pharmacological activity.
Diterpenes also constitute the major components of the
resins. The triterpenes are even more complex in nature
(Ross and Brain, 1977). The sesterterpenes constitute a
small class in the terpenoid family. The tetraterpenes
and polyterpenes, though strictly isoprenoid, are usually
studied separately from the lower classes. The former
also known as carotenoids, are plant pigments; the latter
are polymers such as rubber, gutta-percha and balata
(Templeton, 1966).

As the structure of this group of compounds were
elucidated, it became apparent that many of them could be
regarded as built up of isoprene or isopentane units linked
together in various ways and with different types of ring
closures, degrees of unsaturation, and functional groups.

$$CH_3$$
$$-CH_2-CH-CH_2-CH_2-$$

Isopentane unit
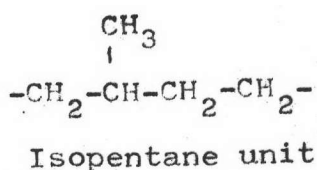
The commonest arrangement appeared to be "head-to-
tail" (Robinson, 1980).

$$C \qquad\qquad\qquad C$$
$$C-C-C-C \quad\rule{3cm}{0.4pt}\quad C-C-C-C-$$
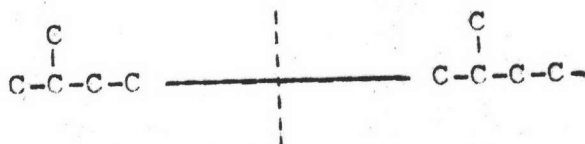
The monoterpenes, sesquiterpenes, diterpenes and sesterterpenes contain the isoprene units linked in a head to tail fashion. The triterpenes and tetraterpenes are made up of two C_{15} and C_{20} units respectively linked in the middle head to head. There are a number of apparent exceptions to this regular isoprenoid backbone. These, however, can be seen to originate in the rearrangement of regular isoprenoid precursors during biosynthesis (Hanson, 1972). All could be accommodated by a "Biogenetic Isoprene Rule" which states that naturally occurring terpenes are derived directly, or by way of stereospecific dimerisations, cyclisations and rearrangements from the acyclic precursor geraniol (C_{10}), farnesol (C_{15}), geranyl geraniol (C_{20}) and squalene (C_{30}) (Banthorpe and Charlwood, 1972).

The biosynthesis of terpenes has been extensively studied using compounds containing C^{14} at "labeled" positions in order to trace the path of particular compounds during biosynthesis. The actual biosynthetic isoprene unit is mevalonic acid, which is synthesised from 3 moles of acetic acid, in the form of acetyl coenzyme A derived mainly from carbohydrate and fat metabolism, *via* normal acylations to a branched skeleton. Formation of the branched skeleton follows a mechanistically sound aldol reaction; this branching constitutes a major biosynthetic, departure from the linear fatty acids and acetogenins (Hendrickson *et al.*, 1970).

The formation of mevalonic acid is shown as follows :-

$$2\ CH_3-CO-S-(CoA) \xrightarrow{\text{C-Acylation}} CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-S-(CoA)$$

$$\xrightarrow[\text{Aldol}]{CH_3CO-S(CoA)} CH_3-\overset{OH}{\underset{CH_2COS(CoA)}{\overset{|}{C}}}-CH_2-\overset{O}{\overset{\|}{C}}-S-(CoA) \xrightarrow{\text{Reduction}}$$
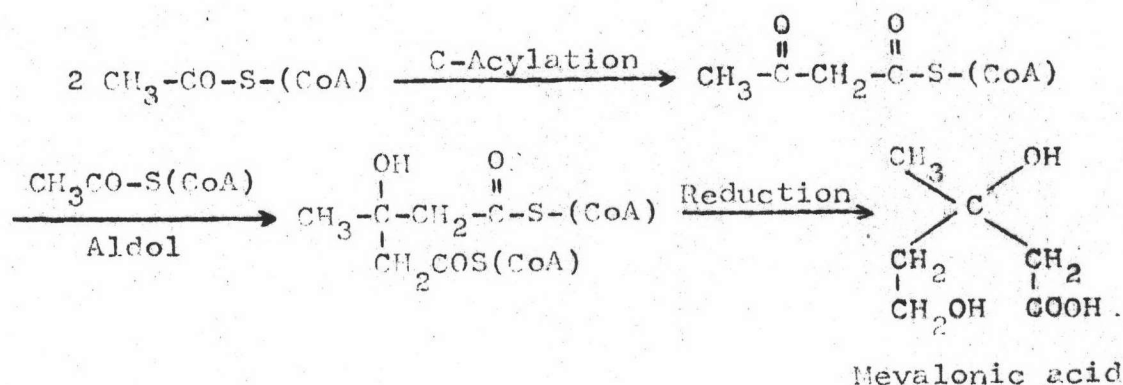
Mevalonic acid

The incorporation of mevalonic acid containing six carbon atoms, into a terpenoid containing a multiple of five carbon atoms obviously requires the loss of one carbon atom per mevalonate unit, and isotope experiments have shown that it is the carboxyl group, C-1 which is lost (Templeton, 1966).

Mevalonic acid is then phosphorylated and decarboxylated to isopentenyl pyrophosphate, the actual biosynthesis isoprene unit (Hendrickson *et al.*, 1970). The mechanism of conversion is shown below :-
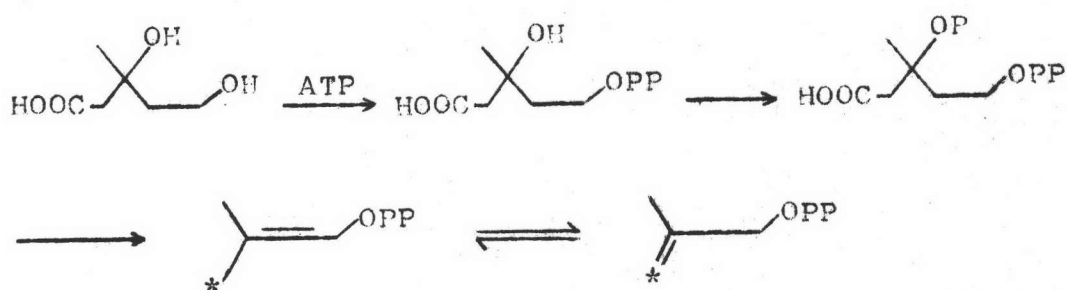
The isopentenyl pyrophosphate isomerises and then dimerises to form geranyl pyrophosphate in an attack of a double bond on the carbonium ion left by ionisation of the

pyrophosphate (Hendrickson et al., 1970). The C_5 units can couple to produce monoterpenes via geranyl pyrophosphate. In the same way as dimethyl allyl pyrophosphate and isopentenyl pyrophosphate can couple, geranyl pyrophosphate can couple with isopentenyl pyrophosphate to produce farnesyl pyrophosphate which affords the sesquiterpenes. Both farnesyl and geranyl pyrophosphate can dimerise. The former yields the triterpenes, via farnesylfarnesyl pyrophosphate and the latter gives the diterpenes, via geranyl geranyl pyrophosphate. Geranylgeranyl pyrophosphate can produce the C_{40} carotenoids by dimerisation (Ross and Brain, 1977). Fig. I
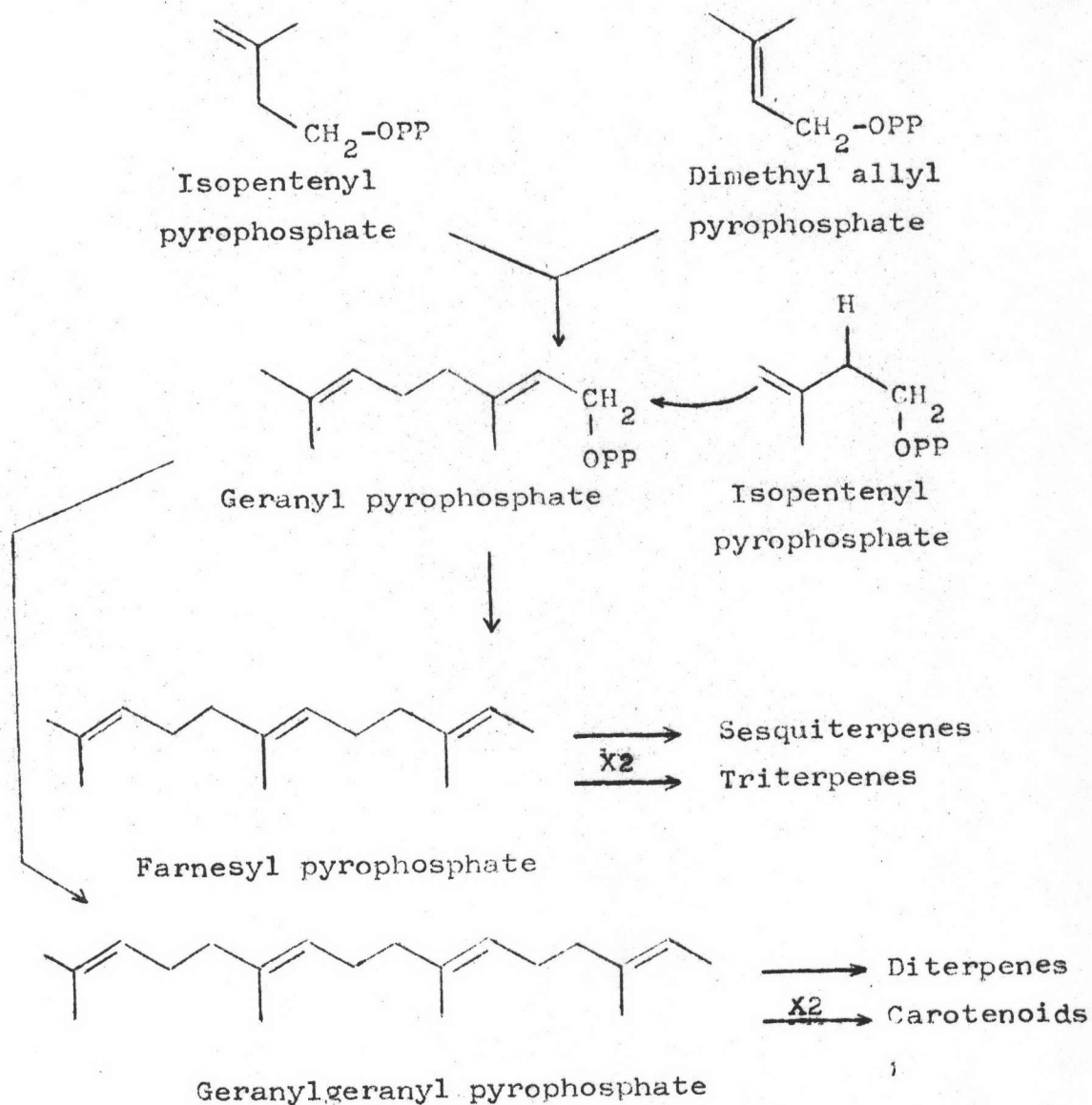
Fig. I Biosynthesis of Terpenoids

Sesquiterpenoids

Sesquiterpenoids are usually characterised as compounds having a basic skeleton of fifteen carbon atoms, formed, similarly to other terpenoids, by a regular repetition of the basic isoprene unit, and occurring mainly in plant material. Such substances have been often encountered in the animal kingdom, especially in insects,

but also in Coelenterata, Mollusca, etc. Not less
numerous are sesquiterpenoids often specifically trans-
formed in the third evolutionary branch of living
organism, the fungi. The occurrence of sesquiterpenoid
derivatives is not limited to moulds, but is even more
frequent in the so-called higher fungi (Herout, 1971).

Many other types of sesquiterpenoids are known to
inhibit plant growth or to be toxic to higher and lower
animals. Some human allergens and agents of contact
dermatitis are in this group. Among the antifungal phyto-
alexins, there are several sesquiterpenoids, particularly
studied in sweet and white potatoes and sweet pepper
plants. Some sesquiterpenoids also have positive effects
(Robinson, 1980). The insect juvenile hormones appear to
be derived from sesquiterpenes and a number of sesquiterpenes
are active against experimental tumours (Hanson, 1972).

Classification of sesquiterpenoids

For the classification of sesquiterpenoid compounds
their carbon skeletons were mainly made use of. Originally
these were grouped according to chemical principles, mainly
the number of rings in the molecule. Nowadays it is
possible to summarise in a very condensed form our present
knowledge of their biogenetical relations (Herout, 1971).

The sesquiterpenes fall chemically into groups
according to the basic carbon skeleton; the common ones
are acyclic, monocyclic and bicyclic (Harborne, 1973).

Acyclic sesquiterpenoids

The most important member is the widely distributed alcohol farnesol which was found in a large number of essential oils. It was the first to be correctly elucidated in the sesquiterpenoid series (**Templeton**, 1966).
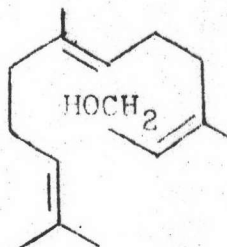
Farnesol

Monocyclic sesquiterpenoids

Most of the monocyclic sesquiterpenoids have the skeleton shown below with variation in double bond location and functional groups (Robinson, 1980).
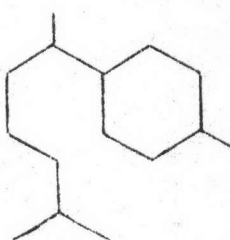
Bisabolane

There are some unusual monocyclic structures found among the sesquiterpenoids that cannot be conveniently constructed from isoprene residues. Presumably rearrangements and oxidation play a part in their formation from isoprenoid precursors. A few examples are given below (Robinson, 1980).
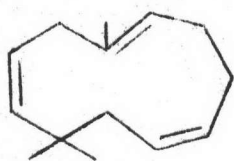
Humulene
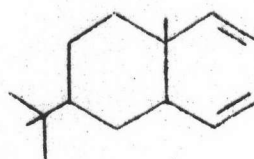
Elemol

Bicyclic sesquiterpenoids

Most of the bicyclic sesquiterpenoids can be divided into naphthalene type and azulene type according to which of these two aromatic structures they give on dehydrogenation. Further subdivision takes into account the locations of substituent groups on the rings. Low temperature distillation may be sufficient to convert some azulenogenic terpenoids into azulenes, and it is generally believed that the azulenes themselves never occur in nature (Robinson, 1980).

Naphthalene type :
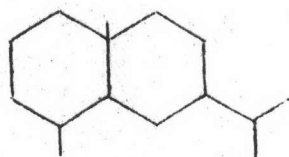
Eudalene
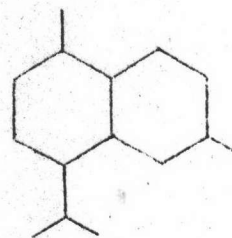
Cadalene

Azulene type :
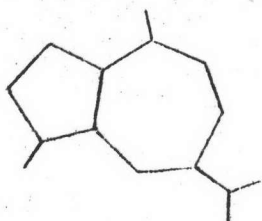
Guaiazulene
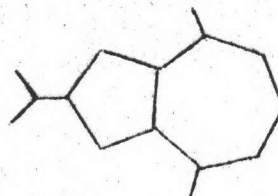
Vetivazulene
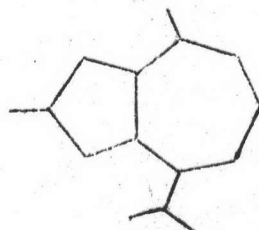
Zierazulene

Additional examples of bicyclic sesquiterpenoids
are also shown to indicate some of the more unusual
structures that are found (Robinson, 1980).
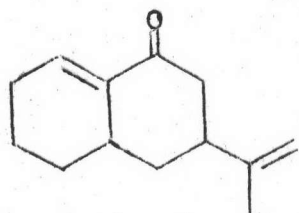
Eremophilone
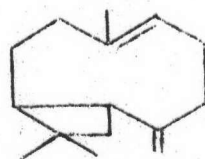
Caryophyllene
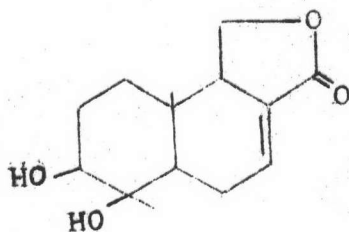
Iresin
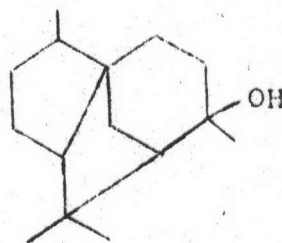
Cedrol

3.2 Biosynthesis of Sesquiterpenoids

The precursor of the sesquiterpenoids, geranyl
pyrophosphate readily condenses with another molecule of
the allyl pyrophosphate to give *trans*-farnesyl pyro-
phosphate (Templeton, 1966). All sesquiterpenes were
originally considered to be derived from cyclisation and
rearrangement of either *trans-trans* farnesol or its *trans-*
cis isomer. More recently the *cis-trans* isomer has been
invoked to account for the stereochemical details in a few

compounds, and the role of farnesyl pyrophosphate rather than the free alcohol has been accepted (Banthorpe and Charlwood, 1972).

The sesquiterpenoids are best classified according to their basic carbon skeletons, virtually all of which can be derived from one or other of the six simple carbonium ions (IV), (V), (VI), (VII), (X) and (XI); these in turn arise from *cis*-farnesyl pyrophosphate (I) *via* the non-classical ions (II) and (III), or from *trans*-farnesyl pyrophosphate (VIII) *via* the ion (IX) (Templeton, 1966).

Fig. II

(II)   (I)   (III)

(IV)   (V)   (VI)   (VII)

(VIII)   (IX)   (X)   (XI)
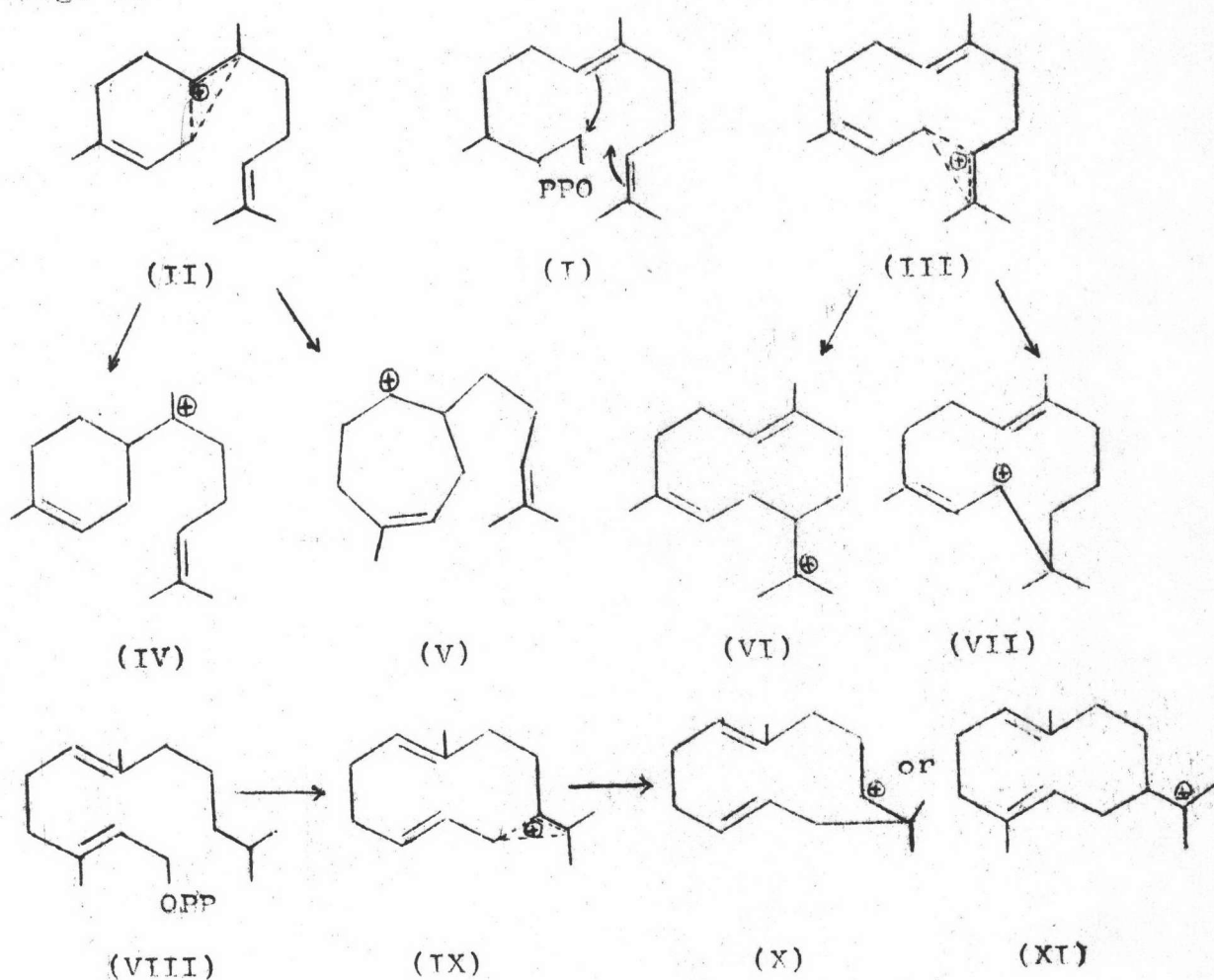
Fig. II   Basic carbon skeleton of sesquiterpenoids

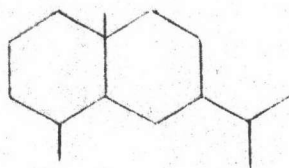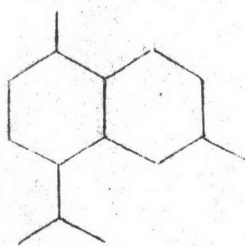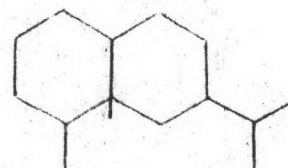The major basic hydrocarbons of the sesquiterpene series are shown below (Nicholas, 1973) :-
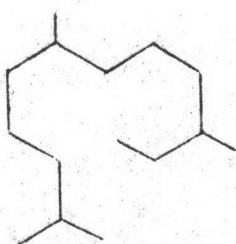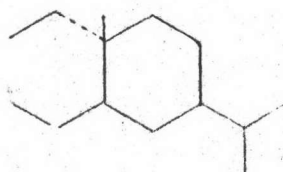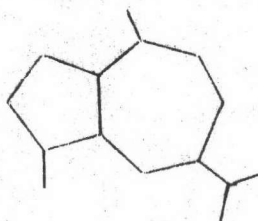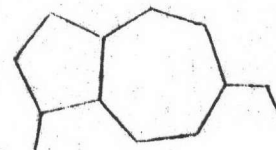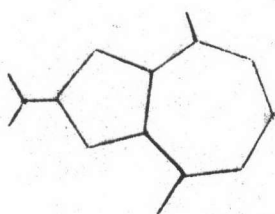
Farnesane
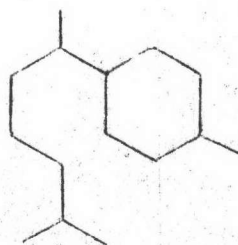
Bisabolane
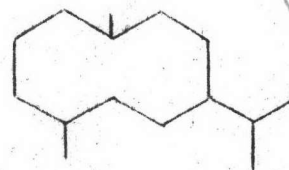
Germacrane

Eudesmane

Cadinane

Eremophilane

Elemane
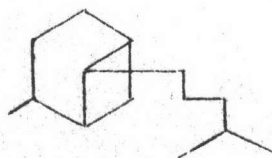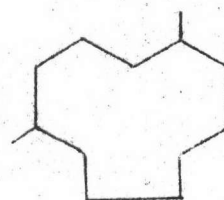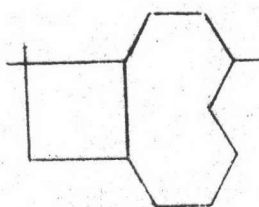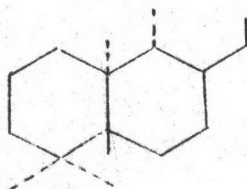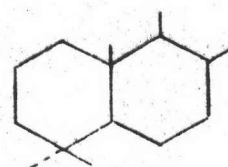
Guai(azulene)

Cham(azulene)

Vetiv(azulene)

Bergamotane

Humulene

Caryophyllene

Iresane

Drimane
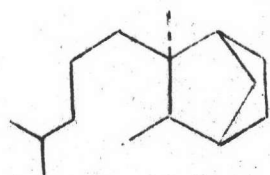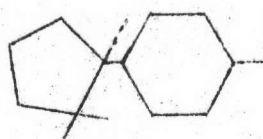
Santalene   Cuparane   Maaline
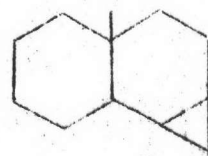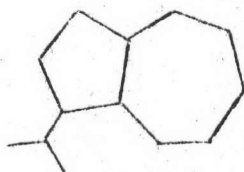
Carotane

3.3 Biosynthesis of Eudesmane
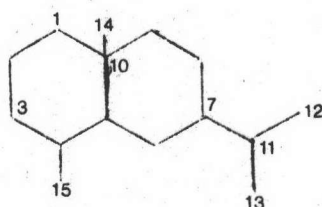
Basic structure of eudesmane

The members of this expanding group give eudalene
on dehydrogenation, with loss of an angular methyl group.
The hydrocarbon β-selinene occurs in the fruit of the
celery plant, and gives a dihydrochloride which, on dehydro-
chlorination, is converted into the isomeric α-selinene.
The structures of the two isomers have been established
from a consideration of their ozonolysis products, and the
natural isomer has been correlated with eudesmol. Among
the numerous alcohols of this group, eudesmol, from which
the group derives its name, was the first to be discovered,
being first isolated in 1897 from eucalyptus oil. Its
carbon skeleton was defined by its dehydrogenation to

eudalene and its conversion into selinene dihydrochloride,
while the position of the double bond followed from its
ozonolysis to the ketone, which could be dehydrogenated in
three steps to 2-isopropyl naphthalene. The location of
the hydroxy group was established by conversion of dihydro-
eudesmol, *via* the chloride, into the isomeric eudesmenes,
which on ozonolysis gave formaldehyde and acetone
respectively, together with the expected ketones (Templeton,
1966). Fig. III

Eudalene

β-Selinene   β-Selinene   α-Selinene

dihydrochloride

Dihydroeudesmol   Eudesmol   Ketone form

Eudesmenes   Eudesmene ketones
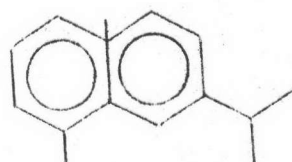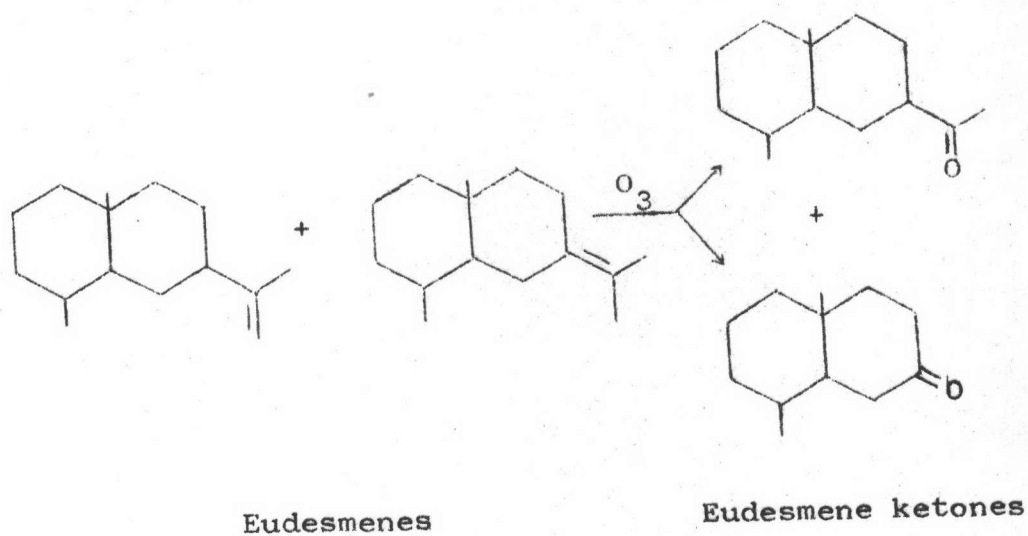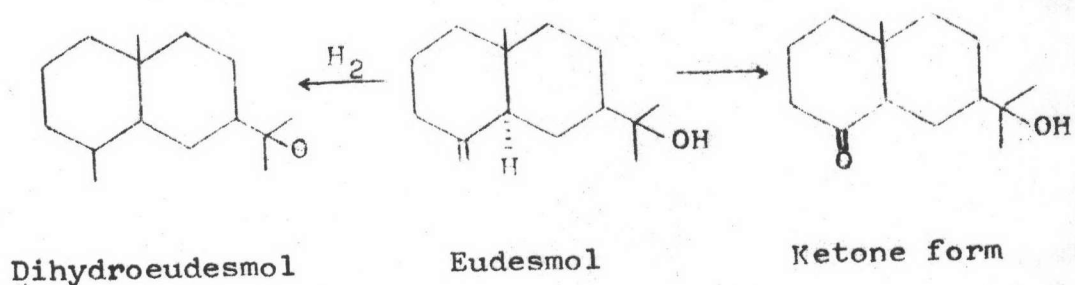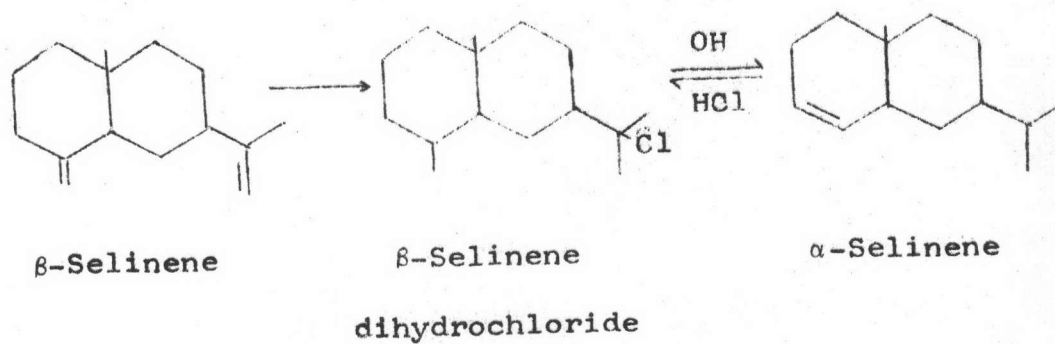
Fig. III   Formation of eudesmene ketones

The generally accepted biosynthesis of eudesmane sesquiterpenes involve first cyclisation of farnesyl pyrophosphate (I) to a cyclodecadiene (germacrane class) (II) followed by further cationic cyclisation to the required skeleton (Schwartz *et al.*, 1972). Fig. IV

(I)   (II)
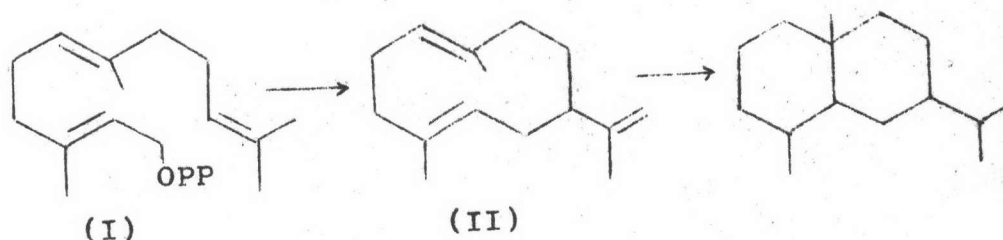
Fig. IV   Biosynthesis of eudesmane

There are many examples of this group including those with furan and lactone rings (usually 6α,12-olides or 8β,12-olides) (Roberts, 1972b).

Eudesmanolides, the sesquiterpene lactone possessing the eudesmane skeleton, owe their origin to an initial cyclisation of farnesyl pyrophosphate to a cyclodecadiene followed by the formation of $-C(COOH)=CH_2$ side-chain and eventual lactonisation after introduction of oxygen at an adjacent position (Gibbs,1974).

The isolation, structural elucidation and total synthesis of sesquiterpene lactone has been a prominent feature of research in the terpenoid area for several years. Much of the interest has been engendered by the fact that many of these compounds are biologically active and exhibit pronounced allergenic fungitoxic, antitumour and antimitotic effects (Money, 1975).

4. Distribution of Eudesmane in Compositae apart from

Pluchea

Arbusculin A

- *Artemisia arbuscula* Nutt.

(Irwan and Geissman, 1971)

Arbusculin E methyl ether

- *A. arbuscula* Nutt.

(Rodriguez *et al.*, 1979)

Arglanine

- *A. douglasiana* Bess.

(Gibbs, 1974)

Artemisin

- *A. maritima* L.

(Gibbs, 1974)

Asperilin

- *Iva asperifolia* Less.

I. texensis Jackson

(Herz *et al.*, 1964)

Atractylon

- *Atractylis japonica* (Koidz ex Kitimura)

Kitakawa

A. ovata Thunb.

(Gibbs, 1974)

Costic acid

- *Saussurea lappa* C.B. Clarke

(Gibbs, 1974)

α-Costol

- *Saussurea lappa* C.B. Clarke

   (Gibbs, 1974)

8-Oxo-β-cyperon

- *Isocoma wrightii* Rydburg

   (Bohlmann and Zdero, 1976)

2β-Acetoxy-8-oxo-β-cyperon

- *I. wrightii* Rydburg

   (Bohlmann and Zdero, 1976)

11-Hydroxy-8-oxo-β-cyperon

- *I. wrightii* Rydburg

   (Bohlmann and Zdero, 1976)

Dihydro-isohelenine

- *Inula helenium* L.

   (Gibbs, 1974)

Douglanine

- *Artemisia douglasiana* Bess.

   (Gibbs, 1974)

Encelin

- *Encelia farinosa* A. Gray

   (Rodriguez *et al.*, 1979)

Eudesmol

- *Atractylis ovata* Thunb.

- *Balsamorhiza sagittata* Nutt.

   (Gibbs, 1974)

- *Tagetes minuta* L.

   (Rodriguez and Mabry, 1977)

(+)-Eudesm-4(14),7(11)-dien-8-one

— *Peteravenia schultzii* (Schmitts) K.et R.

(Endo and Hikino, 1979)

6α-Angeloyloxy-eudesm-4(15)-ene

— *Ageratum fastigiatum* (Gardn.) K.et R.

(Bohlmann *et al.*, 1981)

6β-Cinnamoyloxy-1β-hydroxy-eudesm-3-ene

— *Verbesina luetzelburgii* Mattf.

(Bohlmann *et al.*, 1980b)

6β-Cinnamoyloxy-1β,4β-dihydroeudesmane

— *V. luetzelburgii* Mattf.

(Bohlmann *et al.*, 1980b)

6β-Coumaroyloxy-4β-hydroeudesmane

— *V. macrophylla* (Cass.) Blake

(Bohlmann *et al.*, 1980b)

6β-Feruloyloxy-4β-hydroxyeudesmane

— *V. macrophylla* (Cass.) Blake

(Bohlmann *et al.*, 1980b)

2α-Hydroxy-eudesman-4,6-dien-15-ol

— *Baccharis latifolia* Pers.

B. tricuneata Pers.

(Bohlmann *et al.*, 1979)

5β-Hydroxy-4,15-dehydroeudesmane

— *Senecio rhyncholaenus* DC.

(Bohlmann *et al.*, 1978)

6α-Tiglinoyloxy-4,15-dehydroeudesmane

- *Senecio rhyncholeanus* DC.

(Bohlmann et al., 1978)

Gazaniolide

- *Gazania krebsiana* Less.

(Bohlmann and Zdero, 1979a)

8α-Isovaleryloxy gazaniolide

- *G. krebsiana* Less.

(Bohlmann and Zdero, 1979a)

Ilicic acid

- *Ambrosia ilicifolia* (A. Gray) Payne

(Gibbs, 1974)

Isotelekin

- *A. confertiflora* DC.

(Yoshioka et al., 1970)

Ivangustin

- *Iva angustifolia* Nutt.

(Herz et al., 1967)

Isoivangustin

- *Cyathocline purpurea* Kuntze

(Nagasampagi et al., 1981)

Ivanol

- *Iva annua* L.

(Bohlmann and Zdero, 1979b)

Ivasperin

- *Iva asperifolia* Less.

 I. texensis Jackson

 (Herz and Viswanathan, 1964)

Kudtdiol

- *Flourensia heterolepis* Blake

 (Bohlmann and Jakupovic, 1979)

Pinnatifidin

- *Helenium pinnatifidum* (Nutt.) Rydb.

 (Herz *et al.*, 1962)

Reynosin

- *Ambrosia confertiflora* DC.

 (Yoshioka *et al.*, 1970)

Rothin A

- *Artemisia arbuscula* Nutt.

 (Irwan and Geissman, 1971)

Santamarin

- *Ambrosia confertiflora* DC.

 (Yoshioka *et al.*, 1970)

- *Chrysanthemum parthenium* Bernh.

 (Gibbs, 1974)

α-Epoxysantamarin

- *Ambrosia confertiflora* DC.

 (Yoshioka *et al.*, 1970)

α-Santonin

- *Artemisia brevifolia* Wall.

 A. gallica Willd.

Artemisia mexicana Willd. ex Spreng

A. ramosa C.Sm. ex Link

A. wrightii A. Gray

(Gibbs, 1974)

β-Santonin

- *A. monogyna* Waldst. & Kit.

A. salina Willd.

(Gibbs, 1974)

γ-Selinene-8-one

- *Peteravenia schultzii* (Schmitts.) K. et R.

(Bohlmann and Suwita, 1978)

Torrentin

- *Artemisia herba-alba* subsp. *valentina* Asso.

(Gomis *et al.*, 1978)

Tuberiferine

- *Sonchus tuberifer* Svent

(Gibbs, 1974)

Vulgarin

- *Artemisia vulgaris* L.

(Gibbs, 1974)

5. Other Sources of Eudesmane in Plant and Animal Kingdoms

5.1 Plant Sources

Bromoeudesmane

- *Laurencia* spp. , Rhodophyceae

(Money, 1978)

Canarone

    - *Canarium strictum* Roxb. , Burseraceae

    (Gibbs, 1974)

Carissone

    - *Carissa lanceolata* R.Br. , Apocynaceae

    (Gibbs, 1974)

α-Caryophyllene

    - *Didymocarpus pedicellata* R.Br. , Gesneriaceae

    - *Humulus lupulus* L. , Moraceae

    - *Illicium anisum* L. , Magnoliaceae

    - *Populus nigra* Mill , Salicaceae

    - *Zingiber zerumbet* Rosc. ex Sm. , Zingiberaceae

    (Gibbs, 1974)

Chamaecynone

    - *Chamaecyparis formensis* Matsum , Cupressaceae

    (Roberts, 1972b)

Dehydrochamaecynenol

    - *C. formensis* Matsum , Cupressaceae

    (Roberts, 1972b)

Cryptomeridiol

    - *Cymbopogon proximus* Stapf. , Graminae

    (Locksley *et al.*, 1982)

β-Elemene

    - *Acorus calamus* L. , Araceae

    (Gibbs, 1974)

Ent-5β-hydroxydiplophyllin

   - *Chiloscyphus polyanthus* (L.) Corda , Hepaticae

   - *Diplophyllum albicans* (L.) Dum. , Hepaticae

     (Asakawa *et al.*, 1978)

Ent-3-oxodiplophyllin

   - *Chiloscyphus polyanthus* (L.) Corda , Hepaticae

   - *Diplophyllum albicans* (L.) Dum. , Hepaticae

     (Asakawa *et al.*, 1978)

(+)-Eudesma-4(14),7(11)-diene-8-one

   - *Asarum caulescens* Maxim , Aristolochiaceae

     (Endo and Hikino, 1979)

$4\alpha,5\alpha$-Oxidoeudesm-11-en-3α-ol

   - *Cyperus rotundus* L. , Cyperaceae

     (Hikino and Aota, 1976)

Eudesmol

   - *Baeckea brevifolia* DC. , Myrtaceae

     (Gibbs, 1974)

   - *Eucalyptus piperita* Sm. , Myrtaceae

     (Robinson, 1980)

   - *Leptospermum flavescens* Sm. , Myrtaceae

   - *Machilus kusanoi* Hayata , Lauraceae

   - *Melaleuca uncinata* R.Br. , Myrtaceae

     (Gibbs, 1974)

   - *Pterocarpus santalinus* L. , Leguminosae

     (Kukla *et al.*, 1976)

Cycloeudesmol

    – *Chondria oppositiclada* Dawson , Rhodophyceae

    (Money, 1975)

10-Epi-γ-eudesmol

    – *Rubus rosifolius* Stokes , Rosaceae

    (Money, 1978)

10-Epijuneol

    – *Ferula galbaniflua* Boiss & Buhse , Umbelliferae

    (Thomas *et al.*, 1976)

Gerin

    – *Geraea viscida* (Gray) Blake , Umbelliferae

    (Rodriguez *et al.*, 1979)

(+)-Jujenol

    – *Canarium strictum* Roxb. , Burseraceae

    (Gibbs, 1974)

1-Keto-α-cyperone

    – *Nicotiana tabacum* L. , Solanaceae

    (Roberts, 1972a)

Kudtdiol

    – *Chamaecyparis formensis* Matsum , Cupressaceae

    (Teresa *et al.*, 1980)

Linderalactone

    – *Lindera strychnifolia* Villar , Lauraceae

    – *Neolitsea zeylanica* Merrill , Lauraceae

    (Gibbs, 1974)

Linderane

- *Neolitsea zeylanica* Merrill , Lauraceae

  (Gibbs, 1974)

Neolinderane

- *N. zeylanica* Merrill , Lauraceae

  (Gibbs, 1974)

Linderene

- *Lindera strychnifolia* Villar , Lauraceae

  (Gibbs, 1974)

Linderoxide

- *L. strychnifolia* Villar , Lauraceae

  (Gibbs, 1974)

Lindestrene

- *L. strychnifolia* Villar , Lauraceae

  (Gibbs, 1974)

Magnolialide

- *Magnolia grandifolia* L. , Magnoliaceae

  (El-Feraly *et al.*, 1979)

Maytine

- *Maytenus serrata* (Hochst ex A.Rich)R.Wilczek,

  Celastraceae

  (Money, 1978)

Maytolidine

- *M. serrata* (Hochst ex A.Rich) , Celastraceae

  R.Wilczek

  (Money, 1978)

Maytoline

- *M. serrata* (Hochst ex A.Rich) , Celastraceae

  R.Wilczek

  (Money, 1978)

Occidentalol

    - *Thuja occidentalis* L. , Cupressaceae

    (Roberts, 1972b)

Occidol

    - *J. occidentalis* L. , Cupressaceae

    (Roberts, 1972b)

Opolodiol

    - *Opolopanax japonica* Nakai , Araliaceae.

    (Gibbs, 1974)

Paradisiol

    - *Citrus paradisi* Swingle , Rutaceae

    (Sulser et al., 1971)

Pterocarpol

    - *Daemonorops draco* Blume , Palmae

    - *Pterocarpus macrocarpus* Kurz , Leguminosae

    - *P. santalinus* L. , Leguminosae

    (Nasini and Piozzi, 1981)

Pterocarpdiolone

    - *P. santalinus* L. , Leguminosae

    (Money, 1975)

Pterocarptriol

    - *P. santalinus* L. , Leguminosae

    (Money, 1975)

Reynosin

    - *Magnolia grandifolia* L. , Magnoliaceae

    (El-Feraly et al., 1979)

Rosifoliol

  - *Rubus rosifolius* Stokes , Rosaceae

    (Money, 1978)

Santalene

  - *Santalum album* L. , Santalaceae

    (Gibbs, 1974)

Santalol

  - *Santalum album* L. , Santalaceae

    (Gibbs, 1974)

Santamarin

  - *Magnolia grandifolia* L. , Magnoliaceae

    (El-Feraly *et al.*, 1979)

Selin-3,5-dien-11-ol-2-one

  - *Chenopodium botrys* L. , Chenopodiaceae

    (Teresa *et al.*, 1980)

Selin-4(15)-en-3β,11-diol

  - *C. botrys* L. , Chenopodiaceae

    (Teresa *et al.*, 1980)

Selin-4(15)-en-3α,6α,11-triol

  - *C. botrys* L. , Chenopodiaceae

    (Teresa *et al.*, 1980)

6α-Acetoxyselin-3-en-11-ol-2-one

  - *C. botrys* L. , Chenopodiaceae

  - (Teresa *et al.*, 1980)

6α-Acetoxyselin-4(15)-en-11-ol

  - *C. botrys* L. , Chenopodiaceae

    (Teresa *et al.*, 1980)

Selina-3,7(11)-diene

   - *Humulus lupulus* L. , Moraceae

     (Gibbs, 1974)

5βH,7β,10α-Selina-4(14),11-diene

   - *Aristolochia indica* L. , Aristolochiaceae

     (Govindachari *et al.*, 1973)

(+)-5β,7β,10α-Selina-3,11-diene

   - *Dipterocarpus alatus* Roxb. , Dipterocarpaceae

     (Klein und Rojahn, 1970)

(-)-7β,10α-Selina-4,11-diene

   - *D. alatus* Roxb. , Dipterocarpaceae

     (Klein und Rojahn, 1970)

Selinane-3β,4α,6α,11-tetraol

   - *Chenopodium botrys* L. , Chenopodiaceae

     (Teresa *et al.*, 1980)

β-Selinene

   - *Apium graveolens* L. , Umbelliferae

   - *Libanotis transcaucasia* Schischk , Umbelliferae

   - *Sesili indicum* Wight & Arn. , Umbelliferae

     (Gibbs, 1974)

Selinene-3α,4α,6α,11-tetraol

   - *Chenopodium botrys* L. , Chenopodiaceae

     (Teresa *et al.*, 1980)

5.2 <u>Animal Source</u>

4,11-Epoxy-*cis*-eudesmane

   - *Amitermes evuncifer* Silvestri , Termitidae,

     (Wadhams *et al.*, 1974)