Sesquiterpenes in the perfumery industry

H. R. ANSARI and A. J. CURTIS*

Synopsis—The developments in SESQUITERPENOID CHEMISTRY are reviewed with especial reference to their application in PERFUMERY.

Sesquiterpenes are the group of terpenoids which are formed by the combination of three isoprene units and are found widely distributed in many essential oils in the high boiling fraction. These represent a collection of highly complex and diverse structural systems. Although certain sesquiterpene-based essential oils, such as oil of sandalwood and vetiver, have been used in perfumery since antiquity, the detailed study of sesquiterpene chemistry commenced only about 20 years ago. This progress has been possible mainly due to modern methods of isolation, structural determination and synthesis. It is generally believed that the future of our industry lies in simulating as many essential oils as possible and hence lessen its dependence on the natural oils. In this respect the detailed and more comprehensive analysis of essential oils is revealing that many commercially important oils contain a number of sesquiterpenes which are important to the overall odour of such oils. Consequently, in many cases the scope of commercially producing synthetic oils will depend on the availability of

*Bush Boake Allen Ltd, London E15.

such sesquiterpenes. Another use of sesquiterpene compounds in per-
fumery is to convert the readily available natural sesquiterpenes into various
odoriferous compounds on lines similar to monoterpenes. However, the
complex nature of this class of compounds coupled with the lack of com-
mercially feasible methods of synthesis have prevented a real breakthrough.

The increased demand of perfumery materials has pressurized the
industry to look for, and accept, synthetic equivalents of the natural
products, despite the odour differences between the two. This has led to the
commercial production of materials such as geraniol, nerol, citronellol,
menthol, citral and the ionones whose isolation from natural oils has since
become far less economical. These materials have been produced from
heavy organic chemicals (acetylene and acetone) and by transformation of
natural monoterpenes which are available in large quantities (α- and β-
pinene). There is no counterpart of the versatile monoterpene myrcene in
sesquiterpene chemistry and an advancement comparable to monoterpenes
may appear to be unlikely in the near future. But it is interesting to note
that an increasing number of speciality chemicals are already appearing on
the perfumery scene. In our opinion many perfumery houses use sesquiter-
pene compounds in limited amounts in various formulations which are
often closely-guarded commercial secrets.

During the last 15 years the industry has had benefit from the extensive
research on monoterpenes and perhaps now it is time to explore the ses-
quiterpene field with the same seriousness. It is neither the purpose nor the
scope of this paper to deal with the systematic description of sesquiterpenes
which have been isolated from essential oils and characterized to-date.
Instead, we intend to concentrate on the use and chemistry of those ses-
quiterpenes and their derivatives which occur in commercially important
oils and which have already made an impact on the perfumery industry.
Many of these sesquiterpenoid compounds are commercially available.

It will be pertinent at this stage to mention that the biogenesis of most
sesquiterpenoids in essential oil yielding plants is considered to be based on
the cyclization of *trans-trans* and *cis-trans*-farnesyl pyrophosphate isomers
which in turn are produced from mevalonic acid (1, 2). These biogenetic
transformations give rise to some important sesquiterpene groups which
will be discussed here (*Fig. 1*).

The acyclic olefins α- and β-farnesenes possess interesting odours, which
are generally not known to perfumers because of commercial non-availability.
The latter compound occurs in many essential oils such as lavender, pepper,
hops, copaiba, ylang-ylang and ginger oil (3–5). Peyron, Benezet and
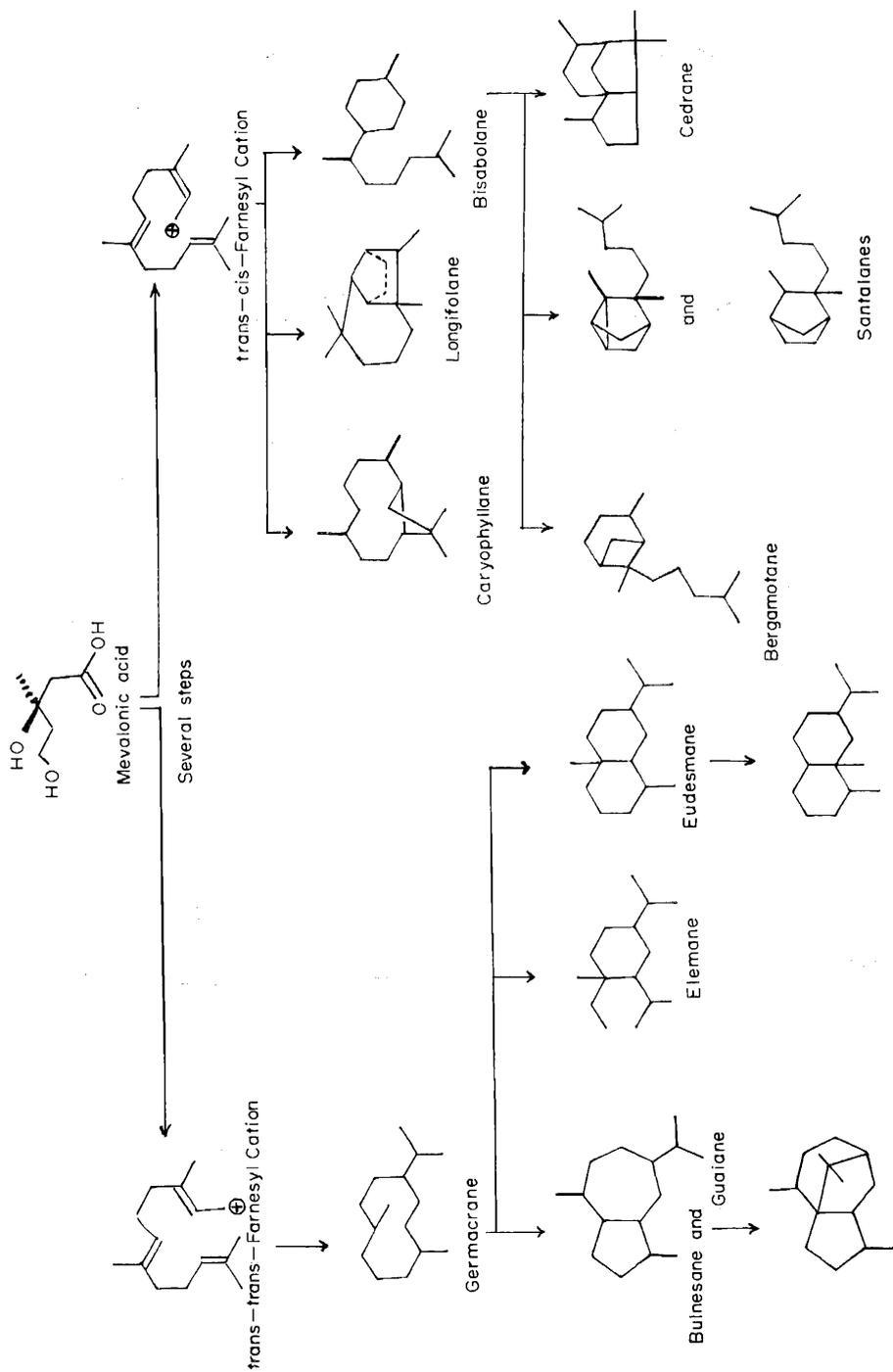
Figure 1.
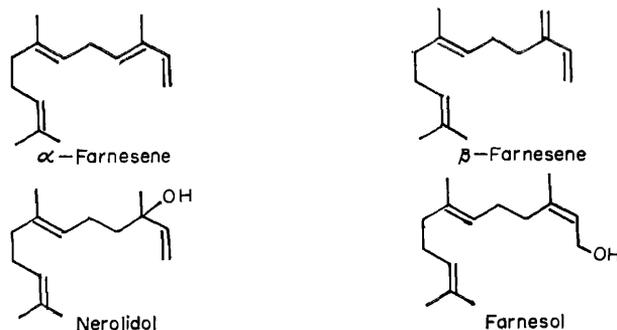
α-Farnesene   β-Farnesene

Nerolidol   Farnesol

Figure 2.

Garnere (6) found β-farnesene to be one of the most important constituents of lavender oil. The α-isomer has not been reported to occur in nature but has been synthesized by dehydration of nerolidol or farnesol (7, 8).

The isomeric alcohols nerolidol and farnesol are important perfumery chemicals. Nerolidol was first isolated from neroli oil (9) and since has been found to occur in several other essential oils, e.g. jasmine, citronella, pepper and cabreuva oil (10–12). According to Arctander (13) it has a mild and woody-floral, slightly green odour with excellent tenacity, and good blending and fixative properties. With the availability of synthetic nerolidol, a drastic reduction in its price has been observed. The synthesis which is based on cheap raw materials such as acetylene and acetone, makes nerolidol a feasible entry into the sesquiterpene field from a commercial viewpoint (*Fig. 3*).

$CH \equiv CH + CH_3COCH_3 \xrightarrow[\text{steps}]{\text{Several}}$ ... $\xrightarrow{Na\,C \equiv CH}$ ... $\xrightarrow{H_2}$ Nerolidol
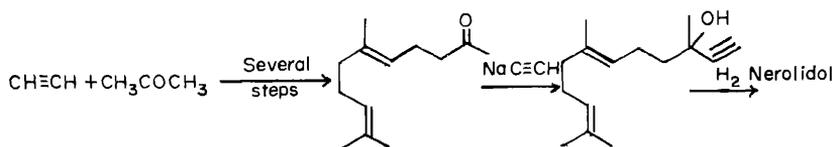
Figure 3.

The chemical possibilities of converting nerolidol into various sesquiterpenes are enormous. Some work has already been carried out on the isomerization to farnesol (15) and cyclization to an interesting range of cyclci terpenes (16). However, unlike nature, the product selectivity in these cyclizations is low, but further research in this area should prove to be extremely useful.

Farnesol occurs in several essential oils, e.g. oils of ambrette seed, neroli, rose, cyclamen, jasmine etc. (17, 18). It has a delicate sweet oily odour developing into a floral fresh-green note and finds uses in floral, oriental and chypre fragrances (13). Biogenetically speaking, this alcohol occupies a very significant position in sesquiterpene chemistry since it has been established that farnesyl pyrophosphate is the *in vivo* precursor of a variety of sesquiterpenes. The acid catalysed cyclization of farnesol, in a manner similar to nerolidol, gives a complex mixture of cyclic products among which bisabolane and cadinane structures are the most prominent (16). Several syntheses of farnesol have been reported in the literature but none of these is commercially attractive. Isomerization of nerolidol to farnesol in acceptable yields should have a significant effect on the usage of this alcohol which is presently restricted because of its high price.

Recently, Stevens, Ludin and Teranishi (19a), isolated and characterized two isomeric aldehydes α- and β-sinesal belonging to the farnesane group which occur in chinese orange oil (19b, c and d). Both aldehydes exist in the all *trans*- form and have attracted the attention of flavourists and perfumers and several commercial syntheses have been accomplished.

a—Sinesal   β— Sinesal

Figure 4.

Several members of the bisabolane group of sesquiterpenes occur in many commercially important essential oils. The parent hydrocarbon bisabolene can have several isomers with regard to the position of double bonds, but the γ-bisabolene is the most important one and occurs in oil of bisabol myrrh, lemon, lime, bergamot, cardamom, sandalwood, etc. It is also obtained by dehydration of nerolidol during the cyclization (16). It is interesting perfumery chemical with a pleasant, warm, sweet-spicy-balsamic odour which makes it invaluable in the reconstitution of essential oils and as a perfumery material in its own right. It is a vital part of the oriental, opopanax, chypre and novelty fragrances (13).

The hydrocarbons zingiberene and ar-curcumene constitute the major part of the sesquiterpene fraction of the oil of *Zingiber officinale* (ginger oil).
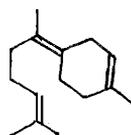
γ- Bisabolene

Figure 5.

Zingiberene has a warm, woody-spicy tenacious odour with deep sweetness. Its structure as shown was assigned by Eischemosher and Schinz and also by Mills (20, 21). Several syntheses of (±) zingiberene have been reported but the most interesting approach is based on citronellal and can lead to the optically active hydrocarbon (22, 23). ar-Curcumene has been synthesized by Honwad and Rao (24, 25) but has an uninteresting odour.
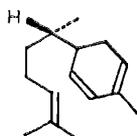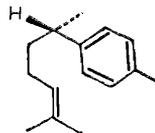

Zingiberene   ar-Curcumene

Figure 6.

α-Bisabolol occurs in oil of camomile (26, 27) and the racemic form is prepared by acid-catalysed cyclization of nerolidol (16). It can be used as a fixative and blender in many formulations with interesting results. Another interesting member of the group is a primary allylic alcohol lanceol which occurs in the oil of *Santalum lanceolatum* (21, 28).
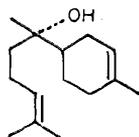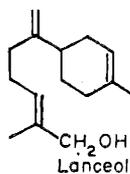
α— Bisabolol   Lanceol

Figure 7.

Germacranes, a group of 10-membered ring compounds, were postulated by Ruzicka, Eschenmoser and Heusser (29) as intermediates of crucial significance in the biogenesis of the elemane-, eudesmane-, and guaiane-type sesquiterpenoids from farnesyl pyrophosphate (29). However, no member of this group was actually isolated and characterized until germacrone and

pyrethrosine were characterized by Ognyanov *et al* and Barton and de Mayo respectively in 1957 (30, 31). Since then several other compounds belonging to this group have been isolated and characterized by careful work-up. Sorm has recently published an excellent review of the chemistry of germacranes (32).

Germacrone   Pyrethrosine

Figure 8.

Germacrone was isolated from oil of *Geranium macrorhizum* in 50% yield (30). It has a faint, sweet-woody, somewhat herbaceous odour of extraordinary tenacity. Although the ketone is not offered as a pure chemical, the oils rich in this material have been suggested to be useful as a modifying fixative in ambre, chypre, and mossy fragrance types. The pure ketone itself blends well with the ionones, geranium, ambergris, vetiver, and cedarwood types (13).

The hydrocarbons germacrene A, B, C and D offer interesting synthetic possibilities of obtaining various well-known sesquiterpenes which are crucially important in simulated essential oils.
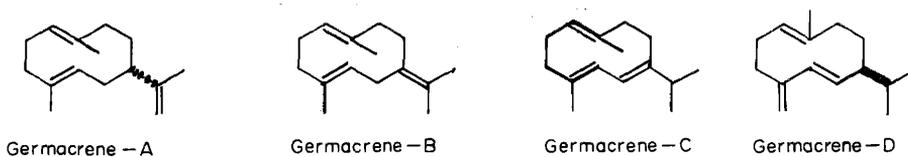

Germacrene – A   Germacrene – B   Germacrene – C   Germacrene – D

Figure 9.

A variety of acid-catalysed and photochemical transformations to systems such as eudesmanes, copaene, ylangane, bourbonane (present in the essential oil of geranium bourbon), cadinane, and muurolane are known and illustrate the biogenetic significance of this group (33).

The elemane group consists of a number of hydrocarbons and oxygenated derivatives including lactones and occur widely in many essential oils. These compounds are closely related to eudesmanes and germacranes, and it is generally supposed that many members are probably artefacts of
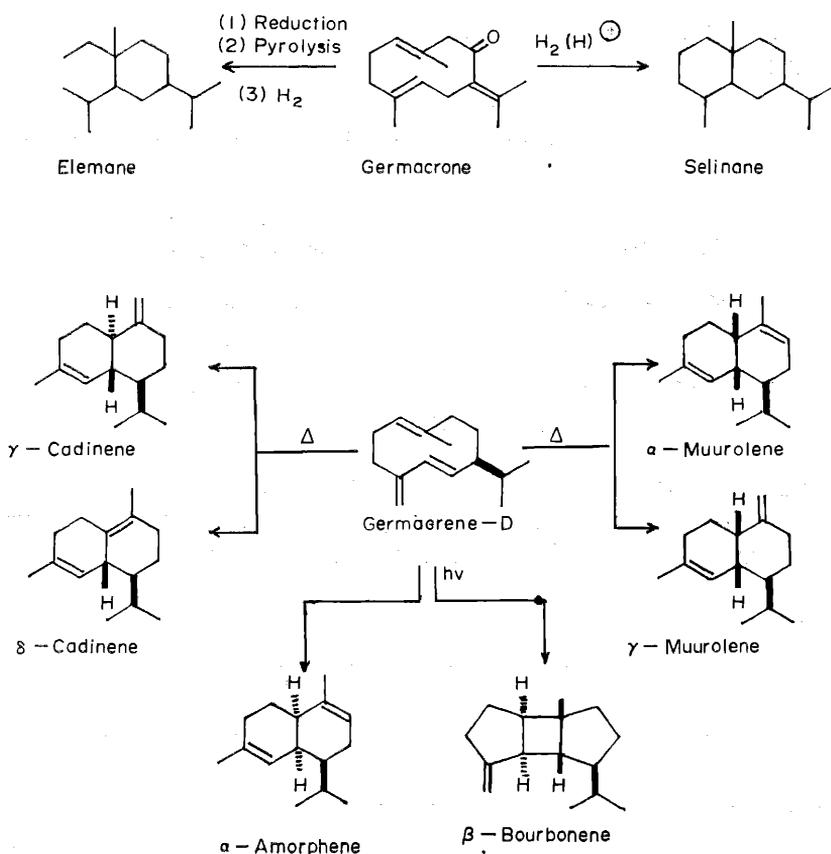
Figure 10.

the latter. The hydrocarbons α- and β-elemene occur in sweet-flag oil (34) and gurjun balsam (35) respectively, but have found no specific use in perfumery so far. The alcohol elemol found in Java citronella oil and elemi oil has the configuration as indicated and affords α-elemene on dehydration (36). Elemol has a faint, sweet-woody odour with an almost floral undertone, and the essential oil fractions rich in this alcohol are used as fixatives, blenders or modifiers in soap perfumery. The total synthesis of elemol was accomplished by Corey and Broger (37).

The eudesmane group is probably the largest of the sesquiterpene groups and can be considered to have been derived from farnesyl pyrophosphate cyclization involving a germacrane skeleton as an intermediate. The hydrocarbons α- and β-selinene are found in Bois de Rose and celery
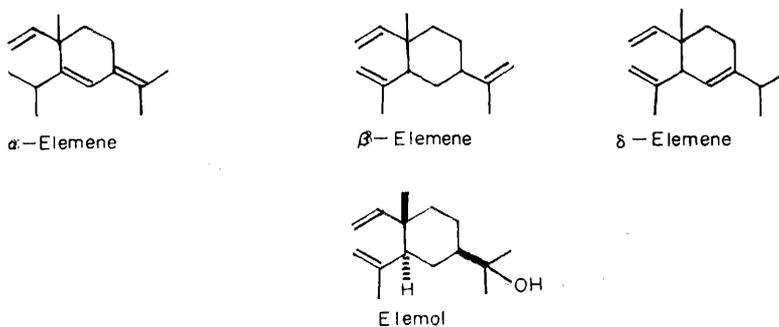
α-Elemene   β-Elemene   δ-Elemene

Elemol

Figure 11.

seed oil (38, 39), whereas the alcohol β-eudesmol occurs in eucalyptus oil (40). α-Selinene has a mild, sweet-woody, and slightly peppery odour, the β-isomer has a similar but warmer and more herbaceous odour (13). β-Eudesmol which finds some use as a fixative offers a delicate, sweet-woody and warm odour. The corresponding acetate ester is also interesting for its linalyl acetate type odour combined with much better tenacity. Both β-
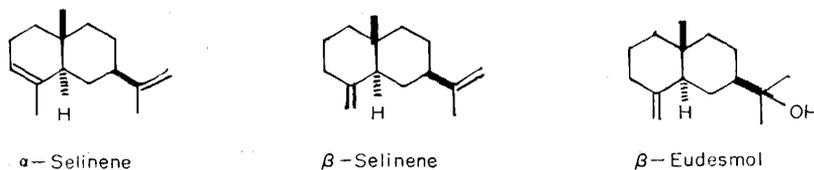
α-Selinene   β-Selinene   β-Eudesmol

Figure 12.

selinene and β-eudesmol have been synthesized by Marshall, Pike and Carroll (41). Cyperene and α-cyperone also offer interesting structural systems, the latter being the main constituent of the oil of *Cyperus rotandus* (42).

Penfold, Robinson and Simonsen (44) speculated a 1,2-alkyl shift in eudesmanes to generate the commercially important group of compounds known as eremophilanes (44). Eremophilene is present in a number of essential oils and has been a subject of several publications and a recent review by Pinder (43). The ketone Eremophilone is a constituent of *Eremophilla mitchelli* (44).

The most commercially important members of the group are valencene, nootkatene, and nootkatone. Valencene has been isolated from orange juice oil and orange peel oil (45), and its structure and absolute configuration has been related to nootkatene, a *t*-butyl chromate oxidation product of
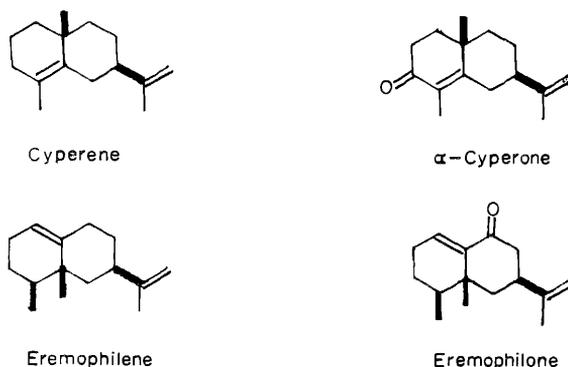
Cyperene

α-Cyperone

Eremophilene

Eremophilone

Figure 13.

valencene. Nootkatone itself is an important flavour chemical isolated from grapefruit oil (46). Nootkatene or dehydrovalencene is readily obtainable from wood of *Chamaecyparis nootkatensis* by steam distillation and can be converted in high yield into nootkatone by hydrochlorination followed by oxidation (47). Therefore, the commercial importance of valencene and nootkatene lies in being readily available starting materials for a convenient synthesis of nootkatone. Nootkatone has an extremely powerful, sweet and citrusy odour of good tenacity and hence in addition to its well established use in flavour, it could undoubtedly find use in certain perfume formulations. Its further detection in other oils such as bergamot, lemon, lime, and tangerine emphasizes its importance in flavour and perfumery (45).
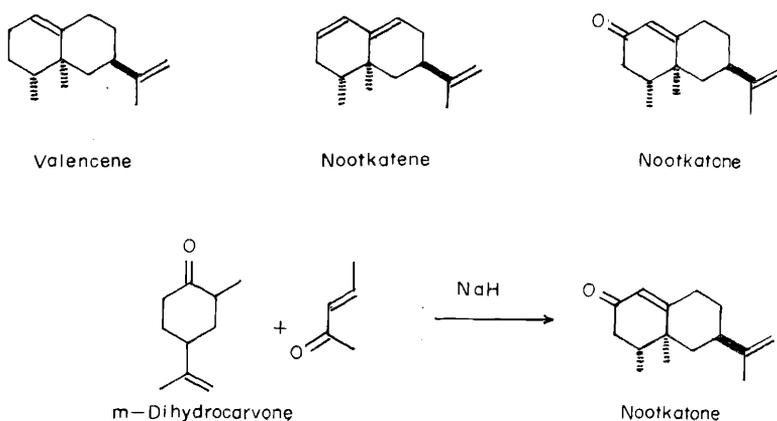

Valencene

Nootkatene

Nootkatone

m—Dihydrocarvone

NaH

Nootkatone

Figure 14.

Several stereospecific syntheses of (±)-nootkatone have been reported in the literature. Pinder and Odom (49) annelated *m*-dihydrocarvone with *trans*-3-pent-en-2-one to obtain nootkatone, which was also synthesized by Marshal and Ruden by a multistep synthesis (50).

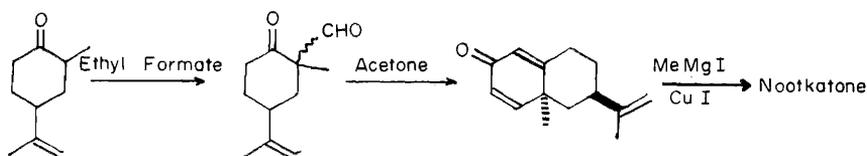A recent patent describes the following synthesis (51).

Figure 15.

Nootkatone has also been the subject of detailed sensory properties. Ohloff and Giersch (52) studied the relationship between odour and structure by comparing the odour and taste of various nootkatone isomers and their derivatives. It was found that those compounds with a fruity odour have a bitter taste, whereas those which are devoid of fruity smell have no taste. Furthermore, the double bond remotely situated from the carbonyl function is of special importance in regard to the odour and taste. Stevens, Guadagui and Stern (53) and Teranishi (54) also arrived at similar conclusions, but add that nootkatone isomers have different odour qualities but have only small differences in potencies.

The compounds belonging to vetispirane and tricyclovetivane are derived mainly from the essential oil of *Vetiveria zizanoides*, a perennial grass which grows wild in India, Ceylon, Burma, Reunion Island, and several other countries. The oil, which has been used in perfumery since antiquity, consists mianly of sesquiterpenes. These sesquiterpenes are α-vetivone (55), β-vetivone (56), tricyclovetivenol or khusimol (57), bicyclovetivenol (58), and vetivenyl acetates. Originally these compounds were assigned wrong structures which have been refuted only recently and the revised structures are as shown below. α- and β-Vetivones are used in perfumery as a mixture derived from the ketone fraction of vetiver oil. They possess an odour which is very much reminiscent of the parent oil but more tenacious. These ketones can be a valuable part of oriental type formulations (13). The chemistry of α-vetivone is closely related to that of nootkatone and hence is also known as isonootkatone. Due to this relationship with nootkatone it would be surprising if we do not see a synthetic material commercially available in the near future. Depending upon their origin and
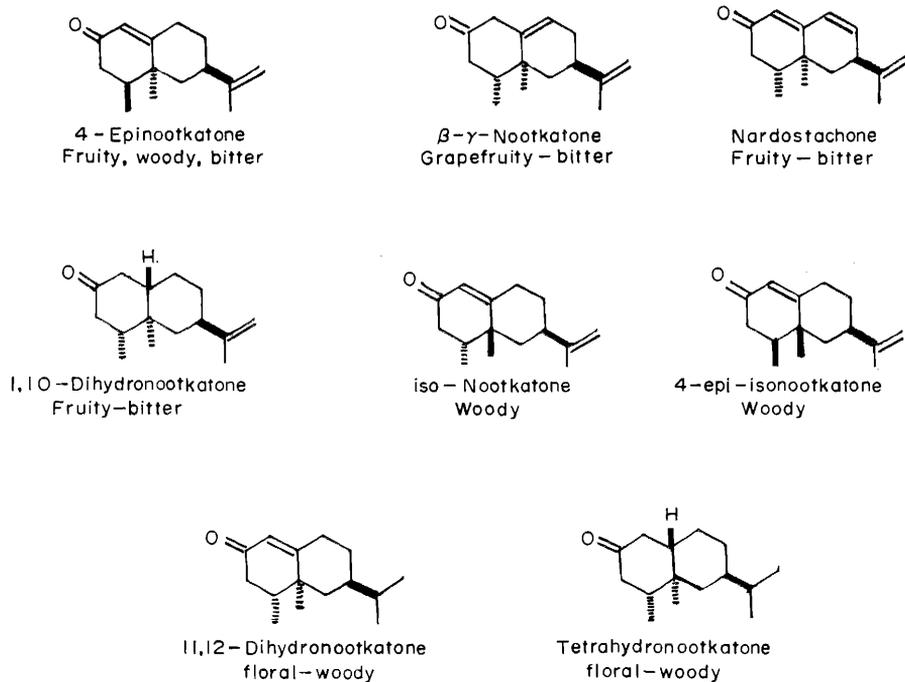
4 - Epinootkatone
Fruity, woody, bitter

β-γ-Nootkatone
Grapefruity - bitter

Nardostachone
Fruity - bitter

1,10-Dihydronootkatone
Fruity-bitter

iso-Nootkatone
Woody

4-epi-isonootkatone
Woody

11,12-Dihydronootkatone
floral-woody

Tetrahydronootkatone
floral-woody

Figure 16.

α-Vetivone

β-Vetivone

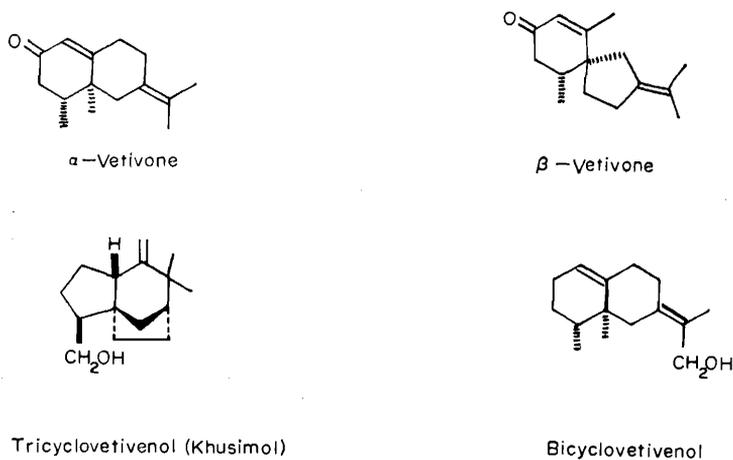Tricyclovetivenol (Khusimol)

Bicyclovetivenol

Figure 17.

quality, vetiver oils contain 45–65% free sesquiterpene alcohols bicyclo-
and tricyclovetivenols. The commercial product is a mixture of these two
vetivenols and has a warm, sweet, mildly earthy-balsamic and extremely
tenacious odour. These alcohols blend well with ionones, styrax, sandalwood
and various materials for oriental and woody bases or perfumes (13). The
corresponding aldehydes are known to have an olibanum type odour. The
mixed acetates obtained by the acetylation of the above alcohols or by
isolation from essential oil are sold under several trade names. The sweet-
dry, fresh-woody odour with excellent tenacity allows its use in all types of
perfumes (13).

Longifolene, a hydrocarbon belonging to the longifolane group, is one
of the few sesquiterpenes commercially available in quantity. Much interest
has been shown by the industry in the new materials that chemical in-
vestigation into longifolene chemistry has presented to the perfumer.

Longifolene was first isolated by Simonsen (59) from *Pinus longifolia*
and the search for commercial uses for the hydrocarbon extends back 50
years. The structure was established by Moffett (60) and Ourisson (61) and
commercial exploitation has followed this breakthrough. The structure of
longifolene has been confirmed by a total synthesis (62) but such syntheses
are of academic interest only.

Two simple longifolene derivatives are on the perfumer's shelf at the
moment: acetyl longifolene and hydroxymethyl longifolene. Acetyl longi-
folene (63) is prepared by the Friedel–Crafts reaction and has a woody-
musky ambergris odour reminiscent of acetyl cedrene.

Longifolene   Acetyl longifolene

Figure 18.

The Prins reaction has been of use in the production of perfumery
chemicals from monoterpenes (*Nopol, Patchenol*) and application of this
reaction to longifolene produces ω-hydroxymethyl longifolene (64, 65). This
alcohol is of use in perfumery.

The simple methods of longifolene oxidation yield complex mixtures
with sesquiterpene acids predominating (66). Direct oxidation of longifolene
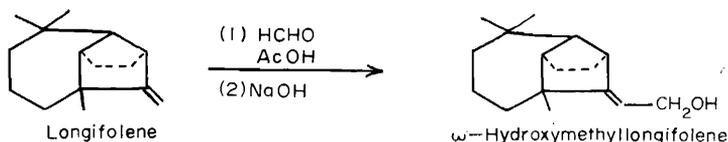has not been of great commercial interest. Formylation reactions have been

Figure 19.

of recent interest in the production of new monoterpene perfumery chemicals (67–69), e.g. dihydromyrcene cyclic esters. Application of these reaction conditions to longifolene produces longibornan-9-ol formed by rearrangement and transannular hydride shift (70). A recent patent claims this formate to be of value in perfumery (71).
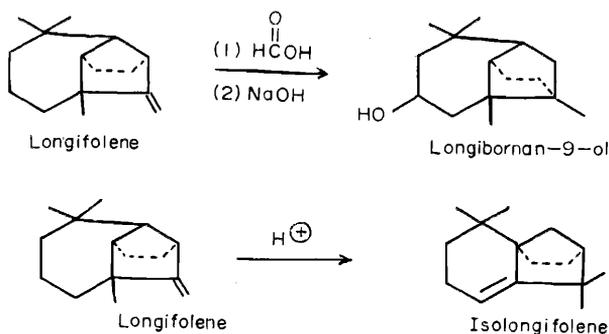

Figure 20.

Early attempts at longifolene acetoxylation did not give good yields of acetates but an isomer of longifolene was produced called isolongifolene (72). The structure of isolongifolene was established by Ranganathan *et al.* (73) who later completed a total synthesis of the hydrocarbon (74). Isolongifolene has proved to be of more commercial interest than longifolene as simple methods of oxidation yield non-acidic products.

If longifolene or isolongifolene are treated with zinc chloride at high temperatures then 1,1-dimethyl-7-isopropyltetralin is formed (75). Acetylation of this tetralin gives the methyl ketones; these are said to have a fine although weak musk odour. The aldehydes have a stronger musk odour but the propionyl compound is odourless (75).

Epoxidation of isolongifolene with peracids yields the α-epoxide (76). This epoxide is of little perfumery interest but rearrangement of the epoxide produces the saturated ketone 8-oxo-7-β-H-isolongifolane which has a desirable woody odour and has found use in perfumery. Epimerization of
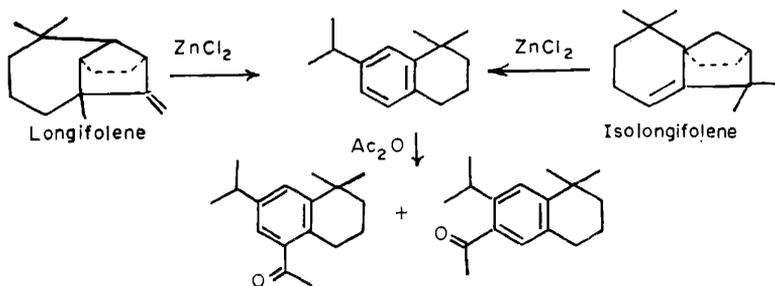
Figure 21.

this ketone to the 7(α)H derivative is simple and this ketone is also of perfumery use as it possesses a sweet-woody odour.

The rearrangement of isolongifolene epoxide has been reported (77–79) to yield two β, γ-unsaturated alcohols. No patents have been published on the rearrangement of the epoxide; under most reaction conditions these alcohols are formed in less than 50% yield, the main product is 8-oxo-7-β-H-isolongifolane (*Fig. 22*).

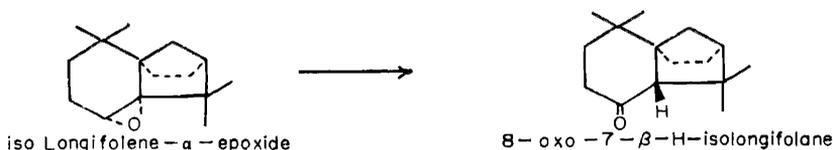iso Longifolene — a — epoxide   8 — oxo — 7 — β — H — isolongifolane

Figure 22.

The sterochemistry of isolongifolene is a subject of academic discussion (76–79) and it is still not known beyond all doubt if the epoxide is, in fact, α- or β. In the author's opinion, the α-structure is the more probable (80).

Sodium dichromate oxidation of isolongifolene yields a complex mixture of ketones with a woody, vetiver type of odour. This mixture has found use in perfumery (81).

Allylic oxidation of isolongifolene with tertiary butyl peracetate gives a mixture of 9α- and β-acetoxy-isolongifolene. This has a woody, vertiveryl acetate odour and has found use in perfumery (82) (*Fig. 23*).

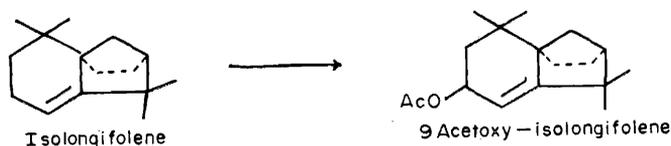Isolongifolene   9 Acetoxy — isolongifolene

Figure 23.

The rapid commercial exploitation of longifolene in the last few years illustrates the interest shown by perfumers in new sesquiterpene products. With the considerable academic and commercial interest being shown in this hydrocarbon, further developments of interest to perfumers may well be expected.

Sandalwood oil is much used in perfumery and has a large production; its odour is too well known to be described in this paper. The main constituents of the oil are known (83); α-santalene had a sweet-woody odour of excellent tenacity; β-santalene has a similar odour but is said to be less sweet than the α-isomer. α-Santalol is considered to have the refined sweet-woody, tenacious sandalwood odour. Impure α-santalol isolated by distillation from sandalwood oil is the santalol of commerce. β-Santalol is said to have a similar odour but it occurs to a smaller extent in sandalwood oil and samples may have been contaminated with the α-isomer. Perfumery opinion is that the α-isomer is the preferred isomer (*Fig. 24*).

α—Santalene   β—Santalene
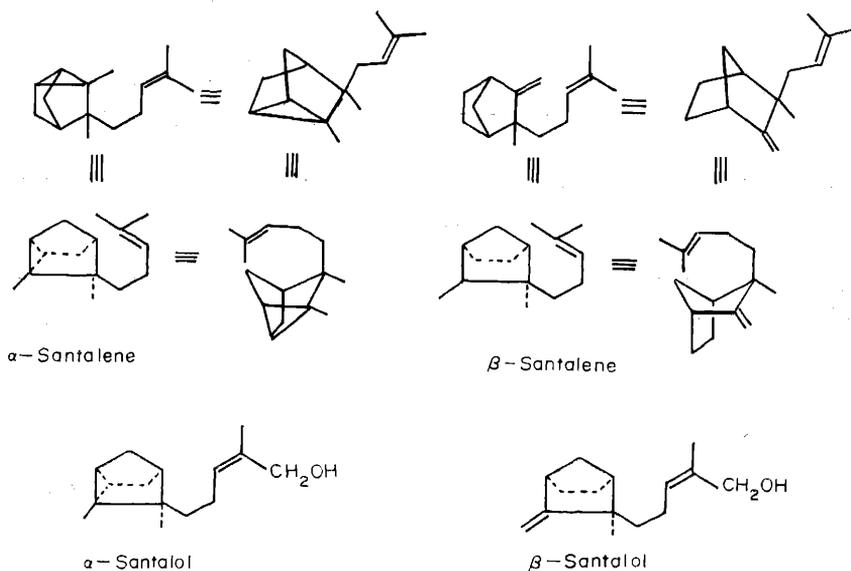
α—Santalol   β—Santalol

Figure 24.

The santalyl structure is related to the structure of longifolene; if it were possible to open the seven-membered ring of longifolene one would have a santalene structure. The sterochemistry is such that the opposite optical isomer to the natural santalene would be produced (*Fig. 25*).
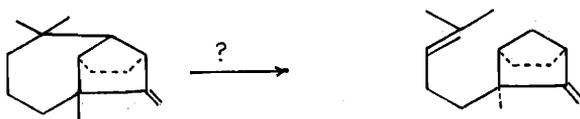
Figure 25.

Sandalwood is a moderately expensive essential oil and its typical bouquet continues to be favoured by the perfumery industry. The search for sandalwood odours have therefore been intense. A number of chemicals with a sandalwood odour have been made. The so-called terpeno-phenols manufactured by the condensation of phenols with camphene followed by hydrogenation (84) have found application in a number of sandalwood bases. These have found a use in the industry but have not depressed the demand for the natural oil.

The last addition to the sandalwood odours is Osyrol (and its homologs), and although this monoterpene is not a direct replacement for α-santalol, this speciality has a fine sandalwood odour and with its good performance in the middle notes it will be of wide interest in the formulation of perfume compounds where the sandalwood character is desired (85) (*Fig. 26*).
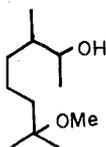

Figure 26.

The commercial synthesis of sesquiterpenes has yet to be achieved but much progress has been made in the academic synthesis of these compounds. Starting from α-bromocamphor French workers were able to synthesize α- and β-santalol in nine steps (86). The reaction sequence is too long for this synthesis to be of commercial interest.
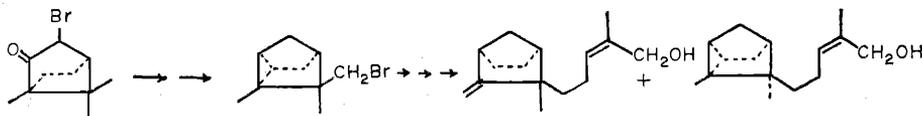

Figure 27.

Canadian workers have devised a route for the synthesis of campherenone. This sesquiterpene is a valuable intermediate for the synthesis of a number of sesquiterpenes and in two steps it may be converted either to α-santalene or β-santalene (87, 88) (*Fig. 28*).
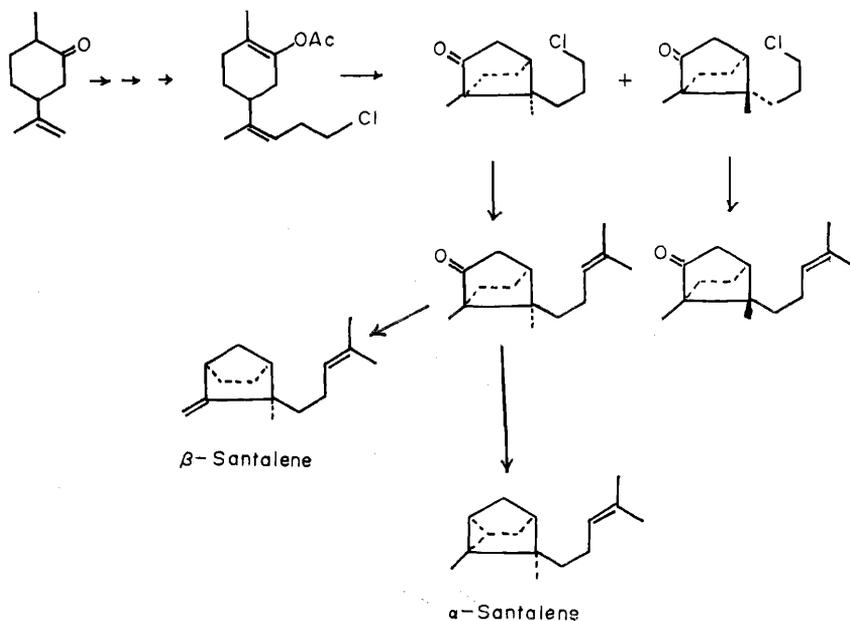

Figure 28.

This synthesis might have been of commercial value but at the key cyclization stage two compounds are produced, one of which gives santalene and the other epi-santalene.

An alternative approach was examined by American workers who synthesized 3-methyl-norcamphor from the Diels–Alder product of methyl cyclopentadiene and ethylene. The construction and addition of the side chain to the camphene structure was more complex and again this synthesis does not offer, at present, any commercial possibility (89).

A more direct synthesis has been described. The key step was the Diels–Alder addition of geraniol to cyclopentadiene; low yields at this stage appear to have discouraged exploitation of this path (90).

The lactonization of camphene-8-carboxylic acid has been reported to yield a lactone with the correct arrangement of functional groups to be a santalene intermediate. Here again the key step produces not only the desired santalene structure but also the epi-santalene structure (91).

As a result of these synthetic studies the odours of a number of santalol derivatives have been reported (89). Dihydro-β-santalol is said to have a sandalwood odour but the α-isomer is said to be much weaker. Tetrahydro-β-santalol has no sandalwood character and has an uninteresting weak woody odour. There is no doubt that the industry would find a synthetic santalol a most welcome addition to the perfumers shelf. It is not possible to say how long it will be before it arrives there.

Cedarwood oil is one of the essential oils whose production exceeds 100 tons/year. The oil is not only of direct use in perfumery; a number of derivatives from the oil have also found a wide use. Although some of these derivatives have been given names in the technical press which would suggest that they are definite chemical entities, many of them are mixtures (e.g. cedrenol) isolated from the oil or the products of reactions on such mixtures (e.g. acetyl cedrene).

Thujopsene and cedrene are the two main sesquiterpene hydrocarbons found in the oil; β-cedrene, β-chamigrene, widdrene, isowiddrene, α-chamigrene, cuprenes and cuparene have been found in smaller quantities (92) (*Fig. 29*).

Cedrol is the main alcohol constituent of the oil; psuedo cedrol, primary cedrol and widderol are also found in the cedarwood oil (92) (*Fig. 30*).
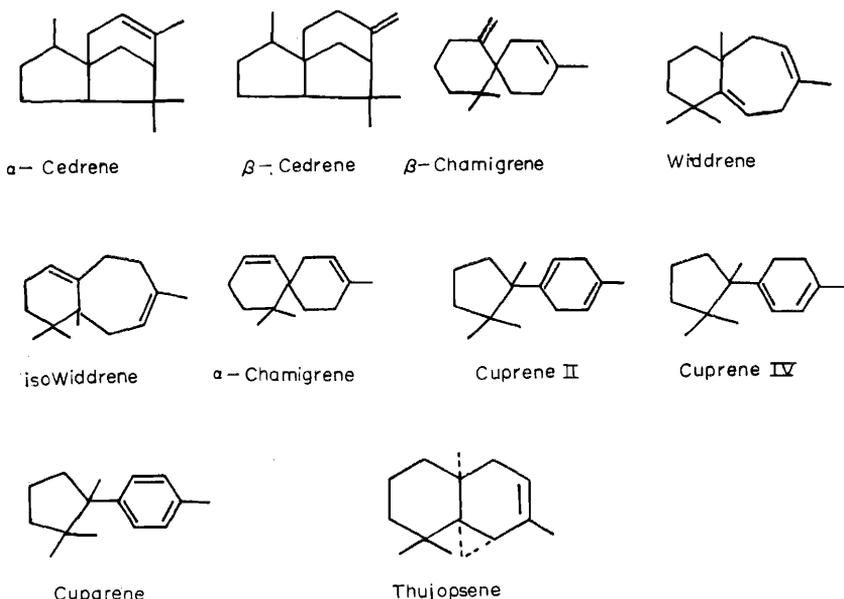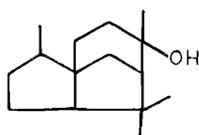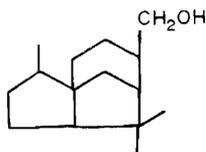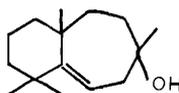

α— Cedrene   β —, Cedrene   β— Chamigrene   Widdrene

isoWiddrene   α — Chamigrene   Cuprene II   Cuprene IV

Cuparene   Thujopsene

Figure 29. Some hydrocarbons from cedarwood oil.

Cedrol

CH$_2$OH

Primary cedrol   Widderol

Figure 30.

Distillation yields two main fractions, the hydrocarbon fraction is the so-called 'Cedrene' of commerce, impure cedrol is obtained as the alcohol cut. Pure cedrol can be obtained by recrystallization of the alcohol fractions and is used in perfumery. Cedrenol is a mixture of cedrol and its isomers, widdrol and some ketonic compounds. Acetylation of this mixture yields cedrenyl acetate. Cedryl acetate is also made by esterification of the alcohol and a number of qualities are sold; they range from the pure recrystallized acetate to acetate mixtures containing almost 50% hydrocarbons.

Epoxy-cedrene has been manufactured by epoxidation of cedrene-rich hydrocarbon fractions followed by recrystallization (*Fig. 31*).

One of the most interesting cedarwood derivatives is the complex mixture of ketones known as 'acetyl cedrene' obtained by acetylation of the hydrocarbon fraction. This has a woody, warm-ambergris and musky odour (94), and is sold under a number of trade names. A number of investigations have been made to find the odour constituents of the mixture. The hydrocarbon cut used in the manufacture has two main components, cedrene and thujopsene. The acetylation product of the purified cedrene is said to have little odour.

The reaction of thujopsene under these conditions is much more complex. With acid catalysts thujopsene isomerizes into a large number of hydrocarbons and it is thought that this isomerization precedes the acetylation step in the production of acetyl cedrene.

At least seven $C_{17}H_{26}O$ ketones have been observed in the acetylation mixture but the structures of only two are known and these account for
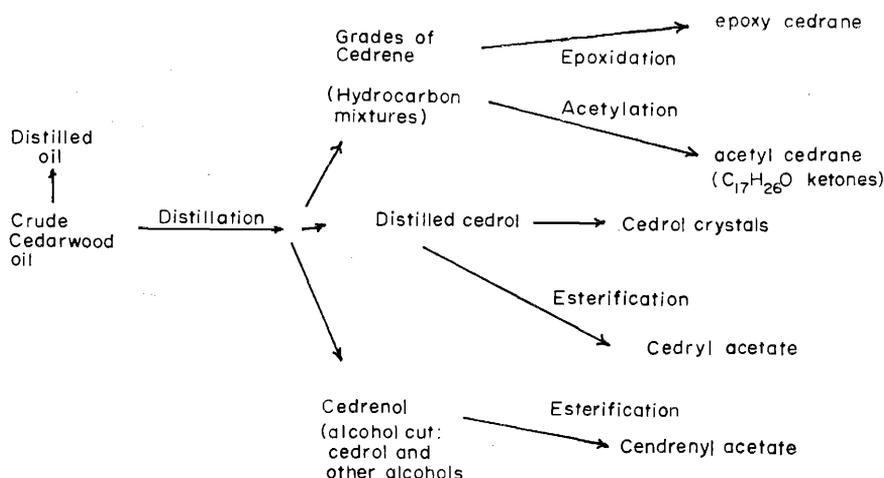
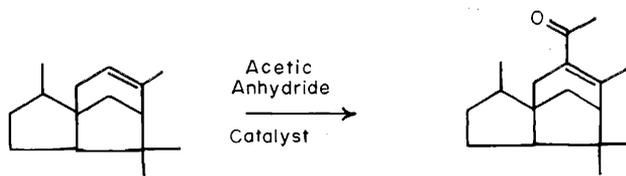Figure 31. Perfumery materials from cedarwood oil (93).

Figure 32.

some 60% of the reaction product. The major ketone is thought to be the active odour constituent of acetyl cedrene. It is said to have a powerful woody, musk-ambergris odour far greater in intensity than any of the other isomers. This acetyl thujopsene isomer has an interesting odour–structure relationship since, although it has a strong musk odour, it has no aromatic ring as have most other tricyclic musks possessing an acetyl group.

Patchouli oil has wide application in the perfumery industry and more extensive use would be made of this essential oil if it were in greater supply. Much effort has been devoted to the analysis of the oil and a number of constituents have been identified. No single compound has the total patchouli odour and any effort to formulate a reconstructed patchouli oil will require the synthesis of a number of sesquiterpene alcohols, ketones and hydrocarbons.

The main alcohol constituent of patchouli oil is patchouli alcohol. A synthesis of this alcohol from homocamphor has been reported (101) but
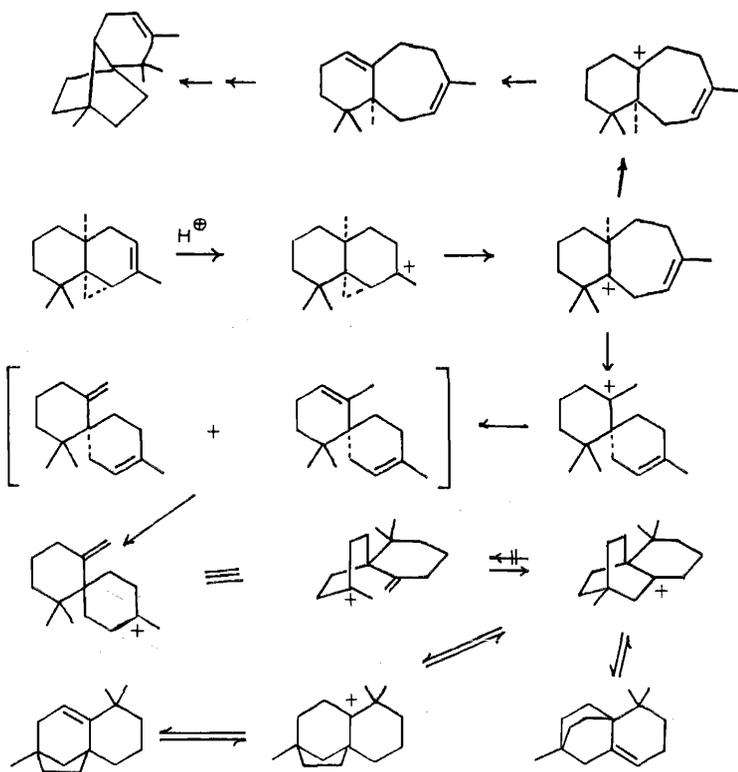
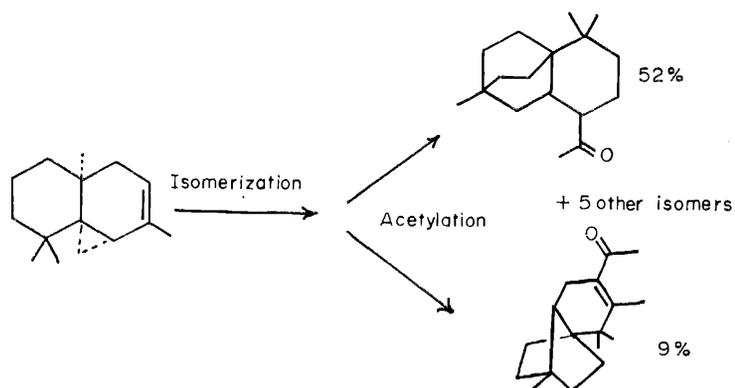*Figure 33.* Products of acid isomerization of thujopsene (95).

Figure 34. The acetylation of thujopsene (96, 97).

α — Patchoulene   β — Patchoulene   γ — Patchoulene

α — Guaiene   Caryophyllene

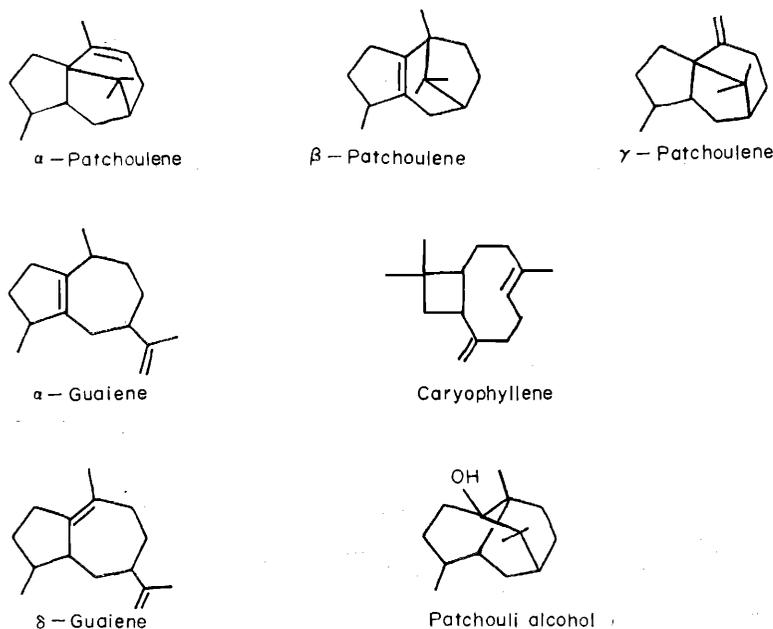δ — Guaiene   Patchouli alcohol

Figure 35. Some constituents of patchouli oil.

the synthesis involves a large number of steps. β-Patchoulene is first synthesized and then converted to the α-patchoulene structure and hence patchouli alcohol. No commercial synthesis of this alcohol appears possible at the present.

Patchouli oil is interesting as it is one of the few oils obtained by steam distillation and is found to contain sesquiterpene alkaloids (102). These alkaloids are formed from the sesquiterpene structures of two hydrocarbons found in patchouli oil, β-patchoulene and α-gauiene; thus they have been called patchoulipyridine and epiguaipyridine. The structures of these products, present in the oil to the extent of 0·1% were determined by physical organic techniques (102) and confirmed by the synthesis of patchoulipyridine and dihydro-epiguaipyridine. Patchoulipyridine was synthesized from β-patchoulene by the action of hydrazoic acid and dehydrogenation of the resulting product. Dihydro-α-guaiene was synthesized (102) from guaiol and subjected to the same reaction steps to yield dihydro-epiguaipyridine.

No odour descriptions have been given for these two alkaloids. An alternative synthesis (103) of patchoulipyridine has been developed by
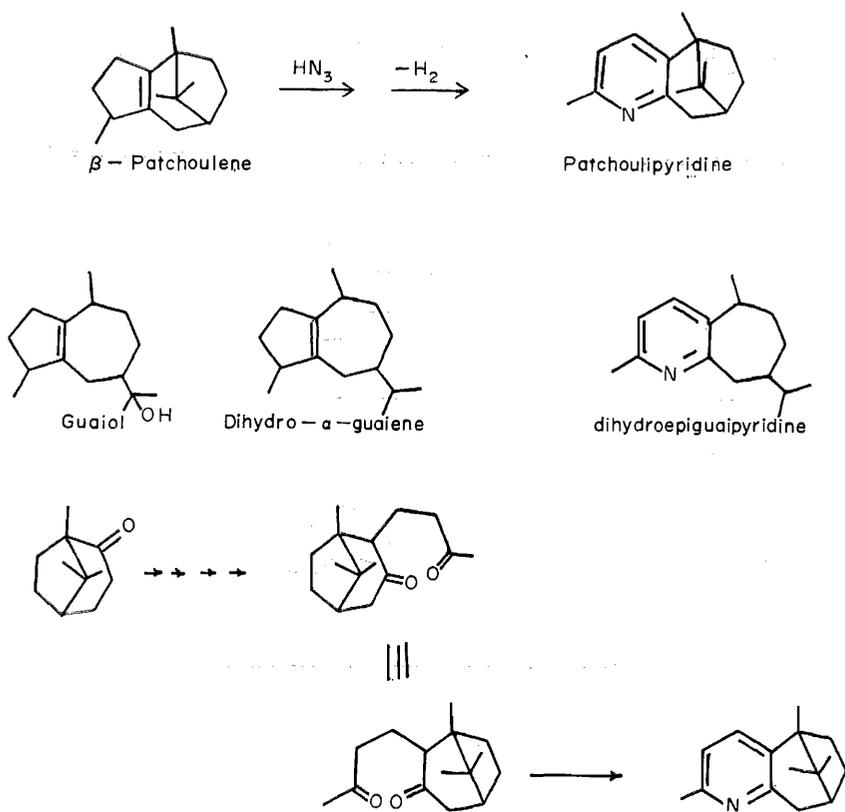
Figure 36

French workers who started from homocamphor. This was converted in a number of steps to a diketone which was then transferred into the pyridine.

Some of the hydrocarbons found in guaiacwood oil have also been found in patchouli oil (104). The main constituents of guaiacwood oil are the two sesquiterpene alcohols guiaol and bulnesol. Treatment of these alcohols with a small quantity (0·01 M) of sulphuric acid produces a number of the hydrocarbons found in patchouli oil. These are obtained as a mixture and isolation of the desired hydrocarbons is difficult (see *Fig. 37*).

A total synthesis (105) of guaiol has been reported but as guaiacwood oil is one of the cheaper sesquiterpene containing essential oils, this work appears to be of academic interest only.

Treatment of guaiol with sulphuric acid, para-toluenesulphonic acid or iodine yields a cyclic ether guaioxide (*Fig. 38*). This ether has been claimed
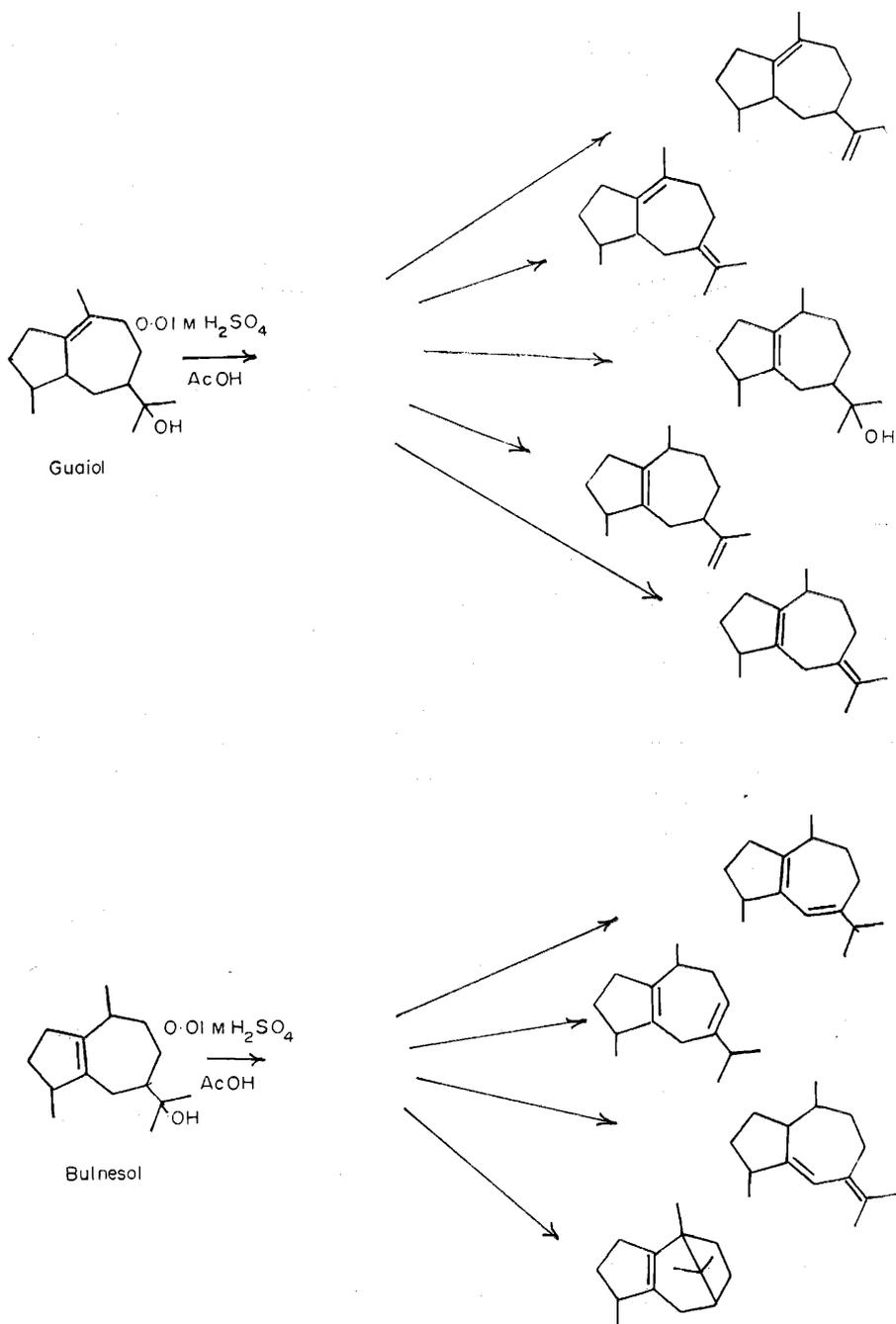
Figure 37. Hydrocarbons from guaiol and bulnesol. (104).

to be of value in perfumery (106). It has a distinctive odour of the warm vetiver type with a warm dry spicy note which is reminiscent of black pepper oil. The cyclic ether has also been reported in guaiacwood oil. A cyclic ether has been isolated from sandalwood oil (107), and it is possible that sesquiterpene ethers will be found to be of some considerable value in perfumery.
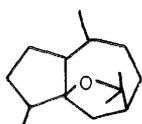
Guaioxide
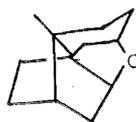
Sandalwood ether

Figure 38

In conclusion it can be said that sesquiterpenes offer a great challenge to the Organic Chemist because of their structural complexity. They are of crucial importance to the perfumery industry as they occur widely in essential oils and individual chemicals offer a wide spectrum of interesting odour types. Therefore, any advancement in the difficult problems of skeletal construction and stereochemical control necessary for such syntheses would have a significant impact on the future of the industry. Undoubtedly during the recent years many new and elegant methods of synthesis have been introduced but unfortunately the majority are of academic interest only. However, one hopes that, in addition to this progress, a better understanding of enzymatic reactions coupled with their commercial exploitation may provide an answer to some of the problems.

(Received: 13th February 1973)

REFERENCES

(1) Parker, W., Roberts, J. S. and Ramage, R. *Quart. Rev.* **21** 331 (1967). and references therein.
(2) Popjak, G. and Cornforth, J. W. *J. Biochem.* **101** 553 (1966).
(3) Sorm, F., Leziva, J. M., Arnold, Z. and Pliva, J. *Collect. Czech. Chem. Commun.* **14** 699 (1950).
(4) Sorm, F. and Arient, J. *Collect. Czech. Chem. Commun.* **15** 175 (1950).
(5) Sorm, F., Zaoral, M. and Herout, V. *Collect. Czech. Chem. Commun.* **16** 626 (1951).
(6) Peyron, L., Benezet, L. and Garnere, J. *Bull. Soc. Chim. Fr.* (8), 3038 (1967).
(7) Naves, Y. *Helv. Chim. Acta,* **49** 1029 (1966).
(8) Brieger, G. *J. Org. Chem.* **32** 3720 (1967).
(9) Hesse, A. and Zeitschel, O. *J. Prakt. Chem.* (ii) **66** 504 (1902).
(10) Katsuragi, H. *Koryo* No. 22 23 (1952).
(11) Calveano, Maria. *Essenz Deriv. Agrum.* **36** (4) 237 (1966).

(12) Lewis, Y. S., Nanbudiri, E. S. and Krishnamurthy, *N. Perfum. Essent. Oil Rec.* **60** 259 (1969).

(13) Arctander, S. *Perfume and flavour chemicals Vols I and II,* (1969) (published by the author, New Jersey, USA).

(14) *British Patent No. 213,250.*

(15) Nazarov, I. N., Gusev, B. P. and Gunar, V. I. *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* 1267 (1957) (CA 52:6150h).

(16) Gutsche, C. D., Maycock, J. R. and Chang, C. T. *Tetrahedron* **24** 859 (1968).

(17) *German Patent No.* 149 603.

(18) Calveano, Maria. *Essenz Deriv. Agrum.* **33** (1) 5 (1963).

(19a) Stevens, K. L., Lundin, R. E. and Teranishi, R. *J. Org. Chem.* **30** 1690 (1965).

(19b) Buechi, G. and Wuest, H. *Helv. Chim. Acta* **50** (8) 2440 (1967).

(19c) Bertele, E. and Schudel, P. *Helv. Chim. Acta* **50** (8) (1967).

(19d) Thomas, A. F. *Chem. Commun.* 947 (1967).

(20) Eischenmoser, A. and Schinz, H. *Helv. Chim. Acta* **33** 171 (1950).

(21) Mills, J. A. *J. Chem. Soc.* 4976 (1952).

(22) Mukherji, S. M. and Bhattacharyya, N. K. *J. Amer. Chem. Soc.* **75** 4698 (1953).

(23) Joshi, G. D. and Kulkarni, S. N. *Indian J. Chem.* **3** 91 (1965).

(24) Honwad, V. K. and Rao, A. S. *Curr. Sci.* **34** (18) 534 (1965).

(25) Honwad, V. K. and Rao, A. S. *Tetrahedron* **21** 2593 (1965).

(26) Sorm, F., Zaoral, M. and Heront, V. *Collect. Czech. Chem. Commun.* **18** 116 (1953).

(27) Tyihak, E., Sarkary-Kiss, I. and Mathe, J. *Pharm. Zeutralhalle* **102** (3), 128 (1963) (CA 59 61956).

(28) Penfold, A. R. *J. Proc. Roy. Soc. N.S.W.,* **62** 60 (1928) and **66** 240 (1932). Murray, A. R. and Birch, A. J. *J. Chem. Soc.* 1888 (1951).

(29) Ruzicka, L., Eschenmoser, A. and Heusser, H. *Experientia* **9** 357 (1953).

(30) Ognajnov, I., Ivanov Verout, D., Horak, M., Pliva, J. and Sorm, F. *Chem. Ind. (London)* 820 (1957).

(31) Barton, D. H. R. and Mayo, P. de. *J. Chem. Soc.* 150 (1957).

(32) Sorm, F. *J. Agr. Food Chem.* **19** (6) 1081 (1971).

(33) Yoshihara, K., Ohta, Y., Sakai, T. and Hirose, Y. *Tetrahedron Lett.* 2263 (1969).

(34a) Sorm, F., Herout, V. and Sykora, V. *Collect. Czech. Chem. Commun.* **21** 267 (1956)

(34b) Rao, A. S. and Patil, L. J. *Tetrahedron Lett.* 2273 (1967)

(34c) Vig, O. P., Matta, K. L., Kapur, J. C. and Vig, B. *J. Indian Chem. Soc.* **45** 973 (1968).

(35) Hirose, Y. and Mosikawa, K. *Tetrahedron Lett.* 1799 (1969).

(36) Paknikar, S. K. and Bhattachayya, S. C. *Tetrahedron* **18** 1509 (1962).

(37) Corey, E. J. and Broger, E. A. *Tetrahedron Lett.* 1779 (1969).

(38) Naves, Y. R. *Bull. Soc. Chim. Fr.* 292 (1956); Klyne, W. *J. Chem. Soc.* 3072 (1953).

(39) Schimmel and Co. News, April, 96 (1910).

(40) McQuillin, F. J. and Parrack, J. D. *J. Chem. Soc.* 2973 (1956).

(41) Marshall, J. A., Pike, M. T. and Carrol, R. D. *J. Org. Chem.* **31** 2933 (1966).

(42) Bradfield, A. E., Hedge, B. H., Rao, B. S., Simonsen, J. L. and Gillam, A. E. *J. Chem. Soc.* 667 (1936).

(43) Pinder, A. R. *Perfum. Essent. Oil Rec.* **59** 280 and 645 (1968) and references therein.

(44) Penfold, A. R., Robinson, R. and Simonsen, J. L. *J. Chem. Soc.* 87 (1939).

(45) MacLeod, W. D. *Tetrahedron Lett.* 4779 (1965).

(46) Hunter, G. L. K. and Brogden, W. B. *J. Food Sci.* **30** (1) 876 (1965).

(47) Ohloff, G. *German Patent* 1,948,033 (*Chem. Abst.* **73** 109933Q).

(48) Van Der Gen, A., Van Der Linde, L. M., Wittleveen, J. G. and Boelens, *H. Recueil* **90** 1034 (1971).

(49) Pinder, A. R. and Odom, H. C. *Chem. Commun.* 26 (1969).

(50) Marshall, J. A. and Ruden, R. A. *J. Org. Chem.* **36** (4) 594 (1971).

(51) Bozzato, G., Pesaro, M. and Schudel, P. *British Patent* 1,236,320.

(52) Ohloff, G. and Giersch, W. *Gustation and olfaction* 184 (1971) (Academic Press, London).

(53) Stevens, K. L., Guadagni, D. G. and Stern, D. J. *J. Sci. Food Agr.* **21** 590 (1970).

(54) Teranishi, R. *Gustation and olfaction,* 165 (1971) (Academic Press, London).

(55) Endo, K. and Mayo, P. de. *Chem. Commun.* 89 (1967); Marshall, J. A., Faubl, H. and Warne, T. M. *Chem. Commun.* 753 (1967).

(56) Marshall, J. A. and Johnson, P. C. *J. Amer. Chem. Soc.* **89** 2750 (1967).

(57) Umarani, D. C., Gore, K. G., and Chakravarti, K. K. *Tetrahedron Lett.* 1255 (1966); Kido, F., Uda, H. and Yoshikoshi, A. *Tetrahedron Lett.* 2815 (1967); MacSweeney, D. F., Ramage, R. and Sattar, A. *Tetrahedron Lett.* 557 (1970).

(58) Ruzicka, L., Capato, E. and Huyser, H. W. *Rec. Trav. Chim.* **47** 370 (1928).

(59) Simonsen, J. L. *J. Chem. Soc.* **123** 2642 (1923).

(60) Moffett, R. H. and Rogers, D. *Chem. Ind.* 916 (1953).

(61) Naffa, P. and Ourisson, G. *Chem. Ind.* 918 (1953).

(62) Corey, E. K., Ohno, M., Mitra, B. and Vitakencherry, P. A. *J. Amer. Chem. Soc.* **86** 478 (1964).

(63) Beyler, R. E. and Ourisson, G. *J. Org. Chem.* **30** 2838 (1965).

(64) Nayak, U. R., Santhanakrishnan, T. and Dev, Sukh. *Tetrahedron* **19** 2281 (1963).

(65) *British Patent No.* 1,225,158.

(66) Ourisson, G. *Recherches* **15** 15 (1966).

(67) Hall, J. B., and Lala, L. K. *J. Org. Chem.* **37** 921 (1972).

(68) *British Patent No.* 1,254,198.

(69) Ansari, H. R. *Tetrahedron* in press.

(70) Prahlad, J. R., Nayak, U. R. and Dev, Sukh. *Tetrahedron* **26** 663 (1970).

(71) *German Patent No.* 2,123,104.

(72) Nayak, U. R. and Dev, Sukh. *Tetrahedron* **8** 42 (1960).

(73) Ranganathan, R., Nayak, U. R., Santhanakrishnan, T. S. and Dev, Sukh, *Tetrahedron* **26** 621 (1970).

(74) Sobti, R. R. and Dev, Sukh. *Tetrahedron* **26** 649 (1970).

(75) Kettenes, D. K., Van Leirop, J. B. H., Van der Wal, B. and Sipma, G. *Recueil* 313 (1969).

(76) Santhanakrishnan, T. S., Sobti, R., Nayak, U. R. and Dev, Sukh. *Tetrahedron* **26** 657 (1970).

(77) Eshinasi, E. H., Shaffer, G. W. and Barteles, A. P. *Tetrahedron Lett.* 3523 (1970).

(78) Lala, L. K. and Hall, J. B. *J. Org. Chem.* **35** (1970).

(79) Santhanakrishnan, T. S., Sobti, R. R., Nayak, U. R. and Dev, Sukh. *Tetrahedron* **26** 657 (1970).

(80) Banthorpe, D. V., Curtis, A. J. and Fordham, W. D. *Tetrahedron Lett.* 3865 (1972).

(81) *British Patent No.* 1,197,579.

(82) *British Patent No.* 1,256,535.

(83) *Die Atherischen Ole Vol. III* 325–9, eds E. Gildemeister and Fr. Hoffman (1960) (Academie-Verlag. Berlin).

(84) Demole, E. *Helv. Chim. Acta* **47** 319 (1964).

(85) *British Patent Application,* 52706/71.

(86) Colonge, J., Descotes, G., Bahurel, Y. and Menet, A. *Bull. Soc. Chim. Fr.* 374 (1966).

(87) Hodgson, C. L., MacSweeney, D. F. and Money, T. *Chem. Commun.* 766 (1971).

(88) Hodgson, G. L., MacSweeney, D. F. and Money, T. *Tetrahedron Lett.* 3683 (1972).

(89) Fanta, W. I. and Erman, W. F. *J. Org. Chem.* **37** 1624 (1972).

(90) Brieger, G. *Tetrahedron Lett.* 1949 (1963).

(91) Vaughan, R., Wolinsky, J., Dueltgen, R. R., Grey, S. and Seichter, F. S. *J. Org. Chem.* **35** 400 (1970).

(92) Kitshens, G. C., Dorsky, J. and Kaiser, K. *Givaudanian* **1** 3 (1971).
(93) Kitshens, G. C., Dorsky, J. and Kaiser, K. *Givaudanian* **2** 9 (1971).
(94) Wood, T. F. *Givaudanian* **1** 3 (1970).
(95) Daeniker, H. U., Hochstetler, A. R., Kaiser, K. and Kitshens, L. C. *J. Org. Chem.* **37** 1 (1972).
(96) Daeniker, H. U., Hochstetler, A. R., Kaiser, K. and Kitshens, L. C. *J. Org. Chem.* **37** 6 (1972).
(97) Dauben, W. L., Freidrich, L. E., Oberhansli, P. and Aoyagi, E. I. *J. Org. Chem.* **37** 9 (1972).
(98) Tsubaki, Naoko, Nishimura, Kiichi and Hirose, Yoshio. *Bull Chem. Soc. Japan* **59** **407** (1967).
(99) Wenninger, J. A., Yates, R. L. and Dolinsky, M. *J. Ass. Offic. Anal. Chem.* **50** 1313 (1967).
(100) Wenninger, J. A., Yates, R. L. and Dolinsky, M. *The Toilet Goods Association,* Proceedings of the Scientific Section 44 (1966).
(101) Buchi, G., MacLeod, W. D. and Padilla, J. *J. Amer. Chem. Soc.* **86** 4438 (1964).
(102) Buchi, G., Goldman, I. M. and Mayo, D. W. *J. Amer. Chem. Soc.* **88** 3109 (1966).
(103) Cren, Marie-Claude, Defaye, G. and Fetizon, M. *Bull. Chim. Soc. Fr.* 3020 (1970).
(104) Bates, R. B. and Slagel, R. C. *Chem. Ind.* 1715 (1962).
(105) Marshall, J. A. and Greene, A. E. *J. Org. Chem.* **37** 982 (1972).
(106) *South African Patent,* 6904,445,07.
(107) Kretschmar, H. C., Barneis, Z. and Erman, W. F. *Tetrahedron Lett.* 37 (1970).