Fragrances Through Hydrochlorination of Terpenes

By James Verghese, Synthite Industrial Chemicals (P) Ltd., Cochin, India

Among the reactions that have enriched terpene chemistry, perhaps the simplest and one of the outstanding is hydrochlorination. This reaction has been used for structural elucidation, for derivatization to identify and/or purify terpenes and for synthesising perfumery chemicals. How the application of hydrochlorination on terpenes has unearthed the treasure caves of fragrances is a vibrant chapter worthy of portrayal.

At the onset, it is of interest to touch upon routes to fragrances which utilise isoprene (I), the fundamental terpene unit, now available prolifically as a petrochemical.[1] Here, the key reaction is the mono-hydrochlorination of the hydrocarbon with aqueous or gaseous hydrogen chloride to give prenyl chloride [1-chloro-3-methyl-2-butene] (2);[2] the latter is obtained in 86% yield by mono-hydrochloroinating (I) admixed with cuprous chloride.[3] Condensation of (2) with acetone at moderate temperature in presence of sodium hydroxide and an amine type catalyst affords methylheptenone (3)[4,5] Ethynylation of (3) with acetylene and sodium hydroxide in N-methyl pyrrolidone solution without pressure gives dehydrolinalool (4).[6] Dehydrolinalool is a very versatile intermediate. By catalytic hydrogenation with 2% Pd/Al_2O_3 in propanol, it gives 99% linalool (5a)[1(c)] and the latter can be rearranged to geraniol and nerol (6a); it condenses with acetone to give ψ-ionone (7) and the ionones (8a). With vanadium catalyst, it rearranges to citral (9)[7]. The pivotal role of this aldehyde as such and in the synthesis of aroma chemicals is well documented.

Entry into perfumery chemicals through hydrocarbons of the 2,6-dimethyl-octane series is a giant step. For this, the exemplary substrates are 2,6-dimethyl-2,7-octadiene (citronellene) (10), 2-methyl-6-methylene-2,7-octadiene (myrcene) (11) and 2,6-dimethyl-2,4,-6-octatriene (allooci-mene) (12).

Inactive citronellene is obtained by selective hydrogenation of myrcene (11)[8] and optically active, by pyrolysis of pinane (13)[9] which in turn results by hydrogenation of optically active α-and β-pinenes (14 & 15). Catalytic hydrogenation of pinenes leads to over 90% of *cis*-pinane.[10] (+)- or (−)-*cis* Pinane thermally isomerises to (+)- or (−)-citronellene but (+)- or (−)-*trans*-pinane affords the corresponding (−)- or (+)-diene.[9c] Also, *cis*-pinane rearranges at a faster rate than the sister isomer.[9c] Under optimum conditions of pyrolysis, the yield of citronellene goes up to about 68-70%.[9]

When citronellene is reacted with anhydrous hydrogen chloride at 20-25°C. in about stoichometric proportion or less, substantially all the hydrogen chloride adds to the tertiary carbon group to give 93-94% of 2-chloro-2,6-dimethyl-7-octene (16a) which lends itself to the preparation of a wide range of aroma chemicals.[12,13]

Hydrolysis of (16a) by stirring with aq. slurry of calcium hydroxide at 100-105°C furnishes 2,6-dimethyl-7-octen-2-ol (16b).[12] Esters can be obtained from this alcohol by the use of acid anhydrides, acid chlorides, etc. By reacting (16a) with an alkoxide or sodium salt of (16b) with an alkylating agent, ethers (16d) are produced. 2,6-Dimethyl-7-octen-2-ol, its esters and ethers possess very pleasant, flowery odours.[12] Moreover, cleavage of the unsaturation in (16b) with ozone gives the hydroxy-aldehyde (17) which on dehydration affords 2,6-dimethyl-1-hepten-7-al (18a), a product known to be valuable in perfumery.[12]

2-Chloro-2,6-dimethyl-7-octene (16a) can be processed to yield hydroxy-citronellal (19a) and citronellal (18b).[14] Thus, the reaction of (16a)

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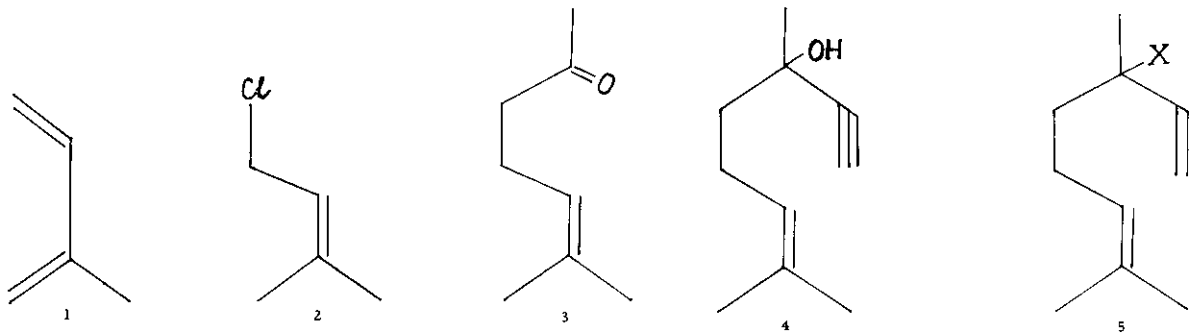
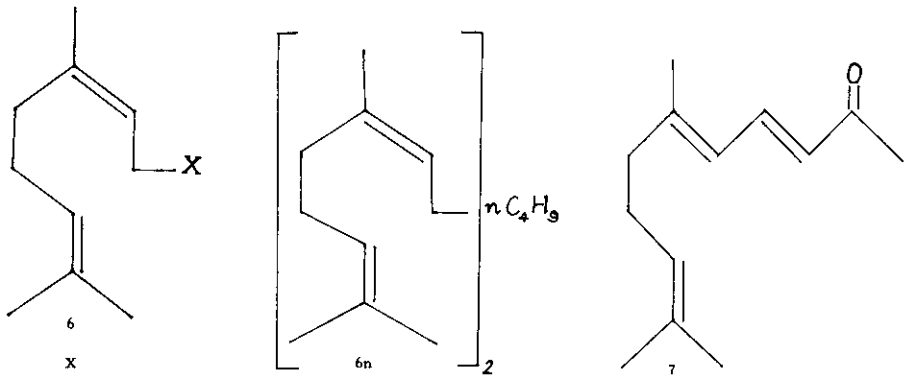


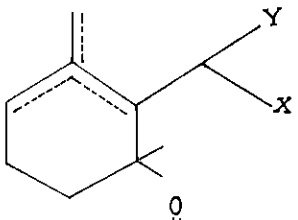
a) X = OH
b) X = Cl

with peracetic acid/anhydrous sodium acetate at 20-30°C gives 2-chloro-7,8-epoxy-2-6-dimethyl-octane (20a) which upon hydrolysis with aq. calcium hydroxide at 100-105°C affords 2,6-dimethyl-7,8-epoxy-octan-2-ol (20b); this epoxy alcohol, when pyrolysed in the vapour phase by passing through a stainless tube with CO_2 as a carrier gas at 490-500°C is converted to hydroxy-citronellal (19a).[14] Reaction of (20b) with traces of acid catalysts such as benzenesulphonic acid, chloroacetic acid, sulphuric acid, phosphoric acid brings about simultaneous transformation of the oxirane ring to aldehyde function and dehydration of the tertiary hydroxyl group to isopropenyl form of citronellal (18b).[14]

Two-way decyclisation of (20b) upon hydrogenation furnishes either 2,7- or 2,8-diol (19b or 19c).[15] Catalysts, e.g., copper chromite or palladium, favour formation of (19b) while Raney type catalysts, of (19c). These alcohols and their lower monocarboxylic esters have pleasant characteristic floral odour, rendering them useful in aromatic compositions for perfumery, including masking agents.



a) OH
b) Cl
c) CH_2COCH_3
d) $CH_2-C(CH_3)(OH)-CH_2-COOR$
e) $CH_2-C(CH_3)=CH-COOR$
f) $CH_2-C(CH_3)=CH-CH_2OH$
g) $CH_2-C(CH_3)=CH-CH_2-O-COCH_3$
h) $N(CH_3)_2$
i) $N(CH_2CH_3)_2$
j) NHC_8H_{17}
k) N
l) $N(CH_3)-CH_2-$
m) N



8

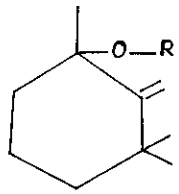
a) XY = O

b) X = NR_1R_2 ; Y = H

c) X = $O\text{-}CO\text{-}R_3$; Y = H

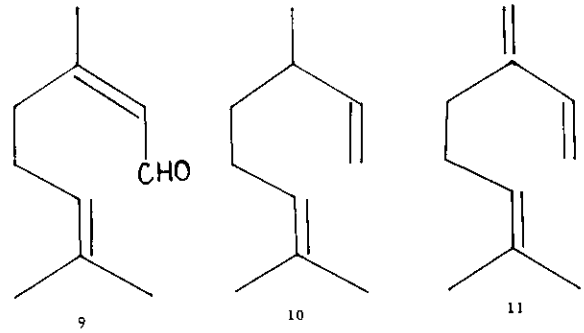
d) X = OH; Y = H

e) XY = O

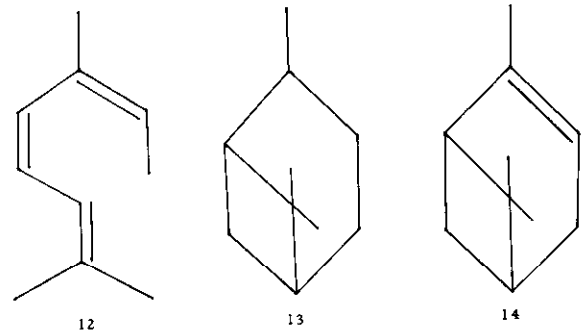


8f) R = COR_3

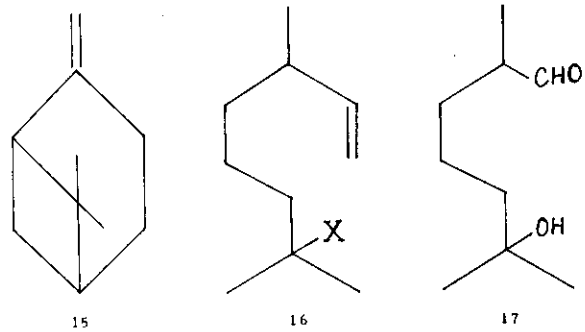
8g) R = H



9 10 11



12 13 14



15 16 17

X

a) Cl c) O-CO-R

b) OH d) O-R

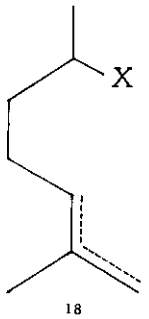
Selective dehydration of the 2,8-diol (19b) with aq. 25% H_3PO_4 gives exclusively the β-form of citronellol (18c); if the dehydration product is separated from the reaction-mass as fast as possible, it will be rich in α-citronellol (18c). Refluxing of α-citronellol for 2 hours with 25% aq. H_3PO_4 changes it to the β-isomer (18c). α- and β-Citronellol (18b) smoothly dehydrate to α- and β-citronellal (18b) by heating with powdered copper and copper chromite respectively.[15]

An alternate route to α- and β-citronellol consists of refluxing the 2,8-diol, with an acid anhydride, e.g., Ac_2O whereby high yields of the citronellol ester is produced; saponification of the latter furnishes the parent alcohol. An α-citronellol ester such as its acetate can also be obtained by controlled pyrolysis of the 2,8-diol derived by reacting the latter with an acid anhydride e.g. Ac_2O in presence of a catalyst such as H_3PO_4. α-Citronellol esters are well-known valuable ingredients of perfumery compositions.

Catalysed by peroxides, (16a) adds hydrogen bromide readily to give 2-chloro-8-bromo-2-6-dimethyloctane (19d).[13]

Citronellyl alkyl ethers [18d, R = CH_3, CH_3CH_2, $(CH_3)_2CH$, $(CH_3)_2CHCH_2$] with pleasant characteristic citronellyl-like odours, useful odorants in soap and the like, are derived from the chloro-bromide by reacting it with appropriate alcohol-KOH reagents. Pyrolysis of (19d) eg. at 400°C at a pressure of 300 mm Hg or hydrolysis with base, e.g., $Ca(OH)_2$ at 120°-130°C gives excellent yield of citronellyl bromide (18e). This on hydrolysis with aq. alkali produces citronellol (18c). Citronellyl esters (18f) are obtained either from (18c) or (19d) by well known procedures. Most desired is the acetate and it can be produced by heating the above alcohol with acetic acid or anhydride and anhydrous sodium acetate. Its saponification affords citronellol (18c). Reaction conditions dictate the proportion of α- and β-forms of citronellyl derivatives. Thus, citronellyl esters or citronellol rich in the α-form can be rearranged to produce a desired ratio of α/β isomers which enables the production of mixed forms of citronellol, highly prized rhodinol.[13] It may be added that the α-form of citronellol has a specific odour and is therefore of selective value in perfumery.[13]

To produce hydroxy-citronellol (19c), the dihalide (19d) is hydrolyzed with excess of an aq. base. Dehydrogenation of (19c) with copper chromite furnishes hydroxycitronellal (19a) and cohobating it with 25% H_3PO_4 leads to citronellol (18c).



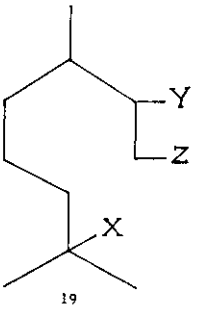
18

X

a) CHO b) CH_2— CHO

c) CH_2— CH_2— OH d) CH_2—CH_2—O—R

e) CH_2—CH_2—Br f) CH_2— CH_2—O—CO—R



19

a) X = OH; Y = H; Z = O b) X = Y = OH; Z = H

c) X = Z = OH; Y = H d) X = Cl; Z = Br; Y = H

e) X = Z = OH; Y = H

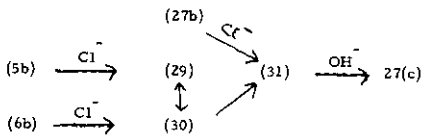
A meritorious feature of the above conversion is that no racemisation occurs in the various steps. Thus by using optically active α- and β-pinenes, optically active citronellols, citronellals, hydroxy-citronellol and derivatives are obtained. This has opened up a route to (−)-menthol (21) involving the following steps: (−)-citronellene (10) → (+)-citronellol (18c) → (+)-citronellal (18b) → (−)-Isopulegol isomers (22) → (−)-menthol isomers (21). From the latter, (−)-menthol can be retrieved by fractional crystallisation of the benzoate esters; the remaining isomers can be equilibrated to generate further quantity of (−)-menthol.

Readily available by pyrolysis of β-pinene,[16] is myrcene which is a pivotal triene for the synthesis of aroma chemicals.

Addition of hydrogen chloride to myrcene can take place at any of its three double bonds, though most of the reaction occurs at the conjugated diene system.[19] It was reported in 1954 that in the absence of a solvent, uptake of one equivalent of hydrogen chloride to myrcene at room temperature leads chiefly to linalyl chloride (5b), and also to the stereoisomers geranyl/neryl chlorides (6b) and 2-chloro-2-methyl-6-methylene-7-octene, mercenyl chloride (23a).[19]

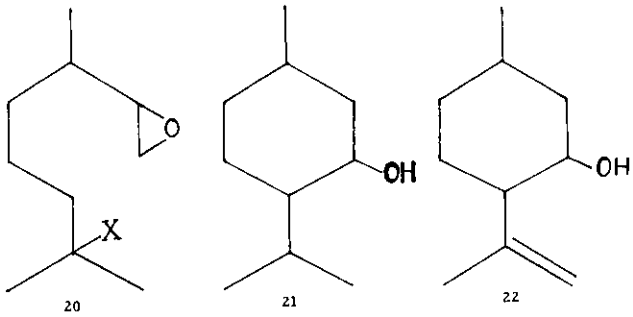
Porsch and Farnow[18] envisage the formation of myrcene hydrochloride initiated according to: (26) ↔ (11) ↔ (24) ↔ (25) followed by addition of the elements of hydrochloride to (24), (25) and (26) resulting respectively in geranyl/neryl, linalyl and mercenyl chloride.

From the above monohydrochlorides, hydrolysis by a slurry of finely divided calcium carbonate releases a cut consisting roughly of ⅓ linalool (5b), ⅓ α-terpineol (27a) and ⅓ myrcenol (23b) and traces of unidentified alcohols. The primary alcohol present appears to be nerol (6a) (<5%) as it does not form a calcium chloride adduct as does geraniol, it can be separated from the reaction mixture.[19] Further, the reaction mixture includes dineryl ether (28) which has a mild sweet odour, valuable as a fixative in perfumery.[19] It is to be noted that α-terpineol (27a) is always formed on hydrolysis of myrcene hydrochloride, even if it is derived from purified myrcene.[19] This alcohol is obtained under hydrolytic conditions from α-terpinyl chloride[27b]—which is formed by cyclization in the presence of hydrogen chloride of linalyl chloride[21] or from linalyl, geranyl/neryl chloride by reaction mechanism:[18, 19, 23]



Of the chlorides constituting myrcene hydrochloride, value is attached only to linalyl and geranyl/neryl chlorides since they are precursors of the desired corresponding acyclic alcohols. Hence, the discovery of cuprous catalysts, e.g., cuprous chloride or broadly any cuprous compound and elemental copper which will produce enough cuprous chloride in presence of hydrogen chloride, in directing the addition of hydrogen chloride to the conjugated system in myrcene to form mainly linalyl and geranyl/neryl chloride, is a unique contribution.[17, 20]

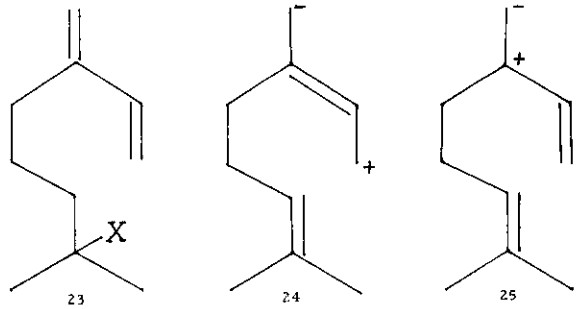
As little as 0.001% of cuprous chloride is effective in suppressing conversion to myrcenyl and α-terpinyl chloride and only stoichometric quantity of hydrogen chloride need be used.[17] To optimise the production of linalyl chloride, the reaction must be carried out at about −15°C with a minimum of catalyst and for the shortest time.



20 21 22

a) X = Cl

b) X = OH



23 24 25

X

a) Cl

b) OH

c) O-CO-R

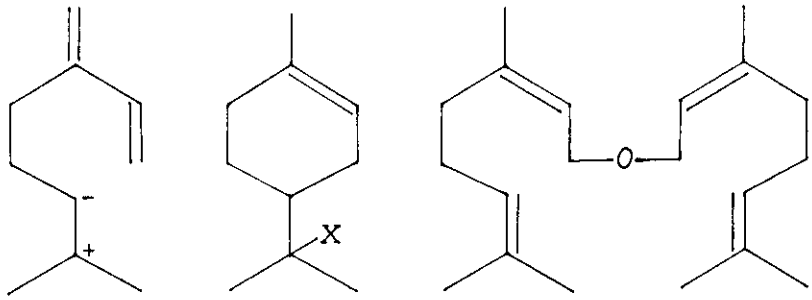
On the other hand geranyl/neryl chloride results if large quantity of catalyst and temperature of 15°C and above are used. Rearrangement of linalyl to geranyl/neryl chloride is provoked if the hydrochloride mixture is allowed to stand or agitated with cuprous chloride. Cuprous chloride eliminates the formation of the undesirable conjugated mercenyl chloride; however it catalyses the rearrangement of linalyl to geranyl/neryl chloride precluding ring closure to α-terpinyl chloride.[17]

Substantially the above results can also be achieved by hydrochlorinating myrcene by using the relatively inexpensive and widely available cupric compound as catalyst in concentration of 0.1 to 10%.[22] The cupric compound must be one convertible to chloride under reaction conditions and it can be an organic or inorganic compound, e.g., chloride, carbonate, oxide, acetate, sulphate, oleate, resinate, naphthanate or the like. Advantageously, the cupric catalyst is the chloride in finely divided state and preferably it is added in the form of cupric acetate. The acetate is soluble in myrcene and when hydrochlorinated, active cupric catalyst precipitates in a virtually colloidally dispersed state affording maximum active cupric surface for the reaction purpose. A significant finding is that, while the overall yield of desirable halide products is comparable with cupric and cuprous catalysed hydrochlorination of myrcene, the cupric copper catalysed reaction furnishes a higher proportion of linalyl chloride than the corresponding cuprous copper catalysed run.

One approach of solvolysis of myrcene hydrochloride consists of treating it with a carboxylic acid and a base capable of neutralising the liberated hydrogen chloride, in the presence of cuprous catalyst.[24] The principle involved may be illustrated by the reaction of myrcene hydrochloride in acetic acid solvent catalysed by cuprous chloride. What is apparently an equilibrium of allylic chloride, acetic acid, ester and hydrogen chloride is eliminated by addition of a base, e.g., a sodium, potassium, ammonium or amine salt of the carboxylic acid, sodium triphosphate, ammonia, amine or an ion exchange resin. Most convenient and economical is the use of a sodium or potassium salt, as it fulfils the dual role of providing both carboxylic ion and necessary neutralising function.[24] As cuprous catalyst, cuprous chloride is preferred though cuprous oxide or copper or mixture of copper and a cupric compound which are equivalent to cuprous chloride to the extent the latter is produced *in situ* in the action mixture can also be used.[24] In so far as linalyl—geranyl/neryl chloride and their esters are exceptionally sensitive to high temperature, it is preferred to conduct these reactions at temperatures <100°C. Ordinarily, in the cuprous catalysed reaction, sodium acetate-acetic acid combination is the best as long as the target is allylic alcohols since the acetates undergo facile saponification to the latter and are themselves useful. Mixed carboxylic acids would, of course, produce mixed esters. In general, this type of solvolysis of myrcene hydrochloride gives a greater proportion of linalyl derivatives.

Using phosphorus trichloride-ammonia addition compound, PCl_5, $5NH_3$ as a novel catalyst in the reaction of myrcene hydrochloride, singly or in combination with alkali salts of fatty acids, conversion to linalyl and neryl/geranyl esters with a high ratio of linalyl ester has been achieved. About 1 to 1.1 mols of fatty acid salt and about 0.001 to 0.1 mol adduct per mol of myrcene hydrochloride are recommended and the reaction is conducted within the range from about 70°C to 100°C.[25]

Trans-esterification of myrcene hydrochloride



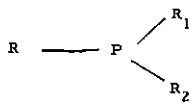
26 27 28

a) X = OH

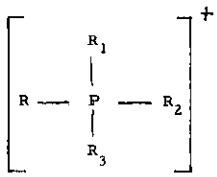
b) X = Cl

to furnish almost exclusively and in high yield up to approximately 95% or more of linalyl acetate leading to linalool upon hydrolysis has been realised by reaction of myrcene hydrochloride substantially between 90-100°C with slightly over equimolar amount of sodium acetate in a tertiary alcohol (e.g., tert-butanol or diethylmethyl carbinol) and an alkaline earth metal such as calcium carbonate and magnesium carbonate and optionally assisted by a catalyst selected from the group consisting of cuprous salts and cupric salts.[26]

Certain trivalent and quaternary phosphorus compounds catalyse the displacement of the chloride group in myrcene hydrochloride by acyloxy group in the treatment of the halide with salts of carboxylic acids under non-aqueous conditions. The catalyst is chosen from the group consisting of phosphorus, phosphonium salts and trivalent phosphorus. Compounds having the formula:

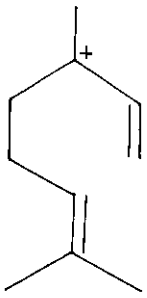


wherein R, R_1 and R_2 are selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, alkylamino, arylamino, cycloalkylamino and amino. Catalysts within the scope of the invention include compounds having the phosphonium radical:



in which R, R_1, R_2 and R_3 have the same meaning as above. Any carboxylic acid salt including the alkali metals such as sodium, potassium, and ammonium or amino salts, preferably about one or two equivalents of the carboxylic acid salt per equivalent of myrcene hydrochloride can be employed. The catalyst concentration prescribed is in an amount greater than 1% based on the weight of the halides substrate. Depending upon the identity of the halide, the reaction proceeds best at 60 to 160°C and may require 10 to 100 hours at 60°C. The terpene halide appears to the stabilised with respect to dehydrohalogenation in presence of the catalyst. Though one may employ the pure components of myrcene hydrochloride *(vide supra)*, it is usually preferred to employ the crude products of the hydrochlorination of myrcene. The mixture of the tertiary chloride (linalyl chloride) and primary chlorides (neryl and geranyl chloride) when subjected to the above process, give far higher yields of ester based on the consumption of the primary chlorides than based on the tertiary chloride. It is to be noted that the catalyst is expensive and hazardous, requiring special safety precautions.[25, 27]

Again, nitrogen base catalysed displacement reaction of myrcene hydrochloride with a salt of a carboxylic acid, tilts the equilibrium in favour of producing geranyl/neryl esters[28, 29] In general, the carboxylic acid salts which have been tested furnished the desired allylic terpenes esters indicating that the identity of the carboxylic acid is not critical. Regarding the nitrogen base, the list includes ammonia, amines, amidines, oximes, hydrazones, imines etc., but the effective and economic are the inexpensive aliphatic amines, notably triethylamine and triethanolamine. Linalyl chloride does not undergo displacement



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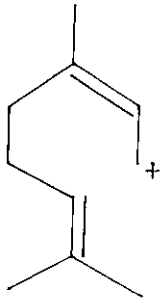

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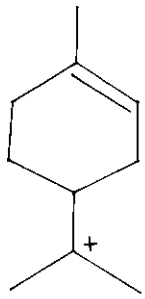

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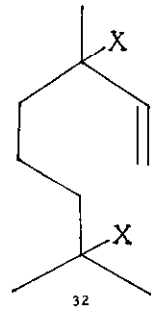


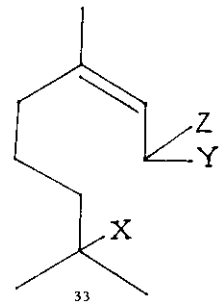
32

X

a) Cl

b) OH

c) O-CO-CH_3



33

a) X = Y = Cl; Z = H

b) X = Y = OH; Z = H

c) X = OH; YZ = O

d) X = Cl; Y = O-CO-R; Z = H

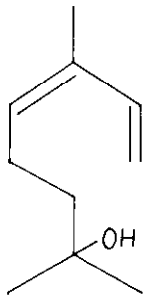
reactions as readily as geranyl/neryl chloride (catalysed or not). Therefore, the process is primarily for the production of geranyl/neryl esters and not for linalyl esters.

By adding to the reaction mixture of myrcene hydrochloride, Na alkanoate, cuprous chloride and a base that liberates ammonia to neutralise acidic impurities prior to distillation, perfumery grade linayl esters such as propionate and butyrate have been prepared.[30]

Synthesis of mixed allylic esters possessing excellent organoleptic and physical properties in good yields from myrcene hydrochloride has been accomplished by the simple and inexpensive processing with a salt of the formula NH_4X wherein X is the acyloxy radical of a lower saturated fatty carboxylic acid, in quantity sufficient to supply one equivalent of acyloxy radical per equivalent of chlorine, in solid or molten form, at a temperature from 0 to 140°C in the presence or absence of the corresponding acid.[31] The ammonium salts function as displacement reagents and have the advantage of possessing mpts 91-118°C which are well below the limits where dehydrochlorination becomes critical. Thus, when myrcene hydrochloride is reacted with ammonium acetate at 105-111°C, the yield of mixed linalyl and geranyl acetate in the oil phase amounted to approximately 75.9%.[31]

Improvements in the conversion of myrcene hydrochloride or its constituents to the corresponding acyloxy compounds by treatment with salts of carboxylic acids in the presence of dimethyl sulphoxide which functions as "solvent catalyst" or "week catalyst" for the displacement have been claimed by Webb.[32] The mechanism of the catalytic effect of dimethyl sulphoxide is not clear, but it may be through an intermediate sulphoxonium halide which reacts with the salt of the carboxylic acid to regenerate dimethyl sulphoxide and form linalyl, geranyl/neryl esters. About 5% and at times quantities up to 200% or more of sulphoxide is required on the basis of the allylic terpene chloride. At least one equivalent weight of the sodium salt of a lower fatty acid per equivalent weight of the chloride and operation temperature of approximately 20 to 120°C are recommended. Sodium carbonate in amounts 5-50% by weight based on the chloride may be added to neutralise any hydrogen chloride in the substrate or formed during the reaction and this renders the reaction mixture less corrosive to metals. By virtue of its water solubility and its convenient boiling point, dimethyl sulphoxide may be readily removed from the reaction mixture. These esters are also formed in the presence of 1,3-diphenyl guanidine.[33]

Except for the contribution of Webb,[19] we were dealing mainly with the modifications of myrcene hydrochloride by a two-step reaction in which the halide is first converted to a lower carboxylic ester and then saponified to the alcohol. A significant improvement is the conversion of myrcene hydrochloride and its components predominantly to allylic alcohols by solvolysis with an aqueous medium involving an inert solvent in which the terpene halide and water are soluble and in the presence of a cuprous halide catalyst.[34a] The preferred solvent is acetone and the catalyst cuprous chloride. Best results are obtained when the reaction mixture has a pH of 7.5-9.0.[34a] Interdependence of the acidity and reaction temperature is significant and higher acidity is better tolerated at low temperature; above 50°C, rearrangements are encouraged. If the pH is controlled by a carbonate or bicarbon-



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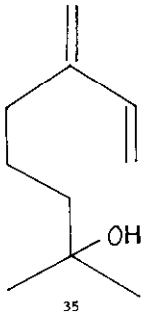

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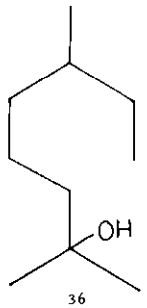

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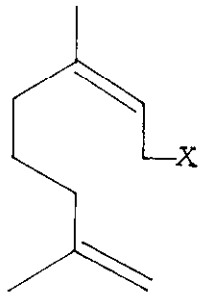

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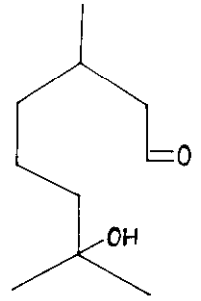
X

a) OAc

b) OH

c) O–R



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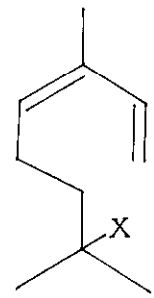


39

X

a) X = OH

b) X = O-CO-R

ate, cessation of CO_2 indicates the completion of the reaction.[34a] The product obtained normally comprises of linalool as the major component. Thus, agitating myrcene hydrochloride (1000 parts), acetone (800 parts), water (1500 parts), sodium bicarbonate (540 parts) and cuprous chloride (50 parts) at 0° for 4 hours, usually affords linalool (480 parts), α-terpineol (120 parts), hydrocarbons (120 parts) and residue (70 parts).[34a]

Kinetics of the hydrolysis of geranyl/neryl and linalyl chloride to oxygen-containing derivatives have been investigated by Soviet chemists.[34b]

Hydrolysis of or mixture of linalyl hydrochloride and myrcene hydrochloride to linalool by reacting with calcium carbonate in aqueous medium, at a pH of 6.0-8.0 and temperature of 0-25°C in the presence of 5-15% by weight of a cuprous or cupric salt and 2-10% of an emulsifying agent has been patented.[35]

In the hydrolysis of linalyl and geranyl/neryl chloride, the common resonating ion (29 and 30), embracing the 6, 7 and 8 carbon atoms, is the intermediate in the solvolysis reaction and therefore the degree to which this can appropriate hydroxyl ion determines the yield of linalool and geraniol/nerol.[36] Stimulated by the polarisation of the isopropylidene double bond, the resonating ion, however, is susceptible to cyclisation to the C_8^+-ion (31) which is the precursor of α-terpineol and ρ-menthadienes.[36] As a consequence, in the solvolysis of myrcene hydrochloride, the overall yield of the acyclic alcohols are lowered.[36]

To offset the above undesired reaction-course of myrcene hydrochloride to ρ-derivatives, myrcene is reached as its dihydrochloride which is devoid of the $C_2 = C_3$ unsaturation.[36, 37]

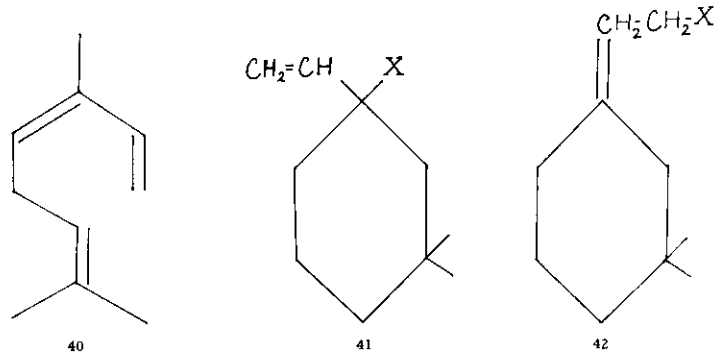
The hydrochloride is prepared by passing two mols of hydrogen chloride into the hydrocarbon containing 0.5% by weight of cuprous chloride at 20-25°C. The hydrochloride is chiefly a mixture of 2-chloro-dihydrolinalyl chloride (32c) and 2-chloro-dihydrogeranyl chloride (33c), with latter predominating.[37] Myrcene dihydrochloride is much more stable thermally than the corresponding monohydrochloride.[38]

Solvolysis of the dihydrochloride leads to allylic alcohols, predominantly 2,6-dimethyl-7-octene-2,6-diol (2-hydroxy-dihydro-linalool) (32b) mixed appreciably with 2,6-dimethyl-6-octene-2,6-diol (2-hydroxy-dihydro-geraniol) (33b) and small quantities of 2,6-dimethyl-5,7-octadiene-2-ol (34) and 2-methyl-6-methylene-7-octene-2-ol (35).[36] The glycols (32b and 33b) have pleasant but weak odours and probably have limited use in perfumery per se, but the conjugated monohydric acyclic alcohols (34 and 35) have pleasant odours and can be hydrogenated to 2,6-dimethyl-octane-2-ol (36) which is also useful in perfumery.[36]

Upon acetylation in benzene solution with Ac_2O/AcONa, (32b) yields practically quantitatively the diacetate (32c). Refluxing of (32c) with Ac_2O, AcONa and glacial AcOH affords geranyl acetate (37c). Saponification of (37c) yields α-geraniol (37b).

Oxidation of (32b) with $Na_2Cr_2O_7$-50% H_2SO_4 at 25-30°C furnishes 2-hydroxy-dihydro-citral (33c) which dehydrates by refluxing with benzene and 20% by weight of cupric chloride to citral (75% α- and 25% β-form). Alternatively (33c) can be condensed with acetone to produce hydroxy-dihydro-ψ-ionone which readily dehydrates and cyclizes to ionones.

The diol (32b), by reaction with 90% formic acid at 0-5°C followed by saponification of the formate esters formed furnishes 2-hydroxy-



40 41 42

dihydro-geraniol (33b). By refluxing with catalytic quantity of copper chromite, (33b) yields 2-hydroxy-dihydro-citronellol (19a) which dehydrates very rapidly with phosphoric acid to pure citronellol.

If myrcene dihydrochloride is processed as the monohydrochloride with ammonium salt of a lower saturated fatty acid in the presence or absence of the corresponding acid *(vide infra)*, the displacement reaction results in 2-chloro-8-acyloxy-2,6-dimethyl-6-octene (33d) which can be further converted almost quantitatively to geranyl ester by dehydrohalogenation with the molten ammonium salt, the geranyl ester produced being approximately 50% the isopropenyl form.[31] The chloro-derivative (33d) is mainly useable for the preparation of hydroxycitronellol.[31]

On the other hand, when myrcene dihydrochloride is submitted to reaction with two or more equivalent of an amine and salt of a carboxylic acid in the presence of a solvent, e.g., acetic acid, esters of geranyl/neryl and linalool in the α-forms are produced.[38] One mole of the carboxylic acid is required for the formation of the allylic ester and the second mole to neutralise the hydrogen chloride released. Instead of the alkali salt, any suitable base, e.g., Na_2CO_3 can be substituted for eliminating or neutralising the hydrogen chloride. As another alternative, the dihydrochloride can be treated with one mole of a monocarboxylic acid plus two moles of a base such as triethylamine. Here, one mole of the base neutralises the carboxylic acid to form the salt which reacts with the allylic chloride group and the second one, neutralises the hydrogen halide formed by dehydrohalogenation of C_2-Cl atom. Sodium acetate, triethylamine at 80-130°C are the preferred metal salt, solvent, organic base and reaction temperature respectively.[38]

Subsitution of myrcene dihydrochloride as the starting material in Webb's processes (vide supra) using phosphorus-containing[27] or dimethyl sulphoxide catalysts[29] leads to 2-chloro-dihydrogeranyl ester and the latter undergoes dehydrohalogenation on heating to approximately 100 to 150°C in the presence of a base; the resulting product on saponification affords allylic alcohols.

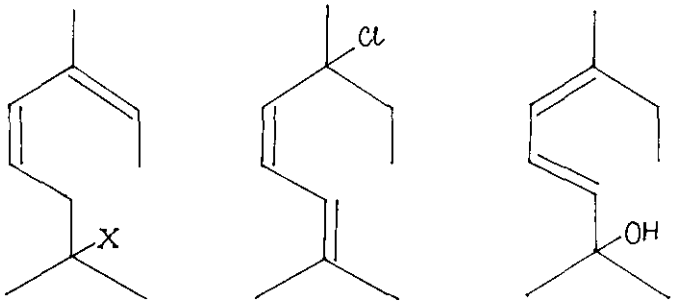
Finally, myrcene dihydrochloride can be transformed to the allylic esters (e.g., 2-chloro-dihydrogeranyl acetate and 2-chloro-dihydro-neryl acetate) (33, X = Cl, Y = CH_3COO) by reaction in benzene* at 75-80°C with anhydrous sodium acetate and trimethylamine which can be further hydrolysed with calcium hydroxide to 2-hydroxy-dihydro-geraniol/nerol (33b).[28]

Reverting to myrcene hydrochloride, another interesting use is its conversion to geranyl ethers (37c, R = CH_3, CH_3CH_2, $CH_3CH_2CH_2$) and their oxidation with alkyl chromate of tertiary alcohols (e.g., t-butyl chromate) at temperature <55°C in solvents such as carbon tetrachloride or petroleum ether to citral.[39]

At this point, mention may be made of the synthesis of farnesol (6f) farnesyl acetate (6g) and farnesol (6h), valuable perfumery ingredients, beginning with geranyl chloride (6b).[40] The steps consist of reacting (6b) with acetoacetic ester. The resulting α, β-dihydro- ψ-ionone (6c) is condensed with chloroacetate in the presence of Mg to give *via* (6d) ethyl farnesolate (6e) which is reduced with $LiAlH_4$ to farnesol (6f). Treatment of the latter with acetyl chloride gives the ester (6g) while oxidation with activated manganese-dioxide, results in farnesal.

Cycloterpenoid amines useful in the synthesis of perfume materials are prepared by ring closure of neryl/geranyl amines which in turn result by reacting neryl/geranyl chloride with appropriate amines.[75] By such alkylation reactions it is possible to obtain neryl dimethyl amine (6h), geranyl dethyl amine (6i), neryl octanyl amine (6j), neryl piperidyl amine (6k), N-neryl-N-methylbenzyl-

Ed. Note: Because of the carcinogenic properties of benzene, its replacement with toluene or another applicable solvent is suggested.



43 44 45

amine (61) N-ethyl-N-2-propyl nerylamine (6m) and dimerylbutyl amine (6n). Cyclisation is accomplished by using an acidic aq. solution, preferably 2-3 equivalents of the acid per equivalent of amine salt, if necessary in the presence of inert solvents such as ethers, cellosolve and the like at a temperature >80°C, preferably between 80 and 120°C but better under reflux conditions. For faster reaction rates, temperatures >120°C are advantageous but this requires pressurized equipment. When a 20 to 30% acid concentration is maintained, temperatures ~100-120°C are quite useful. Acids recommended include HCl, H_2SO_4 and HBr.

By the above process, the cyclized amine generated is a mixture of α, β & γ-cyclogeranyl isomers (8b), where R_1 is hydrogen or a C_{1-4} aliphatic group and R_2 is hydrogen or a monovalent radical, usually a monovalent organic radical or R_1R_2 are joined as a heterocyclic residue. Of the foregoing cyclogeranyl amines, only the β-isomer reacts with carboxylic acid anhydride to form cyclic terpenoid esters of the general formula (8c) where R_3 is a aliphatic group or moiety. Hence, the isomeric mixture of cyclic amines can be processed as such and the unreacted α & β-isomers can be isomerized, e.g., by refluxing with aq. HCl to produce an equilibrium mixture rich in the β-isomer for the addition to the next esterification step.

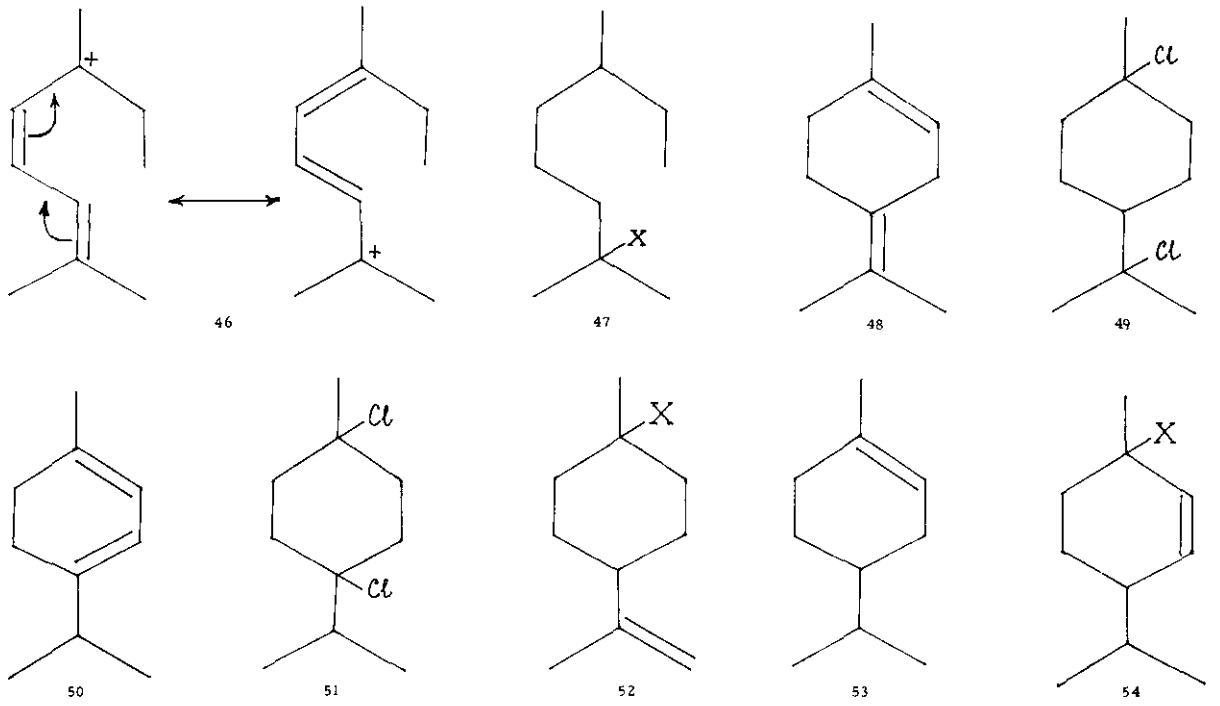
Conventional saponification of cycloterpenoid esters with alkali affords β-cyclogeraniol (8d); this can be oxidized to cyclocitral (8e) which is useful in the synthesis of β-ionone and other important fragrance materials.

Of interest is the "cyclolinayl ester" of the general formula (8f, R = COR_3) where R_3 is a aliphatic group, a minor product of acid ester process. By hydrolysis, this ester can be converted to "cyclolinalool" (1,3,3-trimethyl-2-methylene-1-cyclohexanol) (8f, R = H). "Cyclolinalyl ester" and the corresponding alcohol are a new class of compounds. Thus, by reaction of β-geranyl dimethyl amine with acetyl anhydride, "cyclolinalyl acetate" is formed and this on hydrolysis provides "cyclolinalool"—both useful fragrances.

Selective conducting the addition of hydrogen chloride to the isolated double bond in myrcene to give myrcenyl chloride (23a) has been achieved by applying Lewis acids and/or high surface area catalysts.[41] Examples are Lewis acids such as stannous chloride, bismuth trichloride, mercuric chloride, antimony and arsenic oxide, and high surface area material include silica gel, silicic acid, activated carbon and activated alumina.[41] Combination of a Lewis acid and a high surface area material is especially advantageous. Catalyst concentration may vary from approximately 0.1 to 10% and temperature of hydrochlorination from −20°C to 50°C—at best at 0-20°C. To depress undesirable side reactions, inhibitors, e.g., hydroquinone, 4-hydroxymethyl-2,6-di-t-butyl phenol or 4-methyl-6-t-butyl phenol should be present during hydrochlorination. Hydrolysis of the hydrochlorides affords alcohols with myrcenol (23b) as the major constituent which can be converted to various esters (23c) of great value in the preparation of fragrances, perfumes and other compositions.[41]

The isomerisation of myrcenol and its esters to corresponding ocimenol and esters (39)—are important because of their desirable odour characteristics. The above isomerisation with noble metal catalysts, for example, 2% Rh on carbon, is a notable advance.[42a] This catalytic process when applied to myrcene gives excellent yields of ocimene (40).[42a,b] Hydrochlorination of this triene in the presence of cuprous chloride and then reaction with $CH_3COONa/CH_3COOH/CuCl$ mixture affords linalyl, geranyl/neryl acetates.[24]

Other novel cyclic fragrances have been synthesised from myrcene. Hydrochlorination of myrcene and subsequent hydrolysis as described by Blumenthal and Oakhurst[41] yields, in addition to myrcenol (39a), the interesting alcohol, 3,3-dimethyl-1-vinyl-cyclohexanol (41, X = OH).



Further work has revealed that uncatalysed hydrochlorination of myrcene using 0.8 to 1.1 molar proportion of hydrogen chloride per mol of myrcene at −50 to −70°C under substantially anhydrous conditions affords 3,3-dimethyl-1-vinyl-cyclohexyl chloride (41 X = Cl) and 1-(2-chloro-ethylidene)-3,3-dimethylcyclohexane (42, X = Cl) in an overall yield of approximately 60%. The allylic chloride may be directly hydrolysed, catalysed by a copper compound, e.g., cuprous chloride, before or after purification, to obtain the respective alcohols (41 and 42, X = OH), or they may be reacted with a metal carboxylate salt in the presence of copper or nitrogen base catalyst to form acylates (41 and 42, X = OCOR) and these may be saponified to alcohols. The above allylic derivatives are susceptible to interconversion during various transformations.

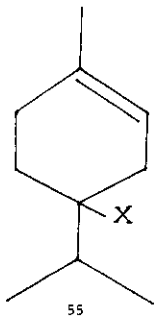
Table I

	Percent acetate	d_{15}	n_D^{20}	Odour
I.	90	0.8700	1.4258	Fragrant
II.	90	0.8709	1.4265	Like anise and basil
III.	90	0.8736	1.4271	Soft linalyl acetate
IV.	88	0.8975	1.4356	Like terpinyl acetate
V.	82	0.9220	1.4458	Disagreeable butyric odour

Earlier it has been mentioned that alloocimene (12) can provide fragrances within a 2,6-dimethyloctane framework. This hydrocarbon is prepared by pyrolysis of α-pinene and contains as impurities 20-25% of other terpenes.[44,45]

The hydrochlorination of alloocimene is characterised by the possibility of polymerisation.[45] In order to avoid this unwanted possibility the process is conducted by combining anhydrous hydrogen chloride diluted with an equal volume of nitrogen with not more than one mole of alloocimene, at −20°C. The hydrochloride formed is a mixture of (44) and (43) (X = Cl); which is prone to decomposition. Hence the next step *viz.* hydrolysis must be carried out immediately. This is effected with a 4% NaOH aqueous solution in the presence of a non-ionic emulsifying agent, e.g. Triton X-100 under moderate agitation. It is best to do the hydrochlorination and subsequent hydrolysis in a continuous manner. The alcohols recovered, designated as allo-ocimenol, consists of two diolefinic tertiary alcohols (43, X = OH) and (45), the latter originating due to the reasonance of the carbonium ion intermediate (46). Allo-ocimenol has the odour of a mixture of lily of the valley and rose.[45] Hydrogenation of allo-ocimenol at 50° with Raney nickel catalyst at 50 atmosphere pressure affords tetra-hydro-ocimenol (47, X = OH), a clear, water-white fragrant oil.[45] By reaction with Ac_2O/H_3PO_4 at 25-45°C, (47) is converted into tetrahydro-ocimenyl acetate (47, X = $OCOCH_3$), b.p. 63-68°C (2 mm) which upon fractionation yields cuts with odour and other characteristics summarised in Table I.

Ethyl ether of allo-ocemenol, having a lime-



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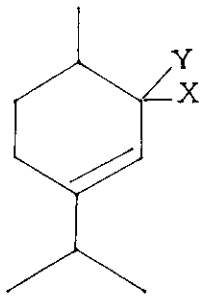

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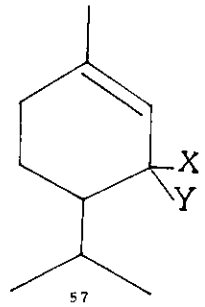
a) X = OH; Y = H
b) XY=O c) X=Cl; Y=H
d) X = Y = H



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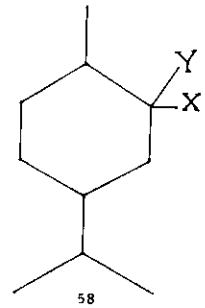
a) X = OH; Y = H
b) XY = O
c) X = Cl ; Y = H
d) X = OCH_3 ; Y = H



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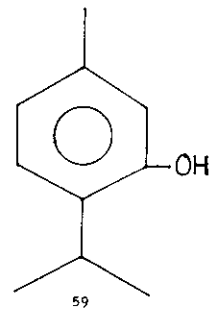
c) XY = O
b) X = OH; Y = H



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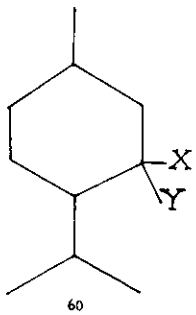

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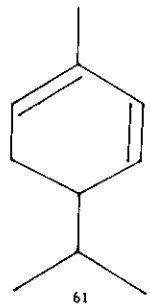
a) X = OH; Y = H
b) XY = O
c) X = OCH_3; Y = H



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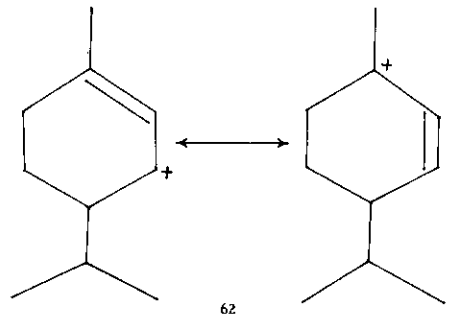

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like odour results when allo-ocimene hydrochloride is treated with aqueous ethyl alcohol.[45]

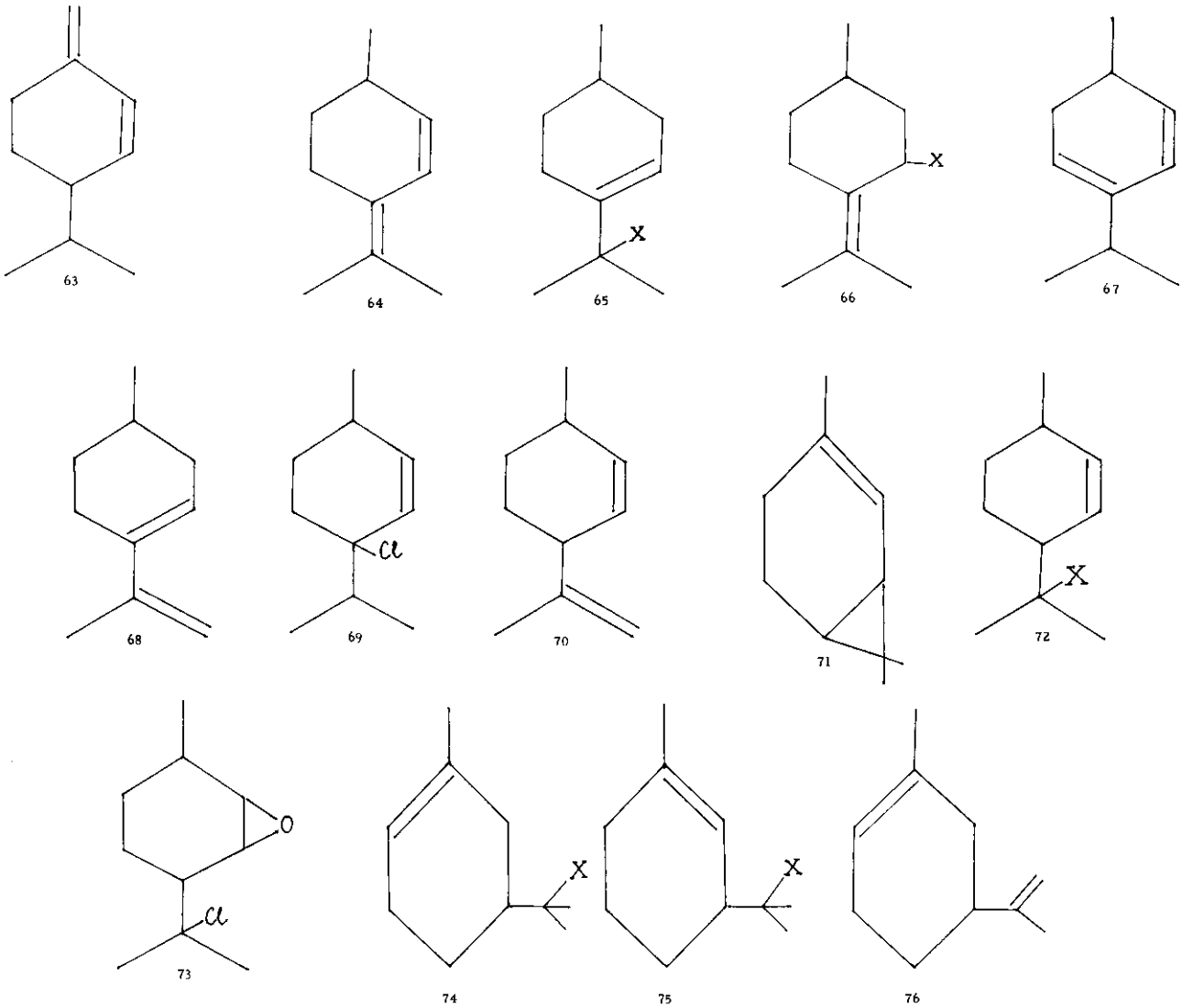
Let us now look at the approaches to aroma chemicals from menthadienes through hydrochlorination.

Of the p-menthadienes, only (+)- (−)- and (±)-p-mentha-1,8 (9)-diene (48) afford crystalline dichloride *viz.* 1,8-dichloro-p-menthane (49). In the light of recent work,[46] α-terpinene (50) is no longer regarded as the precursor of 1,4-dichloro-p-menthane (51). With hot alkali (49) yields α-terpineol (27, X = OH)[47] Best conditions for hydrolysis of (49) to highest yield of tertiary alcohols have been reported by Jerzy and Burkula.[48]

Monohydrochlorides emanating from p-menthadienes are versatile substrates for construction of fragrances.

Controlled hydrochlorination of a solution of (+)-limonene in CS_2 results in a mixture of 8-chloro-p-meth-1-ene (27, X = Cl) and 1-chloro-p-menth-8(9)-ene (52, X = Cl). The halogen atom in these exchanges for hydroxyl by alkaline hydrolysis gives α-terpineol (27, X = OH) and β-terpineol (52, X = OH).[49] α-Terpinyl chloride (27, X = Cl), by refluxing in 80% aq. acetone for 6 hours with ZnO gives α-terpineol in over 85% yield.[50] α-Terpinyl acetate (27, X = $OCOCH_3$), α-terpinyl formate (27, X = OCOH) and α-terpinyl methyl ether; (27, X = OCH_3) are obtained in 90, 95 and 95% yields by heating for 2 hours with ZnO in acetic acid, formic acid (98%) and methanol at 25-30°C. 12-15°C and reflux temperature respectively.[50] Selective reduction of α-terpinyl chloride gives p-menth-1-ene (53)[51] which is a key intermediate for fragrances.[52]

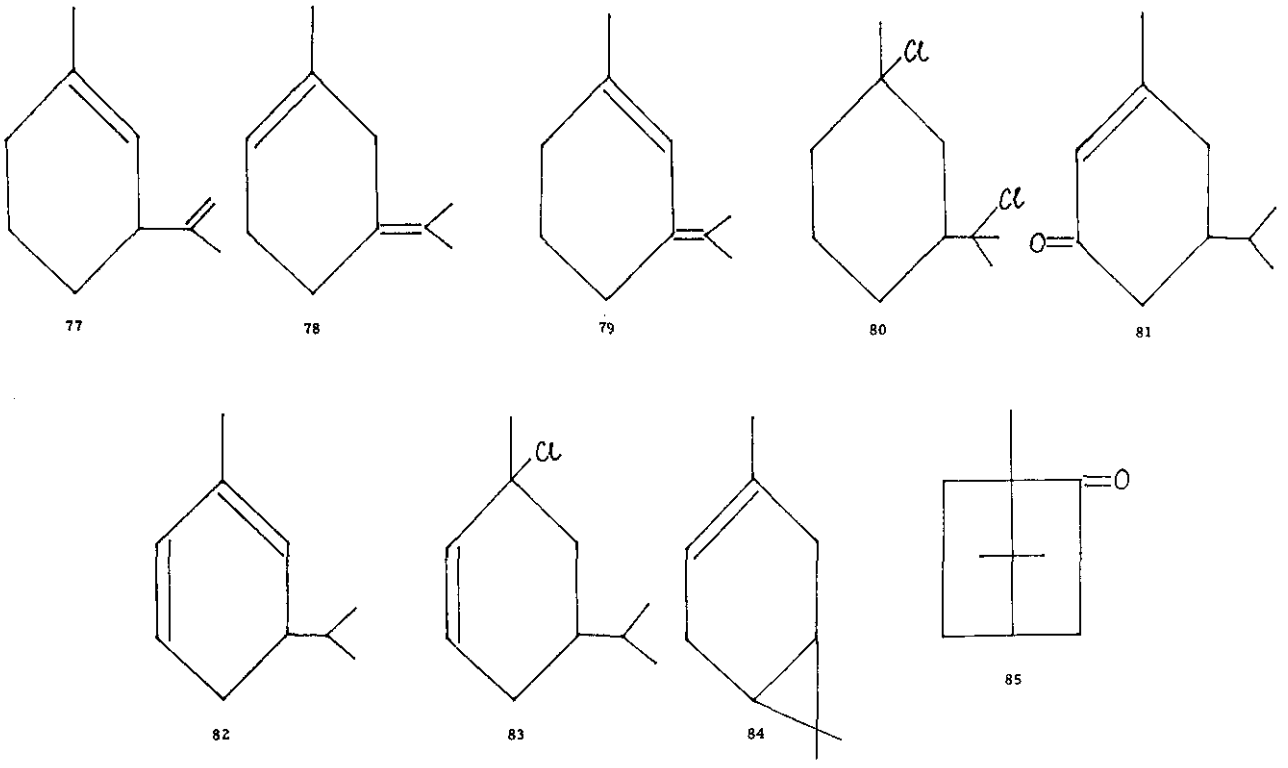
α-Terpinene (50), which is most readily available from monoterpenes,[53] when reacted with dry hydrogen chloride or aq. hydrochloric acid, with or without a solvent, absorbs the halogen acid in equimolecular proportion[54] and gives α-terpinene monohydrochloride, a mixture of 1-chloro-p-menth-2-ene (54, X = Cl) and 4-chloro-p-menth-3-ene (55, X = Cl).[24] Solvolytic reactions of terpinene monohydrochloride by agitation in aqueous phase with sodium, potassium or



calcium hydroxide or their corresponding carbonates or bicarbonates—preferably calcium hydroxide and calcium carbonate, being inexpensive and effective—at 80-120°C, leads to p-menth-2-en-1-ol (54, X = OH) *(cis* and *trans)* and p-menth-3-en-2-ol (56a) (carvenol), with little or no piperitol (p-menth-1-en-3-ol) (57a).[54] On the other hand, esters of (57a) as well as of (54, X = OH) and (56a) are formed if the reaction is conducted under displacement conditions, e.g., with sodium acetate/acetic acid or sodium formate/formic acid plus cuprous chloride,[24,54] and the esters can be saponified to give the corresponding alcohols. Further, the p-menth-2-en-1-ols by careful processing with formic acid buffered with sodium acetate yield piperityl esters which are convertible to mixed piperitols (57a). If terpinene monohydrochloride is allowed to stand for 24 hrs at 20-25°C with sodium alcoholate or alcoholic alkali, a major portion of the oxygenated material produced is composed of ethers of carvenol (56a) and piperitol (57a). These ethers are valuable since they are converted by heating with formic acid buffered with sodium acetate to the formates of (56a) and (57a) which in turn are readily saponified to the parent alcohols. With Beckmann's chromic acid mixture, the alcohols (56a) (57a) are respectively converted to carvenone (56b) and piperitone (57b).[54,55]

A shorter and fascinating route to piperitone is by treating α-terpinene monohydrochloride at room temperature with 35% aq. Na_2Cr_2O under vigorous agitation. The chromium complex which is formed has to be instantaneously decomposed by careful drop-wise addition of 50% H_2SO_4. Piperitone is obtained in 87.8% yield.[59]

Carvenone and carvenol can be reduced to carvomenthone (58a) and carvomenthol (58b) re-



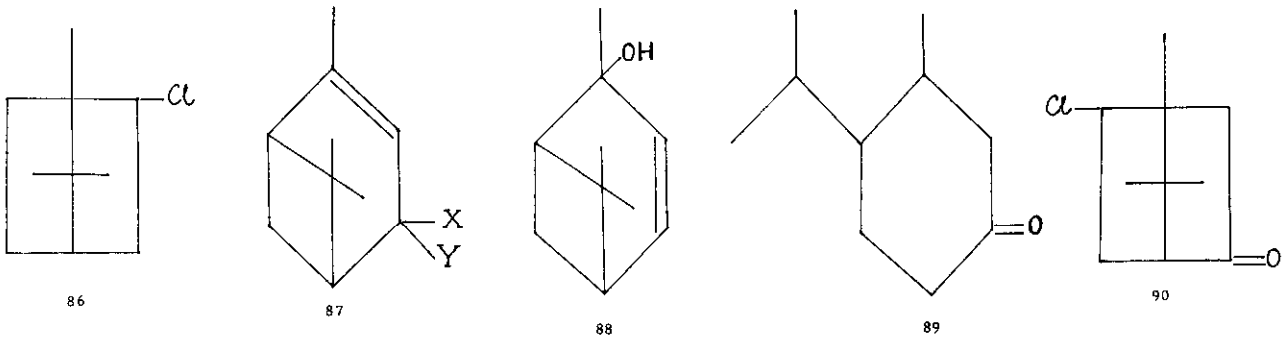
spectively. Piperitols constitute useful parent materials not only for the manufacture of piperitone (57a) but also for thymol (59) and menthols (60a).

As early as 1941, the conversion of (−)-α-phellandrene (61) to piperitols (57a) has been covered by a British Patent.[56] Essentially the process consists of treating the terpene with hydrogen chloride and exchanging the chlorine atom with hydroxyl by reaction with alcoholic caustic alkali, about 15% of strength as calculated as NaOH, at a low or moderate temperature, not exceeding approximately 50°C. Instead of hydrolysing the addition compound directly, it is preferred to replace its halogen first with the radical of an organic acid and then hydrolysing the resulting ester with alcoholic caustic alkali.

Bain and Booth[57] deem the monohydrochloride derived from the terpene as piperityl chloride (57c) and hydrolysis taking place as a displacement reaction. Under solvolytic condition, however, the reaction yields principally p-menth-2-en-l-ol *(cis* and *trans)* (54, X = OH). Here, the transitional resonance complex (62) is envisioned as the progenitor of the allylomeric alcohols which are generated from (62) by acquisition of a hydroxyl ion from water, the ideal solvent for the process. Factors that ensure good conversion are mild alkalies such as lime, soda ash, dilute sodium hydroxide, calcium carbonate etc., temperatures between 85-100°C and good agitation. Economically, it is best to complete the reaction at the highest temperature and recycle the hydrocarbons recovered in the next hydrochlorination step. Since the p-menth-2-en-l-ols can be equilibrated with p-menth-1-en-3-ols by mild acids,[57,58] the solvolysis is conducted under mild acidic conditions to secure a mixture of these alcohols. Beckmann's oxidation of the mixture of alcohols affords a crude product which assayed approximately 75% of (−)-piperitone. Optical activity is retained unless destroyed by improper handling of the piperitone.

By adopting the technique of Ohloff and Schade,[89] the addition compound of hydrogen chloride to phellandrene which is regarded as 1-chloro-p-menth-2-ene (54, X = Cl) can be oxidised by means of alkali bichromate at 0°C to an intermediate unstable chromic acid ester complex of p-menth-2-en-1-ol from which piperitone is obtained through a proton-backed allylic rearrangement by careful addition of 50% H_2SO_4.[60a]

p-Mentha-2,4(8)-diene (64) is another hydrocarbon which has been reacted to valuable alcohols and esters through hydrochlorination.[61] By passing hydrogen chloride into the hydrocarbon in mol-for-mol ratio or by mixing the hydrocarbon with a solution containing 30% or more of hydrogen chloride, the monohydrochloride is obtained. Upon alkaline hydrolysis in aq. system using $Ca(OH)_2$ or $CaCO_3$ at 83-125°C the mono-



86 87 88 89 90

a) X = OH; Y = H

b) X = Cl; Y = H

c) XY = O

d) X = OCH_3; Y = H

hydrochloride yields largely p-menth-3-en-8-ol (65, X = OH) with smaller quantities of p-menth-3-en-2-ol (carvenol) (56a) and p-menth-4 (8)-en-3-ol (66, X = OH).

If pure (64) is hydrochlorinated followed by hydrolysis, mainly p-mentha-2,4-diene (67) and p-mentha-3,8-diene (68) (and some unchanged starting material) are formed as by-products in the course of the reaction. This can be explained that the hydrocarbon (67) and (68) are generated by either dehydrochlorination of the p-menth-2,4(8)-diene monohydrochloride or dehydration of the alcohols produced on hydrolysis. It has been found that the recovered conjugated dienes can be recycled to the hydrochlorination stage of the process since they also furnish the same alcohols as is obtained by treatment of the original pure p-mentha-2,4(8)-diene. This is attested by the fact that a fraction rich in (67) and (68) when treated with hydrogen chloride and hydrolysed yields alcohols (65, X = OH) and (66, X = OH). Therefore, the conjugated dienes (67) and (68) have to be taken as equivalents of (64) for this process. The alcohols (56a) and (66, X = OH) can be converted to carvomenthol (58b) or menthol (60a) by hydrogenation and to carvenone (57b) by oxidation.

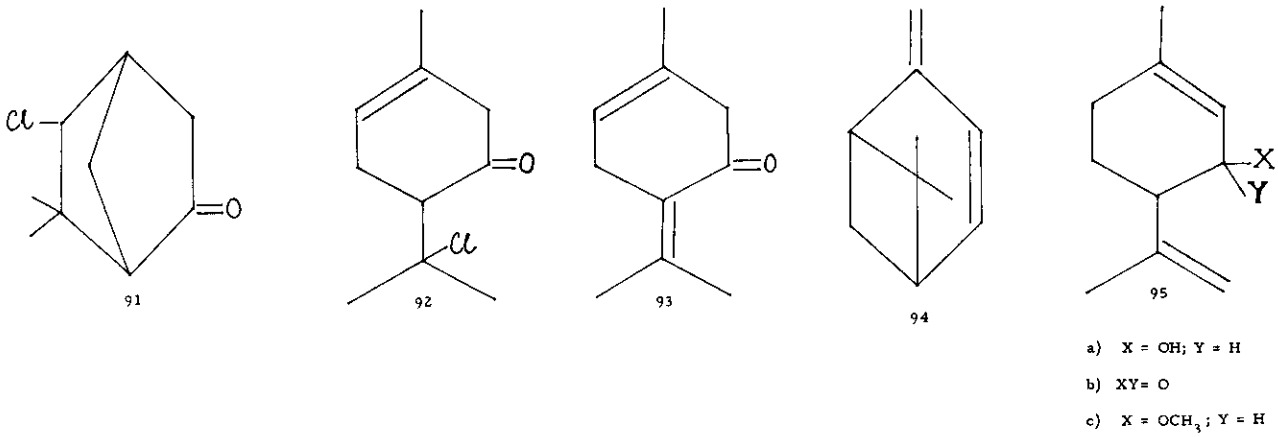
Whereas p-menth-3-en-8-ol does not yield menthol on hydrogenation, by reacting with a lower alkanoic acid under conditions conducive to allylic rearrangement, it is converted into pulegol esters and the latter on saponification gives pulegol, the precursor of menthol.[61]

Webb[61] has left the composition of the monohydrochloride of the conjugated dienes (64), (67) and (68) as individual compounds or mixture of allylic chlorides as an open question. Dragoco School[60b] has investigated the hydrochlorination of p-mentha-1,4(8)-diene once without the addition of solvent and once in glacial acetic acid because 1:4 addition is favoured in acid medium. Immediate oxidation of the hydrochloride with $Na_2Cr_2O_7/H_2SO_4$[59] afforded in both cases carvenone (56b); this conjugated ketone originates, obviously, from 4-chloro-p-menth-2-ene (69)—a product of 1:2 addition of the elements of hydrogen chloride—by oxidation with allylic rearrangement.

It must be emphasized that recent work[76] has firmly established that hydrochlorination of isoterpinolene (64) gives a mixture of 8-chloro-p-menth-3-ene (65, X = Cl) (57%), 4-chloro-p-menth-2-ene (69) (8%) and the two isomers of 2-chloro-p-menth-3-ene (56c) (31%) and that several attempts to convert the 8-chloro-derivative to pulegol acetates were unsuccessful.

Selective addition of hydrogen chloride to the exocyclic bond double bond in (+)-p-mentha-2,8 (9)-diene (70) which is available by pyrolysis of (+)-car-2-ene (71)[62] gives (+)-*trans*-8-chloro-p-menth-2-ene (72, X = Cl) in nearly quantitative yield.[63] (+)-*trans*-p-2-Menthene (72, X = H) is obtained from the monohydrochloride by hydrogenation, e.g. in isopropanol with 5% Rh-C catalyst and (+)-p-mentha-2,4 (8)-diene (64) by isomerisation of (70) with a strong base.[63] Both these hydrocarbons can be modified to (−)-menthol by known methods *(vide supra)*.[64] Recently, epoxidation of (72, X = Cl) to 2,3-epoxy-8-chloro-p-menthane (73) followed by catalytic reduction, e.g., using Raney nickel, at a temperature of 50-160°C and pressure of 20-150 atmospheres, in the presence of an acid acceptor, e.g., sodium acetate or potassium acetate, has been claimed as a convenient route to a mixture of alcohols rich in (−)-menthol.[65]

Odoriferous tertiary alcohols (74 and 75, X = OH) have been synthesised from m-menthadi-



enes (76-79) by hydrochlorination to 1,8-dichloro m-menthane (80) followed by hydrolysis; details of these steps can be gathered from previous publications.[66, 67] Also Ohloff and Schade[59] have developed a process for making 1-menthyl-5-isopropyl-cyclohex-3-one (81), useful in perfumes, by hydrochlorinating m-mentha-1,5-diene (82) to the allylic chloride (83) and then oxidising with aq. sodium dichromate at room temperature.

Abundant availability of (+)-car-3-ene (84) from turpentine has recently catapulted this hydrocarbon to an outstanding industrial raw material.

Reorganisation of the terpene to p- and m-menthenols [27 (a) and 75 X = OH] and to (−)-menthol (60a) involving hydrochlorination has been discussed earlier.[65-67]

We have seen how α-and β-pinenes (14 & 15) provide a wealth of perfumery chemicals by their initial conversion to acylic derivatives.

One need not elaborate here the momentous contribution of the manufacture of camphor (85) from α & β-pinene via isobornyl chloride (86) since this is comprehensively presented in monographs.

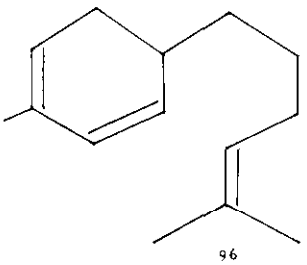
A novel utilisation of α-pinene is through verbenone (87c) and verbenol (87a). Auto-oxidation of the terpene followed by reduction with alkaline sodium sulphite solution results in substantial yield of 3-pinene-2-ol (88) and verbenol. Subjecting the alcohol (88) to oxidation with chromic acid gives verbenone and by isomerisation with acids, verbenol.[68] Optically active verbenol and 3-pinene-2-ol are generated from optically active pinene; these alcohols exist in *cis-trans* forms.[71] By addition of hydrogen chloride to verbenone at 100°C and hydrogenating the mixture in acetic acid with a 5% Pd-C-catalyst p-menthone and isomenthone (60b), o-menthone (89), thymol (59), 5-chloro-*epi*-camphor (90) and 6-chloro-epi-isofenchone (91) are obtained in good yield.[69]

Reaction of hydrogen chloride with verbenone leads to 8-chloro-p-menth-6-en-3-one (92) and from the latter removal of hydrogen chloride using sodium carbonate gives p-mentha-1,4 (8)-dien-5-one (93). On hydrogenation, this ketone affords menthone and isomenthone and then active menthols.[69]

By shaking verbenol, 3-pinen-3-ol or mixtures thereof with aq. hydrochloric acid or by adding dry hydrogen chloride, instead of resulting in a Wagner-Meerwein rearrangement, verbenyl chloride (87b) is obtained in excellent yield; thus, the two allylomers are equivalents for this purpose.[70, 71] When optically active verbenol or 3-pinen-2-ol is used the chloride is optically active and has the same sign as that of the verbenol and the opposite sign for that of the 3-pinen-2-ol.[71]

In spite of the fact that verbenene (94) derived by dehydration of verbenol contains a conjugated diene system, the hydrocarbon on reaction with hydrogen chloride yields almost quantitatively verbenyl chloride.[70] Verbenene, also exists in optically active forms and either form or mixture of these are suitable for conversion to verbenyl chloride and its derivatives.[70]

Verbenyl chloride is a very useful intermediate.[70] When it is reacted with methanol in the presence of ammonia, verbenyl methyl ether (87d) is obtained in approximately 80% yield, a product of pleasant odour.[71] For many applications, optical activity of this ether is not important but when it is employed for the synthesis of optically active menthol, this property is of prime importance. Thermal isomerisation of the ether under non-acidic conditions leads to isopiperitenyl methyl ether (95c) useful as an odorant which can be hydrogenated to menthyl ether



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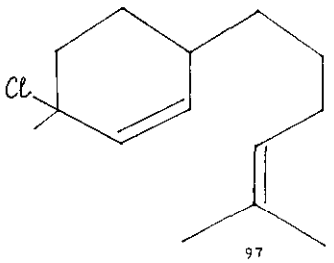

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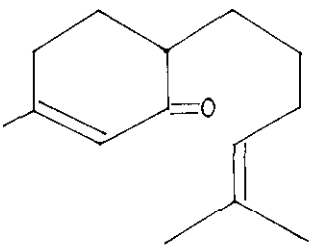

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(60c).[72] By selective choice of the hydrogenation catalyst, it is possible to exercise control over the sterioisomeric form of the methyl ether generated.[72] For example, pyrolysis of (−)-*trans*-verbenyl methyl ether affords (+)-*trans*-isopiperitenyl ether which upon complete hydrogenation in presence of a nickel catalyst under pressure leads to isomenthyl methyl ether and/or (+)-menthyl methyl ether (60c). By cleavage of the ether linkage, (+)-isomenthyl methyl ether furnishes (+)-isomenthol which is convertible to (−)-menthol by known means. Again, hydrolysis of (+)-*trans*-isopiperitenyl methyl ether with non-alkaline aqueous medium and hydrogenation of the (+)-*trans*-isopiperitenol (95a) thus produced gives (+)-isomenthol by hydrogenation or isopiperitone (95b) by oxidation, precursors of (−)-menthol. Selective hydrogenation of the isopropenyl double bond using PtO_2 catalyst to piperityl methyl ether (57d) followed by hydrolysis and oxidation gives piperitone (57b), raw material for menthol manufacture. Finally, demethoxylation of the menthyl ether, e.g., by refluxing with aq. zinc chloride solution gives p-menth-3-ene (56d), retaining optical activity and this is a suitable raw material for the synthesis of (−)-menthol.[72-74]

A further modification of verbenyl chloride is through verbenyl amines (87, $X = N<^{R1}_{R2}$) which result by reacting the former with an amine-compound selected from the class consisting of ammonia and lower alkyl primary and secondary amines.[70] Thermal isomerisation of verbenyl amines to isopiperitenyl amines (95, $X = N<^{R1}_{R2}$) and their hydrogenation afford stereoisomeric menthylamines. By hydrolysis, the menthylamines give a menthol if the amine group is primary; reaction with nitrous acid accomplishes this objective. Otherwise, the isopiperityl amines are treated with Raney nickel and water at reflux or at higher temperatures to replace the nitrogen-bearing moiety with hydroxyl group and the hydrolysate hydrogenated in the presence of Raney nickel at high pressure to menthol.[70]

Only relatively meager work has been done so far on the transformations of sesquiterpenes through hydrochlorination to novel aroma chemicals.

From the sesquiterpene zingiberene (96), the ketone (98) is obtained by hydrochlorinating the hydrocarbon at −5° to −10°C in the absence of solvents and then oxidising the mono-hydrochloride (97) formed with aq. sodium dichromate.[59] This ketone has a similar odour of the highly valuable terpene-free ginger oil.[59]

Finally, reference may be made to a little known utilisation of higher boiling fractions of the Indian Oil of Pinus longifolia (Roxb).[78] Saturation of the fraction of the oil boiling above 180°C with dry hydrogen chloride affords a dark-brown product which is best hydrolyzed with an aq. slurry of lime under pressure to yield a pleasant smelling colourless oil.

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