A peep into p-menth-1-ene chemistry

James Verghese,
Department of Chemistry,
Christian Medical College,
Vellore, India

Backed by a rich and chequered chemistry, p-meth-1-ene (1) enjoys status next to that of the 3-isomer (2) in terpene chemistry. Assignment of the structure to p-meth-1-ene is essentially based on its oxidation with $KMnO_4$ to acetic acid and β-isopropylglutaric acid (3);[1] this is further supported by spectral data.[2-4,13] Though apparently not existing naturally, p-menth-1-ene is synthetically available in (+), (−) and (±)-forms.

The earliest approaches to p-menth-1-ene are centered on carvomenthol (4a). From this alcohol, p-menth-1-ene is liberated by heating with $KHSO_4$,[5,6] boric anhydride,[7] or anhydrous $CuSO_4$.[8,9] Or by reaction with HBr or HCl, it is converted to 2-bromo- (or chloro-)-p-menthane (4b or 4c), which upon digestion with quinoline[10] or alcoholic KOH[11] affords the title compound.

In the above dehydration method, the carvomenthol utilised dictates the optical activity of the generated p-menth-1-ene. This alcohol, originating from carvenone (5) by Na/C_2H_5OH reduction[5,6] or from carvacrol (6) by Raney Ni catalysed hydrogenation, is optically inactive[8] and so also is the derived p-menth-1-ene. To obtain (+)- or (−)-p-menth-1-ene one has to exploit the reaction sequence: carvone (7a) → carvoxime (7b) → carvomethylamine (4d) → carvomenthol (4a) → p-menth-1-ene, the terminal hydrocarbon inheriting the optical activity from the carvone source.[8,9] In fact this laborious—and now outdated—route has been traversed by Dodge and Kremers in their classical study on p-menth-1-ene.[9] Another alcohol that has yielded p-menth-1-ene on dehydration is p-menthan-1-ol (8a).[12,13, see ref. 8]

Sister isomers such as p-menth-1(7)-ene (9a), trans-p-menth-2-ene (10) and p-menth-3-ene (2) are rare precursors of p-menth-1-ene. Florex-S swings the double bond in (9a), into the ring affording 80% p-menth-1-ene;[14] for the other p-menthenes, rearrangement has been noted in the presence of sodium-organosodium catalyst.[15]

Perhaps the most simple, elegant and popular strategy employed for the synthesis of (+)-p-menth-1-ene is by catalytic hydrogenation of the exterior double bond in (+)-limonene (11) which is copiously available as a citrus byproduct.[16,17,18]

A roundabout conversion of (+)-limonene to p-menth-1-ene of dubious optical purity is by hydrochlorination of (+)-limonene into the monochloride (12) and then quantitative exchange of the halogen with hydrogen through reduction by sodium in ethanol.[1,19,20] Alternatively, the hydrochloride is transformed into the Grignard reagent and then hydrolysed to p-menth-1-ene.[21]

Disproportionation of (+)-limonene (11) at reflux temperatures and in the presence of palladium hydroxide-barium sulphate gives a catalysate containing ~ 36% (±)-p-menth-1-ene.[15] Transition metal oxide catalysts also trigger hydrogen transfer in (±)-limonene to yield p-menth-1-ene.[22]

A classical preparation of (+)-p-menth-1-ene is by reaction of (+)-α-phellandrene (13) in amyl alcohol with sodium.[1] More recently, this has been accomplished by controlled catalytic reduction of the p-menthadiene in ethanol at room temperature in presence of PtO_2.[13]

Of academic interest is the reduction of p-cymene (14) to p-menth-1-ene under the action of hexaminecalcium.[23] Decomposition of (−)-pinene hydroperoxide (15) with sodium methylate generates (−)-p-menth-1-ene, apparently via the radicals (16) and (17).[24] By exploiting the sensitive endocyclic unsaturation and reactive C_3 and C_6 methylene hydrogens, p-menth-1-ene has been coaxed to undergo many fascinating reactions.

Stimulated by catalysts such as bleaching earth, pumice, silica gel,[25] sodio-organosodium,[15] and toluene sulphonic acid,[26] p-menth-1-ene isomerises to p-menth-3-ene (2). Over a palladium catalyst, p-menth-1-ene isomerises to p-menth-4(8)-ene (18).[27] Hydrogenolysis of p-menth-1-ene over 2% palladium on pumice catalyst at 150° gives a mixture of cis- and trans-

*Dr. Verghese is presently Director (R&D), Synthite Industrial Chemicals Private Ltd., Ajay Vihar, M.G. Rd., Cochin 682-016, India

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p-menthanes (8b) in 96% yield.[18]

Bromination of p-menth-1-ene has been carried out under a variety of conditions. With pyridine hydrobromide perbromide, the dibromide (19a) is obtained in 50% yield.[28] Boiling of the dibromide with excess of pyridine gives a mixture which according to Raman spectrum contains 96% α-terpinene (20) accompanied by γ-terpinene (21), p-cymene (14), and an unknown hydrocarbon with lateral double bond. Reaction of (19a) with excess sodium acetate in EtOH affords acetyl carvotanacetol (22a).

By reaction with N-bromosuccinimide, p-menth-1-ene yields the allylic bromide (22b) which with quinoline affords mainly α-terpinene (20) and with aq. $CaCO_3$ or with NaOAc-AcOH or sodium formate followed by hydrolysis of the resulting ester, gives carvotanacetol (22c).[29,13]

Theoretically 1,2-dibromo-p-menthane (19a), by dehydrobromination must beget α- and β-phellandrenes (13) and (23) and this expectation has been fulfilled by reaction with $AgNO_3$-DMSO.[30, see also 12,31]

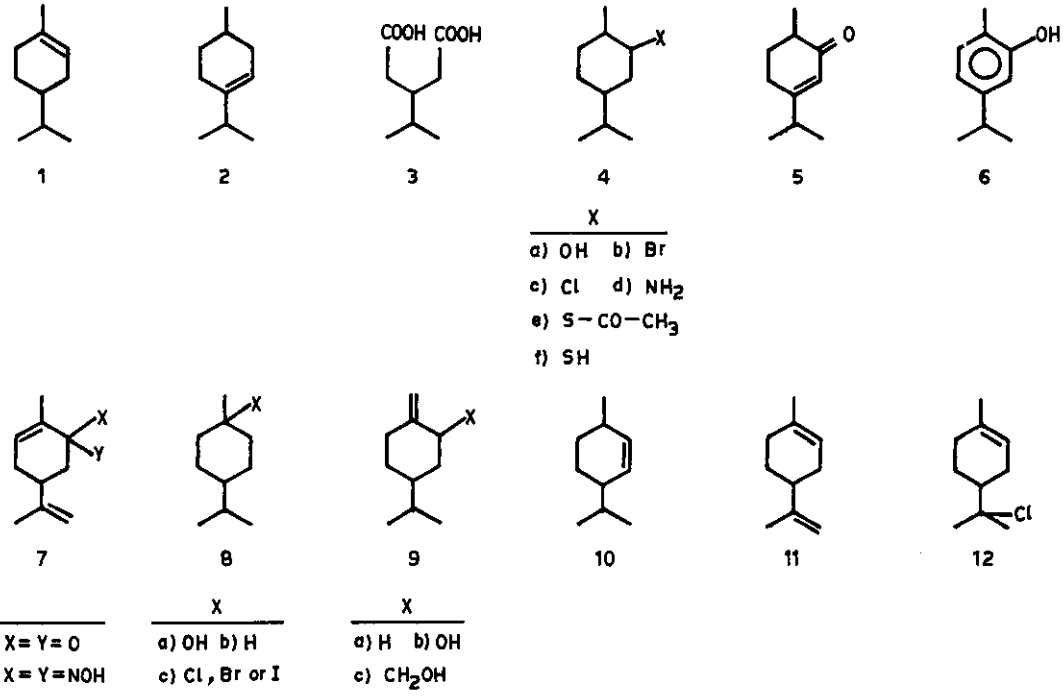
Hydrogen halides combine with p-menth-1-ene in harmony with Markownikoff rule and afford 1-halogeno-p-menthanes (8c).[12,32] The iodo derivative is the precursor of the little known p-menthan-1-ol (8a).[32]

Thioacetic acid adds across the double bond in p-menth-1-ene catalysed by sunlight to give the p-menthyl-thioacetate (4e); this upon saponification affords α-mercapto-p-menthane (4f). Oxidation of the mercaptan with hydrogen peroxide furnishes the disulphide (24).[33]

p-Menth-1-ene adds nitrosyl chloride[34,35,36] and the adduct has recently been assigned structure (25).[37] Reaction of the nitrosochloride with various amines gives two series of products: one with axial amino groups (26 a-g) which form preferentially, to minimize the dipole-dipole repulsions between amino and oxime groups, when the substituents of the amine are small (as in secondary amino products), and a series (27 a-c) of tertiary amines with equatorial amino groups.[37] The two series are readily distinguished by the p.m.r. position of the C_1 methyl, which is coplanar with the oxime and deshielded in the (26) series but which sits above the oxime and at appreciably higher field in the (27) series.[37] Dehydrochlorination of the nitrosochloride (25) gives the oxime (28a) and this upon hydrolysis furnishes carvotanacetone (28b)—thus constituting an elegant synthesis of the α,β-unsaturated ketone.[38,39]

Irradiation of p-menth-1-ene in methanol-benzene causes slow isomerisation to (9a) with a rapid buildup of the esters (29a) and (30a); toluene and xylene, particularly, serve as effective promoters.[40] Ethanol and 2-propanol likewise add to p-menth-1-ene and furnish the ethers (29b), (30b), (29c) and (30c). Isomerisation supersedes ether formation with t-butyl alcohol; only traces of the t-butyl ethers (29d) and (30d) are formed. However, a 50% solution of aqueous t-butyl alcohol readily affords the alcohols (29e) and (30e).

Addition of acetyl chloride to p-menth-1-ene in ethylene chloride in the presence of $AlCl_3$ gives 2-acetyl-1-chloro-4-iso-propyl-1-methylcyclohexane consisting of two principal

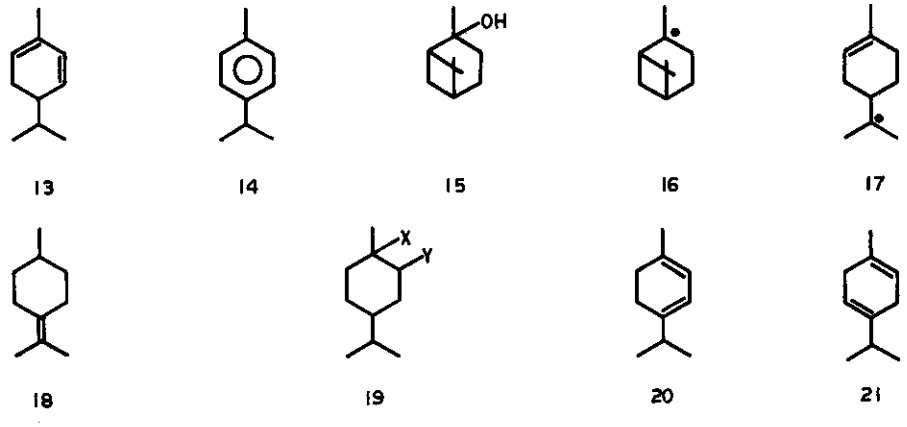


isomers (31a) and (31b) which by loss of HCl give 6-acetyl-4-isopropyl-1-methylcyclohexene (32a) and (32b) respectively plus a small amount of (33).[41] The β, γ-unsaturated ketones (32a) and (32b) are identical with those prepared by the acetylation of p-menth-1-ene with acetic anhydride in the presence of BF_3•O $(C_2H_5)_2$.[41]

Givaudan has patented a process relating to alkyl (1-p-menth-6-en-yl) ketones (34) where R is a lower alkyl group.[42] The process comprises reacting p-menth-1-ene with aliphatic acid anhydride, for example acetic anhydride, propionic anhydride, and butyric anhydride in the presence of condensing catalysts such as zinc chloride, sulphuric, or phosphoric acid at ~ 30° for 2-5 hr. Zinc chloride is preferred as it allows obtaining optically active products from optically active p-menth-1-ene.

2-Propionyl-p-menth-6-ene (34, R = C_2H_5) has been prepared in 48% yield by treatment of p-menth-1-ene with EtCHO in the presence of $ZnCl_2$ at 40-60°.[43]

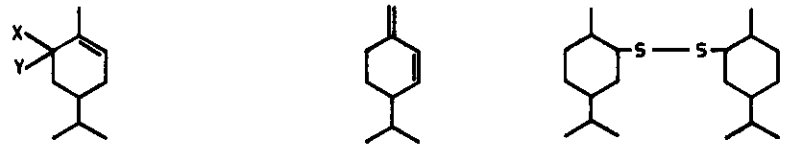
Ozonolysis of p-menth-1-ene is a specific example of one way to obtain perfumery synthetics.[44] Upon reductive decomposition with powdered zinc at 70-80°, the ozonide yields 3-isopropyl-6-keto-heptanal (35). Submission of the latter to an internal aldol condensation furnishes fragrant hay-like smelling methyl-(4-isopropyl-1-cyclopentenyl) ketone (36). Hy-



13 14 15 16 17

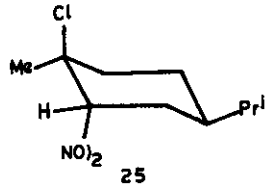
18 19 20 21

a) X=Y=Br b) X=OR, Y=OH
c) X=OH, Y=OR d) X=OCOCH$_3$, Y=OR
(R=CH$_3$ or C$_2$H$_5$)
e) X=Y=OCOCH$_3$ f) X=OH, Y=CH$_2$OH



22 23 24

a) X = O−CO−CH$_3$, Y = H
b) X = Br, Y = H
c) X = OH, Y = H
d) X = H, Y = OOH



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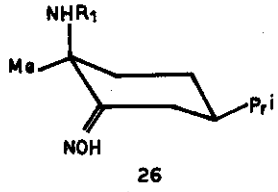

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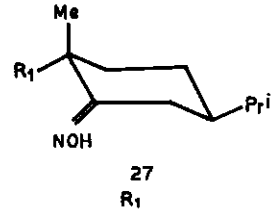
R$_1$	
a) Me	b) Et
c) Pr	d) Bu
e) cyclohexyl	
f) PhCH	g) Ph



27

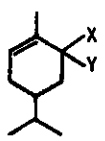
R$_1$	
a) piperidino	
b) morpholino	
c) NMe$_2$	

drogenation of (36) at 150° and 250-400 lbs/sq. in. with copper chromite catalyst yields 1-(3-isopropyl cyclopentyl) ethanol (37) having a linalool-muguet note.

By the application of Simmons and Smith reaction to p-menth-1-ene, cyclopropane derivatives (38) have been synthesised.[45] Formation of 1-azide-2-iodo-trans-p-menthane (39) is realised by combination of iodine azide to p-menth-1-ene.[46]

Epoxidation of p-menth-1-ene by means of organic peroxy acids produces essentially a 1:1 mixture of cis and trans epoxide (40) and (41).[47-54] These epoxides may be separated conveniently on a 15 ft, 15% Carbowax 20M or Chromosorb W GLPC column.[47] Alternatively, catalytic addition of hydrogen to (+)- and (±)-limonene 1,2-oxides (42) also furnishes p-menth-1-ene epoxides.[55-57,63,64]

An economical process giving a good yield of (+)- or (±)-p-menth-1-ene epoxides with a high percentage of the cis variety consists of contacting (+)- or (±)-p-menth-1-ene in acetaldehyde with oxygen or oxygen containing gas such as air.[48,50] The synthesis is preferably carried out at 15-50° and at 1 atm. to 200 psi, in the presence of solvent, for example benzene, hexane, pentane, chloroform, and methylene chloride, facilitated by a transition metal catalyst in amounts ranging from 0.001% to 1.0% by weight of the hydrocarbon. Typical catalysts are cobalt chloride, cobalt acetate, copper chloride, copper acetate, acetylacetonate of Co, Pd, Pt and Cu, nickel acetyllactonate, cobalt benzoylacetonate, and



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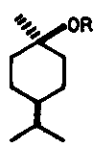
a) XY = NOH
b) XY = O
c) X = H, Y = COR
d) X = OH; Y = H



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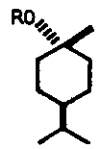
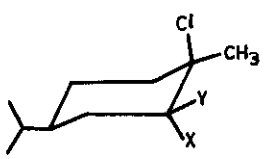


30

R	
a) CH_3	b) CH_3CH_2
c) $(CH_3)_2CH$	d) $(CH_3)_3C$
e) H	



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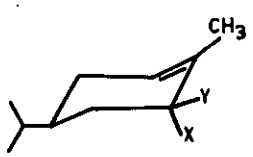

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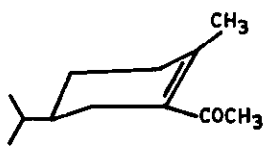

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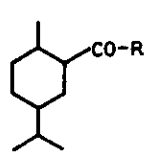
a) X = $COCH_3$, Y = H
b) X = H, Y = $COCH_3$



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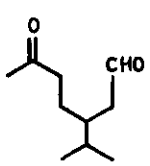

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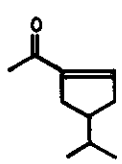

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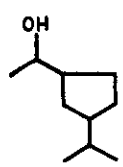

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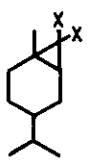
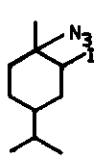


38

X
a) H b) Cl
c) Br



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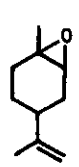

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the like.

Another commercial route to p-menth-1-ene epoxides containing a high ratio of the trans-isomer is through the base-induced ring closure of halohydrin obtained by treating p-menth-1-ene with a hypohalous acid, for example, hypochlorous or hypobromous acid.[51,58] The acids are generally employed in amounts ranging from about 0.1 to 3.0 molar equivalents per mole of the hydrocarbon. The hypohalous acid employed can be either preformed or generated *in situ in the presence of p-menth-1-ene* by use of an appropriate "slow release" halogenating reagent such as N-chloro or N-bromo compounds, for example, N-bromoacetamide, N-bromosuccinimide, N-chlorourea or N-chlorosuccinimide and the like. Use of a solvent such as water, water-acetic acid, water-dioxane mixtures, or water-tetrahydrofuran mixtures at a temperature, preferably at ~ 10-30° is recommended. Conversion of the halohydrin to the epoxide is accomplished with a base such as alkali metal hydroxide or alkoxide amounts of 1.0 to 10.0 molar equivalent per molar equivalent of halohydrin. The halohydrin formation is usually substantially complete from 10 min to 3 hr.

At this stage we shall briefly consider the synthetic approaches to p-menth-1-ene oxides by Polish investigators. Credit must be given to Kuczynski and Walkowicz for the first synthesis of (+)-1,2-epoxy-trans-p-menthane (41) by reaction of the monotosylate of (+)-1-hydroxyneocarvomenthol (43b) with C_2H_5OH/KOH at ambient temperature.[59] More recently, the detosylation has been effected with potassium t-butoxide in pyridine.[60]

Only very meagre yield of the cis-epoxide (40) is realised through the tedious synthesis of Piatkowski and Siemieniuk.[61] The steps involved are the hydroxylation of p-menth-1-ene with H_2O_2/HCOCH to (+)-1-hydroxyneocarvomenthol (43a) and (+)-1-hydroxyneoisocarvomenthol (44a), the splitting of the diols by painstaking fractional crystallisation and finally hydrolysis of the monotosylate of the trans diol (44b) with $C_2H_5OH/ICOH$ to give (+)-1,2-epoxy-cis-p-menthane (40).

Chabudzinski and coworkers have described a simple and convenient synthesis of (+)-1,2-epoxy-cis-p-menthane (40) starting from a mixture of (40) and (41).[62] Hydrochlorination of an ethereal solution of the epoxides simultaneously affords the chlorhydrins (43c) and (43d) which are esterified with p-nitro-benzoyl chloride to afford unilaterally 1-chloro-neocarvomenthol p-nitrobenzoate (43e). Upon treatment with CH_3CH/KOH, this ester undergoes elimination accompanied by Walden inversion at C_1 to furnish the desired cis epoxide (40).

French investigators have rearranged 1,2-epoxy-p-menthane with chromatographic

alumina to carvotanacetol (22c) and carvomenthone (45).[65] By refluxing of the epoxide with 40% H_2SO_4 for 1 hr carvomenthone (45) is obtained in 90% yield.[64] On the other hand, facile cleavage of the oxirane ring with catalytic amounts of aluminum isopropoxide generates ~ 30% cis and trans-carvatonacetol (46) and (47) and cis and trans-p-menth-1(7)-en-2-ol (48) and (49).[66] Also, powdered Na and K-t-butoxide in aprotic solvents convert 1,2-epoxy-trans-p-menthane to cis-p-menth-1(7)-en-2-ol (48).[59,67]

In contrast to the above modifications, zinc bromide induces ring contraction of 1,2-epoxy-p-menthane to 1-methyl-3-isopropylcyclopentyl-1-carboraldehyde (50), methyl (3-isopropyl-cyclopentyl) ketone (51) being formed concurrently.[53,cf. 44,49,50]

Hydrogenation of (+)-1,2-epoxy-p-menthane in acetic acid with palladium hydroxide catalyst shows that the epoxide ring is emancipated preferentially to give jointly (−)-carvomenthol (53a) and (+)-neocarvomenthol (43f), with the latter predominating.[54] Synchronised decyclisation in the other available direction furnishes a small amount of p-menthan-1-ol (8a). The stereoisomeric 1,2-epoxy-p-menthanes are the precursors of p-menth-2-en-ols. (+)-Carvomenthone (45) and trans-p-menthane (8b) are also formed. Excellent yield of (+)-carvomenthone (45) is realised by isomerisation of the epoxide in acetic acid with the same catalyst under hydrogenation conditions.

Isocarvomenthol (54a) apparently devoid of p-menthan-1-ol is formed by the Raney nickel catalysed hydrogenation of 1,2-epoxy-p-menthane.[55,63]

Interesting results have been obtained from study on the reduction of the mixed epoxides of p-menth-1-ene with $LiAlH_4$ in ether medium.[48] The trans-epoxide (41) reacts quickly by axial attack of hydride, furnishing almost exclusively trans-p-menthan-1-ol (55). On the other hand, the cis-isomer (40) yields cis-p-menthan-1-ol (56) and neocarvomenthol (43f) in the ratio 2:1.

With a pure sample of 1,2-epoxy-cis-p-menthane, reduction with $LiAlH_4$ in ethylamine easily affords by bidirectional opening of the epoxide ring, cis-p-menthan-1-ol (56), neocarvomenthol (43f), and isocarvomenthol (54a) in the ratio 18:55:27.[62] Surprisingly, the reduction with $LiAlH_4$ in ether is sluggish, requires extensive heating, and the results are erratic. In one experiment, cis-p-menthan-1-ol (56) and neocarvomenthol (43f) are produced in the ratio 26:74 and in another, 64% cis-p-menthan-1-ol (56), 23% neocarvomenthol (43f), and 13% isocarvomenthol (54a).

As early as 1956 it was known that the hydrolysis of the epoxides derived from (±)-p-menth-1-ene by heating with H_2O at 120° gives a mixture of 1-hydroxyneocarvomenthol (43a) and 1-hydroxyisocarvomenthol (54b).[68] Only recently concentrated efforts were made to decipher the subtle trends in the hydrolysis of the optically active isomeric 1,2-epoxy-p-menthanes. Whereas (+)-1,2-epoxy-cis-p-menthane (40) on hydration gives only (43a), the trans-epoxide (41) furnishes (+)-(43a) and its isomer (+)-1-hydroxyneoisocarvomenthol (44a) in the ratio 8:2.[50] Acetylation of (+)-(43a) gives (+)-1-hydroxyneocarvomenthyl acetate (43, R_1 = OH and R_2 = OAc). Upon pyrolysis, this acetate furnishes 8 parts of trans-p-menth-2-en-1-ol (57) and 2 parts of the cyclopentyl derivative (51).[49,50,56,47] Against this, 1-hydroxyneoisocarvomenthyl acetate (44, R_1 = OH and R_2 = OAc) gives 2.5 parts of cis-p-menth-2-en-1-ol (58) and 7.5 parts of the ring contraction product (51).[49,50] The hydroxyacetates are also available by the reaction of the two isomeric epoxides with acetic acid.[51,56, see ref. 54] From p-menth-2-en-ols, (−)-menthol (59) is readily fabricated by known procedures.[49,50,51]

Hydroxy-ethers (19b) and (19c), in which the latter predominates, are obtained by reacting 1,2-epoxy-p-menthane with methyl or ethyl alcohol in presence of corresponding sodium alkoxide.[69] Pyrolysis of the acetyl ester (19d) gives

the unsaturated derivatives (60) and (61), though the formation of (62) cannot be excluded.[69]

2-Amino-p-menthan-1-ol (63a) and its derivatives (63b) are generated by the decyclisation of 1,2-epoxy-p-menthane with ammonia and amines respectively.[52]

Perhaps it may not be out of place to interpose here the interesting configurational assignments of p-mentha-2-ol geometrical isomers. Encouraged by the fact that cis dialkylated ethylenes undergo asymmetric, stereoselective hydroboration with optically active diisopinocampheylborane in contrast to trialkylated ethylenes which suffer hydroboration stereoselectively but not asymmetrically, the study was extended to (+)-p-menth-1-ene.[70] Isolation of (−)-carvomenthol (53a) and (+)-isocarvomenthol (54a) from the reaction mixture proves that these alcohols are epimeric at positions 2 and that the methyl and hydroxyl groups are in trans configuration.[70,74]

Significant contributions to the hydroxylation of (±)-p-menthane leading to diols (53), (54), (43a), and (44a) are credited to Jefferies and Milligan.[68] Likewise, p-menthan-1,2-diols derived from (+)-p-menth-1-ene have been examined by a number of investigators.[71,72]

A cursory study of the oxidation of emulsified (+)-p-menth-1-ene with molecular oxygen is reported to give p-menth-1-en-3-hydroperoxide (64a) and p-menth-1-ene-6-hydroperoxide (22d).[73] On the other hand, photosensitised oxidation of (+)-p-menth-1-ene has yielded interesting products.[74,75] In addition to 1,2-epoxy-p-menthane, the reduction of the hydroperoxides formed gives cis and trans-p-menth-2-en-1-ol (57) and (58), cis and trans-p-menth-1(7)-en-2-ol (48) and (49), cis and trans-carvatonacetol (46) and (47) and cis-piperitol (64b). The oxidation of (+)-menth-1-ene in acetic anhydride and then hydrolysis affords all the products mentioned above plus carvotanacetone (28b), piperitone (64c), 1-hydroxyneocarvomenthol (43a), carvomenthols (53a), (54a), (43f), and (44c), and cis and trans-p-menthan-1-ol (56) and (55), trans-piperitol (64b), and methyl(4-isopropyl-1-cyclopentenyl) ketone (36).[76] The esters α-ethers (65) and (66) suffer hydrolysis via (67) to the cyclopentene derivative (36).[76]

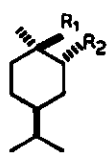
A patent has been granted for the oxidation of p-menth-1-ene under substantially anhydrous conditions at 70-80° to hydroperoxides and then their reduction by stirring vigorously at 85-90° with a saturated solution of sodium sulphite to

give a mixture comprising essentially of 1,2-epoxy-p-menthane, p-menth-2-en-1-ols (57) and (58), carvotanacetols (46) and (47), and carvotanacetone (28b).[64] Through fractional distillation, the p-menth-2-en-1-ols have been separated and these have been modified to members of the menthone-menthol family.

Exclusively α-methylene hydroperoxides are generated by contacting p-menth-1-ene dissolved in a suitable solvent, for example, $CHCl_3$, CH_2Cl_2, CCl_4, pentane, hexane, cyclohexane, petroleum ethers, and the like with triarylphosphite-ozone adducts, preferably at −40° to −20°.[77] Typical triarylphosphites which can form adducts include, for example, triphenylphosphite, tris-(p-methoxyphenyl) phosphite and tris-(p-nitrophenyl) phosphite. Decomposition of the hydroperoxides with conventional reducing agents, for example, sodium sulphite, potassium iodide, and sodium borohydride, affords the allylic alcohols, p-menth-1(7)-en-2-ol and p-menth-2-en-1-ol. The specificity for α-methylene hydroperoxide formation is the most outstanding feature of this reaction, in contrast to the liberation of multiple products by processing with a source of singlet oxygen.

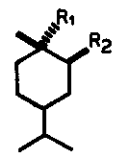
Syntheses of carvotanacetone (28b) and carvotanacetol (22c) by selenium dioxide oxidation of p-menth-1-ene have been achieved.[78,79] Of interest is the fact that asymmetry is retained during this reaction, for SeO_2 oxidation of (+)-p-menth-1-ene of 94% optical purity in aqueous ethanol furnishes carvotanacetone, $(\alpha)_D$ +24.5°-30.6°, equivalent to 44-55% retention of asymmetry, and mechanisms have been proposed.[80]

With t-butyl chromate in CCl_4 p-menth-1-ene yields mainly piperitone (64c) and car-



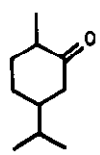
43

a) $R_1 = R_2 = OH$
b) $R_1 = OH$, $R_2 = OTs$
c) $R_1 = Cl$, $R_2 = OH$
d) $R_1 = OH$, $R_2 = Cl$
e) $R_1 = Cl$, $R = OCOC_6H_5$
f) $R_1 = H$, $R_2 = OH$



44

a) $R_1 = R_2 = OH$
b) $R_1 = OH$, $R_2 = OTs$
c) $R_1 = H$, $R_2 = OH$



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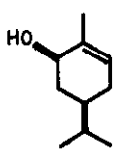

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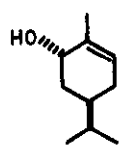

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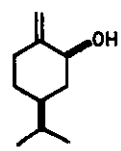

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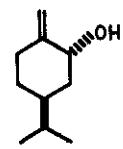

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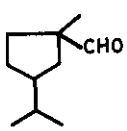

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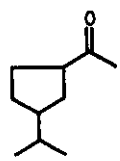

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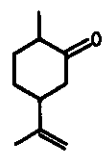

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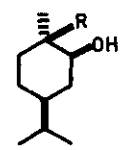

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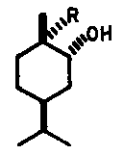
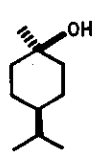


54

R

a) H b) OH



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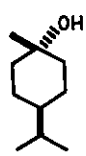
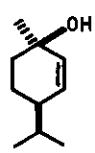


56



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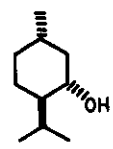
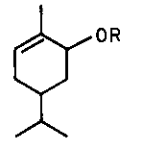
58



59

votanacetone (28b) and probably 2-methyl-5-isopropyl-1,4-hydroquinone.[81] Further work has revealed that with t-butyl chromate in benzene in the presence of anhydrous acetic acid and acetic anhydride, (+)-p-menth-1-ene yields (±)-carvotanacetone (28b), (+)-piperitone (64c) and traces of carvacrol (6), thymol (68), and (+)-phellandric acid (69c).[82,83] Hence, t-butyl chromate concurrently oxidises the active methylene hydrogens at C_3 and C_6 to keto group and, superficially, the active C_1 methyl group to a carboxyl via an aldehyde group. Thus, involvement of the C_6 methylene hydrogens leads to optically inactive carvotanacetone (28b) in contrast to the C_3 methylene hydrogens which afford partially, optically active piperitone (64c).[83]

Acylating oxidation of (+)-p-menth-1-ene by means of mercuric acetate leads to (±)-carvotanacetol acetate (22a) which on saponification gives (±)-p-menth-1-ene-6-ol (22c).[84-86] (+)-p-Menth-1-ene and (+)-carvotanacetol acetate are configurationally stable under the reaction conditions.[80] Through gas chromatography,



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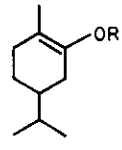

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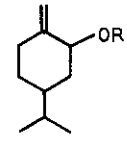

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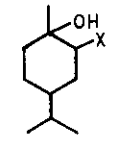
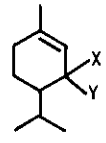


63

X

a) NH_2 b) $NHCH_3$, $N(CH_3)_2$ or

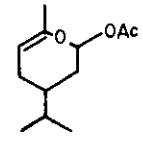


64

a) X = H, Y = OOH

b) X = H, Y = OH

c) XY = O



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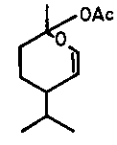

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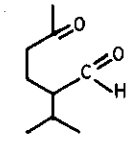

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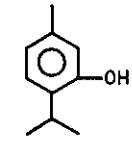

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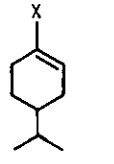
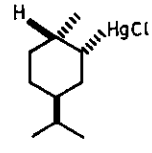


69

X

a) CH_2OH b) CHO

c) COOH



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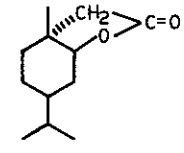

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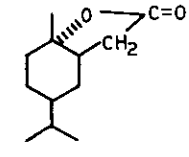

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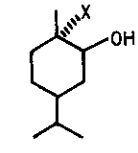
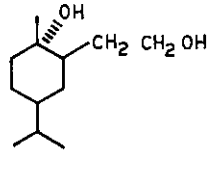


73

X

a) CH_2CH_2OH

b) CH_2COOH



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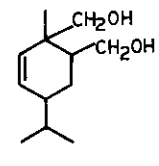

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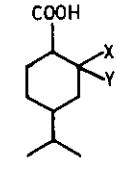
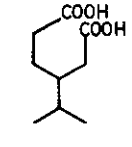


76

X

a) X = H, Y = OH

b) X = Y = O



77

it has been possible to separate the two epimeric carvotanacetol acetates, the ratio of trans to cis being 72:28. This oxidation involves a symmetrical intermediate which is probably formed via the decomposition of an allylmercuric intermediate.

The incorporation of the mercury electrophile across the double bond by the reaction of (+)-p-menth-1-ene with mercuric acetate in water/dioxan is in conformity with Markownikoff rule and diaxial addition rule.[87] Upon treatment of acetoxy-mercuric-intermediate with sodium chloride, crystalline 2α-chloromercuri-1α-methyl-4β-isopropylcyclohexan-1β-ol (70) is obtained in ~ 74% yield. p-Menth-1-ene is regenerated from (70) by reduction with either hydrazine hydrate or Na/Hg.[87]

Though not clean as the mercuric acetate oxidation,[80] carvotanacetol acetate (22a) and p-menthane-1,2-diol diacetate (19e) originate by lead tetraacetate oxidation of (+)-p-menth-1-ene.[86,88] The optically inactive monoacetate (22a) is a mixture of cis and trans isomers.[80] The genesis of this racemate ester appears to be a symmetrical intermediate.[80]

On oxidation with manganese triacetate, p-menth-1-ene affords the lactones (71) and (72) which are reduced by $LiAlH_4$ to the diols (73a) and (74) respectively.[89,90] Alkaline hydrolysis of (71) yields the hydroxy-acid (73b). Spectral data (IR and PMR) and analysis of molecular models back the formulation of (71) and (72) for the lactones. Whether these lactones have interesting and promising cancer inhibitory action deserves scrutiny.[89]

By the action of formaldehyde on p-menth-1-ene in acid medium, the alcohols isolated after saponification include: p-menthan-1-ol (8a), 2-hydroxymethyl-p-menth-6-ene (28d), 2-hydroxymethyl-p-menth-1(7)-ene (9c), and 2-hydroxymethyl-p-menthan-1-ol (19f). It may be added that the formation of 1,2-bis(hydroxymethyl)p-menth-5-ene (75) is not excluded in this reaction.[91-94]

Finally, microbiological transformation of p-menth-1-ene in a Soil Pseudomond (PL strain) has been found to proceed apparently through the main energy-yielding pathway involving a progressive degradation of the C_1 methyl group viz., phellandrol (69a) → phellandral (69b) → phellandric acid (69c) → 2-hydroxy-p-menthan-7-oic acid (76a) → 2-keto-p-menthan-7-oic acid (76b) → β-isopropylpimelic acid (77) → CO_2 + H_2O.[95]

When Semmler elucidated the structure of p-menth-1-ene by oxidative degradation in 1903, little was it thought that this simple hydrocarbon would serve as a substrate for the exciting researches which we have delineated. Today, scientists devoted to aroma chemistry are well

aware of the sensory properties pertaining to odor and taste of the products mentioned in this paper. Available readily in optically active and inactive forms, p-menth-1-ene still challenges us with problems of far-flung consequences.

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