

# Profile of p-menth-3-ene chemistry

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Theoretically p-menthenes,  $C_{10}H_{18}$ , may be regarded as derived from p-menthane (1) by extraction of two neighboring hydrogens. Of the six p-menthenes (2-7) thus generated, (3) and (7) exist in cis- and trans- forms and optical isomerism is displayed by (2), (3), and (4). Outstanding substrates for mechanistic studies and chemical processings, these hydrocarbons are no less valuable and versatile than the much-trumpeted p-menthadienes.

Much literature has focused on p-menthenes since the publication of their chemistry by Windemuth.<sup>1</sup> It is worthwhile to discuss the far-flung contributions in this area. To begin, we will scan the many facets of the fascinating chemistry of p-menth-3-ene (4), the doyen among the p-menthenes.

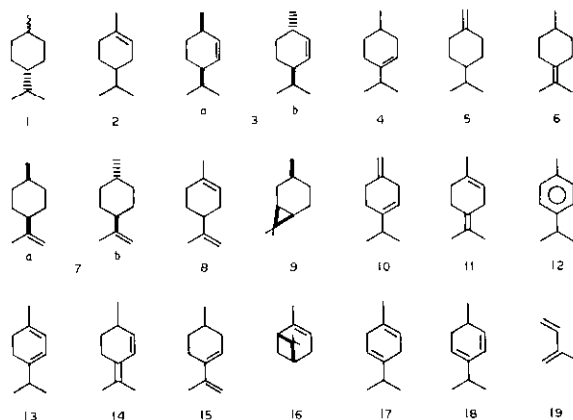
Nature appears to be emphatically reluctant to synthesize p-menthenes. For that reason, all the routes to p-menth-3-ene are modifications of naturally occurring compounds or products derived therefrom. It is to be emphasized that though p-menth-3-ene has a center of asymmetry at the  $C_1$  atom, the optically active compound is difficult to obtain because symmetrical intermediate compounds are usually formed during the syntheses.<sup>2</sup>

## Syntheses

**From p-Menthenes:** Formation of p-menth-3-ene from sister isomers was first observed by Wallach.<sup>3,4</sup> Thus, the conversion of p-menth-4-(8)-ene (6) to the 3-isomer can be substantially achieved by refluxing with ethanolic or 40% aqueous  $H_2SO_4$ .<sup>5,6</sup>

Patents granted to Schering-Kahlbaum A-G cover the manufacture of the title compound from p-menth-1-ene (2) which is readily accessible from (+)-limonene (8) by passing its vapors at a high temperature ( $> 300^\circ$ ) over a catalyst; for example bleaching earth, pumic, silica gel, "Tonsil," magnesium sulfate, copper phosphate, or granular calcium phosphate with phosphoric acid or oxidized copper turnings.<sup>7,8</sup> p-Menth-3-ene is separated from the mixture of isomeric menthenes formed by fractional distillation.

According to Bottoms the isomerization can be



effected by stirring p-menth-1-ene at  $135^\circ$  with catalytic amounts of an organic acid such as p-toluenesulfonic acid.<sup>9</sup> p-Menth-8(9)-ene (7) collapses completely to the 3-isomer by reaction with silica gel at  $150^\circ$ .<sup>10</sup>

Of the base catalysts, sodium-organosodium is the most outstanding and useful to prepare high proportions of p-menth-3-ene from p-menth-1-ene (2) and trans-p-menth-2-ene (3b).<sup>11,12</sup>

**From Carane:** The potentially available raw material carane (9) has been decyclized to p-menth-3-ene by mixing it at  $20-110^\circ$  with a strong acid diluted with the requisite amount of water to function specifically as an isomerization catalyst without oxidizing and polymerizing properties.<sup>13</sup> Aqueous sulfuric, phosphoric, and oxalic acids have been recommended. Thus, reaction of (9) with 50% aqueous  $H_2SO_4$  at reflux temperature for  $\sim 7$  hr furnishes a catalysate containing  $\sim 20\%$  of the title compound.<sup>13</sup>

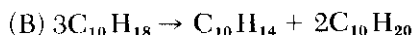
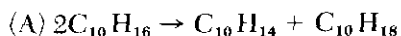
**From p-menthadienes and p-cymene:** 1. Hydrogenation technique—There are reports on the partial hydrogenation of  $\beta$ -terpinene (10) and of terpinolene (11) to p-menth-3-ene with nickel or Adams  $PtO_2$  catalyst and of p-cymene (12) with hexamine-calcium.<sup>14,15,16a</sup>

Bain and Gary have standardized a novel and significant process for p-menth-3-ene production based on p-menthadienes.<sup>6</sup> Conjugated hydrocarbons which involve a double bond at  $C_4$  atom as illustrated by  $\alpha$ -terpinene (13), p-

menth-2,4(8)-diene (14), and p-mentha-3,8(9)-diene (15) can be selectively hydrogenated individually or in admixture with each other in the presence of other non-conjugated p-menthadienes to yield mixtures of p-menthenes in which the 3-isomer predominates over the 2- or 4(8)-isomer (2 or 6).<sup>6</sup> Hydrogenation catalyst, for example Ni, Pd, and Pt in small amounts; hydrogen pressures of 0-200 lb/□"; and temperature of 25-150° are recommended. Ni catalysts are usually preferred. An additional quota of the 3-isomer is obtained by treatment of the cut rich in p-menth-4(8)-ene (6) with an acid isomerization catalyst such as acid clay, sulfuric acid, or benzenesulfonic acid. Mixtures of p-menthadienes with a high proportion of the conjugated members amenable for the above process are derived in general from mono-terpenoids by mixing them with mineral or strong organic acids and earths at a temperature of 50-175°. Thus, p-menthadienes emanating from decyclization of  $\alpha$ -pinene (16) with 50-55% H<sub>2</sub>SO<sub>4</sub> have been successfully converted to (4) over Raney nickel.<sup>17</sup>

The selective hydrogenation of (+)-p-mentha-3(9)-diene (15) with diisobutylaluminum hydride yields (+)-p-menth-3-ene (4).<sup>18</sup> Technically p-menth-3-ene is also produced by reducing p-menthadienes with hexylamine-calcium in an inert solvent.<sup>16(b)</sup>

**2. Disproportionation—Catalytic disproportionation of p-menthadienes provides a very convenient route to p-menth-3-ene.** The mechanism of this transformation emerges from the work of Eschinazi and Pines.<sup>19</sup> Thus, the disproportionation of (+)-limonene (8) with palladium hydroxide-barium sulfate catalyst proceeds in at least two steps, the first of which involves a very rapid and exothermic hydrogen transfer in which two moles of (+)-limonene disproportionate into one mole of p-cymene and one mole of p-menthene, followed by a second slower step in which three moles of p-menthene disproportionate into one mole of p-cymene and two moles of p-menthane:



When the reaction is interrupted at Stage A as a result of thermodynamic equilibrium the p-menthenes liberated include 59% p-menth-3-ene.

What is epitomized in Stage A is the framework of the patent granted to Bain and Gary.<sup>20</sup> p-Menthadienes utilized are from the class consisting of (11), (13), (14), (15), (17), and p-mentha-2,4-diene (18). The process consists of simple refluxing of the selected p-menthadiene and/or mixture containing the same with a small amount of a hydrogenation catalyst, for example Raney nickel, nickel formate, or 5% palladium

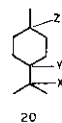
on carbon; the reaction is terminated at the close of Stage A and is tracked through bromine titration; the original non-benzenoid saturation has to be reduced to ~25% and at most to ~75%. Such a drop in unsaturation, which is further monitored by spectrochemical methods, brackets with optimum yield of p-menth-3-ene.

(+)-Limonene has been catalytically disproportionated by transition metal oxide catalysts in a stirring autoclave, fixed bed, or continuous fluid bed at 300-500°. <sup>21-24</sup> A novel and highly selective catalytic system, namely 1:9-nickel-molybdenum oxide (prepared by decomposition of a crystallizable and water soluble ammonium nickel molybdate, (NH<sub>4</sub>)<sub>6</sub>NiMo<sub>9</sub>O<sub>32</sub> • 6H<sub>2</sub>O) supported on silica-chromia or alumina which contains nickel in the uncommon tetravalent state and thus radically differs from other mixed oxide catalysts, yields a high ratio of p-menth-3-ene/p-menth-1-ene. Using this catalytic system, p-menth-3-ene may be obtained as high as 20-30% and may be separated by fractional distillation and further purified by activated silical gel.<sup>25</sup>  $\alpha$ -Pinene (16) and isoprene (19) can also serve as raw materials for this process.

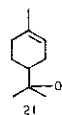
Hydrogen transfer reaction of this p-menthadiene leading to p-menth-3-ene has also been noted in the presence of Chasov-Jarovsky clay; metallic catalysts such as those containing Cu, Ni, and alkali hydroxides; and Japanese acid clay.<sup>112-114</sup>

**From p-menthanols and their derivatives:** A technical route to p-menth-3-ene consists of cycling p-menthan-8-ol (20a), its ether (20b) or ester (20c) derivative, or a mixture of p-menthan-8-ol (20a) and p-menthan-1-ol (20d) over a dehydrating catalyst, e.g., "Tonsil" or Mg<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub> at 300-500°. <sup>26,27</sup> Evidently, the initially formed p-menthenes (6, 7, 2 and 5?) converge on the title compound. In a U.S. patent, p-menthan-8-ol (20a) obtained by refluxing terpineol (21) with menthol (22a) in presence of a hydrogenation catalyst has been successfully converted to p-menth-3-ene with NaHSO<sub>4</sub> at 100°. <sup>28</sup>

Chemetron Corporation exploits slow distillation of dihydro- $\alpha$ -terpinyl ether, e.g., 8-meth-



- a) Y = Z = H, X = OH  
 b) Y = Z = H, X = OR  
 c) Y = Z = H, X = OCO<sub>2</sub>R  
 d) X = Y = H, Z = OH  
 e) X = Z = H, Y = OH  
 f) X = X = H, Y = Cl



oxy-p-menthane (20b,  $x = \text{OCH}_3$ ), in the presence of an alkanesulfonic acid to split off methanol and stimulate the migration of the double bond into the ring to provide p-menth-3-ene.<sup>29</sup>

Of passing interest is the fact that p-menth-3-ene is obtained by dehydration of (20a) under pressure with aqueous  $\text{MgCl}_2$  at  $230\text{--}240^\circ$ .<sup>30</sup> By refluxing with  $\text{KHSO}_4$ , cis-p-menthan-4-ol (20c) is reported to yield exclusively p-menth-3-ene (75%).<sup>31</sup>

Rudloff has comprehensively evaluated the dehydration of a mixture of cis- and trans-p-menthan-8-ol (20a), as well as the pure stereoisomers, using a variety of reagents.<sup>32</sup> For example, the anhydrous salicylic acid-catalyzed reaction affords primarily p-menth-4(8)-ene (6), a smaller amount of isomeric p-menth-8-ene (7), which finally rearranges to p-menth-3-ene.

Transformations of p-menthan-3-ols and their derivatives to p-menth-3-ene have been thoroughly examined. These conversions are briefly projected here, bypassing the subtle reaction mechanism which has been highlighted in advanced monographs.

p-Menth-3-ene is obtained from menthol (22a) by reaction with  $\text{H}_2\text{SO}_4$ ,  $\text{I}_2$ , oxalic acid, boric acid, anhydrous copper sulfate,  $\text{KH}\text{SO}_4$ , anhydrous  $\text{ZnCl}_2$ ,  $\text{PCl}_3$ , activated carbon,  $\text{SiO}_2$  gel, and  $\text{Al}_2\text{O}_3$ .<sup>33-43</sup> Compared to menthol, neomenthol and neo-isomenthol (23a and 25a) undergo more facile dehydration to p-menth-3-ene.<sup>34,43-46</sup> Menthyl chloride (22b) and neomenthyl chloride (23b) undergo dehydrochlorination to p-menth-3-ene, and the conversion approaches as high as 99% with the latter derivative.<sup>47,48</sup> With aniline, 4-chloro-p-menthane (20f) derived by chlorination of p-menthane in  $\text{CCl}_4$  forms ( $\pm$ )-p-menth-3-ene.<sup>115</sup>

We have already emphasized the difficulty of obtaining optically active p-menth-3-ene.

Pyrolysis of the esters, such as methyl-(-)-menthylxanthate (22c), (-)-menthyl acetate (22d), and (-)-menthyl benzoate (22e), is a significant technique to get (+)-p-menth-3-ene.<sup>49-54</sup> Detosylation of the sulfonates (22d, 23a, 24b, and 25b) of the isomeric menthols also leads to p-menth-3-ene.<sup>63,65-67</sup>

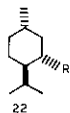
(-)-Menthylamine (22g), (+)-neomenthylamine (23d), (+)-isomenthylamine (24c), and neo-isomenthylamine (25c) may all be utilized as a source of (+)-p-menth-3-ene in varying yields by the action of nitrous acid upon them.<sup>46,62,68-70</sup>



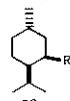
- a)  $\text{R} = \text{OH}$
- b)  $\text{R} = \text{OTs}$
- c)  $\text{R} = \text{NH}_2$
- d)  $\text{R} = ^+\text{NMe}_3\text{OH}^-$



- a)  $\text{R} = \text{OH}$
- b)  $\text{R} = \text{OTs}$
- c)  $\text{R} = \text{NH}_2$
- d)  $\text{R} = ^+\text{NMe}_3\text{OH}^-$



- a)  $\text{R} = \text{OH}$
- b)  $\text{R} = \text{Cl}$
- c)  $\text{R} = \text{O}-\overset{\text{S}}{\underset{\text{H}}{\text{C}}}-\text{SH}$
- d)  $\text{R} = \text{OCOCH}_3$
- e)  $\text{R} = \text{OCOC}_6\text{H}_5$
- f)  $\text{R} = \text{OTs}$
- g)  $\text{R} = \text{NH}_2$
- h)  $\text{R} = ^+\text{NMe}_3\text{OH}^-$

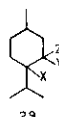
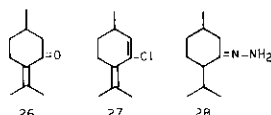


- a)  $\text{R} = \text{OH}$
- b)  $\text{R} = \text{Cl}$
- c)  $\text{R} = \text{OTs}$
- d)  $\text{R} = \text{NH}_2$
- e)  $\text{R} = ^+\text{NMe}_3\text{OH}^-$

Thermal decomposition of the optically active stereo-isomeric menthyltrimethylammonium hydroxides (22h, 23e, 24d, and 25d) discloses the fact that the neomenthyl and neo-isomenthyl derivatives (24d and 25d) undergo massive conversion to (+)-p-menth-3-ene.<sup>71</sup>

**From 1,8-cineole:** Excellent conversion of 1,8-cineole (60) to (±)-p-menth-3-ene has been accomplished by pyrolysis over Japanese acid clay at 200°.<sup>116</sup>

**From p-menthenones:** When pulegone (26) is allowed to react with PCl<sub>5</sub>, it apparently enolizes and yields the chloride (27); the latter by reduction with sodium and alcohol gives p-menth-3-ene.<sup>72-74</sup> Hydrogenolysis of (+)-pulegone (26) with a 3:1 mixture of AlCl<sub>3</sub> and LiAlH<sub>4</sub> in ether affords mainly (+)-p-menth-3-ene.<sup>75</sup> Finally, carvenone hydrazone (28) is converted to p-menth-3-ene by distillation with KOH.<sup>76</sup>



- a) X = Y = Br, Z = H
- b) X = Y = Cl, Z = H
- c) X = I, Y = Z = H
- d) X = OCOCH<sub>3</sub>, Y = Z = H
- e) X = Y = OH, Z = H
- f) X = OH, Y = Z = O
- g) X = OH, Y = H, Z = OCOH
- h) X = H, Y = Z = O

## Reactions

Notwithstanding the great simplicity of structure, p-menth-3-ene has been an interesting and challenging substrate for concentrated and impressive display of synthetic expertise. This phase of the chemistry of the hydrocarbon will now be considered.

**Hydrogenation:** Hydrogenation of (+)-p-menth-3-ene in glacial acetic acid at 4 atm and room temperature over Adam's PtO<sub>2</sub> catalyst gives p-menthane (1) (cis, 55%; trans, 45%).<sup>71</sup>

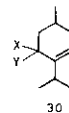
**Bromination:** In glacial acetic acid, (+)-p-menth-3-ene absorbs 1.94 atomic equivalents of bromine with evolution of heat to give (+)-3,4-dibromo-p-menthane (29a), probably a mixture of stereo-isomers.<sup>71</sup> Debromination of this derivative by refluxing with zinc dust in ethanolic solution liberates the parent hydrocarbon.<sup>71</sup> On the other hand, dehydrobromination by refluxing with ethanolic KOH generates the rare p-mentha-2,4-diene (18); by reaction with Na and alcohol, this hydrocarbon reverts to p-menth-3-ene.<sup>77</sup>

Allylic bromination of (+)-p-menth-3-ene by N-bromo-succinimide gives p-menth-3-en-5-yl

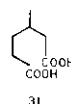
bromide (30a) which by stirring with sodium formate in formic acid in dioxane solution is converted to the formate (30b; R = H). Upon reacting with Na<sub>2</sub>CO<sub>3</sub> in aqueous CH<sub>3</sub>OH, this ester furnishes (±)-trans-p-menth-3-en-5-ol (30c).<sup>51</sup>

**Chlorination:** One of the exciting reorganizations of p-menth-3-ene is through chlorination. Large quantities of 5-chloro-p-menth-3-ene (30d) with smaller amounts of 3,4-dichloro-p-menthane (29b) are formed by chlorination of p-menth-3-ene suitably at 90-120° if the reaction is carried out in the liquid phase, or at 200° if both reactants are to be employed in the vapor phase.<sup>78</sup> These derivatives are precursors of the members of the menthone-menthol family.<sup>78</sup>

Even under mild conditions, the allylic chlorine of (30d) readily exchanges for hydroxyl to give p-menth-3-en-5-ol (30c), but the dehydrochlorination-hydrolysis of the dichloride (29b) demands more rigorous conditions. An economical hydrolyzing system is excess of aqueous slurry of lime. Temperatures recommended are of the order of 125-175° and 175-200° for (30d) and (29b) respectively, and the time required depends on agitation and presence or absence of emulsifiers.<sup>78</sup> The alcohol (30c) is easily oxidized with CrO<sub>3</sub>-H<sub>2</sub>SO<sub>4</sub> mixture to the ketone (30e). Dehydrochlorination of (30d) by refluxing with alcoholic KOH leads to p-mentha-2,4-diene (18), a hydrocarbon which also stems from (29b) by processing with calcium hydroxide.<sup>79</sup> p-Menthenyl amines are formed from (30d) by treatment with ammonia, primary, or secondary amines.<sup>78</sup> Esters and ethers (30d and 30f) are produced from (30d) by heating it with alkali metal salts of carboxylic acids and alkali metal alcoholates under substantially anhydrous conditions respectively.<sup>79</sup> Conversion of p-menth-3-en-5-ol to valuable 3-oxygenated derivatives of p-menthane which are useful in flavors and medicinal preparation is also described.<sup>78</sup>



- a) X = H, Y = Br
- b) X = H, Y = OCOR
- c) X = H, Y = OH
- d) X = H, Y = Cl
- e) XY = O
- f) X = H, Y = OR
- g) XY = NOH



- a) X = H, Y = OOH
- b) X = H, Y = OH
- c) XY = O

**Hydroiodination:** Baeyer noted that the treatment of p-menth-3-ene with an acetic acid solution of hydrogen iodide affords 4-iodo-p-men-

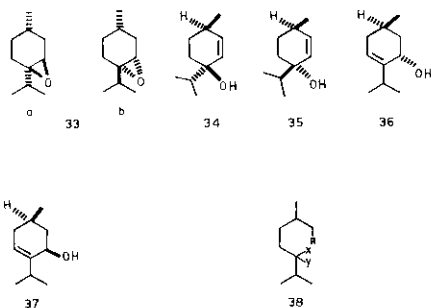
thane (29c).<sup>80</sup> Its decomposition with silver acetate in acetic acid gives the corresponding acetate which upon saponification affords p-menthan-4-ol (20e). Alternatively, the latter is obtained by the action of moist Ag<sub>2</sub>O on (29c).<sup>81</sup> However, the most facile route to this alcohol, known since 1843, is by heating p-menth-3-ene with trichloroacetic acid at 70-90° for 30 min and agitating the product with potash for 12 hrs.<sup>82,83</sup> This simple conversion deserves further scrutiny and appears to be an economic route to this rare alcohol.

**Halohydrin formation:** Application of bromine water to (±)-p-menth-3-ene gives a mixture of 62.9% bromohydrin (C<sub>10</sub>H<sub>19</sub>OBr) and 37.1% dibromide (C<sub>10</sub>H<sub>18</sub>Br<sub>2</sub>).<sup>40</sup> On the other hand, Tanaka has incorporated hypochlorous and hypoiodous acid to the hydrocarbon and secured the respective halohydrins.<sup>84</sup>

**Oxidation:** We owe to Wagner the classical investigation which has thrown light on the constitution of p-menth-3-ene—oxidation with 1% KMnO<sub>4</sub> at ~0° which resulted in the isolation of the glycol (29e), ketone (29f), and β-methyl adipic acid (31).<sup>85</sup>

Autoxidation of (±)-p-menthene at 50° and under the influence of ultraviolet light gives p-menth-3-en-2-hydroperoxide (32a) and smaller quantities of p-menth-3-en-2-ol (32b) and 3,4-epoxy-p-menthane (33).<sup>38</sup> Soviet chemists have studied the kinetics of this autoxidation and have confirmed the formation of the hydroperoxide (32).<sup>86,87</sup> Mn and Co salts of carboxylic acid facilitate the peroxidation step.

According to Ohloff and Uhda, the photosensitized oxidation of (+)-p-menth-3-ene leads to five allylhydroperoxides and these have been reduced by saturated sodium sulfite solution.<sup>60</sup> The alcohols identified are: (-)-trans-p-menth-2-en-4-ol (34), (-)-cis-p-menth-2-en-4-ol (35), (-)-trans-p-menth-4-en-3-ol (36), and (+)-cis-p-menth-4-en-3-ol (37).



- a) R = CHO, XY = O  
b) R = COOH, XY = O  
c) R = CH<sub>2</sub>OH, X = H, Y = OH

of 3,7-dimethyl-6-keto-octanoic acid (38b).<sup>19b,88</sup> Hydrogenation of the former in presence of Raney nickel or copper chromite catalyst gives quantitatively 3,7-dimethyl-1,6-octanediol (38c); this glycol is also obtained from (38b) by reaction with LiAlH<sub>4</sub>. Dehydration of (38c) with Al<sub>2</sub>O<sub>3</sub>, HClO<sub>4</sub> or KIISO<sub>4</sub> furnishes citronellols (39).<sup>19b,88,89</sup> The framework for this exploitation of p-menth-3-ene appears to have been worked out by Siemion, who decomposed the ozonized products with LiAlH<sub>4</sub> to (38c) and distilled the latter with 20% H<sub>2</sub>SO<sub>4</sub> to yield citronellols (39).<sup>90</sup>

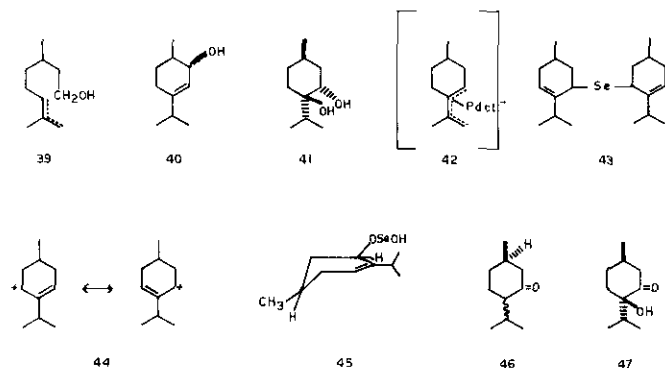
Lead tetraacetate oxidation of p-menth-3-ene has been reported by Sato.<sup>91</sup> The hydrolysate of the reaction mixture included cis- and trans-p-menth-3-en-2-ols (40), p-menthane-3,4-diol (29c), and trans-4-hydroxyneomenthol (41). In passing, it may be mentioned that the reaction of (40) with palladium II chloride, LiCl, and CO gives di-μ-chlorobis-[3,4,8-trihapto-p-menth-3-ene] palladium (II) (42), which contains the only conceivable tetrasubstituted π-allylic system which has not involved drastic rearrangement of the menthane ring system.<sup>92</sup>

Between C<sub>2</sub> and C<sub>5</sub> active methylenes in (+)-p-menth-3-ene, tert-butyl chromate preferentially attacks the one remote from the isopropyl group, presumably due to steric inhi-

A major breakthrough in the modification of p-menth-3-ene is achieved with ozone. Ozonolysis of p-menth-3-ene gives essentially 3,7-dimethyl-6-keto-octal (38a) with a sprinkling

bition—the contribution from the methyl group in this respect being negligible—to give predominantly (+)-carvenone (32c). The sparingly liberated p-menth-3-en-5-one (30e) is optically inactive and its formation is hooked to unspecified intermediate radicals.<sup>52</sup>

p-Menth-3-en-5-one (30e), p-menth-3-en-5-ol (30c), and di-(p-menth-3-en-5-yl)selenids (43) are the products released in the oxidation of p-menth-3-ene with  $\text{SeO}_2$ .<sup>53,93-95</sup> Japanese investigators have found that the oxidation of (+)-p-menthene with  $\text{SeO}_2$  in a mixture of glacial acetic acid and acetic anhydride results in p-menth-3-en-5-yl acetate (30b,  $\text{R} = \text{CH}_3$ ) in addition to the above ketone and alcohol; the hydroxyl group of the alcohol and the acetoxy group of the ester apparently possess trans-configuration with respect to  $\text{C}_1\text{-Me}$ .<sup>54</sup>  $\text{C}_2$ -allylic hydrogens are notably spread in this reaction. The precursors of these optically inactive products involving  $\text{C}_5$ -methylene may be the initially formed resonance hybrid (44). Capture by (44) of the hydroxyl ion of water (which is considered to be produced by the attack of  $\text{SeO}_2$ ) or the acetoxy ion of the solvent leads to the alcohol or acetate respectively. Application of stereo-electronic principles to the formation of selenium (II) ester (45) from (+)-p-menthene and the spectrum of pathways available for its decomposition culminating in racemization has been recently elucidated.<sup>96</sup> However, Ohloff and Uhda have isolated the acetate (30b,  $\text{R} = \text{CH}_3$ ) in their work on p-menth-3-ene; and its saponification with  $\text{KOH}$  followed by oxidation with  $\text{MnO}_2$  gave partially racemized p-menth-3-en-5-one (30e).<sup>60</sup>



Acylating oxidation of (+)-p-menth-3-ene with mercuric acetate gives largely the racemic ester (30b,  $\text{R} = \text{CH}_3$ ) which can be saponified to the corresponding alcohol (30c).<sup>97,98</sup>

It may be recalled that ( $\pm$ )-p-menth-3-ene gives ( $\pm$ )-p-menthan-3,4-diol (29e), m.p. 76.5–77° with 1%  $\text{KMnO}_4$ , apparently by cis addition.<sup>85,54</sup> Decyclization of 3,4-epoxy-p-menthane (33) with 10%  $\text{H}_2\text{SO}_4$  at 0° furnishes a similar diol, m.p. 75–76°. On the other hand, an inactive, trans (?) diol, m.p. 95°, has been prepared from ( $\pm$ )-3,4-

epoxy-p-menthane.<sup>38</sup> Naves added a new dimension to this confusion by isolating in the performic oxidation of ( $\pm$ )-p-menth-3-ene, a diol, m.p. 76–77°, which is assigned cis- structure by slender comparison with Wagner's sample.<sup>99</sup>  $\text{H}^+$  dehydration of the diol yields a mixture of ( $\pm$ )-menthone and ( $\pm$ )-iso-menthone (46) containing 60% of the former.<sup>99</sup> Another route to (46) is by decomposition of the formate (29g).<sup>99</sup> The above stereochemical contradictions were resolved by Japanese workers through infrared spectroscopy.<sup>54</sup> The (+)-p-mentha-3,4-diol, m.p. 76.5–77°, generated by performic acid hydroxylation of (+)-p-menth-3-ene, is deciphered as (+)-trans-4-hydroxyneomenthol (41). Pinacolic dehydration of the latter furnishes a mixture of (–)-menthone (65%) and (+)-iso-menthone (35%).<sup>54</sup> The conversion of the diol and its mono- and di-formates to the menthone isomers is a key step in the synthesis of menthol.<sup>17,100-102,111</sup>

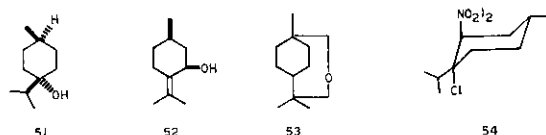
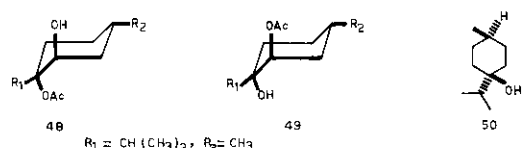
Continuing the chemistry of the diol (47), oxidation with tert-butyl chromate or chromium trioxide-pyridine complex affords (–)-4-hydroxymenthone (47); of interest is the fact that the Huang-Minlon reduction of (47) furnishes (+)-p-menth-3-ene and p-menthan-4-ol (20e).<sup>54,55,103</sup>

Oxidation of p-menth-3-ene with perbenzoic, peracetic, or monoperphthalic acid leads to 3,4-epoxy-p-menthane (33).<sup>83,84,103,106,107</sup> Agitation with methyl-, ethyl-, propyl-, butyl-, or amyl alcohol-hydrochloric acid converts it into p-menth-3-one (29h), essentially an isomerization which is also accomplished at 250–280° in the presence of  $\text{SiO}_2$ ,  $\text{MgSO}_4$  on pumice, Cu pyrophosphate, or  $\text{Al}_2\text{O}_3$ .<sup>83,84,105</sup> Whereas catalytic hydrogenation by Willstätter's method produces p-menthane, conventional reduction with  $\text{LiAlH}_4$  in  $\text{Et}_2\text{O}$  gives mainly p-menthan-4-ol (20e); but if the reaction mixture is deprived of  $\text{Et}_2\text{O}$  and the mass heated to 87°, the product obtained is essentially p-menthan-3-ol (22a).<sup>59,83</sup> On the other hand, hydrogenation of the oxide with a catalyst of  $\text{Pd}(\text{OH})_2$  without a carrier results in a mixture of alcohols, hydrocarbons, and ketones which have not been properly characterized.<sup>107</sup>

The geometrical isomers constituting the epoxide may be separated conveniently on a 15-ft 15% Carbowax 20M on Chromosorb W GLPC column, revealing approximately a 1:1 mixture of the cis- and trans-epoxide (33a) and (33b).<sup>108</sup> Reaction of the ( $\pm$ )-epoxide (33a) with a sodium acetate buffered solution of acetic acid leads extensively to the hydroxyacetate (48) which with pyrolysis at 390° leads to a mixture of ( $\pm$ )-trans-p-menth-4-en-3-ol (36) and ( $\pm$ )-menthon-isomenthone (46) in a product ratio of 7:3. Under similar conditions, the ( $\pm$ )-epoxide (33b) affords ( $\pm$ )-hydroxyacetate (49) which decomposes at 450° to ( $\pm$ )-trans-p-menth-2-en-4-ol (34). The pyrolysis of the hydroxyacetates pro-

vides an excellent route to the allylic alcohols.<sup>108</sup> From a theoretical angle, these epoxide openings disclose a high degree of specificity—as would be expected by an extension of the Furst-Plattner rule—to the monocycle system, assuming that R<sub>2</sub> “fixes” the conformation of the cyclohexene system.<sup>108,109</sup>

Earlier it was mentioned that LiAlH<sub>4</sub> reduction of 3,4-epoxy-p-menthane leads to p-menthan-4-ol (20e). In a comprehensive study, Bowman and Jackson found that the trans-epoxide (33b) is reduced more readily than the cis- isomer (33a).<sup>61</sup> The former affords trans-p-mentha-4-ol (50) and neoisomenthol (23a), and the latter cis- and trans-p-menthan-4-ol (51 and 50). This indicates that the decyclization has occurred with preferential formation of diaxial substituents.<sup>61</sup>



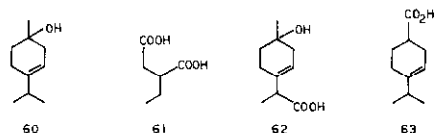
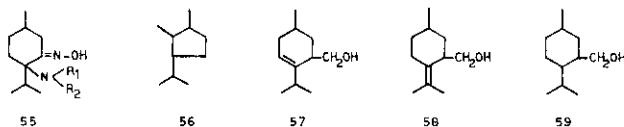
Aluminum isopropoxide (AIP)-catalyzed rearrangement of 3,4-epoxy-p-menthane has yielded interesting results.<sup>110</sup> The electrophilic attack of AIP on the cis-epoxide (33a) at ca 120-130° causes almost unilateral cleavage of the 3-membered ring at the most substituted  $\alpha$ -carbon with synchronized  $\beta$ -proton elimination from the least substituted carbon to yield trans-p-menth-4-en-3-ol (36). Under the same conditions, the sister isomer (33b) remains passive. At elevated temperatures of 150-170°, the trans-epoxide is converted into a mixture of cis-p-menth-4-en-3-ol (37), traces of cis-pulegol (52), and substantial amounts of p-mentha-3,8-diene (15) and p-mentha-2,4(8)-diene (14).

We credit Eschinazi with an exceptionally valuable process for the commercial production of menthol from p-menth-3-ene.<sup>111</sup> This is based on the fact that if a mixture of cis- and trans-3,4-epoxy-p-menthane is hydrogenated in the presence of Raney nickel under suitable conditions, the cis- isomer is substantially converted to a single hydroxy compound such as isomenthol (24a). The isomenthol is then rearranged in the known manner to menthol (22a); H<sup>+</sup> catalyzed isomerization of the unscathed epoxy-p-menthane gives menthone; and the latter can be processed to menthols by hydrogenation in the presence of known catalysts such as copper chromite.

**Nitroschlorination:** Modifications of

p-menth-3-ene through nitroschlorination initiated by Kremers and coworkers have gained momentum over the years.<sup>36,37,117</sup> Both optically active and inactive nitroschlorides of the hydrocarbon are described in literature.<sup>19a,49,71,116,118,119</sup> Spectral data (IR and PMR) are in agreement with structure (54) for the nitroschloride.<sup>120</sup> With primary and secondary amines, the nitroschloride yields nitrolamines of the general formula (55). Dehydrohalogenation of the nitroschloride affords the oxime (30g); upon hydrolysis this oxime furnishes p-menth-3-en-5-one (30e).<sup>19(a),36,37,117,118,121,122</sup>

**Isomerization, disproportionation, dehydrogenation, and dimerization:** Contact isomerization of p-menth-3-ene over SiO<sub>2</sub> at 375-450° to five-membered hydrocarbons has been reported, but the catalysate requires further scrutiny.<sup>42</sup> A mixture of p-cymene (12) and p-menthone (1) is formed by cycling p-menth-3-ene over Pd-asbestos at 175-180° or over reduced Cu at 290-300°.<sup>123,124</sup> Sulfur also dehydrogenates p-menth-3-ene to p-cymene.<sup>125</sup> Heating p-menth-3-ene over activated gumbrin clay gives 1,2-dimethyl-3-isopropylcyclopentane (56) and dimers.<sup>126</sup>



**Prins thermal reaction:** Saponification of the thermal condensation product of p-menth-3-ene, paraformaldehyde, and acetic anhydride at 180-220° affords 3-hydroxymethyl-p-menth-4-ene (57), an assignment clinched from IR and PMR data.<sup>127</sup> However, the formation of the isomeric 3-hydroxymethyl-p-menth-4(8)-ene (58) cannot be excluded.<sup>129,130</sup> The catalytic hydrogenation of

the alcohol, which refused resolution by both fractional distillation and gas liquid chromatography, results in 3-hydromethyl-p-menthane, but in the present context this reaction has no diagnostic value.<sup>127-129</sup> On the other hand, oxidation with potassium permanganate gives acetone, projecting the presence of the iso-propylidene moiety.<sup>128,129</sup> Irrespective of the apparent mixed mixture of the hydroxy derivative generated, this condensation reaction opens up an interesting route to compounds of the p-menthane series.

**Microbiological transformation:** A novel modification of ( $\pm$ )-p-menth-3-ene with a soil pseudomonad (PL strain) results in the formation of p-menth-3-en-1-ol (60),  $\alpha$ -ethyl succinic acid (61), 1-hydroxy-p-menth-3-en-9-oic acid (62), and 1-hydroxy-p-menth-3-en-7-oic acid (63).<sup>39</sup> The hydrocarbon lacks the 1:2-double bond which provides the necessary chemical locus of attack by the bacterial enzyme in bringing about a cleavage of the cyclohexene ring by hydration of an  $\alpha,\beta$ -unsaturation adjacent to carboxyl group derived from the 7-methyl group. Further study in this area is likely to be rewarding.

**Hydroboration:** Finally, we shall consider the most outstanding utilization of ( $\pm$ )-p-menth-3-ene, the preparation of menthols via boron complex. Anti-Markownikoff stereospecific hydroboration of the hydrocarbon leads to a mixture of racemic menthol (22a) and iso-menthol (24a) whose ratio can be varied depending upon the experimental conditions.<sup>25,130,131</sup> Process for preparing optically active menthol from ( $\pm$ )-p-menth-3-ene revolves on boranes having the formula  $BHR_2$  where R is an optically active hydrocarbon radical.<sup>132</sup> A great number of optically active hydrocarbons can form the substituted boranes, but the preferred ones are ( $\pm$ )- $\alpha$ -pinene and (-)- $\alpha$ -pinene.<sup>132</sup> Asymmetric synthesis of (-)-menthols (22a) and (-)-isomenthol (24a) by hydroboration of ( $\pm$ )-p-menth-3-ene with (+)-monoiso-pinocampheylborane derived from (-)-(1S:5S)- $\alpha$ -pinene has been described by Japanese workers.<sup>133</sup>

Introduction of optically active solvent in the hydroboration step is covered by the patent granted to Colgate-Palmolive Company.<sup>134</sup> This results in the production of menthols with greater proportion of the active components. A particularly useful optically active solvent in this process is (-)-menthyl-ethyl ether.<sup>134</sup>

## Summary

Here an attempt has been made to portray the kaleidoscopic chemistry of p-menth-3-ene, the most aristocratic member of the p-menthene series. The exploitation of the reactivity associated with the double bond has sparked investigations of great theoretical and industrial value and more than anything else paved the way for royal entry into the menthenyl, men-

thanyl, and citronellyl series.

## Acknowledgement

Prof. Dr. Manfred Muhlstadt, Dr. Kurt Kulka, Dr. E. Eschinazi, Dr. D. L. Carroll, and Chemetron Corporation are thanked for providing literature.

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