Limonene

A. F. Thomas
Firmenich SA, Research Laboratories, 1211 Geneva 8, Switzerland

Y. Bessière
1261 Borex, Switzerland

1 Introduction

The production of (+)-limonene (1) in Brazil is about 12500 tonnes per year from orange stripper oil, 15000 tonnes per year from cold-pressed orange oil [over 90% of which is (+)-limonene], and about 11000 tonnes per year from other sections of the citrus industry (orange-essence recovery water, etc.).1 making the annual world production of (+)-limonene about 50000 tonnes. Smaller amounts of more or less racemic limonene (dipentene) are produced as a by-product from the hydration of turpentine; distillation of turpentine is a source of (-)-limonene, which can also be distilled from oil of Eucalyptus stagertiana, although the purity is not as high as that of the (+)-enantiomer. (+)-Limonene is one of the cheapest chiral starting materials suitable for organic synthesis, and this review is intended to survey its chemistry.

Until 1877, when Tilden distinguished between terpenes of the ‘turpentine group’ and the ‘orange group’ by the characterization of crystalline nitroso-derivatives,2 there was considerable confusion regarding the hydrocarbons obtained from essential oils. Wallach pointed out that hesperidene, citrene, carvene, di-isoprene, terpilene, kautschine, cycene, cajeputene, and isoteretentine were all identical to (-)-limonene.3 The discovery of (-)-limonene (from Pinus silvestris)4 came a little later, making clear the constitution of the racemate, dipentene, which had been obtained from the distillation of rubber.5 The correct formula was given by Wagner in 1894,6 and the first rational synthesis was by Perkin in 1905.7 Racemic limonene is one of the products of the pyrolysis of (-)-(S)-2-pinene (2),8 and the conversion of turpentine into limonene over catalysts such as sodium sulphide on alumina at 350 °C has been patented.9

We shall use the name ‘limonene’ for both the racemate and optically active forms.

The major uses for limonene are in the flavour and fragrance industries, as a solvent, and in the manufacture of polymers and adhesives. Its uses as a solvent will not be discussed further but there are patents, and such use has been increasing on account of the low toxicity, pleasant odour, and biodegradability of (+)-limonene (1).10 Because (+)-limonene that has been distilled from orange oil is over 95% pure, there is sometimes doubt in the literature as to whether the limonene that was used in any experiment was further purified or not. The major impurity in the material from orange oil is myrcene (3); this can be removed by clathration with tetrakis(4-methylpyridine)dithiocyanatonickel.11 About 1% of aldehydes (mainly octanal) is also present, and there are traces of other monoterpenes. The aldehydes can be removed by distillation over 0.5% sodium hydroxide.

The presence of these impurities has led to widely different values being determined for the flavour threshold concentration in water. This has been given as 0.21 p.p.m., and the effect of non-volatiles on this value has been measured,12 but the limonene was only 96.5% pure, and was probably only distilled orange oil, so the figures are meaningless. Values of 0.01 p.p.m.13 and 229 p.p.b. (also for 96% pure limonene)14 have been published, but in these papers we are not even informed which enantiomer was tested, and it is known that the organoleptic properties of the (+)- and the (-)-isomer are different.15 Again, the promotion of mouse skin tumours by orange oil was long assumed to be caused by (+)-limonene, but pure (+)-limonene does not exert this effect.16 The toxicology of limonene is well known;17 its metabolism is mostly by allylic oxidation or formation of an epoxide.18 One of the major metabolites, uroterpenol glycoside (4), was isolated from urine, especially of subjects with adrenal hyperplasia or in pregnancy; this does not occur as an optically pure enantiomer, presumably because of the variety of enantiomers in dietary limonene.19 Uroterpenol will be discussed later. Other metabolites are known,20 and the conversion of (+)-limonene (1) into (+)-perillic acid (5) by Pseudomonas incognita has been described.21

Limonene is reportedly insecticidal;22 it is toxic to cat fleas (Ctenocephalides felis),23 for example, and may play a part in conferring resistance to trees against attack by insects.24 There is a simple school experiment to demonstrate the insecticidal properties of (+)-limonene.25
An interesting recent application of limonene is in the purification of cyclodextrins from gelatinized starch, with some of which it forms filtrable solids.28

The variation of optical activity of limonene with temperature is known.28 Nuclear magnetic resonance spectrometry in the presence of Ag+ and an optically active lanthanide complex has been used to measure the chirality,29 and the n.m.r. spectrum of limonene, based on 13C-13C couplings, has been reported three times30 with somewhat different figures. Natural-abundance deuterium n.m.r. spectroscopy provides a rapid means of locating the positions from which protons are lost during its biosynthesis; these positions will have excess deuterium, on account of the isotope effect. By this means, Epstein et al. have shown that C-9 and C-10 are not equivalent during the biosynthesis.31 This result was suggested by feeding experiments, but difficult to prove because of the low incorporation of precursors.22

The mass spectrum of limonene appears to consist of two fragments of isoprene, one of which is charged (m/z 68),23 but the situation is complex; this fragment does not arise in the field-free zone directly from the molecular ion that is formed by collision-induced fragmentation.31

2 Hydrogen Shifts and Disproportionation; the Action of Acids and Bases

The carbenium ion (a) that is derived from limonene by the action of acids rearranges as shown in Scheme 1.25 Formation of the ion (a) is also the initiation step in the Friedel-Crafts-catalysed and acid-promoted polymerization of limonene,30 the chemistry of this ion going back to 1789, when turpentine [i.e. α-pinene (2)] was treated with sulphuric acid.27 When (+)-limonene (1) is homopolymerized by Ziegler-Natta catalysts, the resulting polymer is optically inactive, and only has the monocyclic structure (6) and the bicyclic structure (7).30 The properties of such dipentene resins, which are used as tackifiers mainly in hot-melt adhesives (packaging materials), have been summarized by Ruckel et al.31

Although, in principle, all of the hydrogen shifts of Scheme 1 are reversible, in practice (a) - (1) does not occur much, because the formation of terpinolene (6) is preferred, followed by further shifts to α- (9) and γ-terpinene (10).31 Other menthadienes are also formed [particularly isoterpinolene (11), which is better prepared from car-3-ene (12)], but careful distillation of the products is necessary for preparative purposes. There is always some disproportionation (Scheme 1), leading to the menthene and p-cymene (13), and ref. 35 notes how to avoid this.

Much work has been invested in studying the differences between various acids effecting hydrogen transfers and disproportionation,41 and the kinetics have been studied using trifluoroacetic acid.42 The results vary somewhat with the strength of the acid.43 Acid forms of ion-exchange resins effect the same transformations.44 The chirality of limonene is lost in all of these products [ion (b) is already achiral] and the recovered limonene gradually loses optical activity, because of the reaction (a) - (1). Heating limonene in dipolar aprotic solvents also causes slow rearrangement of double bonds and disproportionation.45 These hydrogen shifts are encountered in many other reactions of limonene, and can significantly lower the yields of the desired products (e.g. in the hydration of limonene to α-terpineol, or in catalytic hydrogenation).

Three isomeric dimethylbicyclo[3.2.1]octenes (14) were mentioned after the action on limonene of phosphoric acid on a silica support had been investigated, first in 1947 (with a different structure46) and then in 1974.47 The latter paper includes an identification of the n.m.r. spectrometer that was used, but not a single n.m.r. spectrum; one of us (AFT) repeated this work but found only the usual hydrogen shifts and disproportionations. Many years earlier, phosphoric acid had been reported to give an unidentified compound48 which was dehydrogenated over sulphur to 2,6,9-trimethylphenanthrene,49 the structure of which was confirmed by an independent synthesis.50 The unlikely compound (15) is also reputed to be formed by the action of phosphoric acid.31

Other reactions that have led to the isolation of dimers from limonene or its disproportionation products are treatment with chloranil for 2 hours at 130—170 °C [to form (16)] and the reaction of limonene with p-cymene (13), which has been reported to give the tetracyclic compound (17) in 20—25%
conversion of \( p \)-cymene and in over 40% selectivity.\(^3\) The action of \( BF_3 \cdot OEt_2 \) in \( CC1_4 \) or toluene apparently also gives dimers.\(^5\) The formula in ref. 54 would be the result of the cycloaddition of the two methylene groups, to form a cyclobutane, which seems unlikely. There are a vast number of patents and publications dealing with the copolymerization of limonene with ethylene and propylene,\(^\text{16,17} \) with norbornadiene,\(^\text{18} \) and with other alkenes, as well as on the influence of limonene as a chain-transfer agent in the styrenation of vinyl ether polymers\(^\text{19} \) and the polymerization of vinyl monomers (styrene, vinyl acetate, etc.).\(^\text{20} \)

Double-bond rearrangement of limonene also occurs in the presence of bases\(^\text{21,22} \) such as potassium \( t \)-butoxide in dimethyl sulphoxide\(^\text{23} \) or calcium oxide at 290–380 °C.\(^\text{24} \) Disproportionation to \( p \)-cymene (13) is readily carried out with potassium hydride in pyrrolidine or ethylenediamine,\(^\text{25} \) a reaction which led to the suggestion that limonene could be used to measure the proton-removing power of ‘superbases’.\(^\text{26} \) The formation of the limonene anion (c) by metallation with butyl-lithium and \( N,N,N',N' \)-tetramethylethylenediamine was described by Erman et al.\(^\text{27} \) This anion can be transformed into menth-1,8(10)-dien-9-ol (18)\(^\text{28} \) and was used in several syntheses which will be referred to in later sections. Katzenellenbogen and Crumrine also converted the anion (c) into the alcohol (18) and then into the corresponding bromide for further synthesis.\(^\text{29} \) Other derivatives (including some sulphides) have been made by Suemune et al.\(^\text{30} \) and tin and silicon derivatives have been prepared from the anion (c).\(^\text{31} \) In all of these reactions, the chirality of limonene is retained.

The dianion (d) of limonene can be formed by treatment with butyl-lithium and potassium \( t \)-butoxide (Lochmann’s base) or potassium \( t \)-amyloxide at reflux; quenching this dianion with deuterium oxide yielded 7,10-dideuteriated limonene (19) and some dideuteriated dimethylstyrene (20).\(^\text{32} \)

3 Addition of Water, Alcohols, and other HX-type Molecules

The carbo-cations that are formed by the action of acids on limonene (see Scheme 1) can lead to addition products. Thus \( \alpha \)-terpineol (21; \( R = H \)) can be formed by the addition of water; this is generally accompanied by some \( \beta \)- (22) and \( \gamma \)-terpineol (23) from addition of water to the endocyclic double bond. The reaction was first described by Bouchardat and Lafont in 1886,\(^\text{33} \) and it is surprising that the addition of methanol was only described 50 years later,\(^\text{34} \) although the product, \( \alpha \)-terpinyl methyl ether (21; \( R = Me \)), had been made by etherification of \( \alpha \)-terpineol (21; \( R = H \))\(^\text{35} \) and its odour described\(^\text{36} \) in 1883.

Actually, \( \alpha \)-terpineol was known before Bouchardat’s experiment, having been made by the hydration of turpentine with acid catalysts,\(^\text{37} \) but the structure was only established in 1895.\(^\text{38} \) \( \alpha \)-Terpineol was also known from dehydrogenation of 1,8-terpin (24; \( X = OH \)),\(^\text{39} \) this also being obtained from turpentine. The \( \alpha \)-terpineol that is obtained from limonene is generally (though not invariably; see below) racemic because of the isomerizations in Scheme 1, and the racemate was one of the first substances to be purified (m. pt 35 °C) by low-temperature crystallization.\(^\text{40} \)

Some of these early experiments were conducted in glacial acetic acid, when the main product is terpenyl acetate (21; \( R = Ac \)), from which the alcohol was obtained by hydrolysis.\(^\text{41,42} \) Sulphuric acid in acetic anhydride also yields \( \alpha \)- and \( \beta \)-terpenyl acetates.\(^\text{43} \) The terpineols are themselves hydrated under acid conditions, 5% aqueous sulphuric acid hydrating \( \alpha \)-terpineol, with \( \beta \)- and \( \gamma \)-terpineols reacting more slowly, while limonene is unchanged under these conditions.\(^\text{44} \) This further hydration was well known to the early workers,\(^\text{45,46} \) who believed that \( \alpha \)-terpineol (21; \( R = H \)) gave only \( cis \)-terpin [\( cis \)-(24; \( X = H \)], ‘\( cis \)’ referring to the hydroxyl and the hydroxypropyl groups] while the \( \gamma \)-isomer (23) gave both isomers of (24; \( R = H \)).\(^\text{47} \) More recently it was shown that \( cis \)-terpin is the major, but not exclusive, product of hydration of all of the terpineols.\(^\text{48} \) Consequently, many hydration processes of limonene produce large amounts of the diols (24; \( R = H \)) besides the terpineols, but these diols may be dehydrated to the terpineols. Surprisingly, 1,4-cineole (25), but not 1,8-cineole (26), is said to be
formed in addition, although 1,8-cineole (26) is a major component of the products resulting from treatment of α-terpineol (21; R = H) with an acid. Surprises here are, however, common; for example, terpin of unspecified stereochemistry is dehydrated by aluminium phosphate and aluminium oxide to give limonene (I), p-cymene (13), and unidentified products. The authors of this paper were surprised by the p-cymene, but we are surprised by the limonene, since we would have expected terpinolene (8)!

Innumerable different conditions have been described for the preparation of α-terpineol (21; R = H) from terpene hydrocarbons, mostly from turpentine. The most efficient way from limonene seems to be by using chloroacetic acids and a cation-exchange resin; this gives optically active α-terpineol in 85% conversion and 99% selectivity. Alternatively, formic acid in the presence of zeolites gives 87–100% conversion and high selectivity. From limonene and acetic acid, with ferric sulphate as a catalyst, a 6:4 mixture of α- and β-terpinyl acetates is efficiently made. Oxymercuration of limonene followed by reduction with sodium borohydride gives α-terpineol (21; R = H) (70%), the rest being the diol (24; X = OH) and 1,8-cineole (26). In fact it has long been known that if this procedure is applied to α-terpineol it leads to 1,8-cineole. If the mercuration of limonene is carried out in the presence of sodium lauryl sulphate, the formation of micelles causes the ionized part of the molecule to be exposed to attack by water on the periphery, and monohydration raises the yield of terpineol to 97%.

The addition of methanol to limonene in the presence of an acid could not be repeated by Treibs, who reported that there was mainly dimerization with a small amount of double addition. The reaction was taken up again in 1949, when Royals showed the reaction to be reversible by the fall in the optical activity of the product (21; R = Me) with increasing reaction time. Royals prepared other terpenyl ethers. (See also refs. 54 and 71). By-products from this reaction would be expected; although they have not been described, those from the very similar reaction of pinene and methanol have, notably the ethers (27), (28), and (29). Bicyclic systems arising from the reaction of pinene would, of course, be absent from the products from limonene. Diol monoethers are known, being made, for example, from limonene and ethylene glycol in the presence of an ion-exchange resin. (See also ref. 96). The light-induced addition of methanol to limonene takes a different course from the acid-catalysed reaction, yielding 52% of the ethers (27) and (28) with about 13% of mentha-1(7),8-diene (30). The microbological addition of water to limonene is mentioned later.

The addition of hydrogen chloride to limonene to give its monohydrochloride (31) works well only in the absence of moisture and in a solvent, e.g. carbon disulphide, petroleum ether, or dichloromethane. Hydrogen bromide reacts similarly, and the halides are converted into α-terpineol by the action of magnesium and air, or with 2% potassium hydroxide (a stronger base yields hydrocarbons, mostly dipentene). Zinc oxide (in 80% acetic acid for the acetate) has also been recommended. Because the chloride that is made in this way is optically active, so is the terpineol. The di-addition products (24; X = Cl) and (24; X = Br) have also been known for a long time; they are best made by the action of concentrated halogen acids in methanol or acetic acid on limonene and can be converted into the terpineols by adding a base. The safest route from limonene to γ-terpineol (23) is still the original one from Baeyer, consisting in brominating the dihydrobromide (24; X = Br), to obtain 1,4,8-tribromomenthane (32), and then reducing this with zinc in acetic acid to the acetate of (23), with overall yields of 50–60%. A method that is said to produce 72% of γ-terpineol (23) consists in dehydrating terpin (24; X = OH) in isopropyl alcohol and 95% sulphuric acid at room temperature for 80 hours.

The reaction of limonene with phenols dates from 1922, and the products have been patented as resins and lacquers. These products could arise either by aromatic substitution or by formation of a phenol ether, further reaction giving polymers. The reactions are more complex than those of camphene or pinene (cf. the vague description of the reaction of limonene with 2,4-dimethylphenol compared with the precision of the same reaction with camphene in 1960) and while two products (33) and (34) have been described from the reaction of phenol and limonene in the presence of boron trifluoride, this cannot be the whole story. In the presence of a cationic ion-exchange resin, for instance, limonene reacts with cresols, α-cresol yielding the ethers (35) and (36) another surprise, since these products require a carbenium ion that is derived.
from α-terpinene (9). Dimethylphenols with one free ortho
position,117 and sesamol (3,4-methylenedioxyphenol)118 give similar compounds. The reaction of limonene with phenol has also been studied in the USSR,119 but the publication was not available to us.

Addition of nitric acid to limonene has been examined.120,121 The ester that was obtained was reduced (by zinc dust) to α-

Addition of hydrogen sulphide to limonene was shown to give (+)-1,8-epithio-cis-p-menthane (39) by radical cyclization.120 The acid-catalysed addition of thiophenol to limonene yields 10% of 8-phenylthiomenthene-1-ene (38) but it is 31% of the latter above 82%, and Fourneron et al. preferred to protect the double bond at C-1 of (+)-limonene by treating it with N-bromosuccinimide in

The addition of halogens to limonene has been known since the time of Wallach.131 Addition of chlorine to limonene is a two-stage process,133 but the rate slows well before the first mole has been added, and a mixture of the dibromide (46), two tetrabromides, and some other compounds were identified, but no dibromide arising from addition only to the C(7tC(8) double bond,131 Limonene tetrabromide' has long been used as a crystalline derivative of limonene (cf. Mosher135), and Carman and Venzke showed that the crude bromination mixture consisted of 70% of a crystalline tetrabromide and 30% of another tetrabromide which was only if (+)-limonene was used but crystalline if the racemate was used. At first, they considered the crystalline tetrabromide from (+)-limonene to have the (8S)-configuration,135 but X-ray crystallography showed it to be the (8R)-isomer (47).136 A related dichlorodibromide (48), which was made135 by partial debromination of racemic limonene tetrabromide followed by chlorination of the double bond, was shown similarly to have the same configuration.136

Somewhat similar to halogenation is the addition of iodine azide to both double bonds of (+)-limonene.137

Addition of benzzenesulphonyl chloride to limonene also occurs across both double bonds,138 one mole adds 70% to the C(8)-C(9) double bond and the main isomers of the double addition are (49) and (50).139

The formation of volatile sulphides from the reaction of sulphur with limonene was noted by Nakatsuchi in 1930,140 but it was only in 1959 that Weitkamp deduced the formulae (51)−(54) and discussed the possible mechanism of their formation.141 Weitkamp's major product (54) is isomeric with one of the compounds (39) that were described by Demole and Enggist (see above).142 Actually, Weitkamp had also obtained this isomer (39), mixed with (54), by catalytic reduction of (53).143 These products must have been the main components of a mixture that had earlier been patented as a flotation agent.144 More recently, refluxing limonene with sulphur for two hours was shown to give a complex mixture consisting of ten hydrocarbons and 22 sulphur-containing aromatic and terpenyl compounds. The mass spectra of these substances were taken, and proposals of several new structures were made, including the trisulphide (55),145 but it would be desirable to have further proof. Sulphurized limonene has been patented by oil companies as an additive in lubricating and oxidation-resistant oils.146

The reaction of diphenyl diselenide with hydrogen peroxide gives phenylenezelenic acid, 'PhSeOH', which adds to limonene to yield oxabicyclic selenium compounds (56), reduction of which (by tributyltin hydride) leads to 1,8-cineole (26) in high yield.147

4 Addition of Halogens, Sulphur, etc.

The addition of halogens to limonene has been known since the time of Wallach.131 Addition of chlorine or bromine to limonene in the presence of zinc chloride [which yielded (41)] before acid-catalysed addition of methanol [which yielded (42)]. The acid-catalysed addition of isocyanic acid in the presence of H2SO4 gives phenyl isocyanate.130

Addition of nitric acid to limonene has been studied in the USSR,131 but the publication was not available to us.

Addition of hydrogen sulphide to limonene was shown to give (+)-1,8-epithio-cis-p-menthane (39) by radical cyclization.120 The acid-catalysed addition of thiophenol to limonene yields 10% of 8-phenylthiomenthene-1-ene (38) but it is 31% of the latter above 82%, and Fourneron et al. preferred to protect the double bond at C-1 of (+)-limonene by treating it with N-bromosuccinimide in methanol [which yielded (41)] before acid-catalysed addition of thiophenol and removal of the protecting groups (using zinc and acetic acid) to obtain (−)-(40),127 which they required for a synthesis of car-2-ene (42).

Di(p-tolyl)methyl chloride adds to one double bond of limonene in the presence of zinc chloride (to the double bonds at C-8 and C-1 in the ratio of 2:5:1).128

In three hours, at 55 °C, hydrogen cyanide in 55% sulphuric acid also adds to both double bonds of limonene. From the product (43), 1,8-di-isocyanomenthane was prepared by using phosgene, rearrangement of the isocyanomethanes to 1,8-dicyanomenthane taking place with o-dichlorobenzene at 25 °C. The stereochemy of the products was not discussed.129 The addition of isocyanic acid in the presence of BF3·OEt2 gave only α-terpinyl isocyanate.130

5 Hydrogenation of Limonene

The first catalytic hydrogenations of limonene, which were carried out by Sabatier and Senderens at the turn of the
cymene, occurs in two stages; initially 52-53\% platinum on charcoal as catalyst. The dehydrogenation to menthane (58) has been known since 1924, with palladium or charcoal at 220-230°C, and catalytic reduction generally gives preferentially the cis-isomer. The readiness of hydrogenation more than dehydrogenation (ZrO, and ThO,) led to the discovery of many methods that give high yields of menth-1-ene, for example sodium borohydride and platinum salts (98\% yield) or nickel chloride and polyvinylpyrrolidone with hydrogen. A catalyst that contained neodymium and a silane gave menthene after 1.5 hours and a complex that contained rhodium trichloride and triphenylphosphine which was used as a catalyst in water give menthene after 32 hours and menthane after 76 hours. For preparative purposes, Newhall has confirmed the utility of Vavon’s platinum catalyst rather than palladium or copper for menth-1-ene, and we have found that a small amount of Raney nickel is adequate to give over 90\% of (57). The configuration of the fully reduced menthanes (58) has been well established, and catalytic reduction generally gives preferentially the trans-isomer, but catalytic amounts of cob(1)alamin in aqueous acetic acid give nearly 70\% of the cis-isomer. The readiness of double-bond rearrangement in limonene during reduction has been exploited by using hydrogenation over a deactivated palladium catalyst; this yielded a mixture from which menth-3-ene (59) could be isolated, the unchanged limonene being recycled (racemization was not mentioned, but we can suppose that it to have occurred). The reason for this rearrangement–hydrogenation was to make menthene ([\pm]-60) from the epoxide of (59).

Most of the catalytic reductions that have been mentioned yield optically active menthene, but reducing conditions involving isomerization are known. Thus menth-1-ene slowly racemizes when heated in toluene with sodium and o-chlorotoluene because of the reversible reaction that occurs between menth-1-ene (57) and menth-3-ene (59), the equilibrium mixture containing 63\% of the latter [together with 5\% of menth-4(8)-ene (61)].

Dehydrogenation of limonene to p-cymene is reported to occur best over a catalyst of PdO and sulphur on active charcoal at 220—230 °C, giving 97\% yield of p-cymene (13) in 96\% purity. A small scale, iodine yields 65\% of p-cymene.

The disproportionation of limonene to p-cymene (13) and menthene (58) has been known since 1924, with palladium or platinum on charcoal as catalyst. The dehydrogenation occurs in two stages; initially 52—53\% of p-cymene is formed, together with 40—42\% of menth-8-enes (62). Longer reaction times lead to the menthanes; with mesityl oxide as the hydrogen acceptor, yields of up to 94\% of p-cymene can be obtained. The hydrogen that is available from limonene has also been used in the hydrogenation of double bonds and of nitriles to methyl groups (both with palladium on charcoal as catalyst) and, by adding ferric chloride to the same catalyst, of carbonyl groups to hydrocarbons.

Reductions of limonene other than catalytic ones have not been used; Sewell showed in 1904 that sodium in alcohol was without action. Reduction of limonene via hydroboration is mentioned below.

### 6 Hydroboration and Related Reactions

The first attempted monoaddition of diborane to limonene resulted in a statistical mixture of the diols (63). Using disiamylborane, Brown showed how menth-1-en-9-ol (64) was obtained in 79\% yield after oxidation, similar results having been obtained with aluminium alkyls. Brown did not mention the stereoisomerism at C-8 of (64), which was pointed out by Albaigés et al. Using the addition of di-isobutylaluminium hydride to (+)-limonene followed by aerial oxidation, Ohloff et al. described the stereochemistry of the isomers of (64) and the corresponding aldehydes (65), a diastereoisomeric mixture of which occurs in Bulgarian rose oil. X-Ray crystallography of the (1R,3R,4S,8R)-isomer of the diols (66) and of the (4R,8R)-isomer of menth-1-en-9-ol (64) established the stereochemistry of each of them. More recently it was reported that boron dihydrogen chloride gave 81\% of the alcohols, although thexy! lron hydrogen chloride seems to be more stereoselective, and oxidation of the menth-1-en-9-yl-borane that was obtained with the latter gave 68\% of menth-1-en-9-als directly. Direct reductive alumination of limonene with aluminium and hydrogen in hexane at 160 °C and then aerial oxidation leads to (64). Some methods of reduction of limonene, involving boron and cobalt compounds and then an acid, have been described, but treatment of the adduct of
disiamylborane and limonene with acetic acid at 100 °C gives completely racemized menth-l-ene.\textsuperscript{184} A preliminary note by Brown and Pfaffenberger in 1967\textsuperscript{185} was followed by a rather different full paper in 1975\textsuperscript{186} in which the preparation of the cyclic boron compounds (67) and (68) is described. The diols (69) were obtained from (67) (the stereochemistry at C-8 again not being specified) while 83% of lR,2R,4R)-carvornenthol (70) was obtained from (68), this being the most efficient way of making a single carvomenthol from limonene. Hydroboration of (+)-limonene with BH\textsubscript{4}-H\textsubscript{2}OEt and then reduction with lithium aluminium hydride gives a borane (71) that is said to be useful for asymmetric induction in the hydroboration of alkenes.\textsuperscript{186} Acetoxyborohydride is made from NaBH\textsubscript{4} and Hg(OAc)\textsubscript{2} in tetrahydrofuran.\textsuperscript{187} This reagent hydroborates limonene on the double bond at C-1, then treatment with hydrogen peroxide yields dihydrocarveol (72) (stereochemistry unspecified) and iodoine yields 2-isodimethyl-8-ene (73).\textsuperscript{188}

Hydroboration can be used on functionalized limonenes such as the epoxides,\textsuperscript{189} and the alcohol (64) can be converted into the corresponding chloride with CCl\textsubscript{4} and Ph\textsubscript{3}P,\textsuperscript{190} leading to a wide variety of synthetic routes.

(+)-Limonene has been silylated to (74) with triethoxysilane at 80 °C and a catalytic amount of platinum on charcoal. The product was patented as a waterproofing agent for concrete.\textsuperscript{191}

\section*{7 Oxidation (except Epoxide Formation)}

Since 1914 it has been known\textsuperscript{192} that limonene is very sensitive to air or oxygen, rapidly acquiring a high peroxide number, and it has been used as an antioxidant.\textsuperscript{193} The peroxides are slowly converted into other substances under various conditions (this oxidation is partly responsible for the 'off-flavour' of aged citrus oils). A full explanation has been given by Schenck \textit{et al.}\textsuperscript{194} The effect of an acid on the hydroperoxides was noticed by Bain,\textsuperscript{185, 186} and we have noticed that the rise in temperature that often occurs when limonene is hydrated under mild conditions (weak aqueous acid in organic solvent) is due to the presence of hydroperoxides.\textsuperscript{197} Autoxidation is not stereospecific, racemic alcohols being formed after reduction of the hydroperoxides (cis:trans = ca. 1:1) and racemized through the intermediacy of the radical (e). Decomposition of the hydroperoxides with heavy-metal catalysts can alter the distribution of the products (after reduction) between carvone ([+]-(-75)] and the menthadienol (76), which has predominantly cis hydroxyl and isopropenyl groups.\textsuperscript{199} There are many patents and papers concerning such reactions (with Co, Mn, and Ni compounds).\textsuperscript{198} The products that were formed by leaving a drum of limonene open in Australian sunlight included a trace of perilla alcohol (77).\textsuperscript{199} and heating a solution of limonene in dimethyl sulphoxide at 100 °C in air for 48 hours is reported to give 95% of 4-methylacetophenone, \textit{via} dimethylstyrene (78),\textsuperscript{200} whereas, in dimethylformamide or hexamethylphosphoric triamide as the solvent, cymenol (79) is the main product.\textsuperscript{201} Autoxidation in the presence of ammonia ('ammoniation') yields a complex mixture of terpene hydrocarbons, pulegone (80), and, more interestingly, some trimethylpyridines, including the 2,3,6-isomer.\textsuperscript{202}

Dye-sensitized photo-oxygenation (by \textit{O}2) of limonene leads to hydroperoxides, the stereoisomers of which have been separated and characterized.\textsuperscript{203} The reduction products of the latter are stereoisomers of the menthadienols (76), (81), and (82), but, in contrast to the autoxidation, the alcohols with \textit{cis} hydroxyl and isopropenyl groups are predominant, particularly (76), and they are optically active.\textsuperscript{204} Improvements (of the lamp or by supporting the Rose Bengal catalyst on magnesium oxide) have been claimed.\textsuperscript{205} Reaction rates have been determined.\textsuperscript{206} Uranyl-acetate-catalysed photochemical oxidation of limonene leads to a hydroperoxide (83), hydrogenation of which (over Pd) gives the \textit{trans}-menthane-\textit{trans}-1,2-diol (84).\textsuperscript{207} Catalysis of the photo-oxidation of menth-1-ene with ferric chloride, which has not been reported with limonene, gives 38% of ring-opened products.\textsuperscript{208}

Oxidations that are supposed to permit greater selectivity, especially for avoiding racemization via the radical (e), include the use of \textit{t}-butyl peracetate or perbenzoate in the presence of cuprous bromide. The \textit{cis}-carveol (82) and the \textit{trans}-carveol (85; R = H), which are obtainable from (+)-limonene, were then converted into (-)-carvone (75).\textsuperscript{209} Wacker conditions of oxidation (air and copper chloride, with a catalytic amount of palladium chloride in acetic acid) give a highly stereoselective oxidation to \textit{trans}-carveyl acetate (85; R = Ac) in 63% yield.\textsuperscript{210} PdCl(NO\textsubscript{3})(MeCN)\textsubscript{2} being without catalytic action.\textsuperscript{211}

The oldest method of converting limonene into carvone is through the nitroso-chlorides (86), which were first made by Tilden from gaseous nitrosyl chloride,\textsuperscript{212} this preparation being improved by Wallach by using an alkyl nitrite and HCl.\textsuperscript{213} The action of base then gave carvone oxime,\textsuperscript{214} from which carvone was obtained by the action of an acid. This route is both industri\textsuperscript{215} and academic, there being an undergraduate experiment for making carvone from orange peel.\textsuperscript{216} There are variants, using nitrosylsulphuric acid,\textsuperscript{217} dinitrophenyl tetroxide in formic acid,\textsuperscript{218} and so forth.

Direct allylic oxidation has been carried out with \textit{t}-butyl chromate, this giving 21% of carvone (75) and 13% of isopiperitenone (87),\textsuperscript{219} with the CrO\textsubscript{3}-pyridine complex, to give 36% of (75) and 31% of (87),\textsuperscript{220} with \textit{t}-butyl hydroperoxide and hexacarbonylchromium, to give net yields of 39% of (75) and 28.5% of (87) (with 47.7% of the limonene being recovered),\textsuperscript{221} and with pyridinium chlorochromate, to give (75) and (87) in the ratio of 2:1.\textsuperscript{222} Pyridinium dichromate and
t-butyl hydroperoxide in the presence of Celite is reported to give a 48\% conversion and 23\% yield of piperitenone (88), but the \( ^1H \) n.m.r. figures that are given\(^{224}\) correspond neither to piperitenone (88) nor to isopiperitenone (87). It should be noted that (88) is readily prepared by oxidation by dichromate ion of the major product (76) from the photo-oxidation of limonene.\(^{224}\)

The first experiments on the electrochemical oxidation of limonene concerned the experimental technique, but no products were isolated.\(^{224}\) Later it was suggested that, in an aqueous medium, hydration occurred before oxidation.\(^{226}\) In methanol, a mixture was obtained, mostly of allyl methyl ethers;\(^{226}\) \( \alpha \)-terpineol (21) and one of the carbonyl-containing products have been analysed.\(^{227}\) Later it was suggested that, in an aqueous medium, hydration occurred before oxidation.\(^{225}\) In methanol, a mixture was obtained, mostly of allyl methyl ethers;\(^{226}\) \( \alpha \)-terpineol (21; \( R = H \)) and trans-carveol (85; \( R = H \)) have also been reported.\(^{228}\) On a graphite electrode, in \( \text{NaClO}_4 \), the major products from (\(+\))-limonene are (\(-\))-dihydrocarvone (89) and the trans-diol (90); both antipodes of limonene were examined.\(^{228}\)

The cis-hydroxylating oxidant potassium permanganate yields the tetraol ‘limonite’ (91) (m. pt 192 °C),\(^{229}\) which was also obtained with hydrogen peroxide and catalytic amounts of osmium tetroxide.\(^{230}\) The 1,2-diol that is obtained by the reaction of limonene in acetic acid\(^{231}\) arises by a different mechanism from ring-opening of the epoxide (see below).

The first work on the oxidation of limonene by selenium dioxide contained no spectral data,\(^{232}\) and Sakuda\(^{233}\) and one of us\(^{234}\) showed that the main product from the reaction in ethanol is racemic mentha-1,8-dien-4-ol (92), together with a certain amount of mentha-1,8(10)-dien-9-ol (18) and optically active trans-carveol (85; \( R = H \)). The isolation of supposedly optically active mentha-1,8-dien-4-ol has been described in later papers, one using the same method,\(^{235}\) the other using \( \text{H}_2\text{O}_2 \) and catalytic \( \text{SeO}_2 \).\(^{236}\) This reaction also being described elsewhere.\(^{237}\) Sharpless confirmed our work, and showed that the spurious optical activity was due to impurities.\(^{238}\) The reaction is indeed complex (Sharpless mentions 27 products, and the carbonyl-containing products have been analysed\(^{239}\), but the main product is always (92). Oxidation by selenium dioxide in acetic acid takes a different course, leading mainly to carveyl acetate \([\text{trans} (85; R = \text{Ac})/\text{cis} = 4:1 ; 40\%]\), the acetate of (93) [60\%].

Oxidation of limonene by lead tetra-acetate is useful for making optically active derivatives of mentha-1,8(10)-dien-9-ol (18) from the initial product (94) of the reaction\(^{231}\) (cf. the preparation of lanceol\(^{240}\)), although it was first carried out on the racemate.\(^{241}\) Although the limonene anion (c) makes this reaction apparently redundant, it was still used to make the aldehydes (65) in 1979.\(^{241}\)

Oxidation by manganese(\( \text{III} \)) acetate is discussed in Section 10.

The oxidation of limonene by mercuric acetate in acetic acid leads to a small amount of hydrocarbons (including mentha-1,4,8-triene and p-cymene) and to mentha-1,4(8)-dien-9-yl acetate (95) and trans-carveyl acetate (85; \( R = \text{Ac} \)). Under different conditions (and after reduction with \( \text{NaBH}_4 \)), \( \alpha \)-terpineol (21; \( R = H \)) and \( \beta \)-terpineol (22) were obtained, the terpins (24; \( X = \text{H} \)) also having been reported\(^{242}\) (although the authors did not seem to appreciate the instability of these on gas chromatography).

Oxidation of limonene by thallium(\( \text{III} \)) nitrate is one of the few routes from it to the bicyclo[3.2.1]octane structure (another is mentioned in Section 8, under the 8,9-epoxide). In methanol, 81\% of the limonene was converted into a mixture of stereoisomers of (96) and (97) (1:4), 19\% of the products being unidentified.\(^{243}\)

Early work on the oxidation of limonene by chromyl chloride mentioned a number of products,\(^{244}\) but later work led only to a small amount of dihydrocarvone (89).\(^{245}\)

When passed over vanadium pentoxide on pumice at 425 °C, limonene yields maleic anhydride.\(^{246}\)

The action of \( \text{N} \)-bromosuccinimide on limonene should lead to allylic bromination; the first study reported unstable brominated products, which were converted in 80\% yield into \( p \)-cymene (13) by KOH in MeOH.\(^{246}\) It is likely that the major brominated product is indeed the expected one (98; \( X = \text{Br} \)). Taher and Retamar having converted limonene into carveol by this route; they used aqueous KOH in dioxane for the hydrolysis.\(^{245}\) The action of \( t \)-butyl hypochlorite appears to be cleaner; the production of (\(-\))-trans-carveyl chloride (98; \( X = \text{Cl} \)) has been optimized\(^{246}\) and the latter converted into carveyl esters with zinc carboxylates.\(^{246}\)
Early work on the ozonolysis of limonene was restricted to the possible identification of some (methyloxycyclohexenyl) acetic acids,254 a diozonide was also reported.255 The reaction occurs very rapidly.264 The study of partial ozonolysis seems to date only from 1956, the aldehyde (99) and the corresponding acid being identified after oxidative decomposition (by CrO$_3$) of the ozonide (with a small amount of 4-methylcyclohex-3- enyl methyl ketone, from ozonolysis of the isopropenyl group).257 The aldehyde (100) was mentioned (without its properties), but it was only compared with a degradation product from cembrene.254 The isolation of the C$_4$ acid, after reduction and then esterification to (101), rather than a C$_4$ acid of the early work was also claimed.264 The cyclization of the aldehyde (99) to an aldehyde (102) was also reported259 and a ketone (103) was studied by Wolinsky [who made (99) from limonene epoxide].285 The optical activity of saturated (99) has been used in further syntheses.277 Mono-ozonolysis has been exploited by a Polish group,285 who have also shown that electrochemical reduction of the ozonide of (+)-limonene leads to the optically active alcohol (104), the latter cyclizing to the tetrahydrofuran (105) in acid.286,288 See also the description of the cyclization of (99) to a cyclopentanone (106) with a rhodium chloride catalyst.284

8 The Limonene Epoxides

Direct oxidation of limonene with perbenzoic acid was first described by Prileshajew;287 peracetic acid was later used on (-)-limonene,288 but only in 1957 on the (+)-isomer.289 These and other oxidations with peracids lead to nearly 1:1 mixtures of the cis- and trans-1,2-epoxides (107) and (108) or (in an early case, when H$_2$O$_2$ in acetic acid was used) to the menth-8-ene-1,2-diols.281 The cis-epoxide (107) was prepared stereospecifically by Polish workers, who used the monotosylate of the 1,2-diol,270 and a full investigation of the two isomers was made by Newhall.211 Oxidation by a peracid gives about 10% of the 8,9-epoxides (see below),270 and various other methods slightly alter this proportion. For example, epoxidation of limonene with sodium hypochlorite in the presence of a manganese(III) porphyrin gives a ratio of 7:1 of 1,2-epoxides to 8,9-epoxides,273 and tosodosobenzene with an iron porphyrin (which is more electrophilic than manganese) gives a ratio of nearly 20:1.270 Molybdenum-hexacarbonyl-catalysed t-amyl hydroperoxide yielded 70% of the cis-isomer (107),270 this work having been repeated in order to prepare the menthadienol (76) and the trans-isomer of (81) via the selenoxides (109) and (110)279 (the latter had been briefly mentioned independently elsewhere).270

A 1:1 mixture of (107) and (108) can be obtained from limonene, in 60% yield, with pertungstate-catalysed hydrogen peroxide277 and in 87% yield by the action of superoxide anion (potassium superoxide and o- or p-nitrobenzenesulphonyl chloride) on limonene.279

Although the isomers (107) and (108) can be separated by careful distillation,270 details of several chemical methods have been published. One involved their conversion into the chlorohydrins (111) and (112) with HCl in ether; only (112) [from the trans-epoxide (108)] gives a crystalline p-nitrobenzoate. After separation, KOH in MeOH enabled the pure epoxides to be recovered.290 The greater reactivity of the cis-epoxide towards acids means that this isomer will give trans-dihydrocarvone (89) before the trans-epoxide begins to react, and the latter can then be isolated by fractional distillation.284 The cis-isomer (107) also reacts more rapidly with bromine; treatment of the bromides (113) that were obtained from the epoxide mixture by its reaction with tributyltin hydride gives 1,8-cineole (26) and the trans-epoxide (108).292 The products from treatment of the epoxide mixture with dimethylamine, which were the amino-alcohols (114) and (115), can be readily separated, and the methiodides then yield the pure epoxides with potassium hydroxide.285

The presence of the limonene 8,9-epoxides (116) and (117) among the epoxidation products was suspected as early as 1926,284 but they were in fact only described in 1961 as arising from the oxidation of limonene by air.194 They were later prepared295 by using the Payne epoxidation (H$_2$O$_2$ and PhCN), 40–50% of the epoxidation then occurring in the isopropenyl group, although the conversion is very low. An alternative synthesis from methyl 4-methylcyclohex-3- enyl ketone and dimethylsulphonium methyldide265 has been preferred.186 Methyl 4-methylcyclohex-3-enyl ketone is usually made from isoprene and methyl vinyl ketone, and is racemic, but it can also be prepared from limonene in optically active form (by ozonolysis of limonene 1,2-epoxides and removal of the epoxides after separation of the isomers).264 The two 8,9-epoxides can be separated by careful distillation, and they were assigned configuration by Horeau’s method and correlated with the uroterpenols (limonene metabolites) (118) and (119) by Kergomard and Veschambre.288 Kergomard also converted the uroterpenols into the optically active 3-bisabolols [e.g. (120) from (+)-limonene],289 but there was a discrepancy between the stereochemistries of these and the stereochemistry of bisabolols that had been made in another way.266 An X-ray study showed that the configuration of the bisabolol was not that attributed to it by Kergomard.291 A careful study by Carman has now shown that Kergomard’s assignments of the stereochemistries for the uroterpenols (118) and (119) are correct (as are, therefore, the stereochemistries of the epoxides). The mixture of uroterpenols is not separable, and neither are the dibromides of the uroterpenol dibromides were separable, and X-ray crystallography of the recovered uroterpenols showed clearly that the lower-melting isomer has the stereochemistry (118).292 Carman also showed that the higher-boiling (4R,8R)-isomer of the epoxide (116) was converted into (118) by tetramethylammonium hydroxide in dimethyl sulphoxide in 36 hours at 35–40 °C, the other epoxide (117) yielding (119) under
the same conditions. The bisabolol discrepancy remains unexplained.

The 8,9-epoxides have been used as intermediates in the conversion of limonene into the bicyclo[3.2.1]octane system. Thermal rearrangement of the 8,9-epoxides to the menth-1-en-9-als (65) was described in 1961, and this reaction also occurs with acid ion-exchange resins, the reaction going further to yield optically active 2,6-exo-dimethylbicyclo[3.2.1]oct-2-en-7-endo-ol (121) as the major product together with a little of the 6-endo-methyl isomer. The racemate of (121) had already been prepared from geranyl acetate.

The mixture of the four possible diepoxides has been known as long as the 1,2-epoxides. Little work was carried out until 1955, when it was again described, and from 1956 onwards there are many patents describing the polymerization of 'limonene diepoxide' with Friedel–Crafts catalysts or photosensitized cationic polymerization. Although this is a major use of limonene, there exists no description of the individual isomers of the diepoxides (122) and they have only one Chemical Abstracts Service Registry Number. The 1,2-epoxide group is more reactive towards acid than the 8,9-epoxide group, and the epoxides of (111) and (112) have been obtained by treating the mixture of the diepoxides (122) with hydrochloric acid under mild conditions. When the diepoxides are used in synthesis, the mixture is employed without comment (e.g. the synthesis of hernandulcin by Mori and Kato).

The alcohol (124; R = H) was oxidized by Suga and Watanabe. The corresponding dihydrogenated aldehyde (127) is the main product from hydroformylation of limonene, which was first carried out over Raney cobalt. In methanol (using octacarbonylcobalt as catalyst), the main product is the saturated methyl ether (128), and the aldehydes (129) were reported from the reaction in acetone, although we question this structure. Later, rhodium catalysts, notably RhH(CO)(PPh3), were used, and the rate of reaction of limonene was shown to be rather low compared to those of other alkenes, although the yields were good. After the initial patenting of (127), other patents followed. Phosphite-modified rhodium catalysts increase the rate of hydroformylation of limonene. Esters of the acid corresponding to (127) and a Mannich product (130) have been made.
Although the Vilsmeier reaction of [CICH=\(\text{NMe}_2\)]\([\text{Cl}_2\text{PO}_2\]) with (+)-limonene gives a yield of only 40% after 6 days, it is very useful in that the (E)/(Z) ratio of the aldehydes (131; \(R = H\)) that are formed is 98:2; this fact led Dauphin to a rapid synthesis of (E)-atlantone (132). An earlier synthesis of (131; \(R = H\)) was a multi-step one from methyl vinyl ketone. The isomers of (131; \(R = H\)) have been patented as flavour materials.

Delay and Ohloff used the anion (c) for adding one carbon atom to (+)- or to (-)-limonene. Carbonation gives the \(\beta\)-unsaturated ester (133; \(R = \text{OMe}\)). The corresponding ester is isomerized (by MeONa in MeOH) to the thermodynamic mixture of the conjugated esters (131; \(R = \text{OMe}\)) [(E)/(Z) = 82:18]. After separation, these were used in the synthesis of \(\alpha\)-bisabolones (134) of known stereochemistry.

Carbon tetrachloride reacts with limonene either in the presence of a peroxide or under the influence of ultraviolet light to yield an addition product (135), hydrolysis of which (by ethanolic KOH) leads to the optically active acid (131) \(R = \text{OH}\). This was also used for synthesizing (\(R, E\))-atlantone from (+)-limonene. Distillation of (135) in ethylene glycol (at 200–210 °C) gives methyl 4-methylcyclohex-3-enyl ketone.

Carbon oxysulphide reacts with limonene in a dimethyl- or diethyl-aluminium-catalysed ene reaction to give (136) that had been formed by reaction with the trisubstituted stilbene (137) distilled with the limonene that was recovered, thereby lowering the observed optical rotation. This preference for reaction on the exocyclic double bond is the contrary of that found in 4-vinylcyclohexene, where 81% of the monoaddition takes place on the endocyclic double bond.

Addition of dihalocarbenes is difficult to stop at the stage of monoaddition unless phase-transfer conditions are employed. The products vary with the catalyst: PhCH\(_2\)NEt\(_2\)-Cl gives the diaddition products (140), as does Me\(_2\)NC\(_6\)H\(_4\)-Br. The more hydrophobic Me\(_2\)N\(^+\)CF\(_3\)Cl yielding specifically monoaddition products, (139) being obtained in 68% yield. 1,4-Diazabicyclo[2.2.2]octane leads to 100% of monoaddition.

10 Addition of \(C_2\) or More to Limonene

Acetylation of limonene with acetyl chloride in the presence of stannic chloride at −100 °C was examined by Cookson et al. in 1974. After dehydrochlorination of the product (using LiF and Li\(_2\)CO\(_3\)) they obtained about 30% of the product (141) from reaction at the isopropenyl double bond, with 22% of the unconjugated ketone (142) and 28% of the conjugated ketone (143) that had been formed by reaction with the trisubstituted double bond. With senecioyl chloride (3-methylbut-2-enoyl chloride), the same group synthesized \(\alpha\)-atlantone (132) after dehydrochlorination, about 60% of the reaction occurring in the isopropenyl group against 29% in the ring.

The acetylation was confirmed by Hoffmann, who did not, however, mention Cookson. Acetylation on C-10 can be effected by trapping the limonene anion (c) with trimethyltin. The stannane (144) will then react with acetyl chloride to yield (133; \(R = \text{Me}\)) or with senecioyl chloride to give a ratio of 25:75 of \(\alpha\)-atlantone and the direct coupling product (\(\beta\)-atlantone).

Ermann et al. converted the anion (c) into the alcohol (145) by allowing it to react with ethylene oxide, and into a variety of sesquiterpenes (146) by its reaction with the appropriate alkyl halides RX. The anion (c) was again used for the synthesis of sesquiterpenes; its reaction with a functionalized isoprene (147) added a C\(_5\) unit, giving (148), which is an intermediate in the synthesis of lanceol (146; \(R = \text{CH}_3\text{CH}═\text{CMMeCH}_2\text{OH}\)).

Oxidation of limonene by manganese(III) acetate in acetic acid results in radical addition, giving the acid (149), in 38% yield, and the lactone (150). Despite this relatively good yield, the reported overall yield of the alcohol (145) was only 8%. Gardrat converted (149) into (150) directly by the action of formic acid, in 43% isolated yield from limonene.

The isopropenyl group of limonene reacts in an ene reaction...
with methyl acrylate if aluminium chloride is present as a catalyst; the major product is the ester (151), with a small amount of double-bond-rearranged material (152). This work described the preparation of $\beta$-bisabolene (153) from (151). A similar reaction, using methyl vinyl ketone, yielded the ketone (154), which was also converted into $\beta$-bisabolene (153), but this reaction is difficult to reproduce and unsatisfactory in its application. The corresponding reaction with propargylates is more successful, methyl propargylate in the presence of aluminium chloride giving 39% of the ester (155) with smaller amounts of the two esters (156). Snider has also described the Me$_2$AlCl-catalysed addition of aldehydes. In place of a carbon-carbon double bond, a carbon-oxygen double bond has been used; thus diethyl oxomalonate reacts with limonene in the presence of zinc chloride to give the diester (157) in one week.

Benzylene reacts with limonene in an ene reaction to give the phenyl-substituted menthadienes (158) and (159); these might be optically active, because the symmetrical radical is probably not involved, but, while a very small optical activity was determined in the corresponding reaction with menth-1-ene, it was not measured in the case of limonene. The reaction of 1,2,4-triazoline-3,5-dione with limonene leads to a double adduct, the structure of which was reported as (160); this supposedly arises in a type of ene reaction, the initial attack on the isopropenyl double bond and transfer of the proton at C-4 being followed by a second addition on the C(4)--C(8) double bond. Unfortunately, the published n.m.r. spectrum does not include the signals for the vinyl protons, and it is not clear why a mechanism like that proposed by Mehta and Singh for the benzylene reaction was not considered; this would lead to (161).

This type of reaction is always complicated by the tendency of limonene to polymerize in the presence of Lewis acids or Ziegler catalysts (see above), which is the reason for using low temperatures in the reactions. The ene reaction between limonene and chloral (or bromal) nevertheless gives mostly unrearranged product (162) in the presence of aluminium chloride, although the yield is rather low. In the presence of acids, the tendency to rearrangement of the double bond has to be considered, as well as the addition of water in aqueous milieu.

Despite these problems, Julia and co-workers realized the extremely simple addition of dimethylvinylcarbinol to limonene in formic acid and methylene chloride. They prepared the four isomers of $\alpha$-bisabolol (120) ($\left(+\right)$-$\alpha$-bisabolol from (164) and isomers of the ring-substituted alcohol (163).

The Ritter reaction of (162) in the presence of acetonitrile and dilute perchloric acid gives the chiral iminium salt (164). The racemate of (164) is similarly obtained from terpinolene (8), while $\left(-\right)$-$\beta$-pinene (165) yields the enantiomer. The same reaction, if carried out on $\alpha$-terpineol (21) ($R = H$) with propionitrile, is said to yield a product with the enantiomeric stereochemistry at what was C-1 of the menthene skeleton. An interesting photochemical addition of acetylacetone to (162) has been described by a Brazilian group. The major product (167) (for which full spectral data were given) was used to prepare octalones. It would appear that they were hoping to prepare the eudesmane skeleton, although it was formed, the major isomers that were produced were the cis- and the trans-isomer of (168).

A reaction that has given rise to some discussion is that between limonene and maleic anhydride. Hultzsch reported in 1939 that, with maleic acid, limonene underwent rearrangement to $\alpha$-terpinene (9), which then gave a Diels-Alder product. He also reported a different reaction with maleic anhydride, which
conceivably, the product that Hultzsch obtained was an anhydride of uncertain structure. Alder and Schmitz re-investigated the reaction, but apparently did not obtain the same anhydride. Further re-investigation by Eschinazi and Pines led to the conclusion that limonene did not react with maleic anhydride under the conditions that were used by Hultzsch (i.e., simple heating). Radical cyclo-copolymerization of limonene with maleic anhydride is well known, and probable intermediates are shown in Scheme 2; conceivably, the product that Hultzsch obtained was an anhydride, derived from one of these.

11 Pyrolysis and Miscellaneous Reactions

The pyrolysis of limonene (1) has been known since 1884 to yield primarily isoprene at "just below red heat". Indeed, this was the best way of preparing isoprene for many years. Pines and Ryer made the first serious mechanistic study, and correctly deduced that the main reaction pathway was via allo-ocimene (169), which, at somewhat lower temperatures than those that were required for a good yield of isoprene, then yielded a mixture of products similar to those obtained after the pyrolysis of α-pinene (2) (Scheme 3). The whole problem was re-investigated by Cocker et al., who characterized a vast number of substances in a mixture that was very similar to that obtained from the pyrolysis of pinene. The pyrones (170) and (171) are present, and, under the conditions that were used, the Irish group found up to 25% of compound (172). There are descriptions of a number of addition reactions with metals scattered about the older literature, but mostly nothing definite was identified. We might, however, mention the reaction with antimony trichloride and some colour reactions with phosphomolybdic acid (pink or red-orange, depending on the conditions).

With pentacarbonyliron, limonene forms mixtures of diene-Fe(CO)₅ compounds, the dienes being isomers of the starting material. The reaction of limonene(ricarbonyl)iron with aryl-lithium derivatives has been described. A new method for the addition of alkyl groups to the terminal isopropenyl group of limonene consists in the radical addition of methanesulphonyl iodide and elimination, to form the methyl sulphone (173). Deprotonation (by butyl-lithium) and alkylation, for example with prenyl bromide, leads to the C-C-coupled product (174). The sulphonyl group is removed from (174) by acetylating the anion to the β-oxosulphone (175), which is reduced by aluminium amalgam to the allylic sulphinic acid. This loses SO₃ in situ, giving a regiospecifically defined alkene product. The (E)- and (Z)-α-bisabolenes (134) were made in this way.

12 Biological Reactions of Limonene

It is not the intention of this article to discuss the biogenesis of limonene (leading references are given in a note about the use of natural-abundance deuterium n.m.r. spectrometry to establish the difference between C-9 and C-10 during biogenesis), nor do we deal in detail with its metabolic fate [although the uroterpenols (118) and (119), which are the products of its mammalian metabolism, are mentioned above, and are known to play a central role in the biogenesis of other monoterpenoids, notably the 7-oxygenated menthanes of Perilla frutescens]. Nevertheless, certain microbial reactions lead to possibly useful routes to optically active oxygenated menthanes.

Pioneering work on the transformation of limonene by Aspergillus niger was made by Bhattacharyya et al., who obtained (+)-cis-carveol (82), carvone (75), α-terpineol (21; R = H), and p-mentha-2,8-dien-1-ol (76). Later, Dhavalikar isolated a strain of a member of the Enterobacteriaceae which oxidized (+)-limonene to perilllic acid (5) and a dihydro-acid. This led to the definition of three pathways for the metabolism of limonene: these are allyl oxidation, leading to carveol or to the perilla series (the latter is the main pathway), epoxidation, and rearrangement to dihydrocarvone. Complete degradation by Pseudomonas PL-strain in the presence of arsenite gave a variety of ring-opened products, and ultimately 2-methylproponic acid, for which a mechanism was proposed. A patent covers the efficient conversion of limonene into carvone by Corynebacterium hydrocarbolectasia, which was isolated from soil.

Limonene undergoes microbial hydroxylation with Chrynomona casticola, giving 80% of the trans-1,2-diol fromo (+)-limonene and 76% of (90) from (−)-limonene. Other micro-organisms (members of the genera Fusarium, Gibberella, Aspergillus, Streptomyces, and others are mentioned) also work, and the diols can be dehydrated to mentha-2,8-dien-1-ol (76). The same workers have shown that (+)-limonene is converted into (+)-α-terpineol (21; R = H) with Penicillium digitatum.

13 References

1 These figures have been made available from Brazilian sources by A. N. Henroz, Firmenich Ltda., S. Paulo, Brazil.
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