colorful history surrounding the development of the mentholated cigarette market. Dr. Michael F. Borgerding of R. J. Reynolds Tobacco Company will deliver an overview of the chemical determinations of menthol employed in the tobacco industry from an historical perspective. Dr. Steven A. Wilson of Eastman Chemical Company will discuss the theoretical aspects of menthol migration and transfer. Finally, Mr. Fred W. Best of R. J. Reynolds Tobacco Company makes a presentation dealing with effects of cigarette construction parameters on menthol migration and transfer.

Before turning the program over to our first speaker, let me note that we are all indebted not only to our speakers but also to their sponsors who have supported their participation. Additionally, we are also beholden to a host of individuals, groups and institutions, companies and corporations whose investigations and reports and support of research in this field make this symposium possible.

MENTHOL: ITS ORIGINS, CHEMISTRY, PHYSIOLOGY AND TOXICOLOGICAL PROPERTIES

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ABSTRACT

(-)-Menthol, the main constituent of peppermint oils, is the world's second largest aroma chemical. It is shown that the major types of peppermint oil are different with respect to flavor profile and chemical composition. In the biosynthesis of the main constituents, geranyl pyrophosphate is first cyclized enantioselectively to (-)-limonene and then transformed to the oxygenated *p*-menthanes. The stereochemistry of menthol is a good example of structure-odor relationship. Preparation and sensory impressions of the eight enantiomers are described. Cornmint oil (*mentha arvensis*) is still the main source of (-)-menthol, though a few synthetic processes have to be mentioned which have achieved commercial importance. The major sensory property of (-)-menthol is its cooling sensation on the skin or in the mouth. This effect results from a stimulating action on peripheral cold receptors. Some menthol analogues, possessing a longer lasting cooling effect, have been developed and marketed more recently. The reviewed toxicological and biological studies on menthol show that it is nontoxic at levels used in commercial products, not carcinogenic and easily biodegradable.

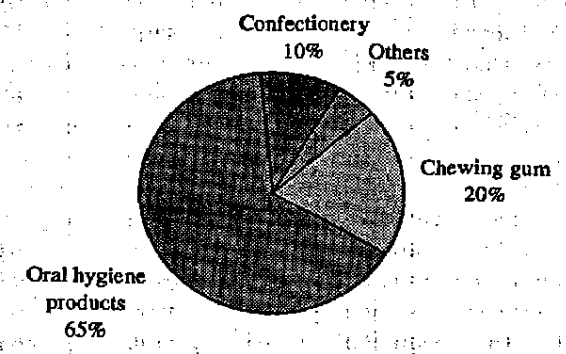
INTRODUCTION

Mint As A Taste Trend

Mint (both peppermint and spearmint) is the world's third most popular flavor complex, being surpassed only by vanilla and citrus flavors. The main applications (Figure 1) consist of oral hygiene products, chewing gum and confectionery. World consumption in 1989 was estimated at more than 10,000 tons (30).

The desire for mint flavors, especially peppermint, was originally an English phenomenon. The *mentha piperita* plant was first cultivated in Mitcham, a town southeast of London (10, 11). From Mitcham, use of this oil as a flavorant spread throughout all English-speaking overseas countries, e.g., Australia, South Africa and the United States. In recent decades, mint flavors have gained increasing popularity on the European continent and in numerous other countries throughout the world. The high acceptance of mint is based not only on its pleasant taste, but also on its association with freshness and cleanliness. An important feature of mint flavor is its cooling sensation in the oral cavity, imparted by (-)-menthol, the main constituent of peppermint oil.

FIG. 1
Main Applications Of Mint Flavors



Peppermint Oils And (-)-Menthol

Besides spearmint oil (from *mentha cardiaca* or *mentha spicata*) which is not reviewed here, peppermint oils and (-)-menthol are the main mint commodities. We have to distinguish between (a) "true" peppermint oil (also known as Mitcham oil, American peppermint oil or *M. piperita* oil) obtained from *mentha piperita* varieties, and (b) cornmint oil (Japanese mint oil, *M. arvensis* oil) obtained from *mentha arvensis* varieties.

The production of *M. piperita* oil is dominated by the United States and amounted there to approximately 3,000 tons in 1992, i.e., more than 90% of the world production. For economic and quality reasons *M. piperita* oil is used almost exclusively as a flavorant.

As a result of its high menthol content of approximately 80%, crude *M. arvensis* oil is always used as a raw material for the production of (-)-menthol. The relatively simple freezing process provides menthol crystals and the remaining oil is known as "dementholated peppermint oil." For years, Brazil (and some parts of Paraguay) was the main growing area with a peak production of around 6,000 tons of crude oil in 1972/1973. Today, China and India contribute 6,000 and 5,000 tons, respectively, to an estimated overall world production of 12,000 tons (Table I).

TABLE I

Suppliers Of (-)-Menthol

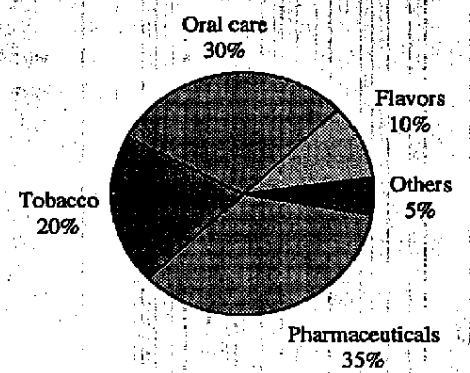
Supplier	1992 Tons[1]	1978 Tons
China[2]	2,300	500
India[2]	750	100
Brazil/Paraguay	350	900
Haarmann & Reimer[3]	1,600	600
Takasago[3]	650	500
Others	650	900
Total	6,300	3,500

[1]Estimated by Haarmann & Reimer Aroma Chemical Division
[2]Not including internal consumption
[3]Synthetic menthol

Though cornmint oil is still the main source of (-)-menthol, many synthetic processes have been developed, starting from natural optically active raw materials, e.g., (+)-citronellal or (+)-3-carene, or from basic organic chemicals, such as *m*-cresol or isoprene. Only a few processes have been commercially successful. In the past, synthetic menthol was only produced on a smaller scale when menthol prices were high due to shortfalls in the production of natural menthol. These fluctuations in (-)-menthol prices did not end until a few manufacturers (Glidden, Haarmann & Reimer and Takasago) made considerable investments to produce on a large scale (-)-menthol by totally synthetic or semisynthetic means. Today, production of synthetic (-)-menthol accounts for approximately 35% of the world market.

(-)-Menthol is widely used in pharmaceutical, oral care, tobacco, confectionery and perfumed products because of its unique cooling and stimulant effect (Figure 2 and Table II).

FIG. 2
Major Uses Of Menthol



Remarkably, none of the other seven enantiomers of *p*-menthan-3-ol gives rise to a comparable cooling sensation. As will be shown later on, for special uses several cooling agents have been developed, which are less volatile and

possess a longer lasting cooling effect compared to (-)-menthol.

TABLE II

Suggested Dosage Of (-)-Menthol In Various Products, Usually In Addition To Essential Oils (e.g., Peppermint Oil), Flavors Or Perfumes

Products	Dosage (%)
Pharmaceuticals	
Drugs	0.1
Medicated Oils	2.0 - 4.0
Liniments	2.0 - 3.0
Oral Care	
Toothpaste	0.5
Mouthwashes (Concentrated)	1.0 - 2.0
Tobacco Goods	
Regular Cigarettes	0.003
Menthol Cigarettes	0.1 - 0.2 (Weak Effect)
Menthol Cigarettes	0.25 - 0.45 (Strong Effect)
Pipe Tobacco	0.3
Chewing Tobacco	0.05 - 0.1
Confectionery	
Chewing Gum	0.5
Cough Drops/Lozenges	0.1
Licorice	0.05 - 0.1
Perfumed Products	
Preshave Lotions	0.2 - 0.3
Handkerchiefs	0.1 - 0.2
Foot Sprays	0.5
Refreshing Towels	1.0
Cooling Gels	1.0

Last but not least, (-)-menthol is used in synthetic substitutes of *M. piperita* oil along with some menthol derivatives and other constituents of peppermint oil.

THE ORIGINS OF PEPPERMINT AND MENTHOL

This part is based chiefly upon the review of Landing (19) on peppermint oil and the standard works of Gildemeister and Hoffmann (10) or Guenther (11) on essential oils.

Peppermint and Japanese mint are members of a complex botanical family referred to as *Labiatae* (two-lipped flowers) which is represented in essential oil production (besides mints) by such well-known and widely used plants as rosemary, lavender, basil, sage, and thyme. The genus *mentha*, which includes the true mints, is believed to have originated in the Mediterranean basin and spread from there to the rest of the world by both natural and artificial means.

The major properties of the mints, a delightful aroma and a mildly stinging fresh taste, have been recognized since ancient days. Mints are mentioned twice in the New Testament (Matthew 23:23 and Luke 11:42) and the distillation of mint oil appeared in the literature as early as 410 A.D. in an account written by Synesius of Alexandria, the Bishop of Ptolemais. In the 10th century A.D., a Japanese medical book described the utilization of mint in an eyewash preparation.

In medieval Europe, mints and other useful herbs were cultivated in the monastery and convent gardens. The monks and the nuns compounded from these herbs numerous medicines for the ailments of the day. But it is doubtful if the plant which we know today as peppermint already existed in those times. Specimens of our cultivated *mentha piperita L.*, which is considered a triple cross between *M. sylvestris L.*, *M. rotundifolia L.* and *M. acquatica L.*, were discovered in 1696 near Hertfordshire, England by a Dr. Eales and later in Essex by a Mr. Dale. They were described by John Ray (28). By 1750 peppermint was being commercially cultivated near Mitcham in the county of Surrey, England. Commercial peppermint production moved outward from England to the Netherlands about 1770 and soon spread into Germany, France and the United States. Today, most of the world's production is derived from the so-called English or black mint (*M. piperita* variety *vulgaris L.*). Menthol obtained from

peppermint oil was first described by Gaubius in 1771 as "Camphora Europaea Menthae Piperitidis."

Menthol from *M. arvensis* oil has been used in Japan for about 300 years. About 350 A.D., Enzan (a Japanese priest) brought mint plants from China to Japan and planted them in the vicinity of Kyoto, but distillation of Japanese mint and preparation of menthol from mint oil probably did not start before the end of the 17th century (17). Japan advanced to the world's dominant supplier of menthol when, starting about 1870, large acreages of mint were planted on the main island and on Hokkaido. The dominant variety grown in Japan was *M. arvensis* variety *piperascens* Malinvaud. Prior to World War II (1935 to 1939) Japan's annual export of menthol amounted to approximately 300 tons, about 70% of the world market. The balance was furnished mainly by China where primarily *M. arvensis* variety *glabrata* Holmes was grown.

The sudden disruption of supply, due to Japan's entry into the war, encouraged Brazilian entrepreneurs to start with the production of cornmint oil and menthol. *M. arvensis* variety *piperascens* was introduced to Brazil by Japanese immigrants and was first planted in the state of São Paulo about 1936 on a small scale. But later on, virgin land and forest were cleared for this new crop, and menthol production increased rapidly, from a few tons in 1941 to 500 tons in 1945. After the war, production was continued at a lower level and increased again since 1955, reaching a peak of around 3,000 tons in 1973. Since then production has fallen rapidly to around 350 tons in 1992. There have been several reasons for this decrease: (a) limited availability of virgin land suitable for mint cultivation, (b) decreasing attractiveness of mint compared with other crops, (c) competition of China and, more recently, India, and (d) competition of synthetic menthol.

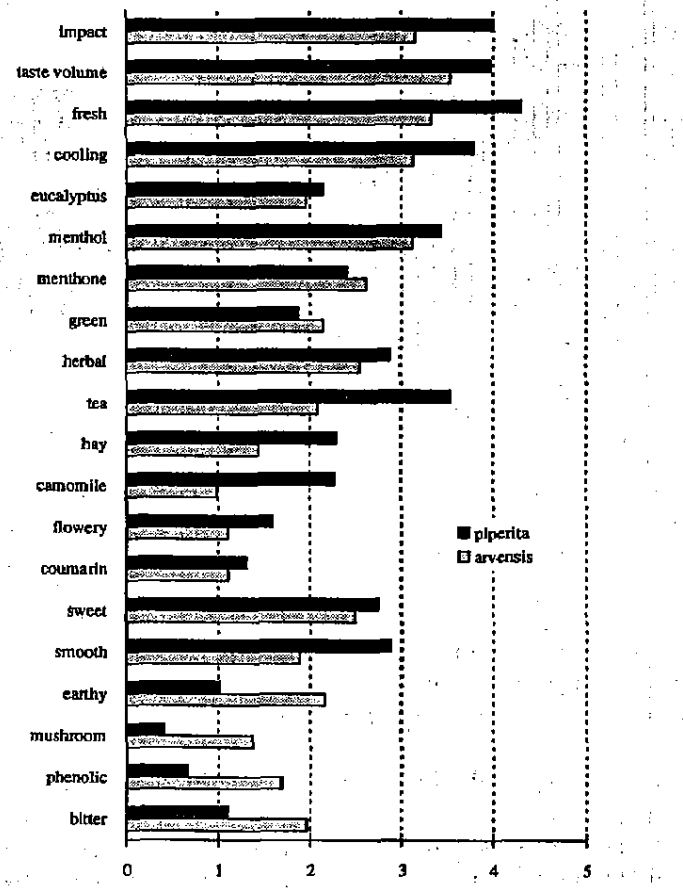
MENTHA ARVENSIS VERSUS *MENTHA PIPERITA* OILS

Flavor Profile

Compared with *M. arvensis*, *M. piperita* oils are significantly more valuable and higher in quality. Their

flavor is fresher, richer, sweeter, and more well rounded. As shown in the comparative flavor profiles (Figure 3) such positive flavor characteristics as impact, taste volume (fullness), freshness, cooling, sweetness, and the notes of tea, hay, camomile and flowers are more pronounced in *M. piperita* oils.

FIG. 3
Flavor Profiles Of *Mentha Piperita* and *Mentha Arvensis* Oil



The harsher flavor of *M. arvensis* oils is characterized by pronounced earthy, mushroomy, phenolic and bitter notes. Some of these differencies can be corrected by rectification; however, the correction is very limited. Therefore, the rectified cornmint oils are merely used as extenders for peppermint oils (30).

Chemical Composition

The chemical compositions of peppermint and dementholized cornmint oil have been the subject of numerous studies (20). As can be seen in Table III, both oils contain similar quantities of the main constituents menthol, menthone, menthyl acetate and neomenthol.

TABLE III

Typical Chemical Compositions Of Peppermint And Dementholized Cornmint Oil: Oxygenated *p*-Menthanes

Compound	Peppermint Oil (%)	Cornmint Oil (Brazil) %
826 Menthol	40	30
X Isomenthol	0.3	Trace
X Neomenthol	3	3
X Neoisomenthol	0.8	0.4
832 Menthyl Acetate	4	4
X Isomenthyl Acetate	0.3	0.2
X Neomenthyl Acetate	0.2	0.05
X Neoisomenthyl Acetate	Trace	Trace
X Isopulegol	Trace	0.4
X Neoisopulegol	Trace	0.6
X Isoisopulegol	-	0.5
X *Trans*-Sabinene Hydrate	0.8	Trace
Eucalyptol → 518 1,8-Cineole	5	0.5
830 Menthone	22	30
X Isomenthone	3	10
X Pulegone	1	1
1259 Piperitone	0.5	2
Mintlactone X Menthofuran	1 - 4	Trace - 0.2
→ 1062 Menthofurolactone	0.05	Trace

1413 Thiomenthone
297 Dehydromenthofurolactone

However, valuable flavoring substances, such as 1,8-cineole, menthofuran, sabinene hydrate and menthofurolactone (mintlactone) are found in much higher concentrations in *M. piperita* oil. They are responsible for the positive flavor characteristics of peppermint oil, together with numerous high-impact flavor compounds which have been detected among a total of around one thousand minor and trace constituents. These have been isolated and characterized using high-performance analytical methods and by the systematic evaluation of the organoleptic properties. This was a decisive step toward high-quality synthetic duplicates of peppermint oil (30, 36).

Chirospecific analytical methods have been used to determine the optical purity of various peppermint components (Figure 4, Figure 5 and Figure 6). Werkhoff *et al.* (38, 39) demonstrated that the menthol and menthone isomers in both *M. piperita* and *M. arvensis* oils are almost optically pure (> 99.5%). That is also true for minor components such as menthofurolactone (40). Today, fused silica GC columns coated with modified cyclodextrins are the most powerful tools for the separation of enantiomers. In flavor and essential oil research, usually a preseparation step is necessary. It is possible either by preparative capillary GC (off-line method) or by multidimensional GC (MDGC) including heart-cutting techniques from an achiral preseparation column onto a chiral main-column (on-line coupling).

Biosynthesis Of C3-Oxygenated p-Menthanes

The high optical purity of peppermint constituents is attributed to the stereoselectively controlled biosynthetic steps involved in their formation. Croteau *et al.* have studied the biosynthesis of C3- and C6-oxygenated p-menthanes in *mentha* species for several years and proposed the pathway outlined in Figure 7 (6).

FIG. 4
Optical Purity Of Peppermint Constituents: Menthol Isomers

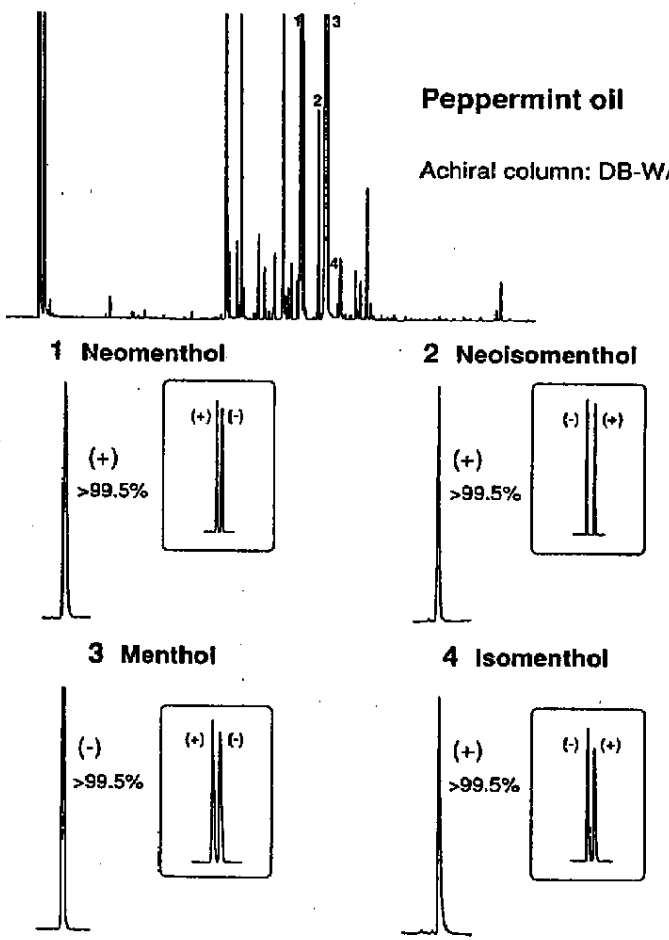


FIG. 5
Optical Purity Of Peppermint Constituents:
Menthone And Isomenthone

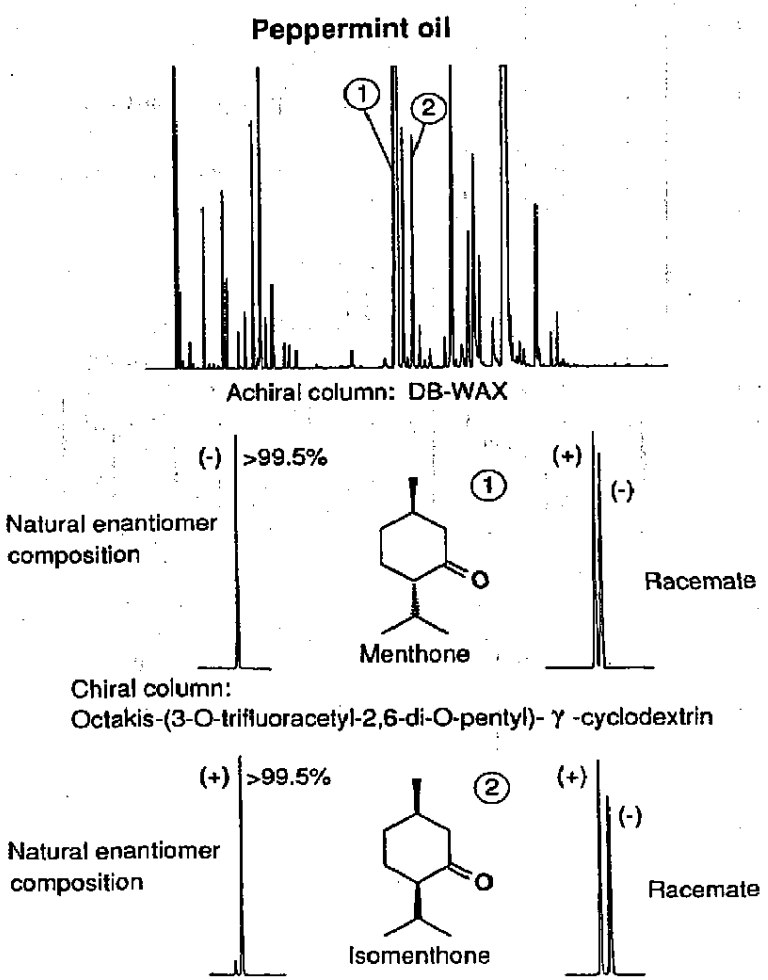
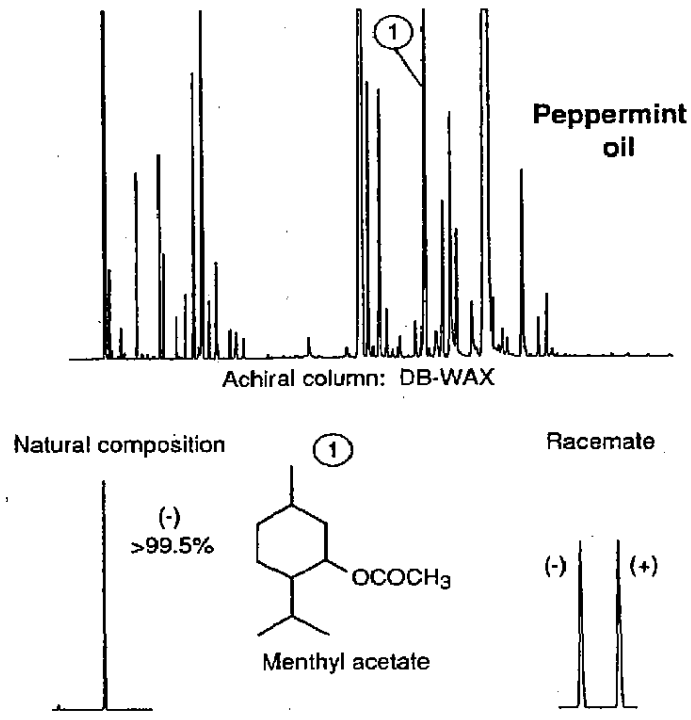
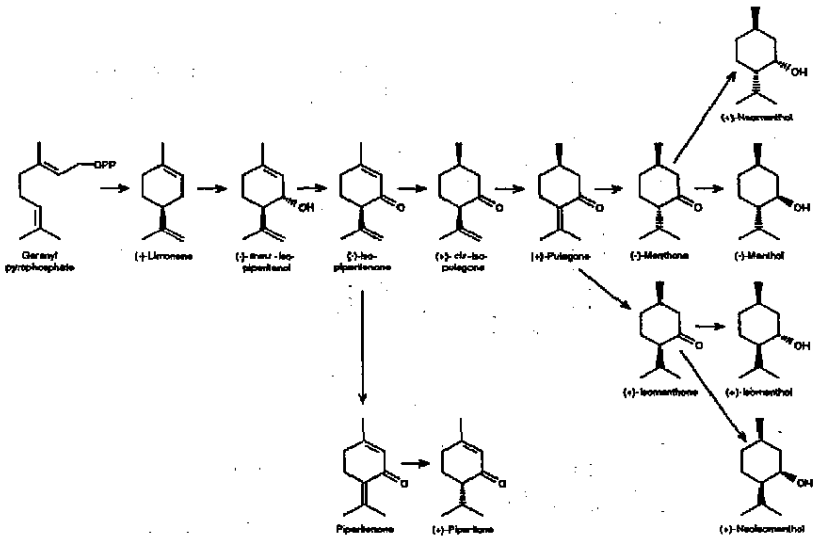


FIG. 6
Optical Purity Of Peppermint Constituents: Menthyl Acetate



The first stage of monoterpene biosynthesis involves a coupled isomerization-cyclization reaction by which the universal C10-isoprenoid precursor geranyl pyrophosphate is transformed to initial cyclic products. In the case of peppermint, (-)-limonene synthase catalyzes the formation of (-)-limonene. The next step, the cytochrome P 450-dependent hydroxylation of (-)-limonene leads specifically to (-)-*trans*-isopiperitenol. An NAD-dependant terpenol dehydrogenase converts (-)-*trans*-isopiperitenol to (-)-isopiperitenone.

FIG. 7
Pathway For The Biosynthesis Of C3-Oxygenated *p*-Menthane Monoterpenes From Geranyl Pyrophosphate



The next step in the sequence is the NADPH-dependent reduction of the $\Delta^{1,2}$-double bond of isopiperitenone to yield (+)-*cis*-isopulegone. The homoallylic double bond of *cis*-isopulegone is then isomerized to the allylic position to afford (+)-pulegone as the product. The enzyme resembles the well-known ketosteroid isomerases in catalyzing an intramolecular hydrogen migration and in requiring no cofactors.

The remaining steps of the sequence are notable for the presence of two stereospecific double bond reductases (NADPH-dependent) for the conversion of (-)-pulegone to (-)-menthone and to (+)-isomenthone, and two stereospecific dehydrogenases responsible for the reduction of (-)-menthone to (-)-menthol and to (+)-neomenthol, respectively. The same two dehydrogenases reduce (+)-isomenthone to (+)-neoisomenthol and to (+)-isomenthol, respectively. The primary metabolites

that accumulate in peppermint are (-)-menthone and (-)-menthol.

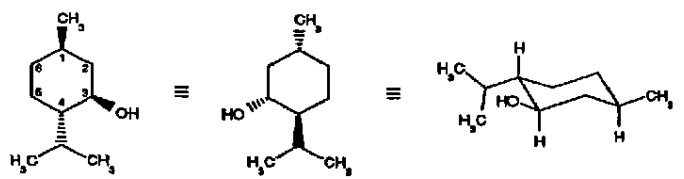
STEREOISOMERS OF MENTHOL

Nomenclature And Graphic Formulas

The work on the structure elucidation and stereoisomerism of menthol, and the preparation of pure stereoisomers, has been shared by many prominent workers, as reviewed by Simonsen and Owen (31) and Merkel.

(-)-Menthol (Figure 8) is one of eight enantiomers of menthol (*p*-menthan-3-ol) owing to three asymmetric centers in the molecule (Figure 9). The *R,S* nomenclature and/or space formulas are used to define the absolute configuration, e.g., (1*R*, 3*R*, 4*S*)-menthol for (-)-menthol. In recent years, *Chemical Abstracts* has adopted a combined *R,S* and α,β nomenclature (the latter is used in steroid chemistry). Menthol is listed under the name cyclohexanol-5-methyl-2-(1-methylethyl) and the configuration of (-)-menthol is characterized as [1*R*-(1α,2β,5α)].

FIG. 8
Various Graphic Formulas Of (-)-Menthol



Preparation And Analytical Data

For sensory evaluations, six of the eight enantiomers of menthol had to be prepared and purified, as both (-) and (+)-menthol were available from the Haarmann & Reimer menthol process. In Table IV, starting materials, methods of preparation and purification procedures are summarized (9).

FIG. 9
The Eight Menthol Stereoisomers

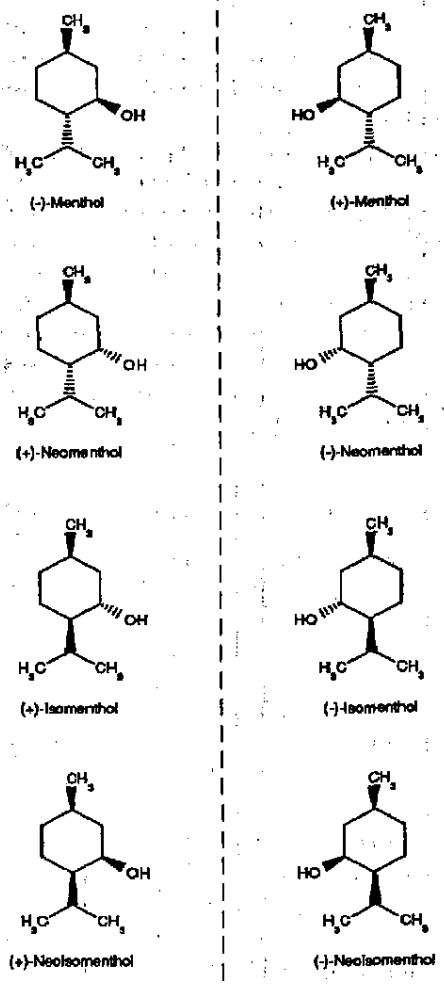


TABLE IV

Preparation And Purification Of Menthol Enantiomers

Prepared Enantiomer	Starting Material, Preparation Method	Separation, Purification
(+)-Isomenthol	Sodium Reduction Of A (-)-Menthone/ (+)-Isomenthone Mixture (77:23)	Rectification, Derivatization (Anisate), Crystallization And Saponification
(-)-Isomenthol	Sodium Reduction Of A (+)-Menthone/ (-)-Isomenthone Mixture (77:23) Which Is Obtained By Oxidation ($Na_2Cr_2O_7$/ H_2SO_4) And Isomerization (NaOH) From (+)-Menthol	
(+)-Neomenthol	$NaBH_4$ Reduction Of (-)-Menthone Provides A 50:50 Mixture Of Menthol And Neomenthol	Rectification, Derivatization, Crystallization (Acetate) And Saponification
(-)-Neomenthol	As Above, Starting From (+)-Menthone Which Is Obtained From (+)-Menthol By Oxidation	
(+)-Neoisomenthol	$NaBH_4$ Reduction Of (+)-Isomenthone Gives 87% Neoisomenthol; (+)-Isomenthone Is Obtained By HPLC Separation	Rectification, Preparative HPLC
(-)-Neoisomenthol	As Above, Starting From (-)-Isomenthone	

Physical and analytical data are listed in Table V.

TABLE V

Physical And Analytical Data Of The Stereoisomers Of Menthol

Substance	Gas Chromatography DB-WAX[1] R.I.[2]	DB-WAX[1] Purity	DB-1[1] R.I.[2]	DB-1[1] Purity	$[\alpha]_D^{20}$	M.P. °C	B.P. °C
(-)-Menthol		100%		100%	-50.2°	} 43	
(+)-Menthol	1632	100%	1160	100%	+50.1°		216.5
(±)-Menthol		100%		100%	-	38	
(-)-Isomenthol		100%		100%	-25.9°	} 82	
(+)-Isomenthol	1659	100%	1174	100%	+24.7°		218.6
(±)-Isomenthol		100%		100%	-	53	
(-)-Neomenthol		99.5%		99.4%	-20.8°	}-15	
(+)-Neomenthol	1596	99.4%	1148	99.5%	+20.9°		211.7
(±)-Neomenthol		99.6%		99.5%	-	52	
(-)-Neoisomenthol		100%		100%	- 2.0°	}- 8	
(+)-Neoisomenthol	1616	99.9%	1171	100%	+ 2.0°		214.6
(±)-Neoisomenthol		98.5%		98.5%	-	14	

[1]Temperature program 60°C - 220°C at 3°C per minute
[2]Retention index

Sensory Characterization Of Menthol Enantioners (9)

For the reconstitution of peppermint oil, it is important to know the flavor properties of all relevant constituents. Besides others, we compared the (1*R*)-menthols which occur in peppermint oil with the (1*S*)-menthols. All enantiomers were tested in 5% sucrose solution by a test panel of seven experienced flavorists.

In the first step, each substance was evaluated by a dilution profile method to determine the concentration levels of (a) taste threshold, (b) noticeable cooling effect, (c) most acceptable dosage range, and (d) bitter taste. The results are summarized in Table VI.

TABLE VI

Taste Properties Of Menthol Enantiomers:
The Dilution Profile (Concentrations: ppm)

	Taste Threshold	Cooling Threshold	Acceptable Dosage	Bitter Threshold
(1*R*)-Menthols				
(-)-Menthol	0.4	0.8	1.5 - 6.0	15
(+)-Isomenthol	0.7	7	1.5 - 4.0	20
(+)-Neomenthol	0.5	2.5	1.0 - 3.0	25
(+)-Neoisomenthol	0.2	> 25	0.5 - 1.5	> 25
(1*S*)-Menthols				
(+)-Menthol	0.3	3	1.0 - 5.0	25
(-)-Isomenthol	0.6	30	1.5 - 5.0	50
(-)-Neomenthol	0.6	25	1.5 - 5.0	30
(-)-Neoisomenthol	1.0	6	2.0 - 5.0	> 25

The taste thresholds of the menthol enantiomers vary within a relatively narrow range of 0.2 to 1.0 ppm. Apart from neoisomenthol, there is only a small difference between the (1*R*) and (1*S*) isomers. However, the cooling level varies significantly and (-)-menthol has by far the lowest cooling threshold. Both (+)- and (-)-neoisomenthol could only be tested up to 25 ppm due to very small amounts of pure substances. The cooling threshold of (-)-neoisomenthol was higher than that concentration. The acceptable dosage range is also quite similar for most of the substances: from about 1 to 5 ppm. The thresholds of bitter tasting were found between 15 ppm and 50 ppm, whereby (-)-menthol surprisingly has the lowest value.

The flavor profiles of (1*R*)-menthols (Figure 10) and (1*S*)-menthols (Figure 11) were determined in a 5% sugar solution at 3 ppm, and each flavor characteristic was scored on a 5 point scale (1 very low; 5 very high). Again, the outstanding flavor properties of (-)-menthol concerning the attributes cool, fresh, minty and sweet were confirmed. (+)-Menthol ranks second with respect to freshness and cooling properties (which is somewhat surprising), but it also has

some negative features such as phenolic, musty and bitter. Nevertheless, this result suggests that a pure racemic menthol is not the worst substitute for (-)-menthol. With respect to the constituents of peppermint oil (+)-neomenthol (3%), (+)-isomenthol (0.3%) and (+)-neoisomenthol (0.8%) contribute to the earthy, woody and musty notes. This opens up the possibility for the flavorist to "correct nature" and to develop tailor-made blends with respect to more freshness, sweetness or other desirable characteristics.

FIG. 10
Flavor Profiles Of The (1R)-Menthol Isomers

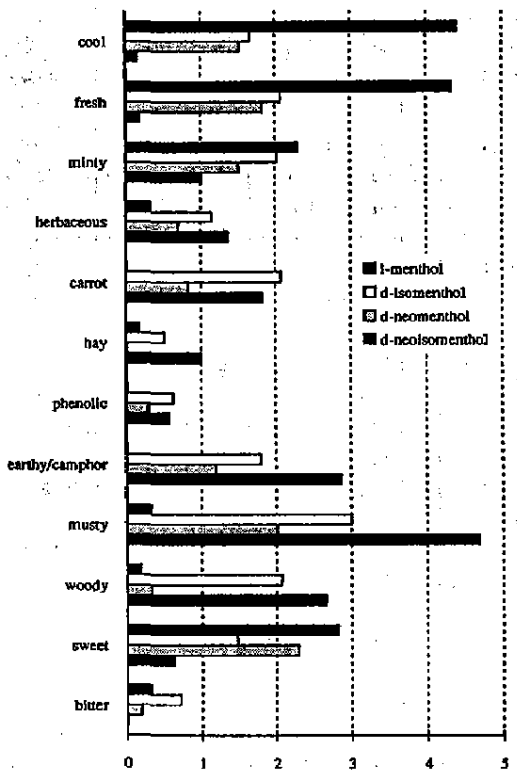
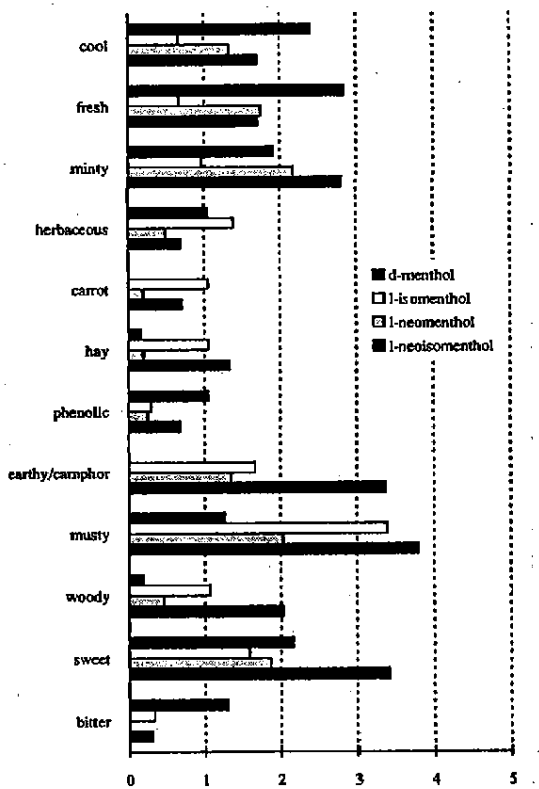


FIG. 11
Flavor Profiles Of the (1S)-Menthol Isomers



SYNTHESIS OF (-)-MENTHOL

Concerning this topic there already exist some excellent reviews (3, 4, 22) which are recommended for in depth studies.

Considerable effort has been devoted to the production of (-)-menthol by synthetic or semisynthetic means from other more readily available raw materials such as (a) dementholized cornmint oil (example *mentha arvensis*), (b) (+)-citronellal (example citronella oil), (c) (+)-3-carene (example Western U.S. and Indian turpentine), (d) (-)-α-phellandrene and

(-)-piperitone (example *eucalyptus dives* oil), (e) (+)-pulegone (example pennyroyal oil), (f) (+)-limonene (example orange oil), (g) racemic menthol (example thymol) via optical resolution, and (h) myrcene (example β-pinene) using an enantioselective isomerization step.

These syntheses, a few of which have been commercially important are shown in Figure 12 to Figure 20 and will be only briefly described here because of the above mentioned reviews. An exception is made with respect to the main processes used today for manufacturing (-)-menthol--the Haarmann & Reimer (Figure 17) and the Takasago (Figure 18 to Figure 20 processes.

"Classical" Menthol Syntheses (Figure 12)

From Dementholized Cornmint Oil: This relatively inexpensive by-product of natural menthol production is still rich in menthol, menthone and some other components which can be transformed to menthol (see Table III). Hydrolysis of menthyl acetate, mild reduction of menthones or hydrogenation respectively, followed by distillation and crystallization, yields additional (-)-menthol.

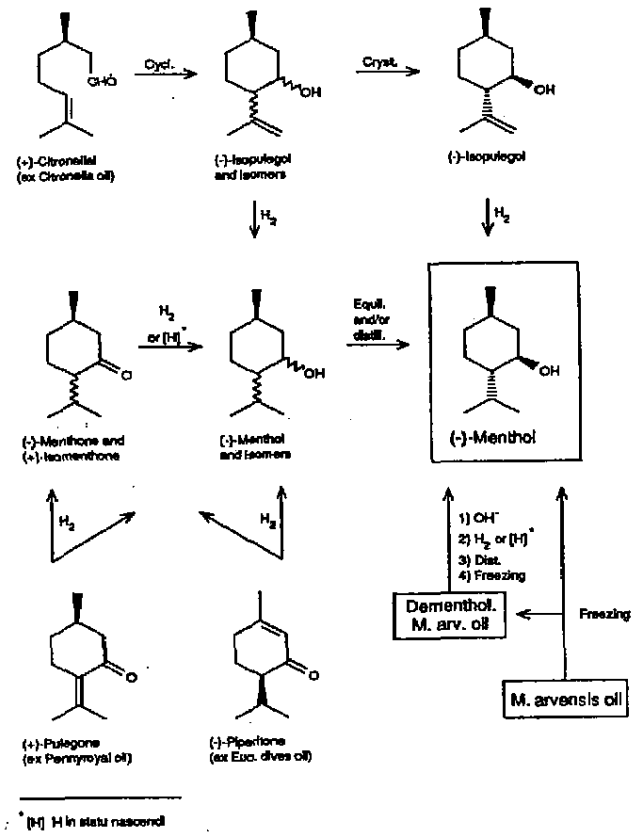
From (+)-Citronellal (Example *Citronella*): This process has been used widely whenever the supply of natural menthol was short. (+)-Citronellal can be isolated with an optical purity of approximately 80% from citronella oil. Accordingly, it is cyclized by acidic catalysts (*e.g.* silica gel) to give a mixture of optically active isopulegol isomers and 20% of the corresponding racemates. Preferably, (-)-isopulegol is separated by crystallization at low temperatures and directly hydrogenated to pure (-)-menthol. The alternative procedure of hydrogenating the isopulegol mixture and separating (-)-menthol from its isomers requires derivatization.

From (-)-Piperitone (Example *Eucalyptus Dives*): This process has been used in Australia on a smaller scale. (-)-Piperitone isolated from *eucalyptus dives* oil usually is already partially racemized, due to the unstable asymmetric center at C4, adjacent to the carbonyl group. Moreover, the hydrogenation to either (+)-isomenthone or to an isomeric mixture of menthols is not completely chirospecific with

respect to the newly formed chiral center at C1. Therefore, (-)-menthol has to be purified via derivatization.

From (+)-Pulegone (Example Pennyroyal Oil): Hydrogenation and reduction of the (-)-menthone/(+)-isomenthone mixture with nascent hydrogen gives predominantly (-)-menthol. However, the actual price of pennyroyal oil is prohibitive for commercial production.

FIG. 12
"Classical" (-)-Menthol Syntheses

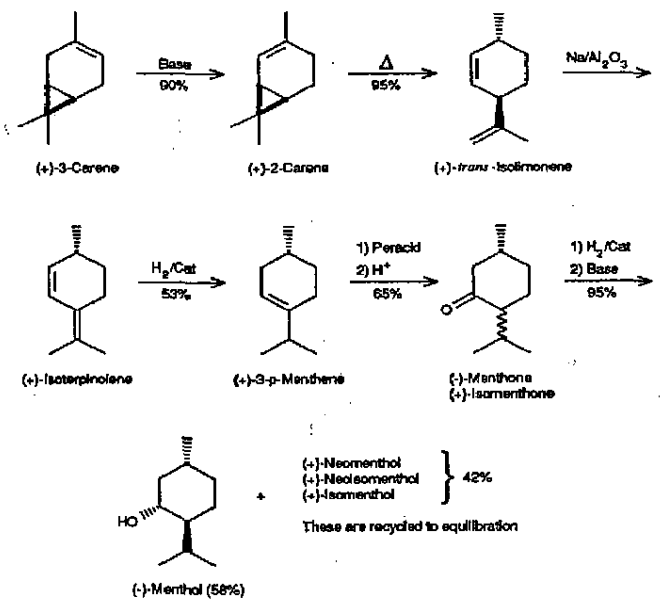


(-)-Menthol From Various Natural Terpenes (Figure 13)

From (+)-3-Carene: The MRC-Process (MRC = Malti-Chem Research Centre, Nandesari, Vadadora, India) starts from (+)-3-carene, the major component of Indian turpentine oil (55% to 65%). Base catalyzed isomerization provides (+)-2-carene which is pyrolyzed to (+)-*trans*-2,8-*p*-menthadiene, followed by an isomerization step to (+)-isoterpinolene in the presence of strong bases. Hydrogenation to (+)-3-*p*-menthane, epoxidation and subsequent rearrangement provide a menthone/isomenthone mixture which is reduced and purified in the usual way (34). A drawback of this process is a partial racemization which has its origin in the isomerization step to isoterpinolene (24). It is obvious that a multistep process like this can only be competitive on a rather large scale. Again, a pure (-)-menthol is only obtained via derivatization.

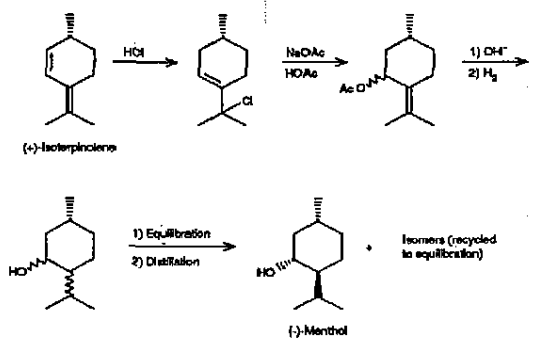
Alternatively, (+)-*trans*-isolimonene can be hydrochlorinated-dehydrochlorinated to give (+)-isoterpinolene. A second hydrochlorination followed by treatment with sodium acetate and acetic acid yields a mixture of *cis* and *trans*-pulegyl acetate which is hydrolyzed to (-)-*cis*- and (+)-*trans*-pulegol. Because the absolute configuration of C1 is fixed in this pathway, hydrogenation of either pulegol provides (1*R*)-menthols which can be equilibrated and separated as previously described. This promising route, developed by Hercules, Incorporated, has not been commercialized (Figure 14).

FIG. 13
(-)-Menthol From (+)-3-Carene: The MRC-Process (India)*



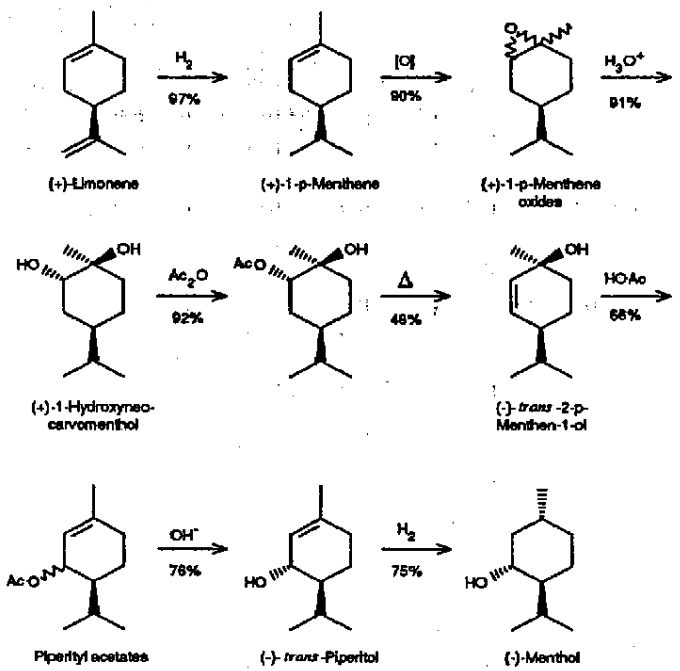
* MRC = Malti-Chem Research Centre, Nandesari, Vadodara, India

FIG. 14
(-)-Menthol From (+)-3-Carene: The Hercules Route



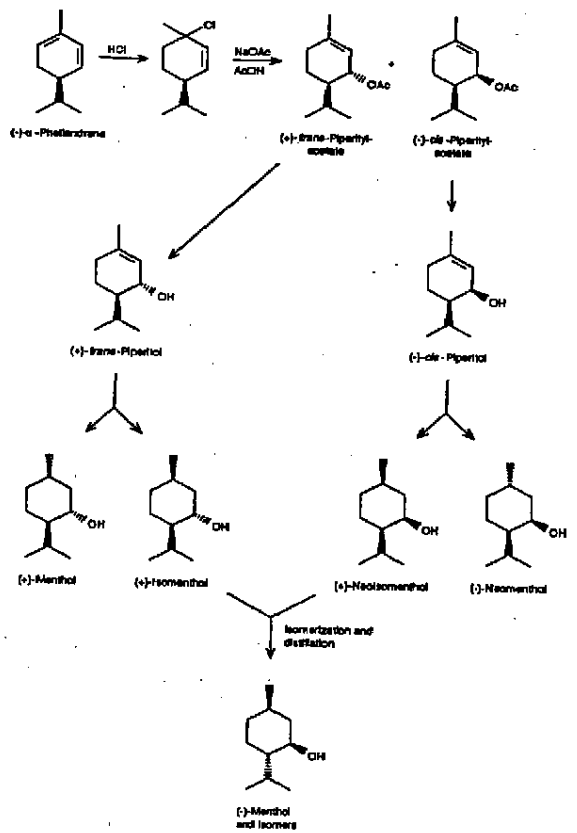
From (+)-Limonene (Figure 15): Optically pure (+)-limonene is an inexpensive by-product from the citrus industry. Hydrogenation to (+)-1-*p*-menthene and air oxidation in acetaldehyde yields (+)-1-menthene epoxides economically. These are hydrolyzed to (+)-1-hydroxyneocarvo-menthol and acetylated to give the desired (+)-1-hydroxyneocarvomenthyl acetate which is then pyrolyzed to (-)-*trans*-2-*p*-menthen-1-ol. Via piperityl acetate (by acetylation and allylic rearrangement) and (-)-*trans*-piperitol, (-)-menthol is finally obtained by hydrogenation containing 25% (-)-isomenthol. This (1*S*)-isomer cannot be transformed to (-)-menthol. The drawback of this interesting route is its low overall yield.

FIG. 15
(-)-Menthol From (+)-Limonene: The Reynolds Route



From (-)-α-Phellandrene (Figure 16): (+)-*Trans*-piperitol obtained via piperityl chloride can be hydrogenated to give a mixture of 97% (+)-isomenthol and 3% (+)-menthol. (+)-Isomenthol can be converted to (-)-menthol by crystallization, equilibration and distillation. The process suffers from the disadvantage of by-products and isomer separation.

FIG. 16
(-)-Menthol From (-)-α-Phellandrene: The Glidden Route



The Haarmann & Reimer (-)-Menthol Process (Figure 17)

Around 1965 Haarman & Reimer decided to develop a total synthesis of (-)-menthol starting from thymol. Hydrogenation of thymol produces a mixture of isomers containing all eight menthol enantiomers, although (-)-menthol is the only target product (16).

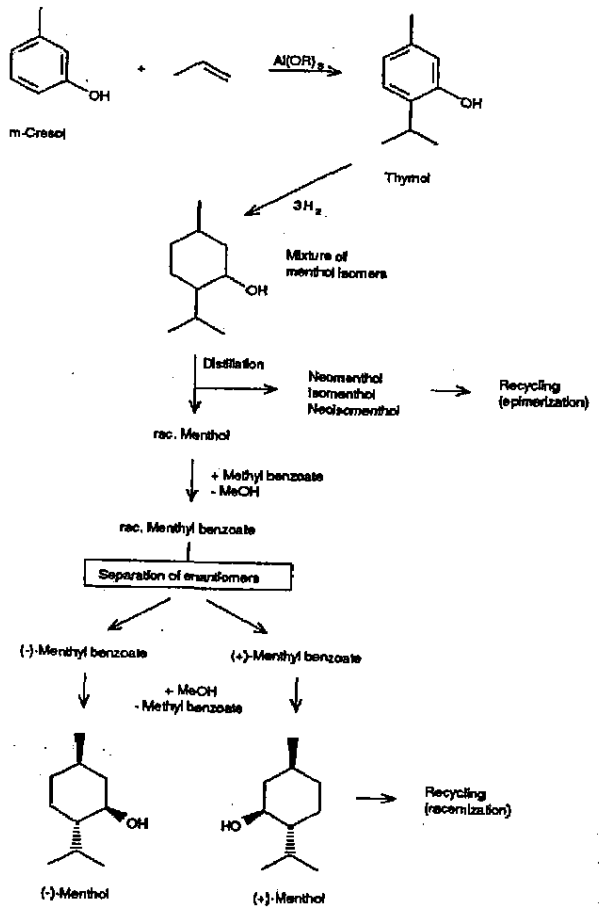
The difficult part of the synthesis is first to separate (±)-menthol from the other isomers and then to separate it into (-)- and (+)-menthol. For economic reasons (+)-menthol and the other remaining menthol isomers have to be recycled.

Figure 17 shows the various stages in the H&R menthol process. *o*-Alkylation of the *m*-cresol produces thymol which, on hydrogenation, gives a mixture of approximately 58% to 60% (±)-menthol, 28% neomenthol, 12% isomenthol and 1% neoisomenthol. After distillation, (±)-menthol of approximately 99% purity is obtained which is esterified to menthyl benzoate. The most important step is then to separate the benzoates into the enantiomers (2). Finally, the benzoates are transesterified once again to form (+)- and (-)-menthol and methyl benzoate which is recycled to the production process.

The crucial step of this process, as mentioned above, is the enantioselective crystallization of (-)- and (+)-menthyl benzoate, carried out continuously in two separate vessels, by seeding a supersaturated solution of (±)-menthyl benzoate with crystals of the (+)- and (-)-form respectively. We did of course attempt the enantioselective crystallization of (±)-menthol, but the melting point diagrams showed that (±)-menthol crystallizes as a racemic compound and not as a mixture of (+)- and (-)-menthol crystals. All our efforts to bring about selective crystallization in a variety of solvents were to no avail. On the other hand, crystallization of (±)-menthyl benzoate, while involving an additional stage of purification, does in fact enhance the quality of menthol. The overall yield of the H&R process, based on the starting material thymol, is more than 90%.

The H&R menthol plant in Bushy Park near Charleston, South Carolina, USA went on stream in 1978. The menthol plant in Holzminden has been in operation since 1973.

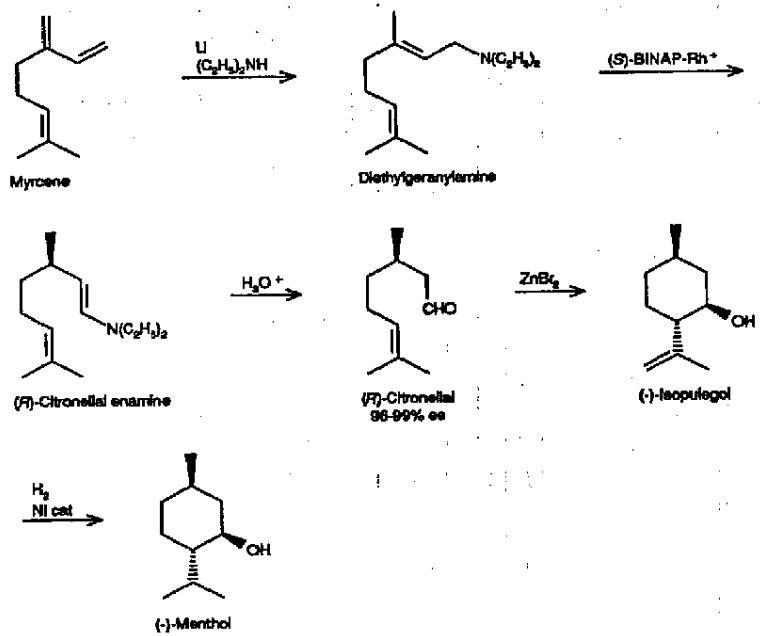
FIG. 17
Total Synthesis Of (-)-Menthol From *m*-Cresol:
The Haarmann & Reimer Process



The Takasago Synthesis Of (-)-Menthol From Myrcene (Figure 18)

Biochemical methods for enantioselective hydrolysis of racemic menthyl esters have been developed by Takasago Perfumery Company (13) in the late 1960's, but we have no confirmed information if this method was utilized for the resolution of (±)-menthol (from thymol) into its optical antipodes on a technical scale.

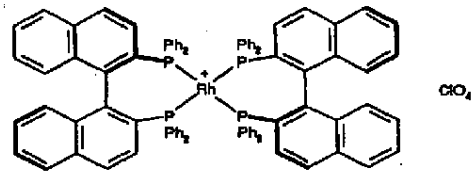
FIG. 18
The Takasago Synthesis Of (-)-Menthol From Myrcene



For about ten years, Takasago International Company has been manufacturing (-)-menthol from myrcene (27). First, the triene is converted in a regio- and stereoselective manner to diethylgeranylamine by lithium catalyzed addition of diethylamine. The key step is the subsequent BINAP-Rh(I)

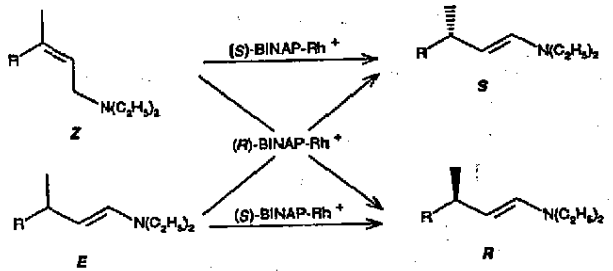
catalyzed enantioselective isomerization of the allylic amine in THF giving (R)-citronellal enamine in 96% to 99%. The chiral catalyst used in this step is shown in Figure 19.

FIG. 19
Chiral Rhodium BINAP Complex, The Key Catalyst In The Takasago Synthesis



Enantiomeric purity of the chiral aldehyde obtained by hydrolysis is much higher than natural citronellal from citronella oil. Stereoselective cyclization of (R)-citronellal promoted by zinc bromide, giving isopulegol, followed by catalytic hydrogenation completes the synthesis of menthol. The technical refinement of the Rh catalyzed asymmetric reaction has enabled the process to work up to a 9-ton scale, where the turnover number (produced enamine mol/Rh catalyst mol in 18 hours) approaches 8,000 per cycle. The BINAP-Rh complex catalyst can be recycled efficiently, giving the overall turnover number of 400,000. This isomerization is chirally flexible leading to either natural or unnatural citronellal enamine. In addition to geranyl- and nerylamines, a variety of allylic amines can be isomerized in an enantioselective and predictable manner. The general scheme is given in Figure 20 (16).

FIG. 20
Rhodium BINAP Catalyst: Stereochemical Correlation Between Substrate, Catalyst And Product



PHYSIOLOGICAL EFFECTS OF MENTHOL

The Response Of Various Receptors To Menthol

Early investigators clearly demonstrated that menthol affects the response of many receptors to stimulation. Like many other substances, the response to menthol is enhanced in small concentrations and depressed in large concentrations or after extended exposure. The electrophysiological response to menthol was first demonstrated for thermal receptors (8, 15). Similar responses to menthol were observed in chemoreceptors of the carotid body. Carotid bodies are regions of receptors located in the neck area which are sensitive to substances that stimulate and transmit information to the brain, particularly the medulla and brain stem (18).

An increase as well as a decrease in sensitivity to menthol after sustained menthol exposure has been observed for the olfactory sense (32) and the gustatory (taste) sense (33). These studies employed psychophysical techniques which require scaling measurements of perceptual responses rather than the recording of impulses from the receptor cells themselves.

To bridge the gap between the electrophysiological technique used in the studies of nongustatory receptors and the psychophysical technique used in the studies of gustatory receptors, Hellekant (14) investigated the electrophysiological effects of menthol on gustatory receptors. The excitability of the gustatory receptors was evaluated by

recording the impulse activity in the *chorda tympani* nerve of the cat. It was observed that menthol elicited a slowly increasing activity in all gustatory fibers. Adding menthol changed the gustatory response to sapid solutions [concentration of sapid solutions (nonoffensive levels of agreeable flavor solutions) was (aqueous) 0.01 M quinine-monohydrochloride, 0.05 M acetic acid, 0.5 M sodium chloride, 1 M sucrose and 2.5 M ethyl alcohol--menthol solution concentrations were 0.05, 0.1 and 0.2 gram per liter (aqueous)] in two respects: (a) it slightly suppressed the initial burst of activity and (b) it enhanced the sustained response. Rinsing with menthol left the gustatory receptors with a changed sensitivity to stimulation with other sapid solutions. This effect on the receptors was related to concentrations and length of the preceding menthol rinse. It also showed variation with regard to stimulus, concentration, and subject.

Recent studies on the sensory transducer mechanism of nasal and lingual cold receptors have demonstrated that menthol activates cold receptors by interfering with the calcium conductance of the neuronal sensory membranes (29, 35).

The Cooling Effect Of Menthol And Menthol Analogues (37)

Menthol does not cool by volatilization. The cooling effect seems to result from chemical action at or near those nerve endings which are associated with the sensation of cold. When menthol is placed on the lingual nerve of the cat, the cold fibers of that nerve are either provoked into firing or, if already firing, respond with a higher rate of firing. Since the neurophysiological basis of the response to cold is essentially the same in all mammals, including man, and since there are many common features in the action of menthol and synthetic cooling agents, it seems reasonable to assume that all such coolants act by a common mechanism, which is essentially that of a stimulant-receptor interaction. Cooling responses can be produced as a result of nasal, oral, or topical application.

Molecular Requirements For Cooling Activity (37): It has been established that four important criteria must be satisfied for a compound to possess effective cooling activity: (a) a hydrogen bonding group, (b) a compact hydrocarbon skeleton, (c) a correct hydrophilic/hydrophobic balance, and (d) a molecular weight in the range 150 to 350.

Hydrogen Bonding: A hydrogen bonding function is essential for cooling action. We believe that the function must contain an oxygen atom capable of acting as a hydrogen bond acceptor. For greatest cooling activity, strong hydrogen bond accepting capability is necessary. There is no indication that the provision of more than one hydrogen bond accepting group in the molecule enhances the cooling effect; some *p*-menthanediols are active, but none is as active as (-)-menthol.

Hydrocarbon Skeleton: It is assumed that the functional group takes part in hydrogen bonding at a receptor site, and that for cooling, the hydrocarbon portion or portions of the molecule must provide a compact hydrophobic region near to the site of hydrogen bonding.

Hydrophilic/Hydrophobic Balance: For strong cooling activity, a compound must have the correct hydrophilic/hydrophobic balance. This balance is important in stimulant-receptor interactions. The most common measure of hydrophilic/hydrophobic balance is the Hansch log P value, where P is the partition coefficient of the compound between *n*-octanol and water. The log P value is well established as an important factor of the pharmacological activity and it is also recognized as one of the factors which determines the rate of transport of compounds through biological membranes, especially the skin.

The log P values of cooling compounds were calculated from published tables of the substituent values. Strong cooling compounds have log P values in the relatively narrow range of 1.5 to 4.0 and values for

nearly all cooling compounds lie in the range of 1.0 to 5.0. The log P value of menthol is 3.1.

Molecular Weight: If a hydrocarbon skeleton capable of giving strong cooling compounds is combined with a strong hydrogen-bond accepting functional group, and if the log P value of the resultant molecule is in the correct range, then cooling will be observed if the molecular weight is in the range 150 to 350. The criterion of molecular weight is more flexible than the criteria for hydrogen bonding, skeleton and log P.

General Properties Of Cooling Compounds: Apart from the cooling effect and a degree of flavor potentiation and odor modification, there are no common sensory properties of cooling compounds. For instance, there is no association between minty smell and cooling.

Because there are many structural variations in cooling compounds, the physical properties of these compounds also vary. Most cooling compounds are solids, although liquids are not uncommon when the functional group is hydroxyl or N,N-dialkylcarboxamide. In addition, most of them are readily soluble in common organic solvents but, due to the requirements of the log P value, all have very limited solubility in water. It should be noted, however, that saturated aqueous solutions have readily perceptible cooling effects. The alcohols and N,N-dialkylcarboxamides are, in general, volatile and some are odorous with odor types ranging from minty to fruity and from earthy to camphoraceous.

Other Sensations Produced By Cooling Compounds

All cooling compounds produce sensations other than pure cooling including tingling, stinging, burning and bitter. These other sensations are most readily described by reference to a strong peppermint candy, which produces tingle in the mouth and, if strong enough, a burning sensation. Compounds differ in the relative degree of cooling and other sensations. Those compounds that produce little sensation other than cooling are (in our terminology) high "quality." The relative degree of cooling appears to correlate to some degree with

compound type. For example, hydroxyesters and hydroxyacetals tend to produce low levels of sensations other than cooling.

These sensations are dose sensitive. In general, increasing the dose of the cooling compound beyond a certain limit gives no apparent increase in cooling. However, it does cause an increase in other sensations, finally to the point where the other sensations dominate the cooling effect.

Sensitivity Of Different Parts Of The Body

Parts of the body differ greatly in their sensitivity to cooling compounds. No attempt has been made to determine their relative sensitivities in absolute terms; however, the suggested order of sensitivity is: eye >> tongue > interior buccal region > ano-genital area > lip > trigeminal area > other face areas > axilla > inside forearm, breast > other arm areas, thigh, back, hands, feet >> palms, soles. The eye is extremely sensitive with thresholds probably measurable in nanograms and a simple test for cooling effect in a volatile compound is to hold the opened bottle near the eye. This test with menthol gives a sharp and very obvious sensation which agrees with consumers' comments on the effect of mentholated shaving foam on the eye.

Like menthol, synthetic cooling compounds also give a cooling sensation in the lungs (when added to cigarettes or inhaled as an aerosol spray) and to the gastrointestinal tract (when ingested).

The order of sensitivity clearly follows a general order of increasing thickness of *stratum corneum*. It seems probable that the sensitivity of an area is determined mainly by the ease with which the compound can penetrate this barrier. For example, abraded or hydrated forearm skin has a reduced threshold compared to intact skin. Although the barrier role of the *stratum corneum* is probably dominant, it is also likely that the number of cold-sensitive nerve endings per unit area and the efficiency with which the central nervous system processes nerve signals vary with the location on the skin.

Mechanism Of Action

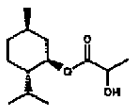
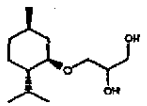
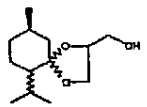
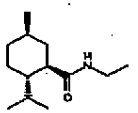
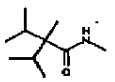
When a composition containing a cooling compound is applied to various body surfaces, three processes must occur

before a cooling effect is perceived: (a) molecules of the compound must transfer from the vehicle and must penetrate the surface of the *stratum corneum*, (b) molecules must diffuse through the skin, and (c) molecules must interact with the receptors.

The role of each of the three processes in producing the cooling effect is dependent upon (a) the properties of the compound, (b) the kind of solvent or formulation in which the compound is used, and (c) the properties of the body surface to which it is applied.

Some commercialized cooling compounds are shown in Figure 21 including one which is in the development stage.

FIG. 21
Various Cooling Compounds

Structure	Trade Name	Origin / Patents
	Frescolat ML Trivent ML	HAARMANN & REIMER TRIVENT, USA
	Cooling Agent No. 10	TAKASAGO PERFUMERY CO. EP 80 148 (1981)
	Frescolat MGA –	HAARMANN & REIMER DOS 41 10 973 (1991) WRIGLEY EPA 485 170 (1991) US Priority: 1990
	WS 3	WILKINSON SWORD, GB (STERLING ORGANICS / PRODUCER) US 4 150 052 (1979) UK Priority: 1973
	WS 23	WILKINSON SWORD, GB (STERLING ORGANICS) UK 1 421 744 (1972) UK 1 421 671 (1974)

TOXICOLOGICAL AND BIOLOGICAL PROPERTIES OF MENTHOL

Menthol is one of the most thoroughly studied flavor and fragrance materials with respect to toxicology and biological properties. Many of these data are summarized in a monograph (26) and other reviews (5, 7). The essential results are briefly reported.

Regulatory Status: Menthol has been given generally recognized as safe (GRAS) status and is approved as a direct food additive by the FDA. The Council of Europe (1981) has also approved menthol for food use, giving an acceptable daily intake (ADI) of 2 milligrams per kilogram for total menthol and menthyl esters. In addition, the Joint FAO/WHO Expert Committee on Food Additives (1968) has published a monograph and specifications for menthol listing an unconditional ADI of 0.2 milligram per kilogram.

Acute Toxicity: The oral, sc and ip LD_{50} values are in the range of 0.8 gram per kilogram to 6 grams per kilogram in rats, mice and cats. The inhalation RD_{50} level for menthol has been determined to be 760 mg/m^3 (116 ppm) for Swiss-Webster mice (1). The RD_{50} is that concentration capable of inducing a 50% reduction in mean respiratory frequency.

Short-Term Toxicity: No detrimental effects of menthol were observed in short-term biological studies.

Carcinogenity: Menthol is not carcinogenic, as shown in studies by the National Cancer Institute (25).

Genotoxicity: Litton Bionetics (23) conducted a mutagenicity study on menthol using the host-mediated assay, cytogenetic studies, and the dominant lethal assay. The results of all three assays were negative. Menthol pyrolysate was tested against *salmonella typhimurin* strains (21) with negative results.

Metabolism (26): The urinary metabolite of menthol was identified as menthyl glucuronide in several species.

Some test results on Haarman & Reimer menthol, concerning skin irritation and sensitization are summarized in Table VII.

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TABLE VII

Survey Of Safety Studies For H&R Menthol:
Irritation And Sensitization Tests

Test	Dose % Vehicle	Species	Test Results
Skin Irritation (OECD 404)[1]	100, 50, 25 25, 5, 1, 0 DEP	Rabbit	Irritation At 100% And 50%
Skin Irritation (Not OECD)[2]	100	Guinea Pig	No Irritation
Skin Sensitization Buehler (OECD 406)[3]	25 EtOH/DEP	Guinea Pig	No Sensitization
Skin Sensitization (Not OECD)[2]	100	Guinea Pig	No Sensitization
Eye Irritation (OECD 405)[1]	28.6 DEP	Rabbit	No Irritation
Eye Irritation (OECD 405)[1]	50 DEP	Rabbit	Slight Irritation
Eye Irritation (Not OECD)[2]	10, 20, 30 40, 50, 60 Olive Oil	Rabbit	No Irritation

[1]Author - K. Skydshaard; date - August, 1989
[2]Author - G. Hopf; date - April, 1974
[3]Author - J. Cuthbert; date - February, 1991

A few ecotoxicological data are listed in Table VIII, showing that menthol is readily biodegradable.

TABLE VIII

Ecotoxicological Data For H&R Menthol

Test	Results	Author/Year
Biodegradability	100% Degradation After 21 Days	G. Müller/1992
Fishtoxicity (*Brachydanio Rerio*)	LC0 : 13.2 mg/l LC100 : 18.4 mg/l LC50 : 15.6 mg/l[1]	N. Caspers/1992
Bacteriatoxicity (Activated Sludge)	EC50 : 237 mg/l EC50 : 306 mg/l EC5 : 89 mg/l	G. Müller/1992 Bayer AG/1992

[1]Calculated

ACKNOWLEDGMENTS

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REVIEW OF TECHNOLOGIES RELATING TO MENTHOL USE IN CIGARETTES

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ABSTRACT

The patent art relating to the use of menthol in smoking articles for the period from 1924 through 1992 has been reviewed. The majority of the patent documents reviewed have been awarded to cigarette manufacturing companies. However, a significant number of patent documents also are owned by companies which supply materials or machinery for cigarette manufacture. Approximately 100 patent documents which have been reviewed have disclosed methods for applying menthol to tobacco, methods for incorporating menthol into smoking article components, and various menthol compositions. Typically, menthol is applied to tobacco by spraying solutions or dispersions containing menthol onto tobacco. Menthol has been incorporated into papers used to manufacture cigarettes, into cigarette rods and into cigarette filters. Menthol also has been incorporated into cigarette packaging materials. Menthol compositions often use precursor compounds which release menthol when cigarettes incorporating such compounds are smoked.