New Developments in Physiological Cooling Agents

Examining the rapid development in the chemistry and use of cooling agents

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Physiological cooling agents are ubiquitous ingredients in many consumer products, such as chewing gums, toothpastes, mouthwashes, lotions and shampoos. Based on numerous new patents and publications, research and development in the field continues at a fast pace.

The chemistry and use of physiological cooling agents—or coolants—have been reviewed in relatively recent articles that cover literature published before 2005.[1–3] Also, the Web site of Leffingwell & Associates (*www.leffingwell.com*) is frequently updated and continues to be a valuable source of information.[4] The present article, warranted by rapid development in the chemistry and use of cooling agents, will focus mostly on newer publications, patents and patent applications, with references to older sources when necessary. Current patent trends will be reviewed separately at the end of this article.

According to classification suggested in the review "Progress in Physiological Cooling Agents,"[1] commercially available cooling agents with FEMA GRAS status can be divided into two major families: menthoxy and Wilkinson Sword (WS) coolants. Menthoxy coolants include menthyl esters, menthyl ethers, menthone ketals and menthol analogs. WS coolants include p-menthane-3-carboxamides and acyclic carboxamides.

Menthoxy Cooling Agents

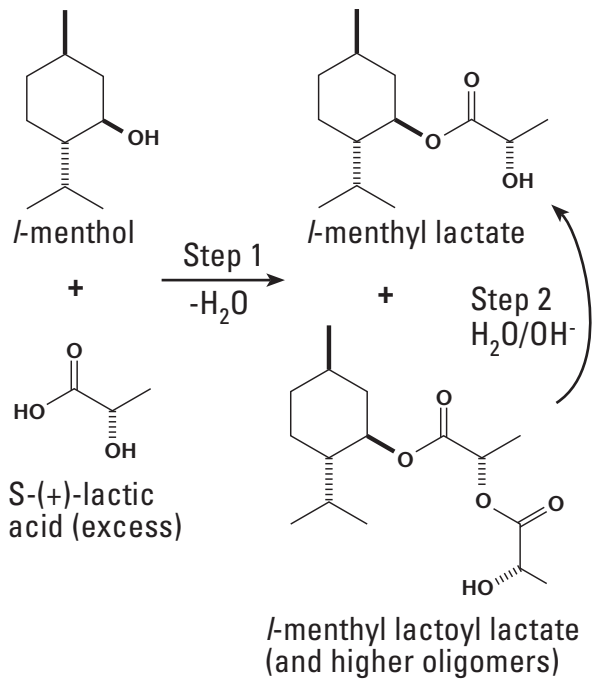
l-Menthyl lactate (FEMA 3748) is one of the most important physiological cooling agents in this family. Although this compound has been on the market for a long time, uncertainty still exists in the literature regarding the configuration of the asymmetric center at the lactic C[2]. The Household Product Database of the National Library of Medicine lists *l*-menthyl lactate under CAS 59259-38-0, which corresponds to the R-configuration.[5] The same R-configuration for the lactic center of *l*-menthyl lactate is shown in recent publications.[2,6] On the other hand, the *Sigma-Aldrich Catalog of Flavors & Fragrances (2003–2004)* lists *l*-menthyl lactate under CAS 61597-98-6, which corresponds to the S-configuration, and the S-configuration is mentioned elsewhere.[7] For clarification, we esterified menthol with S-(+)-lactic acid. The product obtained matched by GC, optical rotation, melting point and spectra the most typical samples of *l*-menthyl lactate from the market, including Frescolat ML produced by Symrise GmbH. Thus, the correct CAS number for commercial *l*-menthyl lactate is 61597-98-6, and configuration of the lactic center is "S" (see structure, scheme **F-1**).

Another "missing link" in the story of *l*-menthyl lactate has been, until now, the lack of published information on its efficient synthesis, as well as for synthesis of its isomers such as *d*-menthyl lactate, neomenthyl lactates, and isomeric mixtures such as *l*-menthyl-*d,l*-lactate. *l*-Menthyl-*d,l*-lactate was first synthesized over a century ago by esterifying racemic lactic acid with *l*-menthol, but neither experimental details nor yield were reported.[8] In a later study, esterification of S-(+)-lactic acid with a 1.75 molar excess of *l*-menthol in chloroform in the presence of an acid catalyst gave only a 39% yield of *l*-menthyl lactate. [9]

l-Menthyl lactate is usually made by reacting lactic acid with an excess of *l*-menthol.[9] Recently, Millennium Specialty Chemicals developed and patented an efficient process for obtaining *l*-menthyl lactate in high yield (over 90%) using excess lactic acid.[10] According to this process, the esterification produces a mixture of 57–68% of *l*-menthyl lactate, 24–32% of previously unknown *l*-menthyl lactoyl lactate, and smaller amounts of higher condensation products. Further, the mixture is carefully hydrolyzed by an aqueous base to convert *l*-menthyl lactoyl lactate and higher condensation products into *l*-menthyl lactate, while minimizing hydrolysis of *l*-menthyl lactate back to *l*-menthol and lactic acid (scheme F-1).

In the course of the work on this method, pure *l*-menthyl lactoyl lactate (m.p. 58–60°C) was isolated and its structure was confirmed by NMR spectroscopy.[11] Formation of *l*-menthyl lactoyl lactate can be explained by condensation of *l*-menthyl lactate with another molecule of lactic acid. Higher oligomers can be formed by further similar condensations. An alternative mechanism of formation of *l*-menthyl lactoyl lactate and higher oligomers is self-condensation of lactic acid to dimers, trimers, etc., followed by esterification of the oligomers with *l*-menthol. Most likely, these two mechanisms coexist under the reaction conditions. It is well known that *l*-menthyl lactate is somewhat unstable on storage. Usually, over the course of several weeks, it develops an acidic, pungent odor and becomes unusable for most intended applications. This loss in quality is frequently accompanied by a rise in the acid number. The shelf life of *l*-menthyl lactate

Millennium Specialty Chemicals process for *l*-menthyl lactate **F-1**



can be improved by adding small amounts of a base, for example $NaHCO_3$.[12] The mixture of *l*-menthyl lactate and inorganic salt obtainable by this method is, however, disadvantageous for some applications, especially if the presence of inorganic salt results in turbidities or precipitates in the consumer products. Recently it was found that the product can be stabilized without the addition of inorganic salts: *l*-menthyl lactate compacted under pressure is stable for a long period (at least six months), does not change from the sensory standpoint, and maintains a low acid number.[13]

Last, but not least, *l*-menthyl lactate has been detected and rigorously identified in natural cornmint oil (*Mentha arvensis*) of Indian origin, which may significantly improve its regulatory status in a number of countries.[7]

l-Monomenthyl succinate (FEMA 3810) and its closest homolog ***l-monomenthyl glutarate*** (FEMA 4006) have also been found in natural products.[6] Thus, *l*-monomenthyl succinate was identified in extracts of dry leaves of peppermint (*Mentha piperita*) and dry fruit of wolfberry (*Lycium barbarum*). *l*-Monomenthyl glutarate and *l*-dimenthyl glutarate were identified in an extract of dry fruit of *Litchi chinensis*. In the latter case, the concentrations of mono- and diester in the extract were 0.9 and 0.2 PPM, respectively, as determined by external standard quantification (monoester/diester ratio = 4.5).[6]

Certain uses of *l*-monomenthyl succinate as a physiological coolant have been patented by V. Mane Fils SA, and it is available from this supplier as a component of flavor blends sold under the trade name Physcool.[14] *l*-Monomenthyl succinate is essentially tasteless and provides a good balance of cooling onset and length of cooling.[6]

Interestingly, many uses of *l*-monomenthyl glutarate have not been patented, probably due to an early publication that gives multiple examples of consumer goods with suggested use levels of *l*-monomenthyl glutarate.[15] According to M.L. Dewis in the article "Molecules of Taste and Sensation,"[2] International Flavors & Fragrances (IFF) sells *l*-monomenthyl glutarate as "Cooler 2." The sensory profile of this product is similar to the succinate, but the onset is slower at about 40 s and the cooling is tenaciously long. From the article,[2] it appears that the commercial product is not pure *l*-monomenthyl glutarate, but rather a mixture of *l*-monomenthyl glutarate (60–70%) and *l*-dimenthyl glutarate (30–40%), with a total of the two components ≥ 97%. Evidently, the monoester/diester ratio in this product is much lower (at best 2.3) than in the natural extract from *Litchi chinensis* (4.5).

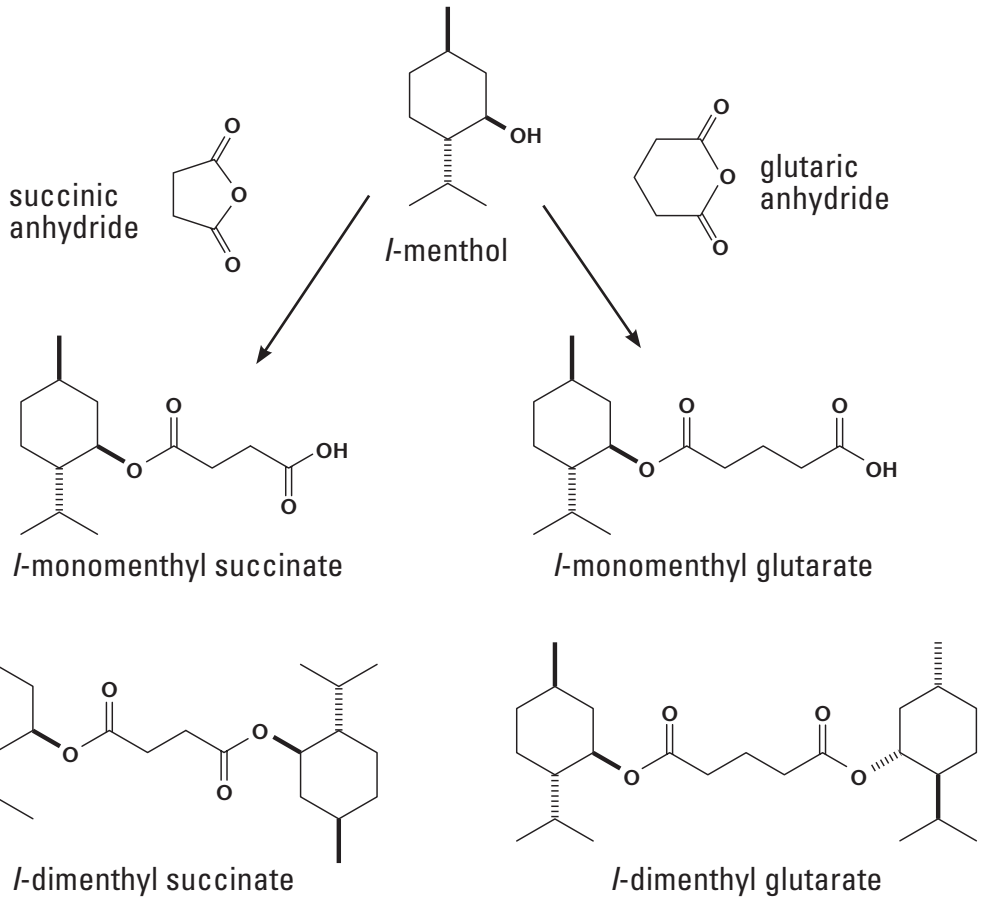
In Millennium Specialty Chemicals' research, we obtained both the mono- and diester compounds in practically pure form and separately tested their cooling properties. While we agreed, in general, with the sensory evaluation of *l*-monomenthyl glutarate given by M.L. Dewis,[2] we concluded that *l*-dimenthyl glutarate has little or no cooling value and its presence in the commercial product provides only diluent value. Therefore, it was worth looking for a synthetic method that would provide a higher ratio of monoester to diester. A few methods are known, applicable to both succinate and glutarate. The best results have been reported with *l*-menthol reacted at room temperature with a triple excess of succinic anhydride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) catalyst.[16] The practical value of this method is limited by the use of toxic materials—pyridine and DMAP—and most importantly, the triple excess of relatively expensive glutaric anhydride.

We developed a simple, economical process for making *l*-monomenthyl succinate and *l*-monomenthyl glutarate by reacting equimolar amounts of *l*-menthol and succinic or glutaric anhydride at elevated temperature in the absence of solvents and in the presence of small amounts of inexpensive base catalysts such as Na carbonate or acetate (scheme **F-2**).[17] The process provides products with a monoester/diester ratio ranging from 9 to 21. The ratio can be reduced to about 4.5, as in the natural extract, by adjusting the reaction conditions.

A new addition to the subfamily of FEMA-approved menthyl esters is ***l-menthyl pyrrolidin-2-one-5-carboxylate*** (FEMA 4154), which can be obtained by esterifying pyrrolidinone-5-carboxylic acid with *l*-menthol in the presence of p-TSA catalyst and benzene solvent.[18–20] This compound has been sold for a long time by Quest International (now Givaudan) under the trade name Questice as a cooling ingredient for cosmetics, but its use in flavors was limited.[21] According to the Quest Ingredient Guide for Cosmetics, beneficial action of Questice on skin is explained by its slow hydrolysis catalyzed by skin enzymes, producing menthol and giving an extended cooling sensation.[22] Another beneficial product formed on skin during this process is pyrrolidinone carboxylic acid, a natural moisturizer. Questice is also known as a mosquito repellent.[23] Questice is available in two forms: liquid with

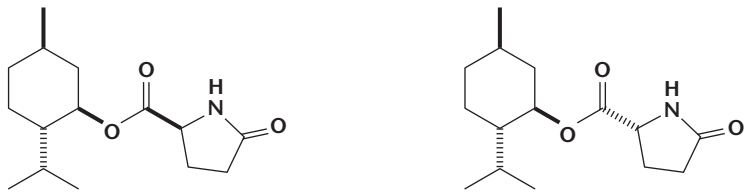
Synthesis of *l*-monomenthyl succinate and *l*-monomenthyl glutarate

F-2



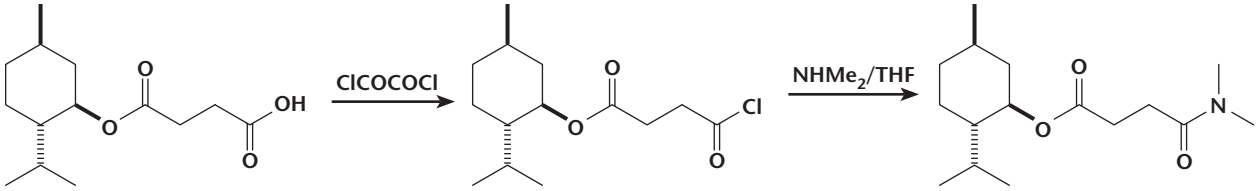
New additions to FEMA GRAS cooling agents of the menthyl ester subfamily

F-3



CAS 64519-44-4 CAS 68127-22-0

stereoisomers of *l*-menthyl pyrrolidin-2-one-5-carboxylate



l-menthyl ester of 4-(N,N-dimethylamino)-4-oxobutanoic acid

CAS 64519-44-4 and powder with CAS 68127-22-0 and 64519-44-4.[22] GC analysis on a Stabilwax column shows two peaks with a ratio of ~91:8 for the liquid form, and ~46:53 for the powder form, which confirms that the powder form is a mixture of diastereomers in nearly equal proportion, while the liquid form is predominantly the diastereomer with the S-configuration at C^5 of the pyrrolidinone ring (scheme **F-3**).

Another newly registered member of this subfamily is the ***l-menthyl ester of 4-(N,N-dimethylamino)-4-oxobutanoic acid*** (FEMA 4230), a half ester/half amide of succinic acid, which has been patented by IFF.[24] Its sensory profile is described as cooling and refreshing on the tongue, palate and front gums; it has a fruity flavor with estery topnotes and sour undertones. Synthesis of this coolant involves conversion of *l*-monomenthyl succinate with an excess of oxalyl chloride into an acid chloride followed by amination with dimethylamine in THF (scheme F-3).

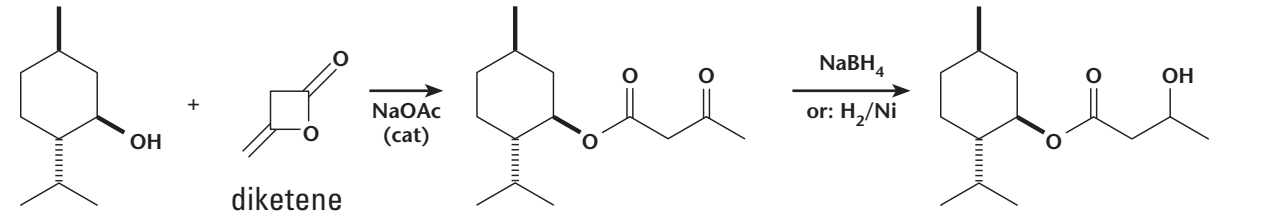
FEMA GRAS status has been also granted to another member of the ester subfamily: ***menthyl 3-hydroxybutyrate*** (FEMA 4308), which has been developed, according to a recent article, by Oxford Chemicals Ltd., in collaboration with Japan's San-Ei Gen FFI, Inc.[25] The publication does not specify stereochemistry of the menthyl group. The material is a liquid with almost no detectable odor and a cooling effect reportedly slightly stronger than that of *l*-menthyl lactate. It has a prolonged cooling effect, although with a delayed cooling sensation onset. It should be noted that this coolant was previously known. Takasago Perfumery Co. patented *l*-menthyl 3-hydroxybutyrate as a cooling agent in 1986 and described it as a colorless, odorless material having a long-lasting cooling effect, excellent safety, stability and solubility.[26,27] According to the Takasago patents, synthesis of *l*-menthyl 3-hydroxybutyrate consists of esterification of *l*-menthol with diketene to *l*-menthyl acetoacetate followed by either the reduction or hydrogenation of the latter (scheme **F-4**).

A major player in the menthyl ether subfamily of physiological cooling agents is ***3-l-menthoxypropane-1,2-diol*** (FEMA 3784), sold by Takasago under names Coolact 10, Cooling Agent 10 and TK-10. Synthetic approaches to Coolact 10 have been discussed in previous publications.[1,2]

A new addition to this subfamily is ***2-l-menthoxyethanol*** (FEMA 4154), which is produced by Takasago under the trade name Coolact 5.[18] The synthesis of this material is far from simple. In the first step, menthol is refluxed with Na hydride or Na metal in toluene. The resulting sodium mentholate is then reacted with chloroacetic acid giving *l*-menthoxyacetic acid. The latter is reduced to 2-*l*-menthoxyethanol by $LiAlH_4$ in ether (scheme **F-5**).[28]

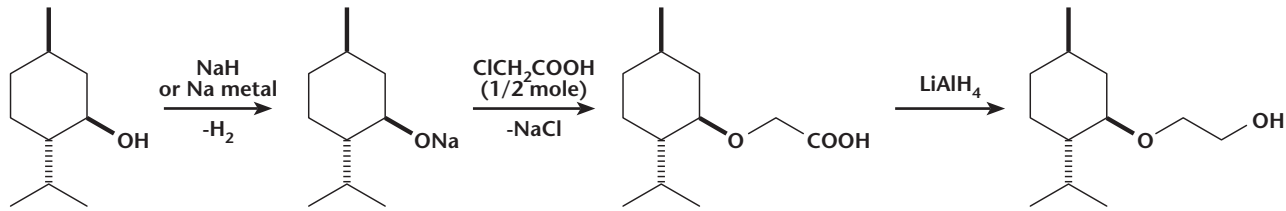
There is little or no important news to report on other menthoxy coolants. Symrise's ***l-menthone glycerol ketal*** (Frescolat MGA, FEMA 3807) and Takasago's ***p-menthane-3,8-diol*** (Coolact 38D, FEMA 4053) and ***l-isopulegol*** (Coolact P, FEMA 2962), appear to firmly

Synthesis of *l*-menthyl 3-hydroxybutyrate **F-4**



l-menthol — diketene — *l*-menthyl acetoacetate — *l*-menthyl 3-hydroxybutyrate

Synthesis of 2-*l*-menthoxyethanol **F-5**



l-menthol — Na salt of *l*-menthol — *l*-menthoxyacetic acid — 2-*l*-menthoxyethanol

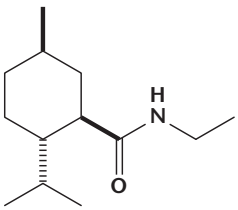
hold their commercial positions. An improved method of crystallizing *l*-isopulegol from its melts was recently claimed by BASF.[29] Moreover, Firmenich has claimed a compound somewhat similar to *l*-menthone glycerol ketal, more specifically a cyclic acylal of menthone and lactic acid, as a flavor enhancer and modifier.[30]

WS Cooling Agents

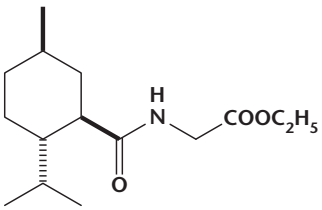
Until recently, commercially available p-menthane-3-carboxamides were represented by a single member: ***N-ethyl-p-menthane-3-carboxamide*** ("WS-3," FEMA 3455), sold by Millennium Specialty Chemicals under the trade name WinSense 3. Another compound of this subfamily, ***N-(ethoxycarbonylmethyl)-p-menthane-3-carboxamide*** ("WS-5"), a derivative of glycine, has been known for a long time as having strong cooling properties, but the compound appeared of no interest to flavorists.[31] After a detailed literature study, a patent application was located that mentions that WS-5 has a more bitter taste compared to WS-3.[32] Importantly, all known sources on the synthesis of WS-5 said to purify the product by vacuum distillation. For example, one patent recommends collecting the product within a boiling range of 150–162°C at 0.1 Torr.[33] We hypothesized that WS-5 tested in previous studies was insufficiently pure. Recrystallization of WS-5 to 96+% purity gave a product that surprisingly had virtually no bitterness and possessed a cooling effect two and a half to three times stronger than WS-3. Highly purified WS-5 has been patented and commercialized by Millennium Specialty Chemicals as WinSense 5.[34] WS-5 has been granted FEMA GRAS status (FEMA 4309) and is included in the GRAS 23 list.

Possible future entrants to the p-menthane-3-carboxamide subfamily include Givaudan's N-aryl-p-menthane-3-carboxamides, especially ***N-(4-cyanomethylphenyl)-p-menthane carboxamide***. According to a patent application, this compound is about seven times stronger as a coolant than WS-3 and is almost two times longer-acting.[35] About the same cooling intensity has been reported for ***N-(4-aminocarbonylphenyl)-p-menthane carboxamide***.[36] Examples of p-menthane-3-carboxamides are shown in scheme **F-6**.

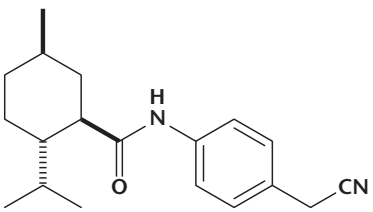
In addition to already well-known uses of p-menthane-3-carboxamides,[1-3] including its insect repellant ability,[4,37] representatives of this subfamily are also gaining ground as medicinal agents. For example, a recent patent application explains that a close analog of WS-5, ***derivative of D-alanine*** (scheme F-6), has a very prolonged cooling action on skin and mucous membranes and can be used for therapeutic purposes, including treatment of irritation, itch, cough and asthma.[38] Carboxamides and other physiological coolants can also be used for treatment of certain cancers due to their ability to activate or suppress Trp-p8 ion channels.[39,40] N-aryl p-menthane-3-carboxamides containing radioactive isotopes such as ^{125}I are especially efficient in targeting diseased cells.[41] An interesting



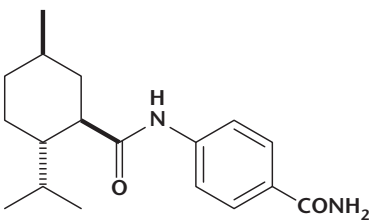
N-ethyl-p-menthane carboxamide



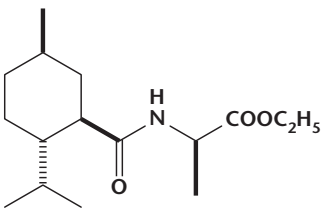
N-(ethoxycarbonylmethyl)-
p-menthane carboxamide



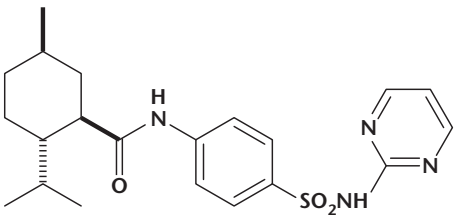
N-(4-cyanomethylphenyl)-
p-menthane carboxamide



N-(4-aminocarbonylphenyl)-
p-menthane carboxamide

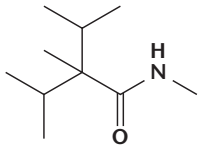


derivative of D-alanine

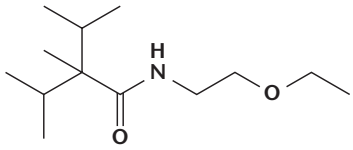


N-(3-p-menthanoyl) sulfadiazine

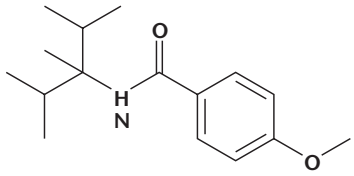
WS-23 and its structural analogs **F-7**



2-isopropyl-N,2,3-trimethylbutanamide



N-(2-ethoxyethyl)-2,3-dimethyl-2-isopropylbutanamide



N-(1-isopropyl-1-methylisobutyl)anisamide

"hybrid" of p-menthane-3-carboxamide with the antibiotic sulfadiazine, ***N-(3-p-menthanoyl) sulfadiazine*** (scheme F-6), also known as CPS-125, is a powerful, long-lasting coolant on skin and mucous membranes and is useful for the treatment of skin and gastrointestinal tract diseases.[42,43]

Among acyclic carboxamides, only one product is currently fully commercialized: ***2-isopropyl-N,2,3-trimethylbutanamide*** ("WS-23," FEMA 3804), which is sold by Millennium Specialty Chemicals under trade name WinSense 23. This compound is used in oral care, confectionary and medicinal preparations.

Qaroma recently patented a number of coolants structurally similar to WS-23, such as ***N-(2-ethoxyethyl)-2,3-dimethyl-2-isopropylbutanamide***, or "ICE 12000" by Qaroma's classification.[44] Some of Givaudan's new N-aryl-substituted carboxamides, for example ***N-(1-isopropyl-1-methylisobutyl)anisamide***, also bear structural similarity to WS-23, although with a reversed configuration of the amide moiety.[45] Structures of WS-23 and some of its analogs are shown in scheme **F-7**.

Patent Trends in Physiological Cooling Agents

Between January 2005 and April 2007, over 300 relevant US patent applications were published and over 80 patents granted. A complete report on these sources would exceed the scope of this review; therefore, some typical examples have been selected.

l-Menthyl lactate (Frescolat ML) maintains a leading position in cosmetics. Numerous examples of its use as a skin sensate in "leave-on" scalp cosmetic compositions are given in one patent.[46] *l*-Menthyl lactate is also claimed as a component of a softening cream,[47] a topical treatment[48] and skin cooling compositions.[49] It can serve as an optional sensate in gel compositions,[50] skin cleansing articles[51] and compositions for combating hair loss.[52] A new example of using *l*-menthyl lactate in flavors is given in a patent application.[53]

l-Monomenthyl succinate (Physcool) is used in coated chewing gums[54,55] and oral care compositions.[56] *l*-Monomenthyl glutarate (Cooler-2) is preferred in certain confectionary compositions,[57–59] breath-freshening tablets and films,[60,61] and methods and compositions for soothing oral and nasal tissues.[62]

Patent literature on the new FEMA additions to the menthyl ester subfamily is scarce. Among other coolants, *l*-menthyl pyrrolidinone-5-carboxylate (Questice) has been claimed[63–65] as a possible additive to a multi-component, controlled-release system for oral care, foods and beverages. The *l*-menthyl ester of 4-(N,N-dimethylamino)-4-oxobutanoic acid and its analogs can be used in chewing gums, toothpastes and candies.[24] Exemplary uses of menthyl 3-hydroxybutyrate include chewing gums, hard candies, sherbets, sodas, creams, lotions, antiperspirants, shampoos, lipsticks, toothpastes and tobacco products.[27]

3-*l*-Menthoxypropane-1,2-diol (Coolact 10) has been in the market for a long time and is used in various consumer goods, for example in cosmetics,[66–69] oral care,[70] disinfectant compositions[71] and flavors for foods and beverages.[72] The latter reference also gives examples of the use of newly registered 2-*l*-menthoxyethanol (Coolact 5) in flavors.

Patenting activity in other menthoxy coolants is illustrated by patent applications claiming *l*-menthone glycerol ketal (Frescolat MGA) and *l*-isopulegol (Coolact P) among flavor additives for beverages[73] and multicomponent, controlled-release systems for oral care.[64] Frescolat MGA and Coolact P are also claimed as cooling agents for absorbent articles.[74] Frescolat MGA is claimed among other coolants for use in chewing gums that provide breath-freshening characteristics.[54] p-Menthane-3,8-diol (Coolact 38D) is useful in antiseptic compositions.[75]

FEMA-approved WS-3 (WinSense 3) and WS-23 (WinSense 23) are abundantly represented in recent patent literature. Their uses extend from traditional flavor[76,77] and oral care[78,79] applications to ophthalmic compositions,[80] lotions for paper tissue,[81] topical patches[82] and cancer medications.[39,40] Various uses of highly purified WS-5 (WinSense 5) are claimed.[34]

An important current trend is controlled-release delivery systems for physiological coolants. One patent

claims a controlled-release cosmetic composition consisting of a plurality of solid nanospheres containing a variety of coolants.[65] A PCT application discloses a chewing gum with a delivery system comprising an encapsulating material and an encapsulated ingredient, which can be any of the known coolants.[83] Another application discloses a multi-modality, center-filled chewing gum with one or more regions containing encapsulated coolants.[84] It also gives examples with encapsulated WS coolants, including encapsulation of a combination of WS-3 and WS-23 (see Example 48 of the Application).

Another significant current trend is the continued quest for combinations of coolants that provide a synergistic effect in consumer products, meaning that the cooling strength and/or longevity of the combination exceeds that expected from the sum of cooling components taken separately. Thus, one PCT application claims a confection comprising *l*-monomenthyl glutarate and one or more other physiological coolants selected from a group consisting of *l*-isopulegol (Coolact P), p-menthane-3,8-diol (Coolact 38D), and mixtures thereof.[85] The application states that the glutarate together with *l*-isopulegol in chewing gums gives cooling properties similar to those of WS-23, a stronger coolant. Also, a three-component blend of *l*-monomenthyl glutarate, *l*-isopulegol, and p-menthane-3,8-diol gave a similar synergy in hard candy. One patent application describes shampoos and soaps in which combinations of WS-3 and *l*-menthol cool more effectively than either WS-3 or menthol alone.[86] A US patent claims synergistic combinations of p-menthane-3-carboxamides with menthyl acetate.[87] Reduced bitterness and unique, long-lasting cooling perception can be achieved in dental articles, for example floss, by using carboxamide coolants and menthol in a ratio from about 1:1 to 2.5:1.[88] Topical compositions containing a warming agent, for example vanillyl butyl ether, and small amounts of cooling agents have an increased warming effect compared to using the warming agent alone.[89] Conversely, topical compositions containing a coolant and a small amount of a warming agent impart a stronger cooling effect compared to using the cooling agent alone.[89] Generally, recent patent literature indicates that combinations of two or more sensates, including coolants, provide a stronger effect compared to that of the sum of the same sensates taken alone.

Additionally, the continued search for marketable, easy-to-use liquid blends of coolants, or "cooling cocktails" is a vital trend. Some of these blends were reviewed earlier.[1] Preferably, the cocktails do not contain solvents and/or significant amounts of *l*-menthol. Millennium Specialty Chemicals developed a series of such liquid cocktails called WinSense Extra based on all solid components: p-menthane-3-carboxamides such as WS-3 or WS-5, acyclic carboxamides such as WS-23, and *l*-menthyl lactate.[90] In addition to synergetic cooling properties, these cocktails boast excellent stability as liquids, which has been confirmed by rigorous tests including not only prolonged storage, but also seeding, freezing/thawing experiments, and mechanical disturbance. The application[90] also gives examples of cocktails that contain additional components, such as *l*-monomenthyl glutarate or 3-*l*-menthoxypropane-1,2-diol. Later, two US patent applications showed liquid combinations of WS-3 and WS-23, preferably in about a 50:50 ratio.[91,92] In this article's control experiments, however, a 50:50 mixture of WS-3 and WS-23 started crystallizing on storage at room temperature within about four weeks and began crystallizing immediately upon seeding.

There are also several new *l*-menthol-based cocktails. For example, liquid flavoring compositions containing from about 25% to about 75% of *l*-menthol and about 25% to 75% of another coolant, preferably WS-3 or WS-23 or mixtures thereof, were reported.[93] Another menthol-based cocktail, a blend of 50 g of racemic menthol, 50 g of racemic neomenthol and 25 g of *l*-menthyl lactate stays liquid at -20°C for 48 h without precipitation or solidification.[94] According to a patent application, "natural" liquid compositions can be obtained by mixing *l*-menthol, *l*-isopulegol and a natural extract imparting a trigeminal effect.[95] Another patent application teaches menthol-based compositions containing mixtures of additional coolants, for example 3-*l*-menthoxypropane-1,2-diol and *l*-isopulegol, and also salicylate esters as additives that alleviate the irritating odor of *l*-menthol.[96]

Yet another patent application employs liquid menthyl esters such as *l*-monomenthyl glutarate or *l*-monomenthyl succinate as solvents for other coolants.[97] Other cocktails composed of *l*-menthyl lactate and p-menthane-3-carboxamides require a solvent—for example, propylene glycol.[98]

Conclusion

Having started their "career" as tobacco additives half a century ago,[1] physiological cooling agents have become key components in innumerable consumer goods, including food products and beverages, cosmetics, oral care and medications. Looking at the growing number of patent applications, the expansion is far from over. Development and registration of new cooling agents continues steadily. New uses for cooling agents continue to grow. Intense studies are ongoing on the biochemical mechanisms of cooling action at the cellular and molecular levels.[99] Thus, we are still at the beginning of a long and winding road to a deeper understanding of the full potential of physiological cooling agents.

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