SUBSTITUTED p-MENTHANE COMPOSITIONS

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Field of Invention

This invention relates to compositions having a physiological cooling effect on the skin and on the mucous membrane of the body particularly those of the nose, mouth, throat and gastrointestinal tract.

Background of the Invention

Menthol is well known for its physiological cooling effect on the skin and mucous membranes of the mouth and has been extensively used as a flavouring agent (menthol being a major constituent of oil of peppermint) in foodstuffs, beverages, dentifrices, mouthwashes, etc., and as a component in a wide range of toiletries, liniments and lotions for topical application. Menthol is also a well known tobacco additive for producing a "cool" sensation in the mouth when smoking.

It is well established that the "cooling" effect of menthol is a physiological effect due to the direct action of menthol on the nerve endings of the human body responsible for the detection of hot or cold and is not due to latent heat of evaporation. It is believed that the menthol acts as a direct stimulus on the cold receptors at the nerve endings which in turn stimulate the central nervous system.

Although menthol is well established as a physiological coolant its use, in some compositions, is circumscribed by its strong minty odour and its relative volatility.

Objects of the Invention

It is an object of the present invention to provide ingestible, topical and other compositions capable of stimulating the cold receptors of the nervous system of the human body thereby to create a desirable "cool" sensation.
It is a further object of the invention to provide a method of stimulating the cold receptors of the nervous system of the human body to create a desirable cool sensation.

Other objects will be apparent from the following detailed description of the invention.

Summary of Invention

In accordance with the present invention, we have discovered a group of compounds having a pronounced physiological cooling effect, which have little or no odour, and which are of relatively low volatility. These compounds are 3-substituted-p-menthanes of the formula:

\[
\text{I} \quad \text{X} \quad \text{Y}
\]

where \(X\) is hydrogen or hydroxyl; and

\(Y\), when \(X\) is hydrogen, is a \(-\text{CHOHR}'\) or \(\text{OC}_n\text{H}_{2n}\text{OH}\) group, where \(R'\) is an alkyl, cycloalkyl, alkenyl aminoalkyl, acylaminoalkyl, carboxyalkyl or alkylcarboxyalkyl radical of up to 8, preferably up to 4, carbon atoms, and \(n\) is an integer of from 1-4; and

\(Y\), when \(X\) is hydroxyl, is an alkyl cycloalkyl, alkenyl, aminoalkyl, acylaminoalkyl, carboxyalkyl or alkylcarboxyalkyl radical of up to 8, preferably up to 4, carbon atoms.

The invention therefore provides compositions, in
particular ingestible compositions and compositions for topical application, capable of stimulating the cold receptors of the nervous system of the human body comprising an effective amount of a cold receptor stimulant and a vehicle therefor, the stimulant comprising one or more of the above defined 3-substituted-p-menthanes.

Particular compositions provided within the scope of this invention are:

1) Comestible compositions comprising an edible base, a flavourant or colourant, and a cold receptor stimulant as defined above.

2) Beverages comprising a potable base, a flavourant or colourant, and a cold receptor stimulant as defined above.

3) Lotions comprising an aqueous, alcoholic, or aqueous-alcoholic carrier, an adjuvant selected from the following: a colourant, an antiseptic or an odourant, and a cold receptor stimulant as defined above.

4) Dentifrices comprising an abrasive, a detergent or foaming agent and a cold receptor stimulant.

5) Toilet preparations, e.g. soaps and creams, comprising an oleaginous base and a cold receptor stimulant as above defined.

6) Pharmaceutical preparations comprising an antacid and a cold receptor stimulant as above defined.

7) Toilet articles, e.g. cleansing tissues and toothpicks comprising a carrier impregnated or coated with a cold receptor stimulant as defined above.

8) Articles and compositions, for chewing, smoking or
inhalation comprising tobacco and a cold receptor stimulant as defined above.

9) Tobacco filter comprising a fibrous or porous filter impregnated with one or more cold receptor stimulants as defined above.

Detailed Description

The 3-substituted-p-menthanes used in this invention may be readily prepared by conventional methods.

The carbinols of Formula I, where X is H and Y is -CHOHR', may be prepared by the reduction of

of the corresponding ketone, e.g. p-menth-3-yl methyl ketone may be reduced to give 3-(1-hydroxyethyl)-p-menthane.

The hydroxyethers of formula I, where X is H and Y is -OC\(_n\)H\(_{2n+1}\)OH may be prepared by the reaction of an alkylene oxide with menthol or by the reduction of a carboxylic acid group.

The tertiary hydroxy compounds of formula I, where X is hydroxy and Y is aliphatic may be prepared by the reaction of menthane with a Grignard reagent R'MgHa, where R' is as above defined and Ha is halogen, or with an organo lithium compound, R'Li.

Other methods of preparing the compounds used in the invention will be apparent to those skilled in the art.

The compounds used as cold receptor stimulants in accordance with this invention exhibit both geometric and optical isomerisation and, depending on the starting materials and
the methods used in their preparation the compounds may be isomerically pure, i.e. consisting of one geometric or optical isomer, or they may be isomeric mixtures, both in the geometric and optical sense.

As is well known, the basic p-menthane structure is a chair-shaped molecule which can exist in cis or trans forms. Substitution in the 3-position gives rise to four configurational or geometric isomers depending upon whether the substitution is axially or equatorially into the cis or trans isomer, the four isomers being related as menthol is to neomenthol, isomenthol, and neoisomenthol. In general it is found that in the compounds where X is H and Y is -CHOHR' or -OCnH2nOH the equatorially substituted derivatives have the greater cooling effect than the axial compounds and are to be preferred.

Substitution in the 3-position of the p-menthane structure also gives rise to optical isomerisation, each of the above-mentioned four geometric isomers existing in d, l and dl forms. The physiological cooling effect is found, in most cases, to be greater in the l-form than in the d-form, and in some cases substantially greater.

The cooling sensation created by the compounds used in this invention on the skin and mucous membranes, for example, in the mouth, varies both in intensity and longevity from compound to compound.

When X is H, Y is preferably an -OCnH2nOH group, especially a 2-hydroxyethoxy group, or a -CHOHR' group in which R' is hydrogen or a C1-C4 alkyl group, especially methyl.

When X is OH, Y is preferably C1-C4 alkyl or C1-C4 alkenyl.
Typical compounds suitable for use in the present invention are listed in Table I.

**TABLE I**

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH₂OH</td>
<td>-CH₂OH</td>
</tr>
<tr>
<td>H</td>
<td>-CHOHCH₃</td>
</tr>
<tr>
<td>&quot;</td>
<td>-CHOH₂H₅</td>
</tr>
<tr>
<td>&quot;</td>
<td>-CHOH₃H₇</td>
</tr>
<tr>
<td>&quot;</td>
<td>-CHOH₄H₉</td>
</tr>
<tr>
<td>&quot;</td>
<td>-OCH₂CH₂OH</td>
</tr>
<tr>
<td>&quot;</td>
<td>-OCH₂CH(CH₃)OH</td>
</tr>
<tr>
<td>OH</td>
<td>-CH₃</td>
</tr>
<tr>
<td>&quot;</td>
<td>-C₂H₅</td>
</tr>
<tr>
<td>&quot;</td>
<td>-C₃H₇(n)</td>
</tr>
<tr>
<td>&quot;</td>
<td>-CH₂CH=CH₂</td>
</tr>
<tr>
<td>&quot;</td>
<td>-C₄H₉(n)</td>
</tr>
</tbody>
</table>

The cold receptor stimulants used in this invention find utility in a wide variety of compositions for consumption by or application to the human body. Broadly speaking, these compositions can be divided into comestible and topical compositions, both terms being taken in their broadest possible sense. Thus comestible is to be taken as including not only foodstuffs and beverages taken into the mouth and swallowed, but also other orally ingested compositions taken for reasons other than their nutritional value, e.g. indigestion tablets, antacid preparations, laxatives, etc. Comestible compositions are also to be taken to include
edible compositions taken by mouth, but not necessarily swallowed, e.g. chewing gum. Topical compositions are to be taken as including not only compositions such as perfumes, powders and other toiletries, lotions, liniments, oils and ointments, applied to the external surfaces of the human body, whether for medical or other reasons, but also compositions applied to, or which, in normal usage, come in contact with, internal mucous membranes of the body, such as those of the nose, mouth, or throat, whether by direct or indirect application or inhalation, and thus include nasal and throat sprays, dentifrice, mouthwash and gargle compositions. Topical compositions also include toilet articles such as cleansing tissues and toothpicks.

A further class of compositions included within the scope of this invention are tobacco and associated articles, e.g. pipe and cigarette filters especially filter tips for cigarettes.

The compositions of this invention will contain an amount of the 3-substituted-p-menthane sufficient to stimulate the cold receptors in the areas of the skin or mucous membrane with which the compositions come into contact and thereby promote the desired cold sensation. As indicated, the degree and longevity of cooling sensation varies from compound to compound and therefore the quantity of stimulant used in each composition will vary widely. As a guide, it may be said that, with the more active compounds of the invention, a significant cooling sensation, which, in some cases, may persist for several hours, is achieved upon application to the skin of as little of 0.05 ml of a 0.2 weight percent solution of
the active ingredient in ethanol. For the less active compounds a significant cooling effect is achieved only with more concentrated solutions, e.g. 5.0% by weight or more of the active ingredient. It must also be admitted that such skin tests are somewhat subjective, some individuals experiencing a greater or lesser cooling sensation than others when subjected to the same test.

In formulating the compositions of this invention the 3-substituted-\(\text{p}\)-menthane will usually be incorporated into a vehicle which may be completely inert or which may be or contain other active ingredients. A wide variety of vehicles will be suitable, depending upon the end use of the composition, such vehicles including solids, liquids, emulsions, foams and gels. Typical vehicles for the 3-substituted-\(\text{p}\)-menthanes include aqueous or alcoholic solutions, oils and fats such as hydrocarbon oils, fatty acid esters, long chain alcohols and silicone oils; finely divided solids such as starch or talc; cellulosic materials such as paper tissue; tobacco; low-boiling hydrocarbons and halohydrocarbons used as aerosol propellents; gums and natural or synthetic resins.

In most compositions according to the invention the vehicle will be or contain one or more of the following: an antacid, antiseptic or analgesic, a flavourant, colourant, or odourant, or a surfactant.

The following illustrate the range of compositions into which the 3-substituted-\(\text{p}\)-menthanes can be incorporated:

1. Edible or potable compositions including alcoholic and non-alcoholic beverages; confectionery, chewing gum; cachous; ice cream; jellies;
2. Toiletries including after shave lotions, shaving soaps, creams and foams, toilet water, deodorants and antiperspirants, "solid colognes", toilet soaps, bath oils and salts, shampoos, lipsticks, hair oils, talcum powders, face creams, hand creams, sunburn lotions, cleansing tissues, dentifrices, toothpicks, mouthwashes, hair tonics and eyedrops;

3. Medicaments and allied compositions including antiseptic ointments, pile ointments, liniments, lotions, decongestants, counter-irritants, cough mixtures, throat lozenges, antacid and indigestion preparations, oral analgesics;

4. Tobacco preparations including cigars, cigarettes, pipe tobacco, chewing tobacco and snuff; tobacco filters especially filter tips for cigarettes;

5. Miscellaneous compositions such as water soluble adhesive compositions for envelopes, postage stamps, adhesive labels, etc.

Particular preparations according to the invention are discussed in more detail below.

**Edible and Potable Compositions**

The edible and potable compositions of this invention will contain the 3-substituted-\(p\)-menthan-6 in combination with an edible carrier and usually a flavouring or colouring agent. The particular effect of the 3-substituted-\(p\)-menthan-6 is to create a cool or fresh sensation in the mouth, and in some cases, even in the stomach, and therefore the compounds find particular utility in sugar-based confectionery such as chocolate, boiled sweets, mints and candy, in ice cream and jellies and in chewing gum. The formulation
of such confections will be by ordinary techniques and according to conventional recipes and as such forms no part of this invention. The 3-substituted-p-menthane will be added to the recipe at a convenient point and in amount sufficient to produce the desired cooling effect in the final product. As already indicated, the amount will vary depending upon the particular compound, the degree of cooling effect desired and the strength of other flavourants in the recipe. For general guidance, however, amounts in the range 0.1 to 10% by weight based on the total composition will be found suitable.

Similar considerations apply to the formulation of beverages. Generally speaking the compounds will find most utility in soft drinks, e.g. fruit squashes, lemonade, cola, etc., but may also be used in alcoholic beverages. The amount of compound used will generally be in the range 0.05 to 5% by weight based on the total composition.

Toiletries

Because of the cooling sensation imparted to the skin, a major utility of the 3-substituted-p-menthanes will be in a wide range of toilet preparations. The particular preparations discussed below are to be taken as exemplary.

A major utility will be in after shave lotions, toilet water, etc., where the compound will be used in alcoholic or aqueous-alcoholic solution, such solutions usually also containing a perfume or mild antiseptic or both. The amount of compound added to the formulation will usually be in the range 1.0 to 12.0% by weight based on the total composition.

Another field of utility will be in soaps, shampoos, bath oils, etc., where the compounds will be used in combination
with an oil or fat or a natural or synthetic surfactant, e.g. a fatty acid salt or a lauroylsulphate salt, the composition usually also containing an essential oil or perfume. The range of soap compositions will include soaps of all kinds, e.g. toilet soaps, shaving soaps, shaving foams, etc. Usually the compound will be added to the formulation in an amount of from 1.0 to 16.0% by weight.

A further class of toilet composition into which the 3-substituted-\(\pi\)-menthanes may be incorporated includes cosmetic creams and emollients, such creams and emollients usually comprising a base emulsion and optionally a range of ingredients such as wax, preservative, perfume, antiseptics, astringents, pigments, etc. Once again the formulation of such compositions, apart from the incorporation of the 3-substituted-\(\pi\)-menthane, usually in an amount of from 1.0 to 20.0% by weight, is conventional.

Compositions for oral hygiene into which the coolants may be incorporated include mouthwash, gargle and dentifrice compositions. The first two may be considered together and will usually comprise an aqueous, alcoholic, or aqueous-alcoholic solution of an antiseptic often coloured or flavoured for palatability, to which the 3-substituted-\(\pi\)-menthane is added in an amount of from 0.10 to 2.0% by weight.

Dentifrice compositions may be of the solid block, powder, paste or liquid type and will usually comprise a finely divided abrasive or polishing material, e.g. precipitated chalk, silica, magnesium silicate, aluminium hydroxide or other similar materials well known in the art, and a detergent or foaming agent. Optional ingredients which may also be included are flavouring agents and colourants,
antiseptics, lubricants, thickeners, emulsifiers or plasticizers. A typical toothpaste formulation to which the 3-substituted-p-menthanes may be added to give a fresh, cool sensation in the mouth, consists of:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitated chalk</td>
<td>20</td>
</tr>
<tr>
<td>Fine Silica</td>
<td>15</td>
</tr>
<tr>
<td>Magnesium Carbonate</td>
<td>4</td>
</tr>
<tr>
<td>Dicalcium Phosphate</td>
<td>6</td>
</tr>
<tr>
<td>Surfactant, e.g. alkylated aryl sulfonate</td>
<td>8</td>
</tr>
<tr>
<td>Starch glycerite</td>
<td>18</td>
</tr>
<tr>
<td>Mineral Oil</td>
<td>1</td>
</tr>
<tr>
<td>Mucilage</td>
<td>4</td>
</tr>
<tr>
<td>Syrup</td>
<td>12</td>
</tr>
<tr>
<td>Glycerin</td>
<td>12</td>
</tr>
</tbody>
</table>

The amount of 3-substituted-p-menthane added in such compositions will generally be from 1.0 to 4% by weight based on the total composition.

Medicaments

Because of their cooling effect on the skin and on the mucous membranes of the mouth, throat and nose and of the gastrointestinal tract the 3-substituted-p-menthanes may be used in a variety of oral medicines, nasal and throat sprays, and topical compositions, particularly where a counter-irritant is required. In particular the compounds may be formulated into antacid and indigestion remedies, in particular those based on sodium bicarbonate, magnesium oxide, calcium or magnesium carbonate, aluminium or magnesium hydroxide or magnesium trisilicate. In such compositions the compounds will usually be added in an amount of from 0.10 to 2.0% by weight.
The 3-substituted-p-menthanes may also be included in oral analgesic compositions, e.g. with acetyl salicylic acid or its salts, and in nasal decongestants, e.g. those containing ephedrine.

**Tobacco Preparations**

The coolants used in this invention may be incorporated directly into tobacco to give a cool effect when smoking but without the attendant strong and characteristic odour which is associated with mentholated tobacco and cigarettes. Such compositions also have considerable storage stability, which is in contrast to mentholated products. However, a more advantageous utilisation is in pipe or cigarette filters, in particular, filter tipped cigarettes. The pad of filter material, which may be of any of the well known types, e.g. cellulose acetate, paper, cotton, α-cellulose or asbestos fibre, is simply impregnated with an alcoholic solution of the coolant dried to deposit the coolant in the filter pad. The effect is to give a pleasant cool sensation in the mouth when the cigarette is smoked. As little as 0.02 mg. of the coolant is effective.

Compounds and compositions of this invention are illustrated by the following Examples. All temperatures are given in degrees Centigrade.

### Example

**Toilet Water**
A toilet water was prepared according to the following recipe:

- Denatured ethanol 75.0%
- Perfume 5.0%
- Water to 100

To the recipe was added 3.0%, based on the total composition, of 3-(2-hydroxy-n-propyloxy)-p-menthane. When applied to the face, a cooling effect was clearly noticeable on the skin well after the termination of any cooling effect attributable to the evaporation of the alcoholic carrier.

II

Deodorant composition

A deodorant composition suitable for formulation and dispensing as an aerosol under pressure of a suitable propellant was formulated according to the following recipe:

- Denatured ethanol 96.9%
- Hexachlorophene 2.0%
- Isopropyl myristate 1.0%
- Perfume 0.1%

To the composition was added 1.3% by weight of 3-allyl menthol. Application of the final composition gave rise to a definite cooling sensation on the skin.

III

Hair Shampoo

Sodium lauryl ether sulphate, 10 g, was dispersed in 90 g. water in a high speed mill. To the dispersion was added 3.3% by weight of 3-(1-hydroxyethyl)-p-menthane. When the hair is washed using the shampoo a fresh, cool sensation is noticed on the scalp.
Solid Cologne

A solid cologne was formulated according to the following recipe:

- Denatured ethanol 74.5%
- Propylene glycol 3.0%
- Sodium stearate 5.0%
- Perfume 5.0%
- Water to 100%

The sodium stearate was dissolved by stirring in a warm mixture of the ethanol, propylene glycol and water. To the solution was added the perfume and 3.0% of 3-ethyl menthol and the mixture then allowed to solidify into a waxy cake.

When applied to the forehead a distinct cooling effect is noticeable.

Eye Lotion

An eye lotion was prepared containing the following ingredients:

- Witch Hazel 12.95%
- Boric Acid 2.00
- Sodium Borate 0.50
- Allantoin 0.05
- Salicylic Acid 0.025
- Chlorobutol 0.02
- Zinc Sulphate 0.004
- Water to 100%

To the formulation was added 0.006%, based on the total composition of 3-(2-hydroxyethoxy)-P-menthane. When used to bathe the eyes a cool fresh sensation is apparent on the eyeball and eyelids.
Mouthwash

A concentrated mouthwash composition was prepared according to the following recipe:

- Ethanol 3.0%
- Berax 2.0
- Sodium bicarbonate 1.0
- Glycerol 10.0
- Flavourant 0.4
- Thymol 0.03
- Water to 100%

To the composition was added 0.1% of 3-allyl menthol.

When diluted with approximately 10 times its own volume of water and used to rinse the mouth a cooling effect is obtained in the mouth.

Toothpaste

The following ingredients were mixed in a blender:

- Dicalcium phosphate 48.0%
- Sodium lauryl sulphate 2.5
- Glycerol 24.8
- Sodium carboxymethyl cellulose 2.0
- Citrus flavourant 1.0
- Sodium saccharin 0.5
- Water to 100%

Shortly before completion of the blending operation 0.5% by weight of 3-(1-hydroxyethyl)-p-menthane was added to the blender.

When applied as a toothpaste, a strong cooling effect is noticed in the mouth.
Toothpicks

The tip of a wooden toothpick was impregnated with an alcoholic solution containing 3-((2-hydroxyethoxy)-p-menthane in sufficient amount to deposit on the toothpick 0.08 mg. of the p-menthane compound. The impregnated toothpick was then dried. When placed on the tongue there is no detectable taste, however, a distinct cooling effect is noticeable after a short period of time.

Boiled Sweet

99.5% sucrose and 0.5% citric acid were carefully fused together in the presence of a trace of water. Just before casting the melt onto a chilled plate 1.5% of 3-methyl menthol
was rapidly stirred in. The melt was then cast. A boiled sweet resulted having a marked cooling effect on the mouth.

**Example XIII**

**Mint Sweet**

Water was added to icing sugar at 40°C to form a stiff paste. 0.05% of 3-(1-hydroxy-n-propyl)-p-menthane was then stirred into the paste and the mixture allowed to set. A soft sweet mass resulted having the characteristic cooling effect in the mouth of peppermint but without the minty flavour or odour.

**Example XIV**

**Chewing Gum**

Leaves of a proprietary chewing gum were leached in running water for 168 hours to remove all water-soluble flavourants. At the end of the leaching operation the chewing gum base had no detectable minty odour or flavour. The chewing gum base was then kneaded with 5.0% of 3-ethyl menthol. When compared with the water-extracted chewing gum base, the final product showed no distinguishable change in flavour but showed a marked cooling effect in the mouth.

**Example XV**

**Cigarette tobacco**

A proprietary brand of cigarette tobacco was sprayed with an ethanolic solution of 3-methyl menthol and was rolled into cigarettes each containing approximately 40 micrograms of active compound. Smoking the impregnated cigarettes produced a cold effect in the mouth characteristic of mentholated cigarettes but without any attendant odour other than that normally associated with tobacco.
EXAMPLE AWE*

Filter tip Cigarettes

The filter tip of a proprietary brand of cigarette was impregnated with an ethanolic solution of 3-(2-hydroxy ethoxy)-\(\beta\)-menthane in an amount sufficient to deposit in the filter 0.02 mg. of the active compound. Smoking the cigarette with the impregnated tip gave rise to a noticeable cooling effect in the mouth.

EXAMPLE XVI

Antiseptic Ointment

An ointment was prepared according to the following formulation:

- Cetyltrimethyl ammonium bromide 4.0%
- Cetyl Alcohol 6.0%
- Stearyl Alcohol 6.0%
- White Paraffin 14.0%
- Mineral Oil 21.0%
- Water to 100%
The ingredients were mixed, warmed to 40°C and emulsified in a high speed blender. Added to the mixture during blending was 0.5% 3-methyl menthol.

The final ointment when applied to the skin gave rise to a marked cooling effect.

**Cleansing Tissue**

A cleansing liquid was prepared having the formulation:

- Triethanolamine Lauryl sulphate 1.0%
- Glycerol 2.0%
- Perfume .95%
- Water to 100%

To this liquid was added 1.0% of 3-(2-hydroxyethoxy)-p-menthan. A paper tissue was then soaked in the liquid.

When the impregnated tissue was used to wipe the skin a fresh cool sensation developed on the skin after a short interval.

The above Examples illustrate the range of compounds and the range of compositions included within the present invention. However, they are not to be taken as limiting the scope of the invention in any way. Other compounds within the general formula will be equally suitable for use in the compositions of Examples I-XIX and the physiological cooling effect obtained with the compounds of the invention will recommend their use in a wide variety of other compositions where the cooling effect will be of value.
Since many of the compounds used as cold receptor stimulants in accordance with this invention are known per se, we make no claim herein to compositions consisting simply of the active ingredient dissolved in a solvent.

SUBJECT TO THE FOREGOING DISCLAIMER
The claims defining the invention are as follows:

1. A composition capable of stimulating the cold receptors of the nervous system of the human body, comprising an effective amount of a cold receptor stimulant and a vehicle therefor, said stimulant being a 3-substituted-p-menthane of the formula:

   \[
   \begin{array}{c}
   X \\
   \text{Y}
   \end{array}
   \]

   where \( X \) is hydrogen or hydroxyl; and

   \( Y \), when \( X \) is hydrogen, is a \(-\text{CHOHR’}\) or \(-\text{OC}_n\text{H}_{2n}\text{OH}\) group,

   where \( R’ \) is an alkyl cycloalkyl, alkenyl, aminoalkyl, acylaminoalkyl, carboxyalkyl or alkylcarboxyalkyl radical of up to 8 carbon atoms, and

   \( n \) is an integer of from 1-4; and

   \( Y \), when \( X \) is hydroxyl, is an alkyl, cycloalkyl, alkenyl, aminoalkyl, acylaminoalkyl, carboxyalkyl or alkylcarboxyalkyl radical of up to 8 carbon atoms.

2. A composition according to claim 1, wherein the cold receptor stimulant is of the formula defined where \( X \) is hydrogen and \( Y \) is \(-\text{OC}_n\text{H}_{2n}\text{OH}\) or \(-\text{CHOHR’}\), where \( R’ \) is \( C_1-C_4 \) alkyl, and \( n \) is 1 or 2.

3. A composition according to claim 1, wherein the cold receptor stimulant is of the formula defined, where \( X \) is hydroxyl and \( Y \) is \( C_1-C_4 \) alkyl or \( C_1-C_4 \) alkenyl.

4. An ingestible composition capable of stimulating the cold receptors of the nerve endings of the mouth and gastrointestinal
tract comprising an edible carrier and an effective amount of a cold receptor stimulant as defined in claim 1.

5. A composition for topical application to the human body and capable of stimulating the cold receptors of the nerve endings in the skin, comprising a pharmaceutically acceptable carrier and an effective amount of a cold receptor stimulant as defined in claim 1.

6. A cleansing tissue comprising a fibrous carrier impregnated with a liquid containing an effective amount of a cold receptor stimulant as defined in claim 1.

7. A tobacco filter comprising a filter pad impregnated with an effective amount of a cold receptor stimulant as defined in claim 1.

8. A tobacco preparation comprising tobacco impregnated with an effective amount of a cold receptor stimulant as defined in claim 1.

9. A toothpick coated or impregnated with an effective amount of a cold receptor stimulant as defined in claim 1.

10. A comestible composition comprising an edible base, a flavourant or colourant, and one or both of the following:
    3-(2-hydroxyethoxy)-p-menthane;
    3-methyl menthol.

11. A beverage comprising a potable base, a flavourant or colourant and one or both of the following:
    3-(2-hydroxyethoxy)-p-menthane;
    3-methyl menthol.

12. A lotion comprising an aqueous, alcholic, or aqueous-alcoholic carrier, an adjuvant selected from the following: a colourant, an antiseptic or an odourant; and one or both of
the following:

3-(2-hydroxyethoxy)-p-menthane;
3-methyl menthol.

13. A dentifrice comprising an abrasive, a detergent or foaming agent and one or both of the following:

3-(2-hydroxyethoxy)-p-menthane;
3-methyl menthol.

14. A toilet preparation comprising an oleaginous base and one or both of the following:

3-(2-hydroxyethoxy)-p-menthane;
3-methyl menthol.

15. A pharmaceutical preparation comprising an antacid and one or both of the following:

3-(2-hydroxyethoxy)-p-menthane;
3-methyl menthol.

16. A cleansing tissue comprising a fibrous carrier impregnated with one or both of the following:

3-(2-hydroxyethoxy)-p-menthane;
3-methyl menthol.

17. An article or composition containing tobacco and one or both of the following:

3-(2-hydroxyethoxy)-p-menthane;
3-methyl menthol.

18. A soap composition containing a surfactant and one or both of the following:

3-(2-hydroxyethoxy)-p-menthane;
3-methyl menthol.

19. A method of stimulating cold receptors of the nervous system of the human body which comprises contacting the cold receptors with an effective amount of a cold receptor stimu-
lant as defined in claim 1.

20. A composition capable of stimulating the cold receptors of the nervous system of the human body substantially as described with reference to any one of the foregoing Examples I to XV.


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