Inhibition of Perspiration


U.S. Cl. 424—65

In the disclosure

The development of perspiration is inhibited by topical application of small quantities of:

\[
\text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O}
\]

wherein \(n\) is from 1 to 3, \(R\) is alkylene of 1 to 5 carbon atoms, \(R^1\) and \(R^2\) are alkyls of 1 to 5 carbon atoms or are conjoined to form a nitrogen-containing ring having from 4 to 6 carbon atoms; such compounds substituted with non-interfering atoms or radicals on the carbon atoms thereof; or salts of the compounds. Preferably, the perspiration-inhibiting compound is 3-phenyl-3-carboxy-(beta-diethylamino)-ethoxy-2,3-dihydrobenzofuran hydrochloride, it is present in a cosmetic composition at a concentration of from 0.02 to 1.0% and application is to the human axillae in sufficient quantity to deposit a total of from 0.1 to 20 milligrams of the perspiration-inhibiting compound. Also described are cosmetic compositions containing the active perspiration-inhibiting compound.

Subject of the invention

This invention relates to a method for inhibiting the production of perspiration, especially human perspiration from the axillae. More particularly, the perspiration-inhibiting method includes topical application to the axillae or other sweat-producing portions of the body of a compound of the formula:

\[
\text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O}
\]

preferably in solution or emulsion in a cosmetic composition. Such composition is also within the invention.

Background of the invention

In most of the commercial antiperspirant cosmetics on the market the active antiperspirant ingredient is usually an astringent salt of aluminum, zinc, zirconium or rare earth metal. Such salts are generally not immediately effective antiperspirants upon first use and often require a number of applications over a period of time to reach a desired level of antiperspirant activity. The salts also tend to react with the skin and change its chemical composition. Therefore, work has been undertaken to discover compounds which will quickly have desired antiperspirant activities, without the need for a series of applications to obtain useful antiperspirant effects. Of course, such products should also be harmless to clothing and the skin.

Various anticholinergic materials have been employed as antiperspirants. They pharmacologically prevent the stimulation of the eccrine sweat glands by interfering with the activity of acetylcholine. Now, the present inventors have discovered that their compounds, and derivatives thereof, which have previously been characterized as being analgesics, hypotensive agents, local anesthetics and antispasmodics, also possess significantly useful antiperspirant properties upon being topically applied to sweat-generating areas of the body.

Description of the invention

In accordance with the present invention a method for inhibiting perspiration comprises applying to the locus of sweat glands and/or ducts a perspiration-inhibiting amount of a compound of the formula:

\[
\text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O}
\]

wherein \(n\) is from 1 to 3, \(R\) is alkylene of 1 to 5 carbon atoms, \(R^1\) and \(R^2\) are alkyls of 1 to 5 carbon atoms or are conjoined to form nitrogen-containing rings having from 4 to 6 carbon atoms; such compounds substituted with non-interfering atoms or radicals on the carbon atoms thereof; or salts of such types of compounds. A preferred compound to be used is 3-phenyl-3-carboxy-(beta-diethylamino)-ethoxy-2,3-dihydrobenzofuran hydrochloride. The antiperspirant compound is preferably applied as a constituent of an aqueous cosmetic solution or emulsion. Such cosmetic is also a part of the present invention.

Detailed description of the invention

The active perspiration-inhibiting compounds of this invention are those wherein \(n\) is from 1 to 5, preferably 1 or 2 and most preferably 1 thereof. The dihydrobenzofuran compounds are considered to be the most active of these materials but in particular applications the compounds based on pyrans are sufficiently active to be preferably employed either in place of or in supplement of the furan based materials. Although in the most preferred embodiments of the invention \(R\) is ethylene, \(n\)-propylene and isopropylene are also acceptable to make an active antiperspirant and often the methylene, butylene and amylene radicals are effective, so that in comparatively broad embodiments of the invention \(R\) may be alkylene of 1 to 5 carbon atoms, straight-chained or branched. The \(R^1\) and \(R^2\) substituents on the amino nitrogen may be any suitable lower alkyls but generally are of 1 to 5 carbon atoms, preferably of 2 to 3 carbon atoms and most preferably, are both ethyl radicals. It is not required that \(R^1\) and \(R^2\) be identical although compounds in which they are the same are preferred. \(R^1\) and \(R^2\) may be conjoined to form a hydrogen-containing ring of 4 to 6 carbon atoms. It is preferred that, in addition to the amino nitrogen, only carbon atoms be in such a ring.

The unsubstituted compounds of the formulas given above are presently preferred but it is within this invention to substitute for hydrogen atoms thereof other non-interfering atoms or radicals. Such substitution will normally be limited to no more than 20% of the hydrogen atoms present, preferably to 10% or fewer thereof. The substitution may be on the aliphatic carbon atoms although it will be more common and more acceptable to
substitute on the aromatic carbon atoms. Substituents may be any suitable atoms or radicals which are non-interfering with the antiperspirant activity of the compound or, in some cases, which may improve the aromatic ring activity; among the substituents which may be present are halogens, including bromine, chlorine, iodine and fluorine; nitro; amino; hydroxy; lower alkyl, especially of 1 to 3 carbon atoms and preferably, ethyl; and lower alkoxy, preferably of 1 to 3 carbon atoms. Normally there will be no more than one such substituent on any one aromatic ring. R₁, R₂, R₃ or R₄ or two or more of these substituents are jointed, the limit will be two substituents for the nitrogen-containing ring, and preferably, only one.

In preferred embodiments of the invention the unsubstituted or substituted active compounds are salt-forming, preferably of such a type as to be substantially water soluble. Such salts are those of acids, such as the hydrohalic acids, e.g., hydrobromic acid, hydrochloric acid, hydriodic acid and, in some cases, hydrofluoric acid. Although the hydrohalic acids are preferred salt-forming acids, especially useful with the unsubstituted compounds, various other well known acids capable of forming salts with amines may be utilized, such as sulfuric acid, sulfurous acid, acetic acid, phosphoric acid, boric acid, gluconic acid and carboxylic acid. Salts resulting from reactions with such acids or similar salt-forming materials will usually be of greater water solubility than the starting active compound and therefore, will be more readily soluble in and compatible with aqueous media usually employed for application of the active compounds to the loci of perspiration glands and ducts.

Representative of the compounds within the invention that may be employed are the following:

<table>
<thead>
<tr>
<th>No.</th>
<th>n</th>
<th>R₁</th>
<th>R₂</th>
<th>Salt-forming acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Ethylene</td>
<td>Ethyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Isopropyl</td>
<td>Propyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>n-Amyl</td>
<td>n-Amyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>n-Amyl</td>
<td>n-Amyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>n-Amyl</td>
<td>n-Amyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>n-Amyl</td>
<td>n-Amyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>n-Amyl</td>
<td>n-Amyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>n-Amyl</td>
<td>n-Amyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>n-Amyl</td>
<td>n-Amyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>n-Amyl</td>
<td>n-Amyl</td>
<td>Ethyl-HCl or HCl</td>
</tr>
</tbody>
</table>

Because most of the active compounds of the types herein described are solids, they are usually incorporated into liquid, paste, gelatinous, spray and other suitable media to assist in their being better applied topically to the locus wherein perspiration is normally generated. Although various vehicles may be utilized, including the water soluble monohydric and polyhydric alcohols, e.g., alcohols of from 1 to 6 carbon atoms and 1 to 5 hydroxyls, such as ethanol, propanol, isopropanol, glycerol, sorbitol, ethylene glycol, propylene glycol; poly-lower alkylen glycols such as polyethylene glycols (Carbowaxes of molecular weights from 300 to 10,000); monoglycerides in which the fatty acid component is of 12 to 18 carbon atoms, e.g., glycerol monolaurate, plus other materials to improve various properties of the cosmetic preparations, the most important carrier for the anhydrotic compound will usually be water. In some cases, it may be used with an additional cosmetic, emulsifier, or "aesthetic" agents but generally such will be present to make the product more attractive and more acceptable to the consumer. The water employed will preferably be deionized water or water low in dissolved salts or hardness ions. Preferably, the hardness of the water will be under 10 parts per million, calculated as calcium carbonate. Although deionized water is used in most such cosmetic formulations to prevent any possible interference of the hardness ions with antiperspirant activity, which might be caused by precipitation of insoluble salts, in many cases it will be possible to employ city tap water, usually having less than 100 p.p.m. of hardness, as calcium carbonate. Waters of greater hardnesses are useful so long as the composition is one in which precipitation of insoluble salts does not adversely affect the final product. Of course, the water employed may be deionized or dispersed a constituent raw material of the product.

To assist the aqueous solution or dispersion of the present anhydrotic compounds in contacting and "penetrating" the skin at the sites of sweat glands or ducts, it is highly preferably that a wetting agent be present. Of such use may be any of the nonionics, preferably, ethylene, amphoteric, anionic or cationic, are also useful.

A preferred nonionic surface active agent is of the type sold under the trade name Pluronic® a condensation product of ethylene oxide with a hydrophobic base portion obtained by condensing propylene oxide with propylene glycol. Various Pluronics are suitable, including those identified as L61, L64 and F68, with the last mentioned being preferred. The molecular weights of such and similar condensation products of lower alkylen oxides with a lower alkylen oxide-lower alkylen glycol hydrophobic base are usually from about 2,000 to 20,000 and the lower alkylenes are of 2 to 4 carbon atoms, with those of three or four carbon atoms being used to make the hydrophobic portion of the molecule, which generally has molecular weight of from about 1,200 to 2,500, preferably 1,500 to 1,800.

Other nonionic surface active agents that are useful in the practice of the present invention include the condensation products of lower alkylen oxides, which are hydrophilic, with organic hydrophobes, either aliphatic or aromatic. Such compounds include detergents that are polyalkylene glycol ethers, ethers or thioethers, wherein the hydrophobic portions of the molecules contain from about 8 to 18 carbon atoms and the number of alkylen oxides, almost always ethylene oxide, is from about 3 to 50. The hydrophobic groups may be long chain fatty alcohols or ethers of 8 to 18 carbon atoms, or alkyl phenols or alkyl thioethers in which the alkyl groups are of 6 to 12 carbon atoms, preferably of eight or nine carbon atoms, either straight chained or branched. Also useful are the tertiary trialkyl amine oxides wherein one alkyl has 10 to 18 carbon atoms and the other two are of 1 to 3 carbon atoms. Specific examples of such useful nonionic surface active agents include lauryl polyoxyethylene wherein there are present 20 moles of ethylene oxide per mole of fatty alcohol, nonyl phenol polyethoxylate containing 15 moles of ethylene oxide per mole and dodecyl dimethylamine oxide.

In addition to or in replacement of the nonionic surface active agents, amphoteric compounds such as the alkyl beta-imino dipropionates, imidazoline compounds of the Miranol® type and alkyl beta-amino propionates, the alkyl groups of which compounds are of 8 to 14 carbon atoms, are also useful. The cationic surface active agents are generally quaternary ammonium salts wherein one or two of the substituents on the quaternary nitrogen are hydrophobic "long chain" radicals and two or three are short chain alkyls, with the salt-forming ion being any suitable such ion, such as halide, including chloride, iodide and bromide, phosphates, nitrates, methosulfate, sulfate or sulfonate. Generally the hydrophobic substituents will contain from 8 to 25 carbon atoms, either as aliphatic or aliphatic-aromatic radicals, e.g., alkyl or alkyl benzene.

Specific examples of quaternary compounds are cetyl trimethyl ammonium bromide, benzethonium chloride, N-cetyl pyridinium bromide, and dodecyl dimethyl benzyl ammonium chloride.

Among the anionic surface active agents that are useful there may be mentioned the sulfated and sulfonated synthetic organic detergents, such as the higher alkyl sulfates; the higher alkyl aromatic sulfonates; the sulfonated amides of higher fatty acids; the higher fatty acid monoglyceride sulfates; the higher alkyl poly-lower alkyl ether
sulfates and sulfonates; the higher olefin sulfonates; and the mono and di-higher alkyl sulfosuccinates. The salt-forming ions will preferably be sodium, potassium, ammonium or lower alkanolammonium. The alkyls will usually be of 8 to 18 carbon atoms and the lower alkoxies will be of 2 to 3 carbon atoms, preferably two carbon atoms. Specific examples of such materials which may be employed include: sodium lauryl sulfate; sodium n-octadecyl sulfate; monothanolammonium pentadecyl sulfate; diethanolammonium oleyl sulfate; sodium dioctyl sulfosuccinate; sodium nonyl benzene sulfonate; potassium pentadecyl benzene sulfonate; sodium tridecyl benzene sulfonate; sodium salt of the lauric acid amide of taurine; sodium coconut oil monoglyceride sulfate; sodium N-lauroyl sarcoside; and the potassium salt of the oleic acid ester of isethionic acid. Also useful are the higher fatty acid soaps, such as those made from mixtures of coconut oil and tallow, saponified by sodium hydroxide or potassium hydroxide.

Although the various vehicles and surface active agents improve the power of the active ingredient to contact the entire surface of the skin to which it is applied and thereby help make it more effective, they also often facilitate the production of the antiperspirant compound of a composition, containing the antiperspirant compound, which is cosmetically desirable and which is in an acceptable physical state for application by the users, solutions, emulsions, gels, powders, sprays, including aerosols, may be made from such ingredients alone. Usually, however, various adjuvants will also be present, either to improve the appearance, physical characteristics or cosmetic acceptability of the product or to give it other desirable properties. Thus, among such adjuvants are: thickening agents, e.g., hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, sodium carboxymethyl cellulose; humectants, e.g., glycerol, propylene glycol; emulsifiers; pH-regulating agents, such as salts of weak acids and strong bases or strong acids and weak bases, e.g., sodium acetate, borates; perfumes; dyes; pigments, preferably water dispersible; carriers, e.g., talc, diatomaceous earth; sequestrants, e.g., trisodium nitrotriacetate, tetrasodium ethylene diamine tetraacetate; fatty materials and oils, e.g., paraffin, petrolatum, monoglycerides, diglycerides, stearic acid; propellants, e.g., propellants 11, 12, 114; bactericides, e.g., orthophenylphenol; fungicides; and antibiotics, e.g., neomycin.

Although not necessary, various "astringent" salts and other anhidrotic compounds may also be employed to supplement the actions of the present active materials. Thus, aluminum chloride, aluminum chlorohydroxide, zincronium chloride, zinc phenolsulfonate, aluminum sulfate and other such astringents may be used. Generally, the astringent metal salts will be salts of aluminum, zincronium or zinc but other similarly effective metal salts and other anhidrotic materials can either be incorporated in the present compositions or may be separately, sequentially applied to loci of sweating to obtain improved anhidrotic actions.

The proportion of active antiperspirant compound of the formula previously given which is present in the antiperspirant compositions will usually be from 0.01 to 2%, preferably from 0.02 to 1.0% and most preferably from 0.05 to 0.5%. Higher concentrations than those will not usually be proportionately more effective than medium or lower concentrations in the ranges set forth and in some cases, the amounts of anhidrotic compound could adversely affect body functions of some users. When lesser amounts than those of the lower portions of the ranges given are used, the quantity of antiperspirant composition necessary to maintain the desired amount of anhidrotic compound may be so great as to be impracticable. The medium for the antiperspirant compositions may constitute the remainder of the product but preferably, because of the utilities of desirable surface active agent components and other adjuvants, the medium, preferably aqueous or aqueous alcohol, will be from 50 to 99.8%, preferably from 75 to 99% and most preferably from 90 to 99% of the final product.

The surface active agent, preferably a nonionic detergent material, although wetting agents and hydrotropic compounds may also be used, will generally be from 0.2 to 20% of the composition, preferably from 0.5 to 10% and most preferably from 0.5 to 3% thereof. Utilizing such ratios, the desired wetting effect is obtained and the amount of wetting agent employed is not so great as to make the composition unduly sticky or otherwise objectionable. The "dryness" and lack of stickiness of the product are useful advantages thereof and therefore, the proportions of adjuvants, non-evaporating vehicles and other constituents will normally be held as low as feasible. If, however, additive or synergistic effects are obtainable by utilizing an astringent metal salt with the active anhidrotic compound and are important, such materials may also be present in these compositions. Generally, the proportions thereof will be from 1 to 20%, preferably from 1 to 10%, and most preferably, about 2 to 5%. Of course, the particular metal salts and other constituents present in the compositions will be chosen so as to be compatible with the active anhidrotic compound utilized. The various adjuvants employed will usually constitute only a minor proportion of the composition. However, in aerosol sprays or powders, this proportion may be increased to as much as 98%. Normally, the proportion of adjuvants present will be from 0.1 to 25%, preferably from 0.1 to 15% and most preferably from 0.5 to 5%. Individual adjuvants, other than those of the two types mentioned specifically above will ordinarily be limited to from 0.1 to 10%, preferably from 0.1 to 5% and most preferably from 0.1 to 2% of the composition.

The amounts of the mentioned compositions which will be applied at any one time will generally be such as to deposit rather evenly on the locus to be treated, usually the axillae, from 0.1 to 20 milligrams of the active anhidrotic compound, e.g., 3-phenol-3-carbo-(beta-diethylamino)-ethoxy-2,4-dihydroxy-3-carbon chloride. Preferably, from 0.1 to 10 milligrams and most preferably, from 0.5 to 5 milligrams will be applied. When application is to the axillae, approximately half the total amount will be applied to each. Applications to other portions of the body will normally be regulated so that the total amounts of the active anhidrotic compound applied will be proportional to the sweating normally observed thereon. However, the application of more than 20 milligrams of the anhidrotic compound to the body at one time will usually be avoided. Although the compositions and methods are most useful in the treatment of human adult sweating and ordinarily would not be used by children or animals, it is also within the invention for them to be so employed. The amounts to be applied in such cases will be adjusted in accordance with the previously given factors and the limits on applications will usually be proportional to the weight of the subject, compared to an adult human being.

The amount of anhidrotic compound or antiperspirant composition being used will satisfy the above-mentioned requirements for effective application of the active ingredient. Usually, from 0.05 to 10 milliliters of the antiperspirant composition will obtain the desired amount of anhidrotic compound. Preferably, the total amount of composition applied will be from 0.1 to 5 milliliters and most preferably, from 0.5 to 2 milliliters. The amounts given will be halved for each axilla when the composition is being applied to both axillae.

Application of the aqueous, aqueous alcoholic or other compositions of this invention in solution, emulsion, spray, powder or other form will normally be made to the locus to be treated at room temperature, preferably from a roll-on applicator or by dabbing or padding the skin. Alternatively, the composition may be applied as a cream or lotion, an aerosol spray, either liquid or powder, or as a "antiperspirant talcum powder". Application may be effect-
ed once a day, although up to three such applications per day, in the case of a severe problem, may be employed. In such instances the total amount of anhidrotic compound applied (which excludes the astringent metal salts, for purpose of description herein) will be limited to the maximum limits previously recited, over a 24 hour period. The locus being treated will usually be the axillae but useful application may be made to the chest, back, buttocks, arms, palms, face, forehead, pubic region, legs and feet. Application is usually topical but may be subcutaneous or iontophoretic, too.

After application of the anhidrotic compound or composition containing it, a diminution of excretion of perspiration will be noted, generally beginning a short time after application of the anhidrotic compound, usually within one to three hours. The effect will gradually increase, with a maximum antiperspirant activity being noted at a time about 4 to 10 hours after application, followed by a gradual diminution of such activity until, after about 20 to 24 hours, little effect is observed. When the anhidrotic compound is employed with other similar materials or with the astringent metal salts, the additive and sometimes, the synergistic effects obtained from the presence of such combinations of materials, allow even more prompt initiation of antiperspirant activity and extend it over a longer period of time. Needless to say, to obtain such desired effects it is important that intermicellar or intermolecular interactions between constituents of the compositions employed should be avoided and the materials will be selected with this consideration in mind.

The anhidrosis resulting from the procedures of the present invention is not perfect and, desirably, some perspiring is permitted which is considered to be beneficial. Thus, the pores are not completely closed but the excessive perspiration which often results in an uncomfortable wetness in the axillae and which gives rise to chemical changes that produce malodorous products, may be avoidable. The diminution of perspiration is noted in panel tests, utilizing a number of human subjects with a variety of problems and is also confirmed in "in vitro" animal tests wherein sweating is stimulated by application of pilocarpine or electrical shock to the loci of the sweat glands and ducts being topically or subcutaneously treated. By means of these tests the significant effectiveness of the present anhidrotic compounds, processes and compositions is established.

The present invention results in several significant advantages and allows the production of antiperspirant compositions which are superior in various respects to those presently on the market. Because the described anhidrotic compounds act to prevent the secretion of perspiration by the sweat glands, their use does not result in milia, which may accompany the antiperspirant use of astringent heavy metal salts, such as those of aluminum, zirconium and zinc, presently employed in most commercial antiperspirants. The very small quantities of material necessarily applied do not feel sticky, heavy or drying to the skin. After about twenty hours the antiperspirant effect of the present anhidrotic compounds completely disappears, showing that the compounds are no longer present. This may often be desirable because chemical reactions by which the antiperspirant compound is held to the skin for long periods of time are avoided and discontinuation of application can soon result in complete elimination of the anhidrotic material. Such a result is not obtainable when utilizing heavy metal astringent salt antiperspirants, which tend to react with the skin and inhibit perspiration on the body to some extent for days after discontinuation of application. Thus, with the present compounds, continued use does not result in a buildup of the anhidrotic compound beyond an acceptable concentration. The present anhidrotic materials are compatible with various cosmetic bases, are safe to use, economical to manufacture and effective selectively at particular sites. They represent a useful advance in the antiperspirant cosmetic art.

The following examples illustrate various embodiments of the present invention. Clearly, the examples should not be interpreted as limiting the invention. Unless otherwise indicated, all parts are by weight and all temperatures are in degrees C.

Example 1

A preferred antiperspirant cosmetic composition is prepared by dissolving 3-phenyl-3-carbo-(beta-diethylamino) ethoxy-2,3-diiodobenzofuran hydrochloride, hereinafter referred to as Compound A, at the rate of 0.5 gram per liter in a deionized water solution containing 1% of the nonionic surfactant active agent identified as Pluronic F68. The product resulting is a clear solution, having a pH of about 6.

Applications of the above solution are made to a panel of human testers whose normal perspiration rates have been established. Shortly before commencement of the test, such perspiration rates are verified by measuring absorption of perspiration by sponges taped to particular regions of the axillae of the subjects. Of course, for such tests, other antiperspirant materials are employed.

To the axillae of each of the subjects, are topically applied one milliliter portions of the subject antiperspirant composition, divided equally between the two axillae (½ ml. applied to each axilla). Then, sponge pads are taped to the axillae and perspiration rates are determined by periodically removing the pads and weighing them to determine the amount of absorbed perspiration. In other tests, ¼ ml. of the anhidrotic composition is applied to one of the axillae and other is left as a control, with perspiration rates being measured from each such axilla.

In a few instances, little antiperspirant activity is noted but in a major proportion of the 15 subject panel employed a significant reduction in perspiration is noted. The maximum average reduction takes place from 3 to 6 hours after application of the antiperspirant. At such times, reductions in perspiration rates as high as about 60% are noted and the average reduction is about 25%.

Continued monitoring of perspiration rates from the treated sites indicates that the significant antiperspirant action disappears about 20 hours after application. At such time, the content of Compound A at the axillae is nil.

Thus, daily or twice daily applications are effected to maintain a low level of perspiration development continuously.

The axillae are observed after use of Compound A and are found to show no evidence of milia or of any other irritation or inflammation. No interferences with autonomic functions are observed except that desired, at the levels of application, nor do the subjects complain of any untoward reactions from the antiperspirant.

When the pads are removed, it is noted that although perspiration is excreted, the diminished rate thereof significantly improves the dryness of the axillae.

The above experiment is repeated, using an increased quantity of Compound A, ten times that previously employed. This is done by repeating the experiment exactly with the exception that the antiperspirant solution contains five grams per liter of Compound A. The antiperspirant and other results obtained are essentially the same as those previously described in this example, indicating that substantial savings in the amounts of Compound A and similar such materials employed may be made by utilizing very low concentrations thereof.

When, in the above compositions, Compound A is replaced by the free acid (instead of the hydrochloride), the content of Pluronic F68 is varied from 0.2 to 10% or is replaced to a similar extent by sodium lauryl sulfate, cetyl trimethyl ammonium bromide, sodium N-lauroyl sarcoside, lauryl dimethyl ammonium oxide or an alkyl beta-imino dipropionate, antiperspirant action is also obtained. Similarly, when from 5 to 25% of the water
is replaced with ethanol, such action is observed and there is an initial drying effect as the product is applied. This also true when topical application is to other parts of the body, e.g., forehead, arms, legs, feet and chest.

The effects described above are also obtained when the active ingredient, Compound A or its acid form, is incorporated in the proportions given in other aqueous cosmetic antiperspirants, such as a roll-on emulsion, a cream, an alcoholic alcoholic spray, an aerosol spray or a solution. Such preparations may also contain metal salt antiperspirants, e.g., 2 to 10% aluminum chlorohydride or anticholinergic agents, e.g., 0.0001 to 0.1% atropine or scopolamine, for an additive or synergistic antiperspirant effect.

Example 2

Other antiperspirant compositions are of the same basic formula as given in Example 1, with 500 or 50 milligrams per milliliter of active ingredient, 1% Pluronic F68 and the balance water. In these compositions, Compound A is replaced by the materials numbered 1–10, listed at column 3, line 35 of this specification. Any of the salt forms mentioned there or the corresponding acid forms are used.

When R1 and R2 are changed from ethyl to lower alkyl, e.g., propyl, isopropyl or n-propyl, substantially the same antiperspirant effect is obtained. When R is changed from ethylene to other lower alkylene, such as isopropylene, n-amylene or n-propylene, similar action obtains. When n is 2 or 3 and when R1 and R2 conjoin, as in the formation of a piperidine ring, antiperspirant effects are obtainable but care should be taken so as to maintain n, R, R1 and R2 balanced for the best antiperspirant action. This also applies when substituents such as bromine, chloride, iodine, nitro, hydroxyl, amino and lower alkyl replace hydrogens on aliphatic or aromatic carbons to the extent of up to 20% of the hydrogen atoms thereof. Best results will generally be obtained when the degree of substitution is limited. For example, Compound A, changed only to include a chloride atom in the para position of the phenyl, will usually be more effective as an anhidrotic agent than more complex substituted analogues.

The above compounds also possess various other desirable properties of the present anhidrotic agents, the most preferred of which are described in Example 1 (Compound A, hydrochloride and acid form). Thus, they counteract the development of perspiration, while not interfering with autonomic functions and not causing miliaria or other adverse effects on the skin. They also may be shown to be useful antiperspirant agents by the Cat Paw Assay test of De Salva et al. (Fed. Proc., 1969) and this test may be used to screen out the less effective of such materials.

Example 3

In addition to in vivo tests on humans, described in Example 1, more accurately reproducible tests of Compound A (see Example 1) are conducted, following the method described by De Salva et al. in Fed. Proc., 1969. By such method, both pilocarpine- and electrically induced perspiration from cat’s paws are measured as water vapor by passing anhydrous air over the surface of the cat’s foot after treatment of the paw with Compound A, applied topically or subcutaneously. Subcutaneous application is found to be most effective, with from 20 to 2,000 micrograms of Compound A reducing perspiration completely, 4–10 micrograms reducing it 96% and 2 micrograms reducing it 60% in those cases where perspiration is induced by pilocarpine injection. With electrically induced sweating, the reductions are less dramatic, ranging from 50 to 85% of the reductions previously mentioned. Topical applications require larger quantities of Compound A or its analogues. Thus, 5 mg. reduce pilocarpine-induced sweating 85% while 1 mg. reduces it 35%. Five mg. reduce electrically induced sweating 65%, when topically applied.

As with the in vivo tests, to maintain useful anhidrotic activities, applications of the active antiperspirant compound are made daily or twice a day. Subcutaneous applications result in almost immediate diminution of perspiration whereas topical applications take about 2 to 4 hours for the greatest effect thereof to be evident.

The above tests indicate the utility of Compound A and the other compounds described in this application for inhibiting perspiration in man and other animals. Example 3 describes a method which may be utilized for screening antiperspirants so as to determine which are most effective. When employed with the antiperspirant acids, as well as the salts, the test is equally valid and shows them to be effective anhidrotic agents.

This invention has been described with respect to specific descriptions, examples and illustrations thereof. However, it is not to be limited to these inasmuch as it is clear to one of skill in the art, with the present disclosure before him, that various modifications may be made and equivalents substituted without going beyond the scope of the invention.

What is claimed is:

1. A method of inhibiting perspiration which comprises topically applying to a locus of sweat glands or ducts a perspiration-inhibiting amount of a compound selected from the group consisting of compounds of the formula:

2. A method according to claim 1 wherein n is 1, R is of 2 to 3 carbon atoms and R1 and R2 are of 1 to 3 carbon atoms.

3. A method according to claim 2 wherein the locus to which the perspiration-inhibiting compound is applied is an axilla.

4. A method according to claim 3 wherein R is ethyl, R1 and R2 are both ethyl and the compound is a hydrohalic acid salt.

5. A method according to claim 2 wherein the compound is a hydrochloride and from 0.05 to 10 milligrams thereof are applied to each of the axillae.

6. A method according to claim 1 wherein from 0.05 to 10 milligrams of the compound are applied to each of the axillae.

7. A method of inhibiting perspiration which comprises applying topically to a locus of sweat glands or ducts a
perspiration-inhibiting amount of a compound of the formula:

\[
\text{R} \quad \text{C} - \text{O} - \text{R} - \text{N}^{+} \quad \text{R}^{1} \quad \text{R}^{2}
\]

wherein \( n \) is from 1 to 3, \( R \) is alkylene of 1 to 5 carbon atoms and \( R^{1} \) and \( R^{2} \) are independently selected alkyls of 1 to 5 carbon atoms.

8. A method according to claim 7 wherein \( n \) is 1, \( R \) is ethylene and \( R^{1} \) and \( R^{2} \) are each ethyl.

9. A method according to claim 4 wherein the compound is the hydrochloric acid salt.

References Cited

UNITED STATES PATENTS

3,103,515 9/1963 Znag et al. \--------- 424--283 X

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424--283, 285, 278