954,268

# PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

## Decongestant Compositions comprising N-Acylated Sulphydryl Compounds

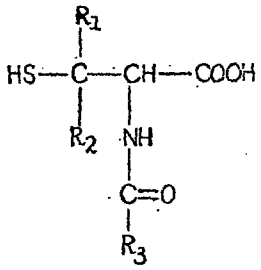
We, MEAD JOHNSON & COMPANY, a corporation organised under the laws of the State of Indiana, United States of America, of Evansville, State of Indiana, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a therapeutic composition and has for an object the provision of a composition for liquefying animal mucus.

The treatment of pathological disorders in the respiratory system is a well-developed medical practice and a number of compositions have been suggested for the treatment of such respiratory diseases as the common cold, allergies, severe bronchitis, and the like. Certain of the heretofore proposed compositions have met with some success, but there is still a wide recognition that the ideal preparation has not been found. For example, it has been discovered in accordance with one embodiment of this invention that an ideal decongestant suitable for use in treating the respiratory system is one which should have marked mucolytic properties. Secondly, the composition should be compatible with other therapeutic agents that may be used in connection therewith, such as vasoconstrictors, vasodilators, antibiotics, sulfa drugs, antihistaminics, enzymes, surfactants and antiseptics. In addition, such agents should be capable of convenient administration as a powder by in-sufflation, or in solution as in nose drops or as sprays or aerosols.

Accordingly, it is an object of this invention to provide a therapeutic composition which may be readily administered which has a high degree of mucolytic activity and which is compatible with other types of therapeutic agents that may be used in connection therewith.

Specifically, the present invention provides a therapeutic composition comprising a solid or liquid pharmaceutical carrier, 0.05 to 25.0% by weight of an N-acylated sulphydryl compound of the d-, l-, or dl-configuration, having the formula



wherein $R_1$ and $R_2$ are each hydrogen or lower alkyl containing up to 6 carbon atoms and $R_3$ is lower alkyl containing up to 6 carbon atoms or phenyl, and, when the carrier is liquid, sufficient of an alkaline material to confer upon said composition a pH in the range 4.0 to 9.0.

The present invention also provides a process for preparing a therapeutic composition as defined above, which comprises admixing the pharmaceutical carrier with an N-acylated sulphydryl compound as defined above.

The present invention also provides a composition for the preparation of a liquid therapeutic composition according to the present invention, made by admixing all of the ingredients other than the liquid pharmaceutical carrier.

With the composition of this invention, animal mucus may be liquefied by contacting it with an N-acylated compound as defined above. Specific compounds that are included within the scope of this invention are N-acetylcysteine, N-propionylcysteine, N-caproylcysteine, N-benzoylcysteine, N-acetylpenicillamine and N-acetyl-β-mercaptoisoleucine. These compounds all contain a

[*Price 4s. 6d.*]

sulphydryl group and a carboxyl group. It will be apparent that the carboxyl group may be partially or completely neutralized by adjustment of pH of the solution to be used for application to the mucous membrane. This pH adjustment is effected by a suitable alkaline-reacting nontoxic substance, such as sodium hydroxide or ammonium hydroxide, and thus the nontoxic salts of the sulphydryl compounds, such as the salts of sodium, ammonium, calcium or magnesium, together with the nontoxic acid addition salts thereof, are included within the scope of this invention.

The invention finds particular applicability in the treatment of mucus on the mucous membrane in animals with the stated compounds in order to reduce the viscosity thereof. As will be apparent from the following description, the invention is particularly useful for decongesting the respiratory and vaginal tracts of animals.

The sulphydryl compounds of this invention may be prepared by conventional procedures. The following methods may be used:

*N-Propionyl-L-cysteine.*

To 35.1 gm. (0.2 mole) L-cysteine hydrochloride (monohydrate) in 100 ml. 4*N* sodium hydroxide at 0°C. is added, with efficient stirring and under a nitrogen atmosphere, 22.2 gm. propionyl chloride and 60 cc. 4*N* sodium hydroxide over a two-hour period. The mixture is stirred in the cold an additional two hours and at room temperature for three hours. The mixture is stored in the refrigerator overnight, acidified with 33.3 ml. 6*N* hydrochloric acid and concentrated under reduced pressure at room temperature until solids begin to appear. Ethanol is added and the mixture filtered to remove the insoluble salts. The filtrate is evaporated to an oil which is redissolved in 40 ml. water and passed through a 24 inch × 2 inch "Dowex" (registered Trade Mark) 50—X8 (200—400 U.S. Standard mesh) column, ($H^+$ cycle). The column is eluted with water and that volume giving a positive nitroprusside reaction is collected. The eluate is concentrated under reduced pressure to an oil which after refrigeration for three months gives a crystalline product melting indefinitely (hygroscopic) at 75—85°.

*N-Acetyl-L-cysteine.*

A process may be used for the preparation of this compound which is essentially the same as that for the preparation of N-propionyl-L-cysteine described above except that acetic anhydride or acetyl chloride may be substituted for the propionyl chloride. The method of Pirie et al., Biochemical Journal, 27, 1716—18 (1933) may also be used.

*N-Caproyl-L-cysteine.*

This product may be employed by the same general method indicated above except that *n*-caproyl chloride is used as the acylating agent.

*N-Benzoyl-L-cysteine.*

L-cysteine hydrochloride (monohydrate) is reacted with benzoyl chloride and sodium hydroxide under general Schotten-Baumann reaction conditions. Upon acidification of the reaction mixture a material is obtained which is contaminated with benzoic acid. Washing with benzene and ether and recrystallization from these solvents gives a final product melting at 105—110°.

*N-Acetyl-DL-penicillamine.*

N-Acetyl-DL-penicillamine is prepared according to the procedure described by Leach and Hunter, Biochemical Preparations, *3*, 111 (1953) by reacting 4-isopropylidene-2-methyl-5(4)-oxazalone (prepared from N-chloroacetyl-DL-valine) with hydrogen sulphide followed by hydrolysis.

*N-Acetyl-β-mercapto-DL-isoleucine.*

N-Chloroacetyl-DL-isoleucine is converted to the azlactone with acetic anhydride. Reaction of hydrogen sulphide in sodium methoxide with the azlactone followed by hydrolysis gives the N-acetyl-β-mercapto-DL-isoleucine. This is essentially the procedure described by Clark et al., The Chemistry of Penicillin, Princeton University Press, 1949, page 469. The product is probably a mixture of the two racemic pairs. M.P. 143—145°.

In order to demonstrate the mucolytic properties of N-acetylcysteine, small globules or clots of viscous pulmonary secretions were placed on glass slides inclined at an angle of 53°. At this angle the clots did not move on the slide. One half of the globules were contacted with drops of water and one half with drops of aqueous 0.25M N-acetylcysteine. The globules treated with water retained their rigidity while those treated with the N-acetylcysteine solution immediately collapsed due to loss of viscosity and ran down the slides.

Drops of N-acetylcysteine solution (0.25M, pH 7.5) were administered intranasally to a young woman with congested sinuses (chronic condition), a young man with congested sinuses and nostrils from a common cold, and a seven-month-old baby girl with severe bronchitis. Immediate clearing of the nostrils and sinuses took place in each instance. In the case of the child, the bronchitis was severe enough to warrant placing her in an oxygen tent; also, the administration of an aerosol containing a commercially available surface active agent had been unsuccessful. The beneficial effect of the N-acetylcysteine solution lasted 2½ to 3 hours in the adults and

approximately 45 minutes in the child.

Tests have been made on the other sulphydryl compounds as defined above and it has been found that they also have mucolytic properties. The N-acylated cysteine compounds which are not substituted in the beta position (i.e. $R_1=R_2=$hydrogen) appear to be more effective than the beta-substituted compounds (i.e. $R_1$ and/or $R_2$ equal lower alkyl).

In accordance with this invention, a therapeutic composition has been provided which comprises the N-acylated sulphydryl compound and a pharmaceutical carrier, thereby ~~reulting~~ resulting in a compositon which may be used readily in the above-indicated process. The pharmaceutical carrier may comprise water, or in the event that it is to be sprayed, may comprise a suitable aerosol propellant, as is well known. Other inert pharmaceutical carriers may be employed, such as lactose, starch, calcium carbonate, cream or jelly base carriers, talc, or hydrated alumina, the type of carrier being dependent at least in part upon the type of composition desired and the place and method of its application to the mucus. If desired, the N-acylated compound can be combined with various known therapeutic agents which may include (1) vasoconstrictors for reducing mucosal swelling and diminishing the secretion of viscous mucus in the respiratory tract, (2) bronchodilators to aid in the passage of air to the lungs, (3) antibiotics, antiseptics and chemotherapeutic agents to prevent infection and the resultant secretion of purulent fluids, (4) antihistaminics or steroids to reduce allergic and other inflammatory reactions, (5) surfactants, and (6) various enzymes, such as deoxyribonuclease and/or proteolytic enzymes which under certain conditions may supplement the action of the N-acylated compounds.

The N-acylcysteines, and particularly the compound N-acetylcysteine, are particularly useful as mucolytic agents in accordance with this invention since these compounds do not have an obnoxious odour. They do not have a nauseating taste and they are relatively stable to oxidation in aqueous solution. Because of this stability the mucolytic properties of the compounds are retained in compositions containing water, especially in the presence of sodium ethylenediamine tetraacetic acid (EDTA) or other chelating agents, and the compounds do not form a precipitate on standing which could produce irritation in the respiratory tract upon use. The compositions are relatively innocuous and are nontoxic. They can be used as often as required to remove mucus from the respiratory tract or other areas of the body where the presence of the viscous mucus is a clinical problem. For a more complete understanding of this invention, reference will now be made to a number of specific examples showing compositions which may be prepared and used in accordance with this invention but applied to the animal by the usual techniques, as will be understood in the art.

EXAMPLE 1.

An aqueous solution for use in the treatment of the respiratory tract by inhalation has the following composition:

| | |
|---|---|
| N-Acetylcysteine | 3.0 gm. |
| Distilled water q.s. ad | 100.0 ml. |
| Sodium hydroxide in an amount sufficient to impart pH 7.5 to the solution | |

EXAMPLE 2.

An aqueous solution for use in the treatment of the respiratory tract by inhalation containing a chelating agent to increase the stability of the mucolytic agent has the following composition:

| | |
|---|---|
| N-Acetylcysteine | 20.0 gm. |
| Sodium EDTA | 0.1 gm. |
| Distilled water q.s. ad | 100.0 ml. |
| Sodium hydroxide in an amount to impart pH 7.5 to the solution | |

EXAMPLE 3.

A composition suitable for inhalation as a powder aerosol from a pressurized container in which the mucoyltic agent is present as a micronized powder suspension and in which the aerosol contains the conventional lubricants and excipients and has the following composition:

| | |
|---|---|
| N-Acetylcysteine, sodium salt | 1.0 gm. |
| Freon 12 | 23.0 ml. |
| Freon 14 | 77.0 ml. |

EXAMPLE 4.

A composition suitable for intranasal instillation has the following composition:

| | |
|---|---|
| N-Acetylcysteine | 10.0 gm. |
| Sodium EDTA | 0.1 gm. |
| Cetyl pyridinium chloride (a bacteriological preservative) | 0.02 gm. |
| Distilled water q.s. ad | 100.0 ml. |
| Sodium hydroxide in an amount to impart pH 7.5 to the solution | |

The above preparation may be instilled as drops or sprays or by use of nitrogen pressure (nitrosol).

EXAMPLES 5 AND 6.

N-Propionylcysteine or N-caproyl-L-cysteine may be substituted for N-acetylcysteine in Example 4.

EXAMPLE 7.

A suitable composition for inhalation containing a bronchodilator has the following composition:

| | |
|---|---|
| N-Acetylcysteine | 3.0 gm. |
| Epinephrine hydrochloride | 0.1 gm. |
| Sodium EDTA | 0.1 gm. |
| Distilled water q.s. ad | 100.00 ml. |
| Sodium hydroxide in an amount to impart pH 7.5 to the solution | |

EXAMPLES 8 AND 9.

N - Propionylcysteine or N - caproyl - L-cysteine may be substituted for N-acetylcysteine in Example 7.

EXAMPLE 10.

A suitable composition containing an antihistaminic for intranasal instillation has the following composition:

| | |
|---|---|
| N-Acetylcysteine | 3.00 gm. |
| Chlorpheniramine maleate | 0.02 gm. |
| Sodium EDTA | 1.10 gm. |
| Distilled water q.s. ad | 100.0 ml. |
| Sodium hydroxide in an amount to impart pH 7.5 to the solution | |

EXAMPLES 11 AND 12.

N-Benzoyl-L-cysteine or N-acetyl-DL-penicillamine may be substituted for N-acetylcysteine in Example 10.

EXAMPLE 13.

A composition containing a vasoconstrictor for intranasal instillation has the following composition:

| | |
|---|---|
| N-Acetylcysteine | 3.00 gm. |
| Phenylephrine hydrochloride | 0.25 gm. |
| Sodium EDTA | 0.10 gm. |
| Distilled water q.s. ad | 100.00 ml. |
| Sodium hydroxide in an amount to impart pH 7.5 to the solution | |

EXAMPLE 14.

N - Acetyl - DL - penicillamine may be substituted for N-acetylcysteine in Example 13.

EXAMPLE 15.

A composition containing an antibiotic for intranasal instillation has the following composition:

| | |
|---|---|
| N-Acetylcysteine | 3.0 gm. |
| Neomycin sulphate | 0.3 gm. |
| Sodium EDTA | 0.1 gm. |

Prepare the above as a concentrate, add a bacteriological preservative and lyophilize. At the time of use the composition is reconstituted with a sufficient quantity of water to bring the solution to a total volume of 100 millilitres.

EXAMPLES 16, 17 AND 18.

N-Propionylcysteine, N-caproylcysteine or DL-N-acetyl-beta-mercaptoisoleucine may be substituted for N-acetylcysteine in Example 15.

EXAMPLE 19.

A composition containing an anti-inflammatory agent for intranasal instillation has the following composition:

| | |
|---|---|
| N-Acetylcysteine | 3.0 gm. |
| Prednisolone-21-phosphate | 0.1 gm. |
| Sodium EDTA | 0.1 gm. |
| Distilled water q.s. ad | 100.0 ml. |
| Sodium hydroxide in an amount to impart pH 6.5 to the solution | |

EXAMPLE 20.

A suitable solution for vaginal application either by swab or nitrogen-propelled spray has the following composition:

| | |
|---|---|
| N-Acetylcysteine | 3.0 gm. |
| Sodium EDTA | 0.1 gm. |
| Distilled water q.s. ad | 100.0 ml. |
| Sodium hydroxide in an amount to impart pH 6.5 to the solution | |

EXAMPLES 21 AND 22.

N - Benzoyl - L - cysteine or N - acetyl-DL - penicillamine may be substituted for N-acetylcysteine in Example 20.

EXAMPLE 23.

An effervescent vaginal insert tablet having the following composition per tablet is as follows:

| | |
|---|---|
| N-Acetylcysteine | 100.0 mg. |
| Cetylpyridinium chloride | 4.0 mg. |
| Tyrothricin | 5.0 mg. |
| Sodium bicarbonate | 50.0 mg. |
| Sodium EDTA | 1.0 mg. |
| Lactose (powdered) q.s. | 1.0 gm. |

EXAMPLE 24.

N-Propionylcysteine may be substituted for N-acetylcysteine in Example 23.

EXAMPLE 25.

A powder for preparing a vaginal cleansing solution has the following composition in grams for each four grams of powder:

| | |
|---|---|
| N-Acetylcysteine | 1.0 gm. |
| Sodium bicarbonate | 0.75 gm. |
| Tyrothricin | 0.15 gm. |

| | |
|---|---|
| Cetylpyridinium chloride | 0.010 gm. |
| Sodium EDTA | 0.020 gm. |
| Lactose (powder) q.s. | 4.0 gm. |

As a vaginal cleansing agent, dissolve four grams of the above composition in 1000 millilitres of water and use as a douche.

EXAMPLE 26.

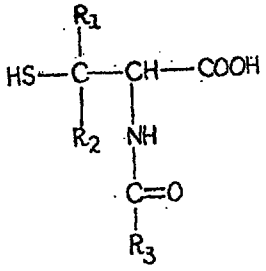
N-Propionylcysteine may be substituted for N-acetylcysteine in Example 25.

The concentration of the active N-acylated compound is between 0.05 and 25 per cent by weight. Also, the composition prepared for administration should have a pH between 4 and 9 and the pH is adjusted as desired by the use of a suitable alkaline-reacting material.

In the foregoing description, particular reference has been made to the treatment of the respiratory and vaginal tracts in order to effect the desired decongestion by the above defined compounds. However, it will be apparent that they may be used for the treatment of the mucous membranes in animals in other types of disorders, such as various topical ulcerations accompanied by mucopurulent discharge, such as occur in bedsores and draining sinuses, debridement, and otitis media serosa.

WHAT WE CLAIM IS:—

1. A therapeutic composition comprising a solid or liquid pharmaceutical carrier, 0.05 to 25.0% by weight of an N-acylated ~~sulphydryl~~ sulphyd. compound of the d-, l-, or dl-configuration, having the formula



wherein $R_1$ and $R_2$ are each hydrogen or lower alkyl containing up to 6 carbon atoms and $R_3$ is lower alkyl containing up to 6 carbon atoms or phenyl, and, when the carrier is liquid, sufficient of an alkaline material to confer upon said composition a pH in the range 4.0 to 9.0.

2. The composition according to claim 1, including sodium ethylenediamine tetraacetic acid.

3. The composition according to either of claims 1 and 2 wherein the sulphydryl compound is N-acetylcysteine.

4. A therapeutic composition according to any of the preceding claims comprising water as the pharmaceutical carrier and sodium ethylenediamine tetraacetic acid in an amount from 0.002 to 1.1 per cent by weight.

5. The composition according to any of the preceding claims, which is liquid and includes an aerosol propellant.

6. A process for preparing a therapeutic composition according to any of the preceding claims which comprises admixing the pharmaceutical carrier with an N-acylated sulphydryl compound as defined in claim 1.

7. The ~~threapeutic~~ composition according to claim 1, substantially as herein described with particular reference to the Examples. therapeu

8. The process for preparing a therapeutic composition according to claim 6, substantially as herein described with particular reference to the Examples.

9. A solid composition for the preparation of a liquid therapeutic composition according to claim 1, made by admixing all of the ingredients other than the liquid pharmaceutical carrier.

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| | |
|---|---|
| Cetylpyridinium chloride | 0.010 gm. |
| Sodium EDTA | 0.020 gm. |
| Lactose (powder) q.s. | 4.0 gm. |

As a vaginal cleansing agent, dissolve four grams of the above composition in 1000 millilitres of water and use as a douche.

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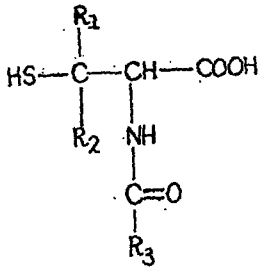
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In the foregoing description, particular reference has been made to the treatment of the respiratory and vaginal tracts in order to effect the desired decongestion by the above defined compounds. However, it will be apparent that they may be used for the treatment of the mucous membranes in animals in other types of disorders, such as various topical ulcerations accompanied by mucopurulent discharge, such as occur in bedsores and draining sinuses, debridement, and otitis media serosa.

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wherein $R_1$ and $R_2$ are each hydrogen or lower alkyl containing up to 6 carbon atoms and $R_3$ is lower alkyl containing up to 6 carbon atoms or phenyl, and, when the carrier is liquid, sufficient of an alkaline material to confer upon said composition a pH in the range 4.0 to 9.0.

2. The composition according to claim 1, including sodium ethylenediamine tetraacetic acid.

3. The composition according to either of claims 1 and 2 wherein the sulphydryl compound is N-acetylcysteine.

4. A therapeutic composition according to any of the preceding claims comprising water as the pharmaceutical carrier and sodium ethylenediamine tetraacetic acid in an amount from 0.002 to 1.1 per cent by weight.

5. The composition according to any of the preceding claims, which is liquid and includes an aerosol propellant.

6. A process for preparing a therapeutic composition according to any of the preceding claims which comprises admixing the pharmaceutical carrier with an N-acylated sulphydryl compound as defined in claim 1.

7. The ~~threapeutic~~ therapeutic composition according to claim 1, substantially as herein described with particular reference to the Examples.

8. The process for preparing a therapeutic composition according to claim 6, substantially as herein described with particular reference to the Examples.

9. A solid composition for the preparation of a liquid therapeutic composition according to claim 1, made by admixing all of the ingredients other than the liquid pharmaceutical carrier.

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