## Description

The present invention relates to an expectorant comprising a hydroxyalkylcysteine derivative as an active ingredient.

Up to the present time, S-(2-hydroxyethyl)-L-cysteine [Journal of Pharmaceutical Sciences, 50, 312 (1961)] and S-(3-hydroxypropyl)-L-cysteine [Biochem. J., 100, 362 (1966)] are known as hydroxyalkylcysteine derivatives. However, all that has been reported concerning their pharmacological effects is that S-(2-hydroxyethyl)-L-cysteine has anti-seborrheic activity (West German Laid-open Patent No. 2,219,726) and that S-(3-hydroxypropyl)-L-cysteine is effective against anti-cholesterolemia and arteriosclerosis (U.S. Patent No. 3,892,852).

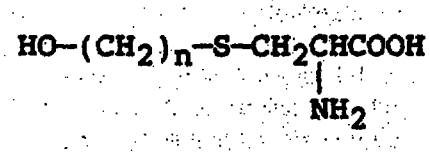
On the other hand, cysteine derivatives such as carbocysteine, N-acetylcysteine and cysteine ethyl ester hydrochloride are being used as expectorants.

The cysteine derivatives described above when used in expectorants are not completely satisfactory, particularly both N-acetylcysteine and ethyl ester hydrochloride have the problems of strong toxicity and chemical instability.

Therefore, the development of an expectorant possessing stability, little side effects and toxicity, as well as an excellent expectorant effect, has been desired.

In view of such circumstances, the inventors of the present invention synthesized a number of compounds and examined their pharmacological effects. As a result of these investigations, it was found that the hydroxyalkylcysteine derivative shown by the following formula (I) fulfilled the above conditions and possessed an excellent expectorant effect.

Accordingly, the present invention refers to the use of a hydroxyalkylcysteine derivative of the following formula (I),



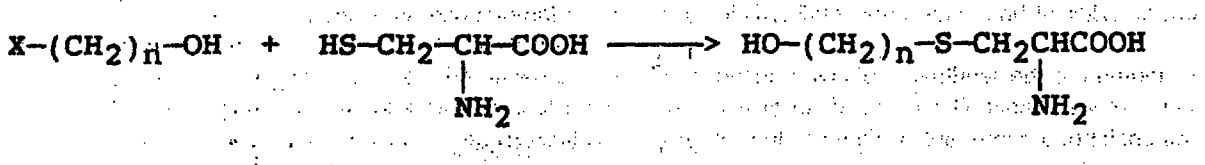
(I)

wherein n represents an integer of 1 to 4. For the manufacture of an expectorant.

Other objects, features and advantages of the invention will hereinafter become more readily apparent from the following description.

In formula (I) above, n is an integer of 1 to 4, and especially preferably of 3 or 4.

Compound (I) used in the present invention is prepared by the reaction involving a substituted alkyl alcohol (II) and cysteine (III) according to the following reaction formula,



(II) (III) (I)

wherein X represents a halogen atom, a tosyloxy group, or a methanesulfonyloxy group, and n is an integer defined above.

This method is carried out by reacting 1 mol of a compound (III) per 1-1.2 mols of a compound (II) for 4-24 hours in an appropriate solvent at a pH of about 9 using an alkali at room temperature, or if required, with heating.

Sodium bicarbonate, potassium carbonate, sodium carbonate, potassium hydroxide, or sodium hydroxide can be used as an alkali. Water, a water-methanol solvent, or a water-ethanol solvent are desirable as the solvent.

After the reaction is completed, the reaction mixture is washed with an organic solvent (ether, ethyl acetate, chloroform or methylene chloride) and the pH of the aqueous layer is adjusted to between 4 and 5 using hydrochloric acid. If crystals precipitate out, they are collected by filteration and refined by recrystallization. In the case where the crystals do not precipitate out, the aqueous layer is concentrated

under reduced pressure and the residue is extracted using absolute methanol. After concentrating the extract, ether is added to precipitate crystals, which are then purified by recrystallization or the like. Alternatively, crystals are produced from the residue with acetone and then purified by ion-exchange column chromatography or by recrystallization. Compound (I) used in the present invention is obtained using these methods.

Hereinafter are presented experimental examples to illustrate the expectorant effect of Compound (I) of the present invention. These examples are given for illustration of the invention.

Test Method:

The expectorant effect was investigated based on the method of Sakuno [Manchurian Medical Journal, 33, 779 (1940)].

The test compound was suspended or dissolved in an aqueous solution of 0.5% carboxymethylcellulose sodium (CMC-Na). The solution was administered orally to rabbits at 500 mg/kg. At the same time, 1 mg/kg of a 0.6% phenol-sulfonphthalein (PSP) injection solution was administered into the ear vein of the rabbits. Thirty minutes later, the carotid artery was severed and the rabbits were sacrificed by exsanguination. A cannula was placed into the trachea and a heated (38°C) aqueous solution of 5% sodium bicarbonate (12.5 ml/kg) was infused through cannula. After leaving for 10 mitutes, the infused solution was slowly drawn out and then infused again. This procedure was repeated a total of 3 times. The final solution collected was centrifuged at 10,000 rpm for 30 minutes at 4°C. After adjusting the pH of the supernatant thus obtained to 8.0 with 1 N hydrochloric acid, the absorbance was measured using a spectrophotometer at a wavelength of 557 nm in order to assay the amount of PSP. The amount of PSP was measured in the same way as described above in the control group after orally administering 10 ml/kg of an aqueous solution of 0.5% CMC-Na. The expectorant effect of the test compound was judged by the rate of increase in the amount of PSP which effused into the respiratory tract.

The rate of increase in PSP amount was calculated according to the following formula,

$$\text{Rate of increase in PSP amount (\%)} = (S-C)/C \times 100$$

wherein S is the amount of PSP in the test compound group and C is the amount of PSP in the group given 0.5% CMC-Na (control group).

Test Results:

The results are presented in Table 1.

Table 1

| Test compound | PSP concentration (μg/ml) | Rate of increase in PSP (%) |
|---|---|---|
| Compound 1 | 0.59 | 28 |
| Compound 2 | 0.65 | 42 |
| Compound 3 | 0.79 | 72 |
| Carbocysteine | 0.57 | 23 |
| Control | 0.46 | - |

Compound 1: S-(2-hydroxyethyl)-L-cysteine
Compound 2: S-(3-hydroxypropyl)-L-cysteine
Compound 3: S-(4-hydroxybutyl)-L-cysteine

As can be seen from Table 1, compared to the control group, rabbits to which Compound (I) was given showed a significant increase in the amount of PSP in the airway, thus evidencing that the compounds of this invention possess an excellent expectorant effect.

In addition, the toxicity of the compounds of formula (I) was extremely low. In particular, the values for acute toxicity ($LD_{50}$) of the Compound (I) in which n = 3 or 4 in formula (I) were greater than 10 g/kg when orally administred to mice or rat.

When Compound (I) is used as an expectorant the dose is different depending upon the administration route or the symptoms. However, in the case of oral administration in normal adults, a daily administration of 0.1-5 g once or over several doses is desirable, while for non-oral administration, the daily dose range is 0.02-1 g, also either given as a single dose or over several doses.

The present expectorant can be given by either oral or non-oral administration in any type of preparations. For oral administration forms such as tablets, capsules, powders, granules, troches or liquids can be used. For non-oral preparations hypodermic injections, intramuscular or intravenous injections, mixed transfusion or infusion preparations, suppositories are used. They can be prepared by commonly known methods. In other words, tablets, capsules, powders, granules or troches can be prepared by formulating appropriate combinations of Compound (I) and excipients such as starch, mannitol, lactose, binders such as carboxymethylcellulose sodium, or hydroxypropylcellulose, disintegrators such as crystalline cellulose, carboxymethylcellulose calcium, lubricants such as talc, magnesium stearate, and fluidity increasing agents such as light anhydrous silicic acid. In addition, aqueous liquid preparations and injection preparations can be prepared by utilizing the water-soluble property of Compound (I). Suppositories can be prepared by dispersing Compound (I) into a commonly used base material such as cacao butter, synthetic fats and oils and solidifying the mixture using common procedures.

Other features of the invention will become apparent in the course of the following description of the exemplary embodiments which are given for illustration of the invention.

## EXAMPLES

[Example 1]

A small amount of water was added to 20.0 g ($1.65 \times 10^{-1}$ mol) of L-cysteine to make a suspension and the pH was adjusted to 9 by adding an aqueous solution of 2 N sodium hydroxide. To this solution, 22.7 g ($1.82 \times 10^{-1}$ mol) of 2-bromoethanol was added, followed by stirring for 4 hours at 60 °C. Upon completion of the reaction, the resulting mixture was cooled and washed with ether. The aqueous layer was adjusted to pH 4 with 10% hydrochloric acid and the solvent was evaporated under reduced pressure. The residue was extracted with 80 ml of absolute methanol 3 times, and the extract was concentrated to a 1/3 volume. To the residue the equivalent amount of ether was added and the supernatant was removed by decantation. This procedure was repeated and the resulting viscous residue was recrystallized in a water/ethanol mixture to produce 21.7 g (yield: 80%) of colorless crystals of S-(2-hydroxyethyl)-L-cysteine (Compound No.1).

[Example 2]

20.0 g ($1.65 \times 10^{-1}$ mol) of L-cysteine was suspended in a small amount of water and the suspension was adjusted to pH 9 with an aqueous solution of 2N sodium hydroxide. To this suspension, 40 ml of ethanol and 25.2 g ($1.82 \times 10^{-1}$ mol) of 3-bromo-1-propanol were added to produce a homogeneous solution, followed by stirring all night at room temperature. Upon completion of the reaction, the pH was adjusted to 5 with 10% hydrochloric acid and the solvent was evaporated under reduced pressure. The residue was pulverized after repeated washing with acetone. The resulting powder was subjected to ion-exchange chromatography (Dowex-50W®) and eluted with 2 N ammonia water. The fraction which eluted was collected and concentrated under reduced pressure. The residual material was recrystallized in water-ethanol to obtain 25.2 g (yield: 85%) of colorless crystals of S-(3-hydroxypropyl)-L-cysteine (Compound No.2).

[Example 3]

A small amount of water was added to 10 g ($8.26 \times 10^{-2}$ mol) of L-cysteine to make a suspension and the pH was adjusted to 9 by adding an aqueous solution of 2 N sodium hydroxide. To this solution, 9.9 g ($9.1 \times 10^{-2}$ mol) of 4-chloro-1-butanol was added, followed by stirring for 4 hours at 60-70 °C. Upon completion of the reaction, the resulting mixture was washed with ether. The aqueous layer was adjusted to pH 4 with 10% hydrochloric acid and the solvent was evaporated under reduced pressure. 11.65 g (yield: 73%) of colorless crystals of S-(4-hydroxybutyl)-L-cysteine (Compound No. 3) was produced in the same way as described in Example 2.

## FORMULATION EXAMPLES

[Example 4] (tablets)

Tablets were prepared using known procedures and the following ingredients. These tablets can be prepared into film coated or sugar coated tablets.

| | |
|---|---|
| Compound No.3 | 250 mg |
| Crystalline cellulose | 50 mg |
| Lactose | 40 mg |
| Hydroxypropylcellulose | 15 mg |
| Magnesium stearate | 5 mg |
| Total | 360 mg/tablet |

[Example 5] (capsules)

Granules were prepared using known procedures and the following ingredients, and then filled into No. 1 capsules.

| | |
|---|---|
| Compound No. 2 | 125 mg |
| Crystalline cellulose | 87 mg |
| Light anhydrous silicic acid | 35 mg |
| Talc | 3 mg |
| Total | 250 mg/capsule |

[Example 6] (granules)

Granules were prepared according to known procedures using the following ingredients.

| | |
|---|---|
| Compound No. 1 | 250 mg |
| Lactose | 600 mg |
| Starch | 135 mg |
| Polyvinylpyrrolidone | 15 mg |
| Total | 1,000 mg |

[Example 7] (troche)

Troches were prepared according to known procedures using the following ingredients.

| | |
|---|---|
| Compound No. 3 | 250 mg |
| Magnesium stearate | 20 mg |
| Polyvinylpyrrolidone | 50 mg |
| Sucrose | 680 mg |
| Total | 1,000 mg/troche |

[Example 8] (powder)

Powder was prepared according to known procedures using the following ingredients.

| | |
|---|---|
| Compound No. 2 | 250 mg |
| Light anhydrous silicic acid | 30 mg |
| Lactose | 250 mg |
| Starch | 70 mg |
| Total | 600 mg |

[Example 9] (syrup)

Syrup was prepared according to known procedures using the following ingredients.

| | |
|---|---|
| Compound No. 3 | 200 mg |
| Ethyl paraoxybenzoate | 1 mg |
| Sucrose | 5 g |

Syrup was produced by adding purified water to a volume of 10 ml.

[Example 10] (suppositories)

Suppositories were prepared according to known procedures by forming and solidifying after the following ingredients were melted and stirred.

| | |
|---|---|
| Compound No. 1 | 250 mg |
| Cacao butter | 1,250 mg |
| Total | 1,500 mg/suppository |

[Example 11] (injection)

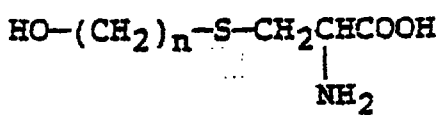
Injection was prepared according to known procedures and the following ingredients.

| | |
|---|---|
| Compound No. 3 | 250 mg |
| Physiological saline | 1,750 mg |
| Total | 2,000 mg |

**Claims**

**Claim for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, NL, SE**

1. Use of a hydroxyalkylcysteine derivative of the following formula (I):



(I)

wherein n represents an integer of 1 to 4, for the manufacture of an expectorant.

[Example 8] (powder)

Powder was prepared according to known procedures using the following ingredients.

| | |
|---|---|
| Compound No. 2 | 250 mg |
| Light anhydrous silicic acid | 30 mg |
| Lactose | 250 mg |
| Starch | 70 mg |
| Total | 600 mg |

[Example 9] (syrup)

Syrup was prepared according to known procedures using the following ingredients.

| | |
|---|---|
| Compound No. 3 | 200 mg |
| Ethyl paraoxybenzoate | 1 mg |
| Sucrose | 5 g |

Syrup was produced by adding purified water to a volume of 10 ml.

[Example 10] (suppositories)

Suppositories were prepared according to known procedures by forming and solidifying after the following ingredients were melted and stirred.

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|---|---|
| Compound No. 1 | 250 mg |
| Cacao butter | 1,250 mg |
| Total | 1,500 mg/suppository |

[Example 11] (injection)

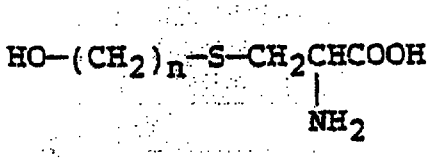
Injection was prepared according to known procedures and the following ingredients.

| | |
|---|---|
| Compound No. 3 | 250 mg |
| Physiological saline | 1,750 mg |
| Total | 2,000 mg |

**Claims**

**Claim for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, NL, SE**

1. Use of a hydroxyalkylcysteine derivative of the following formula (I):



(I)

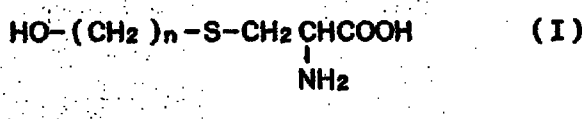
wherein n represents an integer of 1 to 4, for the manufacture of an expectorant.



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**Claim for the following Contracting State : ES**

1. Use of a hydroxyalkylcystein derivative of the following formula (I):

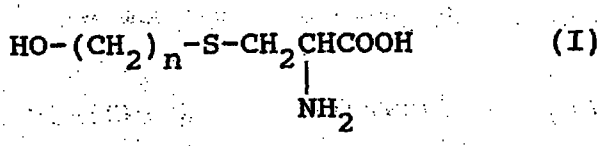


(I)

wherein n represents an integer of 1 to 4, for the manufacture of an expectorant by
blending said hydroxyalkylcysteine derivative (I) with one or more pharmaceutically acceptable components selected from excipients, binders, disintegrators, lubricants, and fluidity increasing agents, and
forming the mixture into tablets, capsules, powders, granules, or troches; or by
dissolving said hydroxyalkylcysteine derivative (I) in water or a physiological saline; or by
dispersing said hydroxyalkylcysteine derivative (I) into one or more base materials selected from cacao butter, synthetic fats and oil, and
solidifying the mixture into a suppository.

**Patentansprüche**
**Patentanspruch für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, NL, SE**

1. Verwendung eines Hydroxyalkylcystein-Derivats der folgenden Formel (I):

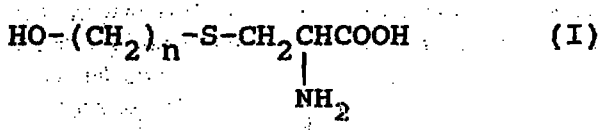


(I)

in der n eine ganze Zahl von 1 bis 4 darstellt, für die Herstellung eines Expektoranz.

**Patentanspruch für folgenden Vertragsstaat : ES**

1. Verwendung eines Hydroxyalkylcystein-Derivats der folgenden Formel (I):



(I)

in der n eine ganze Zahl von 1 bis 4 darstellt, für die Herstellung eines Expektoranz durch
Mischen des Hydroxyalkylcystein-Derivats (I) mit einer oder mehreren pharmazeutisch annehmbaren Komponenten, die ausgewählt sind aus Hilfsstoffen, Bindemitteln, Auflösungsmitteln, Gleitmitteln und fluiditätssteigernden Mitteln, und
Formen der Mischung zu Tabletten, Kapseln, Pulvern, Granula oder Pastillen; oder durch
Auflösen des Hydroxyalkylcystein-Derivats (I) in Wasser oder physiologischer Kochsalzlösung; oder durch
Dispergieren des Hydroxyalkylcystein-Derivats (I) in einem oder mehreren Basis-Materialien, die aus Kakaobutter, synthetischen Fetten und Öl ausgewählt sind, und
Verfestigen der Mischung zu einem Suppositorium.

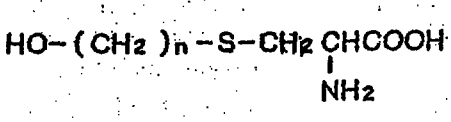


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**Revendications**

**Revendication pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, NL, SE**

1. Utilisation d'un dérivé d'hydroxyalkylcystéine répondant à la formule (I) suivante :

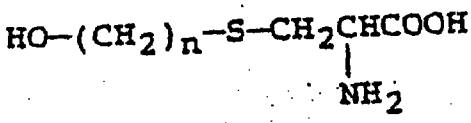


(I)

dans laquelle n un entier de 1 à 4, pour la fabrication d'un expectorant.

**Revendication pour l'Etat contractant suivant : ES**

1. Utilisation d'un dérivé d'hydroxyalkylcystéine répondant à la formule (I) suivante :



(I)

dans laquelle n représente un entier de 1 à 4, pour la fabrication d'un expectorant

en mélangeant ledit dérivé d'hydroxyalkylcystéine (I) avec un ou plusieurs composants pharmaceutiquement acceptables choisis parmi les excipients, les liants, les agents de désintégration, les lubrifiants et les agents améliorant la fluidité, et

en formant le mélange en comprimés, gélules, poudres, granulés, ou pastilles ; ou

en dissolvant ledit dérivé d'hydroxyalkylcystéine (I) dans de l'eau ou dans une solution saline physiologique ; ou

en dispersant ledit dérivé d'hydroxyalkylcystéine (I) dans un ou plusieurs produits de base choisis parmi le beurre de cacao et les graisses et les huiles synthétiques, et

en solidifiant le mélange pour obtenir un suppositoire.



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