

PATENT SPECIFICATION

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International Classification:—C07c.

COMPLETE SPECIFICATION

Bismuth Salts and their preparation

We, MINING AND CHEMICAL PRODUCTS LIMITED, a British Company, of 86, Strand, London, W.C.2, 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 new bismuth salts of aliphatic α -amino carboxylic acids, for example the bismuth glycinates, which are therapeutically useful in that they have properties which make them of value in the treatment of gastric and duodenal disorders. Amino acids, being amphoteric, are capable of controlled acid neutralization. We have found that the bismuth salts of these acids combine the antacid effect with the inactivation of pepsin thereby preventing auto-digestion, which may play some part in the persistence of duodenal ulceration.

According to this invention there are provided bismuth salts of aliphatic α -amino carboxylic acids. Also according to the invention there is provided a method of preparing bismuth salts of aliphatic α -amino carboxylic acids, the method comprising reacting a moist bismuth hydroxide with a solid aliphatic α -amino carboxylic acid.

Three series of salts may be prepared, depending on the number of hydroxyl groups in bismuth hydroxide that are replaced by acidic groupings. This depends on the relative amounts of bismuth hydroxide and aliphatic α -amino acid that are reacted together. For example, with glycine the following compounds can be prepared: (a) bismuth triglycinate, (b) bismuth monohydroxy glycinate, (c) bismuth dihydroxy glycinate. With glutamic acid, among the compounds that may be prepared is tetrahydroxy dibismuth glutamate. Other acids which may be used include alanine, valine, norvaline, lysine and arginine.

The basis of the method of preparation is the reaction of moist bismuth hydroxide with a solid aliphatic α -amino carboxylic acid. Bismuth hydroxide is prepared by precipitation from an acid solution of water soluble salt

[Price 3s. 6d.]

of bismuth such as nitrate, sulphate or chloride, with an aqueous solution of an alkali such as sodium hydroxide or ammonium hydroxide. The precipitated gel of bismuth hydroxide is then washed free from undesirable impurities such as sodium nitrate, sodium sulphate and sodium chloride. The bulk of the water is removed by filtration, centrifuging or other well known method. The bismuth hydroxide is then mixed with the requisite amount of an aliphatic α -amino carboxylic acid. A reaction takes place and the mass liquefies to produce a thin slurry. This slurry will solidify to a gel if left undisturbed. The gel may then be used as such or a powder can be obtained by spray drying the slurry. Other known methods of drying can be used providing the compound is not subjected to high temperatures for any length of time.

EXAMPLE 1

485 grams of bismuth nitrate are dissolved in 1,000 mls. of water containing 200 mls. of nitric acid sp.gr. 1.42. 50 grams mannitol is dissolved in the nitrate solution which is then diluted to 30 litres. This solution is poured into excess dilute ammonia solution and the bismuth hydroxide is precipitated and is then washed free from ammonium nitrate. The hydroxide is filtered and the moist gel is mixed with 75 grams of glycine. The mass becomes fluid at first but will then set to a firm paste. This paste is then dried, but should not be subjected to high temperatures for any length of time. The product obtained is bismuth dihydroxy glycinate.

EXAMPLE 2

The bismuth hydroxide prepared as in Example 1 is mixed with 73.5 grams glutamic acid. The mass becomes fluid and again sets to a firm paste. This paste is then dried and the product obtained is tetrahydroxy dibismuth glutamate.

EXAMPLE 3

The bismuth hydroxide prepared in Example 1 is added to a hot aqueous solution containing 225 grams of glycine in 450 mls. of water. The solution is then spray dried and the

product obtained is bismuth triglycinate.

WHAT WE CLAIM IS:—

1. Bismuth salts of aliphatic α -amino carboxylic acids.
2. A process for the preparation of bismuth salts of aliphatic α -amino carboxylic acids, wherein moist bismuth hydroxide is reacted with a solid aliphatic α -amino carboxylic acid.
3. A process for the preparation of bismuth salts of aliphatic α -amino carboxylic acids, comprising the steps of precipitating a gel of bismuth hydroxide from an acid solution of a water soluble bismuth salt with an aqueous alkali solution, washing the gel, removing most of the water to leave moist bismuth hydroxide, reacting the moist bismuth hydroxide with a predetermined amount of an aliphatic α -amino carboxylic acid to produce a thin slurry.
4. A process according to claim 2 or claim 3 in which the aliphatic α -amino carboxylic acid used is one of the following: glycine, alanine, valine, norvaline, lysine, arginine, glutamic acid.
5. A process according to claim 3 wherein the water soluble bismuth salt used is one of the following: bismuth nitrate, bismuth sulphate, bismuth chloride.
6. A process according to claim 3 wherein the alkali used is sodium hydroxide or ammonium hydroxide.
7. A process according to claim 3 wherein the thin slurry produced is allowed to solidify to a gel which is then reduced to powder by spray drying.
8. Processes for the production of bismuth salts of aliphatic α -amino carboxylic acids, substantially as described herein with reference to the examples.
9. Bismuth triglycinate.
10. Bismuth dihydroxy glycinate.
11. Tetrahydroxy dibismuth glutamate.

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PROVISIONAL SPECIFICATION

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According to this invention there are provided therapeutically useful bismuth salts of amino carboxylic acids, in which the molecule of the salt comprises one or more bismuth atoms and one or more amino carboxylic acid groupings. Also according to the invention there is provided a method of preparing bismuth salts of amino carboxylic acids, the method comprising reacting a moist bismuth hydroxide with a solid amino carboxylic acid.

Three series of salts may be prepared, depending on the number of hydroxyl groups in bismuth hydroxide that are replaced by acidic groupings. This depends on the relative amounts of bismuth hydroxide and amino acid that are reacted together. For example, with glycine the following compounds can be prepared (a) bismuth triglycinate (b) bismuth monohydroxy glycinate (c) bismuth dihydroxy

glycinate. With glutamic acid, among the compounds that may be prepared is tetrahydroxy dibismuth glutamate. Other amino acids which may be used include alanine, valine, norvaline, lysine and arginine.

The basis of the method of preparation is the reaction of moist bismuth hydroxide with a solid amino carboxylic acid. Bismuth hydroxide is prepared by precipitation from an acid solution of water soluble salt of bismuth such as nitrate, sulphate or chloride, with an aqueous solution of an alkali such as sodium hydroxide or ammonium hydroxide. The precipitated gel of bismuth hydroxide is then washed free from undesirable impurities such as sodium nitrate, sodium sulphate and sodium chloride. The bulk of the water is removed by filtration, centrifuging or other well known method. The bismuth hydroxide is then mixed with the requisite amount of an amino carboxylic acid. A reaction takes place and the mass liquifies to produce a thin slurry. This slurry will solidify to a gel if left undisturbed. The gel may then be used as such or a powder can be obtained by spray drying the slurry. Other known methods of drying can be used providing the compound is not subjected to high temperatures for any length of time.

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EXAMPLE 3

15 The bismuth hydroxide prepared in Example 1 is added to a hot aqueous solution containing 225 grams of glycine in 450 mls. of water. The solution is then spray dried and the product obtained is bismuth triglycinate. 20

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