PATENT SPECIFICATION

NO DRAWINGS

883,283

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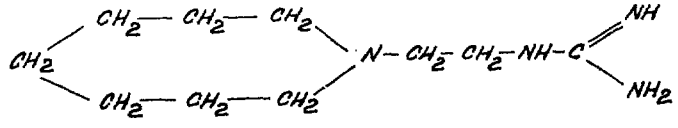
International Classification:—C07d. A61k.

COMPLETE SPECIFICATION

A new Guanidine Compound

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, 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:—

The present invention provides 2 - heptamethyleneimino - ethyl - guanidine of the formula



and physiologically tolerable acid addition salts thereof.

The new guanidine derivative and the aforesaid salts thereof have a hypotensive action and can therefore be used to reduce the blood pressure, particularly in cases of neurogenic or renal hypertension. A special characteristic of the new compound and the said salts is their strong and long-lasting action and low toxicity.

As physiologically tolerable salts there may be mentioned those of inorganic acids, especially sulphuric acids or nitric acid, phosphoric acids, hydrohalic acids, such as for example hydrochloric or hydrobromic acid, and also perchloric acid, thiocyanic acid etc., or of organic acids, for example, formic, acetic, propionic, glycollic, lactic, pyruvic, oxalic, malonic, succinic, fumaric, maleic, hydroxymaleic, dihydroxymaleic, malic, tartaric, citric, ascorbic, methane - sulphonic, ethane - sulphonic, hydroxyethane - sulphonic acid, or benzoic, 4-hydroxybenzoic, 4 - amino - benzoic, salicylic, 4 - aminosalicylic, benzene sulphonic, anthranilic, sulphanilic, phenylacetic, cinnamic, mandelic, 2-phenoxybenzoic, 2-acetoxybenzoic, ~~paratoluene~~ - sulphonic or naphthalene - sulphonic acid or methionine, tryptophane, lysine or arginine. Mono- or poly-salts may be formed.

2 - ~~Heptamethylene-imino~~ - ethyl - guanidine or its sulphate or other physiologically tolerable salts thereof, may be used as medicaments in the form of pharmaceutical preparations which contain the new compound or salt thereof in admixture with an inorganic or organic, solid or liquid carrier suitable for enteral, for example, oral administration, or parenteral administration. As carriers there are used substances that do not react with the new compound or salt thereof, for example water, talc, vegetable oils or fats, magnesium stearate, gelatine, lactose, starches, gums, benzyl alcohols, polyalkylene glycols, cholesterol and other usual excipients. The pharmaceutical preparations may be in the form of tablets, dragees, capsules or in liquid form as solutions, emulsions or suspensions. They may be sterilized and/or contain auxiliary substances, such as preserving agents, stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain other therapeutically useful substances.

The new compound can be obtained by reacting 2 - heptamethyleneimino - ethylamine with an S - alkylisothiourea, e.g. S - methyl- or S - ethylisothiourea, or a salt thereof, especially with mineral acids, such as hydrohalic acids, e.g. hydrochloric acid, hydrobromic acid, or more especially nitric or sulphuric acid. According to a preferred method, 2 - heptamethyleneimino - ethylamine is re-

para-toluene

heptamethyleneimino

[Price 3s. 6d.]

acted with S - methylisothiourea sulphate. The reaction can be carried out in the absence of a solvent, but is preferably performed in the presence of a solvent, such as water, an organic solvent miscible with water, e.g. an alkanol, such as methanol, ethanol, propanol, isopropanol or tertiary butanol, an ether, such as *p* - dioxane, a ketone, such as acetone or methyl ethyl ketone or a lower alkane-carboxylic acid, such as acetic acid, at room temperature or a raised temperature, e.g. the boiling temperature of the solvent, and at atmospheric or superatmospheric pressure, or in the presence of an inert gas, such as nitrogen.

The starting materials used for this reaction are known or can be prepared in a manner known *per se*. Thus, for example, an S-alkylisothiourea can be obtained by alkylating thiourea with an alkyl halide, for example methyl or ethyl chloride, bromide or iodide, or with a dialkyl sulphate, such as dimethyl or diethyl sulphate. The 2-heptamethyleneimino-ethylamine is claimed in Specification No. 7462/60 (Serial No. 883284).

Depending on the conditions used, the new guanidine derivative is obtained in the form of the free base or a salt thereof. A salt may be converted into the free base by reaction with a basic agent, such as an alkali metal hydroxide, e.g. lithium, sodium or potassium hydroxide, or an alkali metal carbonate, for example lithium. sodium or potassium carbonate. The free base can be converted into its acid addition salts, for example by reaction with an inorganic or organic acid, such as for example one of those mentioned above, if desired, in the presence of a solvent such as an alcohol, e.g. methanol, ethanol, propanol or isopropanol, an ether, for example diethyl ether or *p* - dioxane, or an alkyl alkanoate, e.g. ethyl acetate, or in a mixture of such solvents, if desired, in the presence of water.

The following Example illustrates the invention:

To a solution of 98 grams of 2 - heptamethyleneimino - ethylamine in 300 cc. of water there are added 87 grams of S-methylisothiourea sulphate, and the reaction mixture is heated for 8 hours. Upon cooling, 2 - heptamethyleneimino - ethyl - guanidine sulphate precipitates. After filtering and recrystallisation from aqueous ethanol the product melts at 276—281° C. with decomposition.

In Specification No. 19907/59 (Serial No. 883,282) there are claimed alkyleneimino-alkyl-guanidines in which the alkyleneimino ring contains 4 to 10 carbon atoms in the ring and the alkyl radical contains 1 to 7 carbon atoms, and physiologically tolerable salts of these compounds, and also pharmaceutical preparations which contain the aforesaid compounds ~~of~~ or salts thereof.

WHAT WE CLAIM IS:—

1. 2 - Heptamethyleneimino - ethyl-guanidine.

2. Physiologically tolerable salts of 2 - heptamethyleneimino - ethyl - guanidine.

3. 2 - Heptamethyleneimino - ethyl-guanidine sulphate.

4. ~~Pharamaceutical~~ Pharmaceutical preparations which comprise 2 - heptamethyleneimino - ethyl-guanidine or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutical carrier suitable for enteral or parenteral administration.

5. Pharmaceutical preparations which comprise 2 - heptamethyleneimino - ethyl - guanidine sulphate in admixture or conjunction with a pharmaceutical carrier suitable for enteral or parenteral administration.

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2. Physiologically tolerable salts of 2 - heptamethyleneimino - ethyl - guanidine.

3. 2 - Heptamethyleneimino - ethyl-guanidine sulphate.

4. ~~Pharamaceutical~~ Pharmaceutical preparations which comprise 2 - heptamethyleneimino - ethyl-guanidine or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutical carrier suitable for enteral or parenteral administration.

5. Pharmaceutical preparations which comprise 2 - heptamethyleneimino - ethyl - guanidine sulphate in admixture or conjunction with a pharmaceutical carrier suitable for enteral or parenteral administration.

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* C L M S *

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