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PATENT SPECIFICATION

NO DRAWINGS

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Inventors: HANS ALFRED NIEPER and FRANZ KÖHLER

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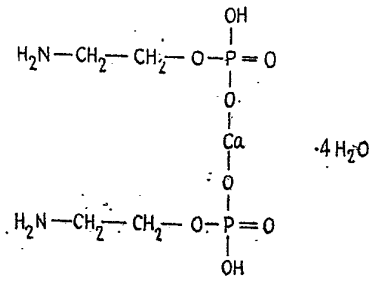
COMPLETE SPECIFICATION

A Salt of a Nitrogen-Containing Ester of Phosphoric Acid and the Therapeutic Applications thereof

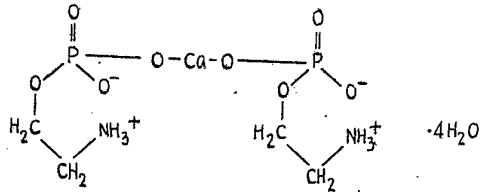
We, HANS ALFRED NIEPER, of Sedanstrasse 21, 3 Hannover, Germany, (formerly of Krankenhaus Silbersee, Langerhagen-Hanover, Germany), and FRANZ KÖHLER, of Dr. Köhler Chemie, Alsbach, Germany, both German citizens, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new compositions of therapeutic value.

According to the present invention there is provided, as a new therapeutic agent, a composition comprising the mono calcium salt of phosphoric acid monoaminoethyl ester and potassium and/or magnesium aspartates. For brevity this ester compound is referred to herein as Ca—AEP. Its formula may be written as:



However the stability of the 2-aminoethyl phosphoric acid, and its salts, to hydrolysis suggests that the compound may have an internal ring structure and be represented by the formula:



The compound may be made by the treatment of 2-aminoethylphosphoric acid with calcium carbonate or other convenient water-soluble calcium salt or calcium hydroxide. When calcium carbonate is added gradually to an equimolecular amount of 2-aminoethylphosphoric acid in aqueous medium the solution remains clear for a short time and then the Ca—AEP precipitates rapidly. The precipitate may conveniently be separated by filtration and dried *in vacuo* at a temperature not exceeding 40°C. The product may thus be obtained in the form of a white or greyish-white powder of polygonal crystals. It has no ascertainable melting point as it decomposes on

heating. It is insoluble in most common solvents but soluble in water to the extent of 3.8 to 3.9% at room temperature.

The combination at Ca—AEP and K and/or Mg aspartates has valuable therapeutic properties and can be used for the treatment of various clinical conditions as set out below. New therapeutic compositions according to the invention may comprise in addition to the Ca—AEP and K and Mg aspartates, a therapeutically acceptable diluent or extender. The diluent or extender may be an aqueous medium, e.g. a sterile aqueous medium, or a solid, the composition being in the form of tablets, or a resorbable material such as cocoa butter.

Suitably, such compositions may take any of the following forms. In each of these the quantity of Ca—AEP is indicated; the quantity of K and Mg aspartates is in each case adjusted to provide a daily dosage of 1 to 2g. for internal administration.

a) Sterile aqueous vials (preferably 10 ml) for intravenous and/or intramuscular injections, containing, for example, 4 per cent of Ca—AEP,

b) Liquid oral preparations containing, for example, 1 to 4 per cent of Ca—AEP in solution in a suitable vehicle, or up to 10 per cent as a suspension. The vehicle may be flavoured.

c) Tablets, uncoated, scored or not, or entericoated (gastric juice resistant), containing, for example from 0.2 to 0.4 gm (preferably 0.35 gm) of Ca—AEP. Such tablets may contain for example talc, and/or magnesium stearate. A suitable daily dose is 0.8 to 2 gm.

d) Suppositories containing, for example, from 0.4 to 1 gm. of Ca—AEP, preferably in a highly resorbable mass e.g. cocoa butter. A suitable daily dose is from 0.8 to 8 gm.

e) Compositions for application to the skin or to mucous membranes containing, for example, from 0.5 to 10 percent of Ca—AEP, such as a lotion in aqueous resorbable solution, emulsion or ointment bases.

f) Ophthalmic preparations, such as ointments in a suitable base or collyrium, containing, for example, 0.05 to 4 per cent of Ca—AEP in a solution of adequate tonicity and buffer capacity.

The compound Ca—AEP was found to have a toxicity (determined l.p in the mouse) of $LD_{50} = 0.5$ gm/kg and $LD_{100} = 1.25$ gm/kg.

The compositions of the present invention, in their various dosage forms have been found to be active in the treatment of:

(1) *Autoimmune Diseases*
- Colitis ulceros and mucosa
- Hepatitis (chronic and non cirrhotic)
- Chronic nephritis and associated hypertension
- Nephrosclerosis, malignant, and associated fixed hypertension
- Myocarditis, Jaffe's myocarditis, post-infarct syndrome
- Post-cardiotomy syndrome
- Multiple sclerosis
- Osteonecrosis
- Rheumatic manifestations, including rheumatoid arthritis, rheumatic fever, myocarditis
- Sclerodermia
- Chronic inflammation with or without tuberculosis.

(2) *Allergic Diseases*

(3) *Inflammatory Diseases*
- Hemorrhoids (suppositories)
- Skin inflammatory diseases (topical). Dermatitis
- Eye diseases.

(4) *Eczema*

(5) *Smooth Muscle Spasma*
- Intestinal
- Gastric
- Bronchial (asthma)

(6) *Lupus erythematosus*

(7) *Gastritis*

(8) *Tuberculosis*

(9) *Osteoporosis*

(10) *Aging*

(11) *Juvenile Diabetis*

(12) *Treatment and diagnosis of Cancer*

(13) *Progressive Muscle Dystrophy*
(14) *Angiosmastic Hypertension*
(15) *Chronic Encephalitis*
(16) *Spondylitis Osteoporosis*
(17) *Intersticial Pulmonary Fibrosis*
(18) *Myalgia*
(19) *Breast Induration*
(20) *Consolidation of Bone Fracture*

In copending Application No. 48613/64 (Serial No. 1,079,569) we have described as a new therapeutic agent, the compound calcium di-aspartate. In the preferred form the said agent consists of a mixture of 25% by weight of the D-form of that salt and 75% by weight of the L-form of that salt.

For some indications such as in dermatology, arthritis and colitis Ca—AEP represents a therapeutic improvement over such Ca aspartate. The therapeutic applications are similar to those described for Ca aspartate, but in some cases, therefore, the therapeutic doses of Ca—AEP are lower. Comparison of effects have been conducted on the same patients.

In the treatment of inflammatory conditions of internal organs and limbs, 3 gm of Ca 1,dl, aspartate are equivalent to 1 gm of Ca—AEP. In the treatment of eczema or skin inflammation, very high doses of Ca 1, dl, aspartate, at least 10 times greater than doses of Ca—AEP, are unable to achieve the same results as the latter.

Following clinical experience with calcium aspartate, and particularly with Ca 1, dl-aspartate and the Mg and K-2-aminoethylphosphate (Mg—K—AEP), Ca-2-aminoethyl-phosphate (Ca—AEP) was used in all inflammatory, rheumatic, autoimmune and allergic conditions. Since it has been observed in the past that cancer patients reacted to a mixture of Mg and K—AEP by episodes of intense shivering, but that this sympton was only observed in these conditions, Ca—AEP was tested for this purpose in cancer cases. It was concluded that tumor tissues are probably capable of liberating ethanolamine more rapidly from the AEP salt than other tissues. Pharmacological tests have proven that ethanolamine leads to such temperature increase reaction and to shivering.

It has been observed that the repeated use of Ca—AEP, particularly through the i.v. route, leads occasionally to cardiolvascular side-effects or gall bladder side effects that appear to be associated with K and Mg deficiency. This is corrected or avoided by the simultaneous administration of a mixture of K and Mg dl-aspartates i.e.

$$HOOC—CH_2—CH(NH_2)COOK.\tfrac{1}{2}H_2O \text{ and}$$
$$(HOOC—CH_2—CH(NH_2)COO)_2Mg.4H_2O$$

preferably in equal parts by weight.

K and Mg, as their corresponding aspartic acid salts, have been demonstrated to be much more effective than their other salts in correcting disturbances associated with K and Mg deficiency. Moreover the combination of these two cations shows definite potentiation of effects and occasionally therapeutic activity of a nature not observed with the use of either one of the cations alone.

It is generally recommended not to administer more than one i.v. injection of Ca—AEP every other day. I.V. administration should be alternated with oral or rectal administration.

Ca—AEP:

All parts are parts by weight.

The following procedures will serve to illustrate the production of the compound

PROCEDURE 1.

500 parts of calcium-carbonate are slowly added with continuous stirring to a solution composed of 141 parts of phosphoric acid-mono-aminoethyl ester in 2000 parts of water.

The carbonate starts reacting with liberation of CO_2 and then in a short time an almost clear solution is obtained in which the calcium salt of phosphoric acid-mono-aminoethyl ester is rapidly precipitated. Once the liberation of CO_2 has subsided, the reaction mixture is cooled at room temperature and the reaction product is separated. After vacuum drying, 150 parts of the desired calcium salt is obtained in the form of a snow-white crystalline product.

PROCEDURE 2.

163 parts of the sodium salt of phosphoric acid-mono-aminoethyl ester are dissolved at room temperature in 1500 parts of water, to which are added with rapid

stirring 73.5 parts of crystallized calcium chloride. The calcium chloride is rapidly dissolved and reacts with the sodium salt. The mixture is then warmed to about 50° and stirred for about one hour at this temperature, cooled, and the precipitate separated by filtration.

After drying of the precipitate under vacuum, 151 parts of calcium salt of phosphoric acid-mono-aminoethyl ester are obtained in the form of snow-white glistening crystals.

WHAT WE CLAIM IS:—

1. A therapeutic composition which comprises the mono-calcium salt of phosphoric acid monoaminoethyl ester and magnesium and/or potassium aspartates.

2. A therapeutic composition according to claim 1 which comprises a therapeutically acceptable diluent.

3. A therapeutic composition according to claim 2 wherein the diluent is an aqueous medium.

4. A therapeutic composition according to claim 2 wherein the diluent is a sterile aqueous medium.

5. A therapeutic composition according to claim 2 wherein the diluent is solid and the composition is in the form of tablets.

6. A therapeutic composition according to claim 5 wherein the tablets contain talc and/or magnesium stearate.

7. A therapeutic composition according to claim 2 wherein the diluent is a resorbable material and the composition is in the form of a suppository.

8. A therapeutic composition according to claim 7 wherein the diluent is cocoa butter.

Agents for the Applicants,
V. GALLAFENT & CO.,
Chartered Patent Agents,
8, Staple Inn, London, W.C.1.

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