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AMINE SALT PREPARATIONS FOR INTERNAL MEDICATION

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This invention relates to means for the treatment of infections of the kidney and urinary tract, such as, for example, pyelitis. In the medical treatment of matters of this kind, usually the treatment includes rendering the urine distinctly acid and applying an antiseptic agent, the two working together better than if either be used alone. This well known type of medication has heretofore employed methenamine, or the sodium or ammonium salt of mandelic acid for the medication and sodium acid phosphate, ammonium chloride or ammonium nitrate for rendering the urine distinctly acid. As between methenamine and a salt of mandelic acid, the latter has the advantage of being less irritant and possibly less toxic to the patient.

Heretofore, in such medication, and the acid producing constituents thereof usually require the employment of the stronger acids; thus ammonium chloride and ammonium nitrate have been preferred to sodium acid phosphate. However, these two salts, as is well known, while neutral, upon oral administration, are as a class quite irritating to the mucous tissue. These salts, from the manufacturer's standpoint, are objectionable in that they are subject to deterioration, the chloride being quite appreciably volatile and the nitrate on occasion becoming violently explosive. Their high acid content, however, makes them convenient and effective in rendering the urine acid and has outweighed the disadvantages as compared with heretofore known equivalents.

The present invention includes the production of the ethylene diamine salt, or salts, of hydrochloric or nitric acid and/or mandelic acid. These salts may be of the mono-acid or basic type or of the neutral or di-acid type. Ethylene diamine has the advantage that it is commercially available in large quantities, it is commercially available at a relatively low cost and also it is among the least toxic amines known. Also, it has the advantage that by reason of its lower molecular weight, it may be combined with a larger proportion of a given acid than any other amine. These amine salts of hydrochloric and nitric acids have been found to be highly efficient in producing acidity of the urine. The amine salts of mandelic acid have been found to be highly efficient as an antiseptic agent in the treatment of infections of the character described and it has been determined that these last mentioned salts require less dosage for a given antiseptic action than other antiseptics heretofore employed for the same when the antiseptic is accompanied by the use of a medicament for rendering the urine acid. The invention, therefore, is primarily directed to the ethylene diamine salt, or salts, of hydrochloric or nitric acid, in combination with an antiseptic such as methenamine or the ethylene diamine salt or salts of mandelic acid.

Experimentation has demonstrated that in certain types of infection of this general class, a mixture of ethylene diamine dihydrochloride and methenamine was much more effective in curing the infection than was ammonium chloride and methenamine. Why this should be true, is not understood. In other words, the antiseptic action of methenamine in the presence of the ethylene diamine salt of hydrochloric acid was increased. The ethylene diamine salt of mandelic acid, when used with the ethylene diamine neutral salt of hydrochloric acid, should produce substantially the same equivalent desirable effect.

While the invention up to this point has been stressed primarily as one of combination, the invention is not limited thereto, because the acid producing medicament of the medication has certain inherent advantages per se which will be referred to hereinafter and the antiseptic medicament of the medication has certain advantages per se over the corresponding well known antiseptic portions of such medication.

For example, with respect to the acid producing medicament of the medication, ammonium chloride and ammonium nitrate, like most ammonium salts, are irritating to the mucous tissues and, therefore, undesirable for such use, if their use can be avoided. Other objections have been heretofore mentioned; likewise, their advantages, to-wit, the high acid content.

The product of the present invention retains this advantage of high acid content and eliminates the disadvantage just mentioned, to-wit, irritancy, and the ethylene diamine salts do not have the toxic effect that other amine compounds may have when used internally. In addition to having the foregoing advantage of high acidity and low irritancy, if any, these salts have the further commercial advantage of stability and in that respect markedly differentiate from the ammonium salts previously mentioned.

Ethylene diamine is capable of forming two salts with either hydrochloric or nitric acid. One is the basic salt, being the mono-acid salt, and the other is the neutral or di-acid salt. So that when high acidity is desired, naturally the neutral salt is preferred for medication, solely because of the higher percent of acid it contains. The basic salt, however, qualitatively has the same action and could be used satisfactorily. It has also been experimentally determined these salts are not volatile and large quantities of these salts may be taken orally without injury. Also, as heretofore mentioned, these salts may be administered alone or with an antiseptic agent. These salts have the property, due to their stability, of being capable of incorporation with a solid antiseptic agent, such as methenamine, in

the form of compressed tablets. One particular combination peculiarly effective, has been hereinbefore mentioned. Usually these salts are produced by the batch process.

By way of illustration only, the following example of the preparation of the dihydrochloride will now be given. To 73 lbs. of hydrochloric acid (about 37%) was added, with stirring, 23 lbs. ethylene diamine (about 70%). To this mixture was added the mother liquor from a previous similar lot. Titration of a sample of the mixture, using meta cresol purple as an indicator, then showed 6 lbs. hydrochloric acid must be added to render the whole solution neutral to this indicator. When this amount of acid was added to the mixture, the latter was heated on a water bath until a crystal crust over the surface of the solution or the pellicle was formed. The mixture was then cooled and allowed to crystallize. This resulted in relatively large size crystals. If the mixture is stirred while cooling, the size of the crystals will be reduced. For tablet preparation or use as a powder, the latter procedure is preferred. The resulting crystals were then removed by filtration, washed thoroughly with alcohol and then dried. When tested in the body, the ethylene diamine portion of the molecule is apparently broken down as it cannot be recovered in the urine as such, except when given in excessively large amounts. Presumably the carbon chain is burned to carbon dioxide while the amino carbons are converted to urea. Thus, the basic portion of the molecule is destroyed, leaving the free acid.

In a similar manner, the di-nitrate, of this amine may be prepared.

With respect to the new amine antiseptic agent, and its preparation, the following is given by way of illustration only. Ethylene diamine and mandelic acid are mixed and warmed until the acid is completely dissolved. The proportions utilized are preferably molecular proportions. The neutral salt is a white powder and very soluble in water.

In substantially the same manner that ethylene diamine forms dual salts with hydrochloric or nitric acids, set forth herein or with hydriodic acid, as set forth in a copending application, Serial No. 119,271, filed January 6, 1937, ethylene diamine forms dual salts of mandelic acid. Naturally, the neutral salt is preferred for medication over the basic salt because of the greater acid content. To the query as to why mandelic acid per se might not be used direct, the same objection applies thereto as stated in the before mentioned copending application with reference to hydriodic acid—that is, it has an objection if used as a free acid, and in this instance the objection is that when so used it is too irritating to the stomach.

Sodium mandelate requires that some other substance must be administered simultaneously to produce acidification. Ammonium mandelate has the objection previously mentioned with respect to the other ammonium salts noted hereinbefore—that is, it is irritating to the mucous tissue. The ethylene diamine salts of mandelic acid of this invention on the other hand ordinarily require no additional agent for acidification, since the ethylene diamine portion of the molecule is broken down in the body, leaving the free mandelic acid and these salts of mandelic acid are not irritating to the mucous tissue.

By way of illustration only, the following example of the preparation of the neutral salt of mandelic acid (ethylene diamine mandelate) will now be given. 152 parts of mandelic acid (white and crystalline) and 43 parts of an aqueous solution of ethylene diamine (about 70%) were mixed and warmed until the acid dissolved completely. The mixture was then cooled and allowed to stand until crystallized. The crystals resulting therefrom were then filtered, washed with small amounts of alcohol and dried. The resulting new salt is a white crystalline powder and very soluble in water.

It is to be noted, however, that inasmuch as the ethylene diamine salts of mandelic acid are for commercial purposes used in solution form, the precipitation step herein described need not be practiced but by the use of proper proportions of the two reagents and water, the desired strength of solution of the ethylene diamine salt of mandelic acid can be prepared. This solution then can be used with any non-conflicting acid-increasing medication such as hereinbefore described.

It has been determined that the neutral salt becomes increasingly effective as an antiseptic as the acidity of the patient's urine increased. As a result the proportion of the neutral salt of mandelic acid required for a given antiseptic action can be materially reduced, if there is administered therewith an agent for rendering the urine distinctly acid.

The term "acid producing" as used herein and in the claims, specifically refers to a product which in itself is neutral or but slightly acid, and but which when subjected to metabolic action, the end product thereof is of a definite and relatively high acid type and is in solution, as in the urine.

The salts of ethylene diamine and hydrochloric acid or nitric acid have been found extremely useful for their diuretic action.

While the invention has been described in great detail in the foregoing specifications, the same is to be considered as illustrative and not restrictive in character. Various modifications of the method of preparation of the compounds prepared will readily suggest themselves to persons skilled in this art and the same as well as the modifications herein before mentioned specifically, are all considered to be within the broad scope of the invention reference being had to the appended claims.

The invention claimed is:

1. A composition suitable for use in internal medication including a mandelate of ethylene diamine.

2. Ethylene diamine mono-mandelate.

3. Ethylene diamine di-mandelate.

4. A product including ethylene diamine mono-mandelate and ethylene diamine di-mandelate.

5. A composition suitable for oral administration including an acid-producing ethylene diamine salt of a strong acid and an ethylene diamine salt of mandelic acid.

6. A composition suitable for oral administration including an acid-producing ethylene diamine salt of hydrochloric acid, and the ethylene diamine salt of mandelic acid.

7. A composition suitable for oral administration including an acid producing ethylene diamine salt of nitric acid and the ethylene diamine salt of mandelic acid.

8. A white, stable, crystalline mandelate of ethylene diamine.

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