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HEXAMETHYLENE TETRAMINE SALTS OF AROMATIC ACIDS

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10 Claims. (Cl. 260—501)

This invention relates to improvements in hexamethyl tetramine salts of aromatic acids, particularly to non-toxic antiseptics for the treatment of infections of the urinary tract.

5 A few years ago ketogenic diet was recommended for the treatment of certain urinary infections. It has been found that the bactericidal agent in the urine, resulting from the ketogenic diet is beta hydroxybutyric acid. It appears, therefore, that by the administration of this acid one would obtain similar results. However, when beta hydroxybutyric acid or similar aliphatic acids are administered orally they are largely oxidized in the body into carbon dioxide and water before reaching the kidney, therefore they are not eliminated in the urinary tract. Some of the orally administered beta hydroxybutyric acid may get to the urinary tract when the patient is on the ketogenic diet, that is, when the patient's metabolism is not normal.

15 The case is different with the aromatic acids having the carboxyl group on the side chain. These acids eliminate through the urinary tract unchanged and it has been shown that if the side chain does not contain a hydroxy group the body will add such a group to it before it is passed out through the urine.

Such an aromatic acid with the hydroxy group on the side chain is, for instance, mandelic acid. This acid is recommended for the treatment of infections of the urinary tract, but to accomplish satisfactory results it is necessary to administer not less than 12 gms. daily. Besides this large dose it is found to be necessary to administer simultaneously a large amount of ammonium chloride or other acidifying agents to lower the pH of the urine. The gastric disturbance caused by this treatment makes its use very undesirable.

40 It is known that the bactericidal action of aliphatic acids is increased with the number of the carbon atoms in it. We have found that similar conditions exist when the length of the side chain is increased in aromatic acids.

45 Another well known urinary antiseptic is hexamethylenetetramine, hereafter called shortly, methenamine. Methenamine itself is a valuable urinary antiseptic because it liberates formaldehyde in the acid or acidified medium of the urinary tract.

50 An object of this invention is to combine methenamine with aromatic acids in such a form that they will be eliminated unchanged through the urinary tract, where the acid, combined with

the methenamine, will liberate formaldehyde and so exert combined antiseptic action.

Another object of this invention is to prepare compounds which will produce satisfactory therapeutic results, if administered in relatively small quantities.

A further object of this invention is to increase the bactericidal action of side chain aromatic acids by combining them with methenamine.

Further objects will be seen from the specification.

We have found that aromatic acids combined with methenamine exert bactericidal action whether the side chain is saturated or unsaturated, and whether a hydroxyl group is attached to it or not.

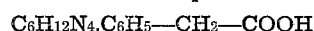
Methenamine itself shows very little bactericidal action when tested in vitro, by the agar plate method. When a salt of methenamine is made with side chain organic acids, the bactericidal action increases considerably when tested by the same method. The increase of bactericidal action seems to be depending, to a certain extent, on the length of the side chain, and for practical purposes a chain consisting of not less than two and not more than six carbon atoms is preferred.

These salts of methenamine with side chain aromatic acids are prepared by dissolving equimolecular quantities of methenamine and the acid in non-aqueous solvents, such as absolute alcohols, acetone, chlorinated hydrocarbons, etc., refluxing the solutions from five (5) minutes to one-half an hour, depending on the quantities, cooling the solution and collecting the crystals on a filter. They form white crystalline products which can be purified by recrystallizing from suitable solvents. As methenamine is monobasic it combines with one molecule of the aromatic acid used.

Example 1

6.8 g. phenylacetic acid and 7.0 grams methenamine were dissolved in 40 cc. dry methanol, filtered and concentrated on the steam bath until the solution became saturated. After cooling the crystals were collected on a filter, washed and recrystallized out of chloroform, and dried at room temperature. The white crystalline plates have no definite melting point. They soften to a viscous gummy substance at about 80 to 90° C.

The formula of the new product is



methenamine phenylacetate.

Example 2

5 grams hydrocinnamic (phenylpropionic) acid and 4.67 grams methenamine were dissolved in 30 cc. hot chloroform and refluxed for five minutes. The solution was filtered and concentrated on the steam bath until beginning of crystallization. After cooling on ice the crystals are collected, washed and recrystallized from chloroform. The melting point of the crystalline plates is 124–125° C.

The formula of the new compound is

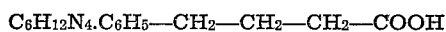


methenamine β phenyl propionate.

Example 3

7 grams methenamine are dissolved in 50 cc. chloroform. To this solution, while heated on a steam bath 8.2 grams γ phenylbutyric acid are added and the mixture is stirred until all the acid is dissolved. The solution is then filtered and the filtrate concentrated until crystal formation. After cooling the crystals are collected, washed and recrystallized out of chloroform or benzene. The crystalline plates begin to char at 205° C., but do not melt when heated as high as 250° C.

The formula of the new compound is:



methenamine γ phenylbutyrate.

Example 4

7.4 grams cinnamic (phenyl acrylic) acid and 7.1 grams methenamine are dissolved in 40 cc. chloroform and boiled for five minutes to obtain a complete reaction. The solution is filtered and the chloroform is evaporated until crystals begin to appear. After cooling, the crystals are collected, washed and recrystallized out of chloroform or benzene. The melting point of the crystalline plates is 133 to 134° C.

The formula of the new compound is:



methenamine cinnamate.

Example 5

4.2 grams β oxyhydrocinnamic (β oxy β phenyl propionic) acid and 3.5 grams methenamine were dissolved in 25 cc. hot chloroform. The solution was filtered and concentrated to a small volume on the steam bath. After cooling on ice the crystals are collected, washed and recrystallized out of chloroform. The crystalline plates begin to soften at 115 to 120° C., and the melting point is 141 to 143° C.

The formula of the new compound is:



methenamine β oxy- β -phenyl propionate.

The products described in the above examples are of similar character. They all form white crystalline plates, soluble in water, alcohol, chloroform, benzene, insoluble in ligroin.

The new compounds show a decided bactericidal action against cocci and bacilli, which is considerably higher than either of its components alone.

The preferred compound, methenamine phenylpropionate, when tested by the agar plate meth-

od will show a bactericidal action of 1:3000 against *B. coli* and *Staphylococcus aureus*. The compounds described are non-toxic and are well tolerated by experimental animals and are valuable as therapeutic agents.

We have described our invention in detail and with respect to preferred forms, as many widely different embodiments of this invention may be made without departing from the spirit and scope therein. We do not intend to limit ourselves to the specific embodiments herein set forth, except as indicated in the claims.

What we claim is:

1. As a new medicinal product, the compound obtained by reacting methenamine with an aromatic acid of the formula: ARCOOH where A is an aromatic radical and R is a member of the class consisting of saturated aliphatic hydrocarbon radicals, unsaturated aliphatic hydrocarbon radicals and hydroxy-substituted aliphatic hydrocarbon radicals.

2. As a new medicinal product, the compound obtained by reacting methenamine with an aromatic acid of the formula: ARCOOH where A is an aromatic radical and R is a saturated aliphatic hydrocarbon radical.

3. As a new medicinal product, the compound obtained by reacting methenamine with an aromatic acid of the formula: ARCOOH where A is an aromatic radical and R is an unsaturated aliphatic hydrocarbon radical.

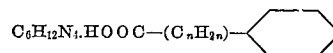
4. As a new medicinal product, the compound obtained by reacting methenamine with an aromatic acid of the formula ARCOOH where A is an aromatic radical and R is a hydroxy-substituted aliphatic hydrocarbon radical.

5. As a new medicinal product, methenamine phenyl propionate, a white crystalline compound obtained by reacting methenamine and phenylpropionic acid in a non-aqueous organic solvent.

6. As a new medicinal product, methenamine cinnamate, a white crystalline product obtained by reacting methenamine and cinnamic acid in a non-aqueous organic solvent.

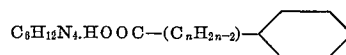
7. As a new medicinal product, methenamine phenyl hydroxy propionate, obtained by reacting methenamine with oxyphenyl propionic acid in a non-aqueous solvent.

8. As a new medicinal product an aromatic acid salt of methenamine of the following general formula:



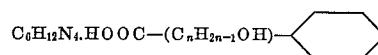
where n is less than 7.

9. As a new medicinal product, an aromatic acid salt of methenamine of the following general formula:



where n is less than 7.

10. As a new medicinal product an aromatic acid salt of methenamine of the following general formula:



where n is less than 7.

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