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DI-GUANIDINO-PHENOL ETHERS

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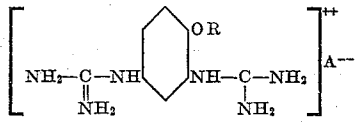
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Claims priority, application Italy July 25, 1951

3 Claims. (Cl. 260—565)

It is an object of the present invention to provide new surface active agents analogous to the so-called "cationic detergents." These new surface active agents have particular bactericidal properties that extend to types of micro-organisms against which known cationic detergents are scarcely active and that are less irritating than the known detergents.

More particularly, the new compounds according to the present invention are salts of ethers of 2,4-diguanidinephenol, corresponding to the Formula I



(I)

wherein R is an alkyl radical, in particular a straight chain radical with a number of carbon atoms from 8 to 16, and A^{--} is an acid radical of a strong acid (such as hydrohalogenic acids, sulfuric acid, nitric acid), for example 2 Cl^-.

One feature which imparts particular interest to the compounds of type I is the presence of the diguanidinephenol-ether group, with the two guanidine radicals conveniently positioned at the benzene nucleus. These applicants and others (see report to the 23d Congress of Applied Chemistry, September 1950, published subsequently: A. Di Marco, G. Boretti, C. Pasini, "Il Farmaco," 6, 300 (1951)) had previously found that, in case of compounds of the foregoing type wherein R represents methyl or propyl, the diguanidinophenol-ether group imparts definite although disconforming antibacterial properties. These applicants have now made the unexpected discovery that, in the series of compounds corresponding to Formula I, if R is a straight chain hydrocarbon of 8 to 16 carbon atoms, these properties are enhanced to such an extent that materials of this type are equal and even superior in bactericidal activity, as far as certain species of micro-organisms are concerned, to the most active cationic detergents.

When comparing, for example, cetyl pyridinium chloride, which is one of the most active cationic agents known (and which, like the new agents of this invention, but distinct from the other known agents, remains constant in its action even though the pH of the medium varies), with a representative of the new series of compounds, such as a compound wherein R represents 12 carbon atoms (di-hydrochloride of the lauryl ether of 2,4-diguanidinephenol), the applicants established that, while the bactericidal activity upon Gram-positive and upon acid-resistant organisms is about the same in both cases, the bactericidal action of the herein-disclosed compound is remarkably higher upon Gram-negative germs.

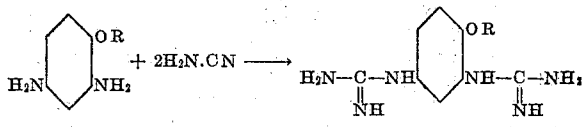
As far as the irritative action is concerned, in degree as well as in persistence of the local irritation phenomena, the comparison between cetyl pyridinium chloride and di-hydrochloride of lauryl ether of 2,4-diguanidinephenol is greatly in favor of the latter.

The fact that solutions of compounds according to this

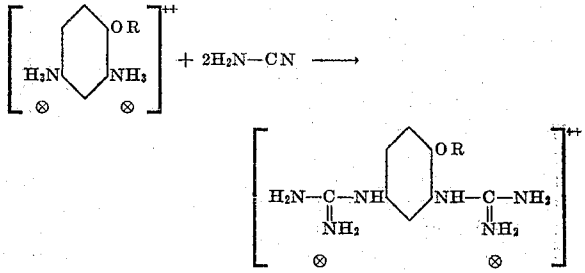
invention are less irritating is probably due in part to their pH being close to neutrality.

Compounds according to the present invention have not been previously prepared.

It is a further object of the present invention to provide a process for obtaining compounds corresponding to Formula I wherein R is an alkyl as described. Substantially, the process consists in reacting ethers of 2,4-diaminophenol with cyanamide, either starting from the free bases, according to the reaction scheme:

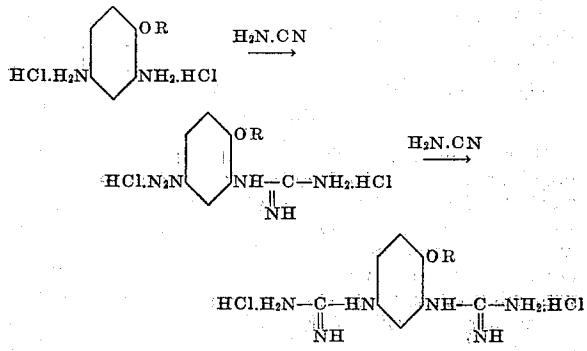


and obtaining salts of these products, or, preferably, starting from the ionic form, that is to say from a salt of 2,4-diaminophenol, according to the scheme:



and effecting the treatment in the heat with cyanamide in solvents. The salts are those of strong acids, and the ethers are alkyl ethers as previously set forth.

Cyanamide reacts in two stages with the salts of 2,4-diaminophenyl-ethers, according to the following reaction scheme, taking a di-hydrochloride salt as example:



It has been found that if even an excess of cyanamide is added to the hot solution of 2,4-diaminophenyl-ethers, considerable heat is developed for about 10–15 minutes, at which time the first guanidine group forms, in the ortho-position with respect to the O-R-group, and that, in order to obtain the desired product, the heating period must be extended.

With the first members of the series (R=methyl, ethyl, propyl, butyl), the influence of the lateral chain is scant; they represent, substantially, no more than salts having the particular property of dissolving well in ethyl alcohol. For these, the method of preparation is essentially as follows: reaction in ethyl alcohol, concentration (if needed), and precipitation by addition of a non-polar solvent (ether). The presence of water in small quantities is required (except for the methyl-derivative) for the formation of the crystal structure of these compounds.

If, however, the lateral chain comprises from 8 to 16 carbon atoms, the compounds in question acquire, as it were, properties intermediate between salts and paraffins. In fact, it has been found that in the case of products

having a lateral chain comprising from 8 to 16 carbon atoms, if the reaction is carried out in the presence of alcohol as the only solvent, the subsequent precipitation with a non-polar solvent does not yield satisfactory results.

On the other hand, the separation by precipitation is important because it permits an easy elimination of the by-products of the reaction. However, it has been found that good yields are obtained if the reaction medium employed is a mixture of solvents, consisting predominantly of a non-polar solvent with the addition of small quantities of polar solvents, particularly ethyl acetate, as well as small quantities of water and methyl alcohol. The non-polar solvent should have a boiling point of between about 50° C. and about 150° C., so as to not unduly extend the reaction time. Moreover, this method affords the advantage of recovering the reaction product directly from the reaction liquid, and recovering a product of sufficient purity at a good yield.

The following examples are furnished to illustrate the present invention, but in no way to limit the scope of the appended claims.

Example 1

10 g. di-hydrochloride of the n-propyl ether of 2,4-diaminophenol are dissolved in 100 cc. of hot 96% ethyl alcohol. 9 g. anhydrous cyanamide are added to the solution which is refluxed for about 5 hours and is then treated with decolorizing carbon while hot and filtered. The filtrate is concentrated to one-half of the volume and diluted cautiously, while stirring, with ethyl ether, until it becomes turbid. By rubbing the walls of the flask, the separation of the di-hydrochloride of the n-propyl ether of 2,4-diguanidine-phenol is started. This compound is white, and is filtered and washed with a small amount of acetone. On analysis, it is shown to possess 1 mol of water of crystallization. It has no definite melting point but starts sintering at about 190° C. and decomposes above 220° C.

The product can be obtained in a different form — which loses crystallization water at 130–135° C., with simulating fusion with decomposition — if heating it under refluxing for 30 minutes in a 1% aqueous solution, concentrating rapidly at 13–15 mm. Hg pressure and at 30–35° C. to almost dryness, treating with some alcohol and precipitating with ether.

Example 2

10 g. di-hydrochloride of the n-butyl ether of 2,4-diaminophenol are dissolved in 100 cc. of hot 96% ethyl alcohol. 8 g. anhydrous cyanamide are added and the solution is refluxed for about 5 hours and is then treated with decolorizing carbon and filtered. 2 cc. of water are added to the filtrate, which is then cautiously diluted with ethyl ether, while stirring, until it becomes turbid. By rubbing the walls of the flask, the separation of the di-hydrochloride of n-butyl ether of 2,4-diguanidine-phenol is started. The white product is filtered and washed with a small amount of acetone. On analysis, it is shown to possess 1 mol of water of crystallization. It has no definite melting point, but starts sintering above 170° C. and decomposes at more than 230° C.

Example 3

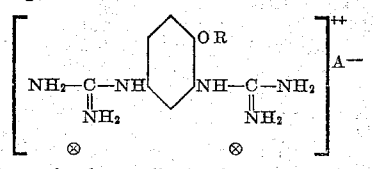
10 g. of the di-hydrochloride of diamino-phenyl lauryl ether are heated on the water bath, while refluxing, with 100 cc. of ethyl acetate, 2.5 cc. water and 5 cc. methyl alcohol. When boiling commences, 5 g. anhydrous cyanamide are added and refluxing is carried on for 2 hours. An additional 5 cc. of methyl alcohol are added to the hot liquid, which is then allowed to cool; after standing for some time, crystallization begins and is carried to completion by leaving the sample at 0° C. overnight. Filtration is then effected on a Büchner funnel and the cake is washed with 5 cc. of acetone. The filtrate is crystallized from water and a small amount of alcohol, after previous treatment with decolorizing carbon. The di-hydrochloride of lauryl ether of 2,4-diguanidine-phenol thus obtained possesses one molecule of water of crystallization, has no definite melting point but shows initial sintering at about 135° C., which goes to completion at about 210° C., then it becomes dark and decomposes at about 250° C.

Example 4

10 g. of the di-hydrochloride of 2,4-diaminophenyl-cetyl ether are heated while refluxing with 80 cc. of ethyl acetate, 2.5 cc. of water and 4 cc. of methyl alcohol. When boiling commences, 4 g. of anhydrous cyanamide are added and refluxing is carried on for two hours. After adding another 12 cc. of methyl alcohol to the hot liquid, the latter is allowed to cool, whereby crystallization starts which is carried to completion by leaving the sample at 0 C. overnight. The product is then filtered on a Büchner funnel, washed with 5 cc. of acetone, and the filtrate crystallized from methyl alcohol and water, after previous treatment with decolorizing carbon. The di-hydrochloride of the cetyl ether of 2,4-diguanidine-phenol thus obtained possesses one molecule of water of crystallization, has no definite melting point but sinters between 80 and 100° C. and decomposes at about 275° C., after darkening slowly.

We claim:

1. A compound of the formula:



wherein A^{--} is the radical of a strong inorganic, not strongly oxidizing, acid, and R is an alkyl radical with a straight chain having from 8 to 16 carbon atoms.

2. The di-hydrochloride of the lauryl ether of 2,4-diguanidine phenol.

3. The di-hydrochloride of the cetyl ether of 2,4-diguanidine phenol.

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