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AROMATIC QUATERNARY AMMONIUM SALTS WITH DISINFECTANT ACTIVITY

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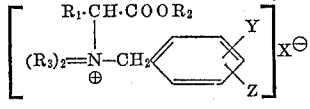
ABSTRACT OF THE DISCLOSURE

Quaternary ammonium salts with disinfectant activity, of the general Formula I:



I

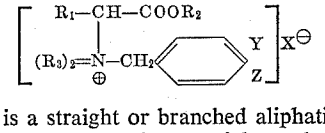
wherein R_1 is a straight or branched aliphatic chain with 10–16 carbon atoms, R_2 is a straight or branched alkyl with 1–8 carbon atoms, cycloalkyl or aralkyl, R_3 is alkyl with 1–4 carbon atoms, and the substituents Y and Z, identical or different, stand for hydrogen, halogen, or methoxy, and X is halogen.

The compounds of the invention are useful as disinfectants and can be made in solid crystalline form.

An example of the compounds of the invention is α-carbethoxypentadecyl - benzyldimethylammonium chloride.

The invention relates to new quaternary ammonium salts with disinfectant activity and to the method of preparing same.

Said salts are represented by the general Formula I:



I

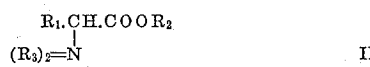
wherein R_1 is a straight or branched aliphatic chain with 10–16 carbon atoms, R_2 is a straight or branched alkyl with 1–8 carbon atoms, cycloalkyl or aralkyl, R_3 is an alkyl with 1–4 carbon atoms, and the substituents Y and Z, identical or different, stand for an atom of hydrogen, halogen, or a methoxy group, and X is a halogen atom, preferably chlorine.

The quaternary salts of the above quoted general Formula I represent altogether definable crystalline substances showing disinfectant effect enhanced by their surface activity. They are readily soluble in water, lower alcohols and glycols, capable of forming solutions of 30 percent or even higher concentrations, stable at normal temperature.

Crystalline and chemically homogenous substances of this kind are advantageous above all in that they can secure constant effectiveness of disinfectants prepared with them, that they can be used mostly in the form of aqueous solutions of various concentrations, and in that they offer the possibility of determining the disinfectant effect by external conditions, permitting the study of the mechanism of their effect, etc. From an economical standpoint also the shipment of crystalline substances appears more advantageous and easier than the expensive, uncomfortable, and sometimes difficult to handle aqueous solutions.

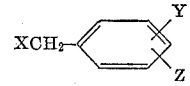
Compared with known disinfectants, e.g. with N-alkyl-benzyl-dimethylammonium halides, cetyltrimethylammonium bromide or cetylpyridinium halides and similar substances known under various trade names, which usually are amorphous mixtures hardly obtainable in anhydrous form, a number of the new substances of the general Formula I are soluble to a substantially higher degree, and antibacterially more effective. Noteworthy and interesting is also the antivirus activity of several substances of this group.

According to the invention, the new quaternary ammonium salts with disinfectant activity of the general Formula I are prepared in the manner that a compound of the general Formula II:



II

wherein R_1, R_2 and R_3 have the same definition as in Formula I, is brought into reaction with a compound of the general Formula III



III

wherein X, Y, and Z have the same definition as in Formula I.

In carrying out the method according to the invention it is preferable to use a molar ratio of 1:1 for the two components of the general Formulas II and III.

The reaction can be carried out either without any medium, or in the medium of polar organic solvents, such as acetone, ether, ethly acetate, or dimethyl formamide, at a temperature within the range of normal temperature of 15–25° up to 100° C., and at atmospheric pressure, or with pressures up to 5 atm.

Under the conditions usually practised in the preparation of quaternary ammonium salts, the reaction of the components proceeds very slowly, and isolation of the product from the reaction mixture, containing still a large part of unreacted starting substances, is very difficult.

The advantageous preparation of substances of the general Formula I, according to the invention, is rendered possible by adjustment of the reaction conditions by addition of a slight amount of suitable solvents, application of a suitable temperature and concentration of the reacting components. Except for the solvents listed in the examples (i.e. acetone, ether, and dimethyl formamide), also other polar solvents can be used, such as higher ketones, alcohols, esters, acetonitrile, nitromethane, and the like. Of special advantage are such solvents, by which the reaction of the two components is accelerated, and in which at the same time the reaction product is insoluble. In some instances the reaction can be effected without the use of any organic solvent.

In pharmacological testing the substances of the general formula I proved to have a relatively low toxicity in peroral application (LD_{50}=144–380 mg./kg.—mice), and to be non-irritating. In bacteriological testing with *Staphylococcus pyogenes aureus* and *Salmonella typhi* there was shown at least double activity compared with known preparations, e.g. dodecylbenzyldimethylammonium bromide (Zephirol), or α-carbethoxypentadecyl-trimethylammonium bromide (Brit. Pat. No. 961,353).

EXAMPLES

(1) 20 g. ethylester of α-dimethylaminopalmitic acid is dissolved in 20 ml. acetone, and to the solution 7.7 g. freshly redistilled benzyl chloride is added. The solution is left to stand for 14 days in a closed vessel at normal temperature (15–20° C.). After that the reaction mixture containing the crystallized product is stirred up with additional 20 ml. acetone, filtered, and the crystalline quaternary salt thus obtained, i.e. the α-carbethoxypenta-

decylbenzyl-dimethylammonium chloride, is washed with acetone. The united filtrates are concentrated by evaporating the acetone, whereby a further portion of the crystalline quaternary salt is obtained. The total yield of the final product, which on twofold recrystallization from acetone has M.P. 106° C., amounts to 15 g.

(2) By reacting the butylester of α-dimethylaminopalmitic acid with benzyl chloride under the same conditions as in Example 1, there is obtained by stirring up the reaction mixture with ether, in which the quaternary salt formed is insoluble, filtration, washing with ether and drying, the α-carbobutoxypentadecyl-benzyldimethylammonium chloride in the form of a white crystalline substance with M.P. 74° C.

(3) By reacting 20 g. ethylester of α-dimethylaminopalmitic acid with 10 g. p-chlorobenzyl chloride under the same conditions as in Example 1, and using ether for isolation of the product, likewise as in Example 2, there is obtained α - carbethoxypentadecyl - p - chlorobenzyl-dimethylammonium chloride in the form of a white crystalline substance with M.P. 126° C.

(4) 52.5 g. ethylester of α-dimethylaminopalmitic acid is dissolved in 25 ml. acetone, and to the solution the product is added that had been obtained in the known way by chloromethylation of 54 g. anisole by means of paraformaldehyde and gaseous hydrogen chloride, and containing in the mixture p-methoxybenzyl chloride with unreacted anisole. The reaction mixture is left to stand for 3 days at room temperature. The product crystallized is filtered off by suction, washed with acetone and dried. There is obtained 13 g. of α-carbethoxypentadecyl-p-methoxybenzyl-dimethylammonium chloride in the form of a white crystalline substance with M.P. 112° C.

(5) 15 g. butylester of α-dimethylaminolauric acid is dissolved in 15 ml. acetone, 6.3 g. benzyl chloride is added with stirring, and the reaction mixture is then left to stand at rest for several days at room temperature. If there does not come to elimination of a crystalline product, crystallization is initiated by any of the known methods, e.g. inoculation. In that case the liquid reaction mixture does quickly crystallize throughout the mass under spontaneous warming up. After standing for 24 hours at room temperature the reaction product is filtered by suction, several times thoroughly washed with ether, and dried. There is obtained 9.2 g. α-carbobutoxyundecyl-benzyl-dimethylammonium chloride in the form of a white crystalline substance with M.P. 87° C. On recrystallization from acetone the M.P. is 92° C.

(6) The quaternary salt described in Example 5 can be prepared also by heating 12 g. butylester of α-dimethylaminopalmitic acid with 5 g. benzyl chloride to 90° C. for 6 hours. After cooling down the reaction mixture is allowed to stand for 12 hours at room temperature, in order to get crystallized the major part of the quaternary salt formed, thereupon it is stirred up with ether, and further processed to the final product in the way already described.

(7) 8 g. cyclohexylester of α-dimethylaminolauric acid is stirred up with 3.2 g. benzyl chloride to a homogeneous solution, which is then kept at a temperature of 40° C. for 7 days. The crystallized quaternary salt is filtered by suction and washed with ether. The united filtrates are freed of the ether by evaporation, and the liquid residue is heated to 60° C. for 3 days. There crystallizes a further portion of the quaternary salt, which is then sucked off and washed with ether. There is obtained altogether 6.3 g. of crude quaternary salt having M.P. 118° C. By repeated crystallization the pure α-carbocyclohexyloxyundecyl-benzyldimethylammonium chloride is prepared, in the form of a white crystalline substance with M.P. 133° C.

The mother liquor obtained in the crystallization of the crude quaternary salt is evaporated and the residue extracted with 15 ml. water and 7.5 ml. ether. The aqueous extract is washed with ether, the ethereal extract in turn with water, and both evaporated. From the aqueous extracts further 1.5 g. of the crude quaternary salt is obtained, and from the ethereal extracts 2 g. of the unreacted starting cyclohexylester of α-dimethylaminolauric acid recovered.

(8) The quaternary salt described in Example 7 can be obtained also by heating 8 g. cyclohexylester of α-dimethylaminolauric acid with 3.2 g. benzyl chloride in 10 ml. acetone or dimethylformamide at 40° C. for 4 days.

(9) 8 g. benzylester of α-dimethylaminolauric acid is dissolved in 10 ml. acetone, to which solution 3.1 g. benzyl chloride is added with stirring, and the mixture heated for 2 days at 45° C. to be then allowed to stand for 4 days in a closed vessel without heating. The crystallized product is filtered by suction, washed with ether, and dried. There is obtained 6 g. α-carbobenzyloxyundecyl 1-benzyldimethylammonium chloride with M.P. 105° C.

(10) 20 g. ethylester of α-dimethylaminopalmitic acid is added to a solution of 11 g. 3.4-dimethoxybenzyl chloride in 40 ml. acetone, and after thorough mixing is allowed to stand for 3 days at normal temperature. Thereupon the acetone is distilled off from the reaction mixture under reduced pressure without heating, whereby a yellowish-brown amorphous substance is obtained, which crystallizes after some time. The thus obtained crude quaternary salt is readily soluble in water, giving a clear solution, which forms a heavy sediment by shaking; the salt is soluble in alcohols, acetone and ether, while insoluble in petroleum ether; therefore it is purified by precipitation with petroleum ether from the ethereal solution, thus yielding an amorphous substance, which after some time crystallizes to form a light-yellow substance of fat-like consistence with a low M.P., the α-carbethoxypentadecyl-/3.4-dimethoxybenzyl/ - dimethylammonium chloride.

(11) 20 g. ethylester of α-dimethylaminolauric acid is dissolved in 20 ml. acetone, and under stirring 17.5 g. 3.4-dichlorobenzyl bromide is added. The reaction mixture is left in closed vessel for several days at normal temperature. The portion of the reaction product crystallized from the reaction mixture is filtered off and washed with ether, the latter then being united with the mother liquor, the organic solvents are evaporated, and the residue is left for several hours to crystallize. The crystallized quaternary salt is filtered off and washed several times with ether. In this way there is obtained 20.3 g. of a quaternary salt with M.P. 104° C.

(12) Using the same procedure as in Example 11 there is prepared a quaternary salt from 3.4-dichlorobenzyl bromide and n-propylester of α-dimethylaminolauric acid.

(13) Using the same procedure as in Example 11 a quaternary salt is prepared of 3.4-dichlorobenzyl bromide and isopropylester of α-dimethylaminolauric acid (having M.P. 98° C.).

We claim:

1. α-carbethoxypentadecyl - benzyldimethylammonium chloride, with M.P. 106° C.
2. α-carbobutoxypentadecyl-benzyldimethylammonium chloride, with M.P. 74° C.
3. α-carbethoxypentadecyl-p-chlorobenzyl - dimethylammonium chloride, with M.P. 126° C.
4. α-carbethoxypentadecyl-p-methoxybenzyl - dimethylammonium chloride, with M.P. 112° C.
5. α-carbobutoxyundecyl - benzyldimethylammonium chloride, with M.P. 92° C.
6. α - carbocyclohexyloxyundecyl - benzyldimethylammonium chloride, with M.P. 133° C.
7. α-carbobenzyloxyundecyl-benzyldimethylammonium chloride, with M.P. 105° C.
8. α-carbethoxylpentadecyl - (3.4-dimethoxybenzyl)-dimethylammonium chloride.
9. α-carbethoxyundecyl-(3.4-dichlorobenzyl)-dimethylammonium bromide, with M.P. 104° C.

10. α-carbopropoxyundecyl - (3.4-dichlorobenzyl)-dimethylammonium bromide.

11. α-carboisopropoxyundecyl-(3.4-dichlorobenzyl)-dimethylammonium bromide, with M.P. 98° C.

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