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Ecsery et al.

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[45] **Nov. 18, 1975**

[54] **QUATERNARY AMMONIUM COMPOUNDS**

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[30] **Foreign Application Priority Data**

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[52] **U.S. Cl.** ..... **260/256.4 N;** 260/256.4 C; 260/256.4 R, 424/251

[51] **Int. Cl.²** **C07D 239/42**

[58] **Field of Search** ..... 260/256.4 N, 256.4 C, 260/256.4 R

[56] **References Cited**

UNITED STATES PATENTS

3,020,200	2/1962	Rogers et al.	260/256.4 N
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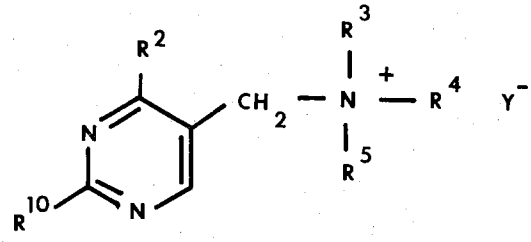
Primary Examiner—Sherman D. Winters
Attorney, Agent, or Firm—Karl F. Ross; Herbert Dubno

[57] **ABSTRACT**

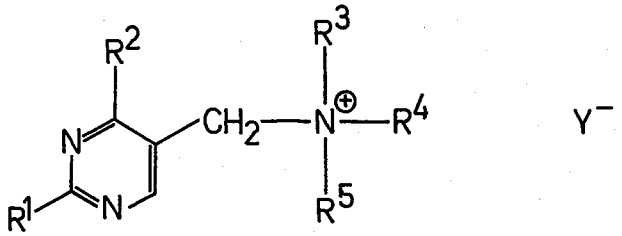
A quaternary ammonium compound of the formula:



wherein

R^{10} is propyl, R^2 is hydrogen, halogen, hydroxy, alkoxy or amino, R^3, R^4 and R^5 are each aryl, aralkyl, heteroaralkyl or alkyl and Y^- is an acid or hydroxyl anion. The compound has superior coccidiostatic properties.

6 Claims, 1 Drawing Figure



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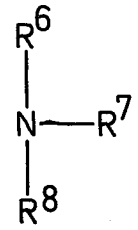

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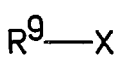

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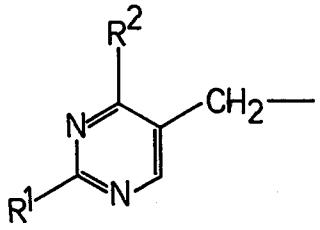

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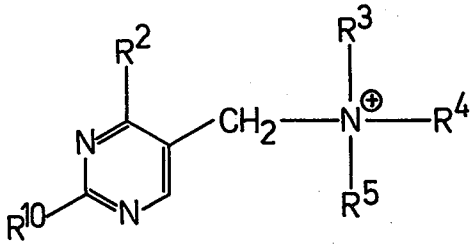
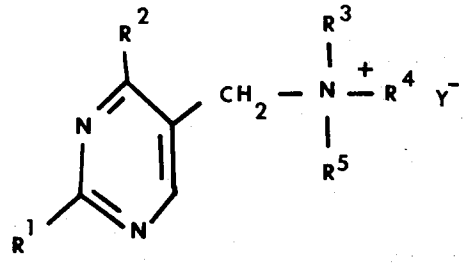


(V)

QUATERNARY AMMONIUM COMPOUNDS

This invention is directed to new quaternary ammonium compounds and a process for the preparation thereof. The compounds are useful in the preparation of pharmaceutically active compounds and also exhibit themselves coccidiostatic activity.

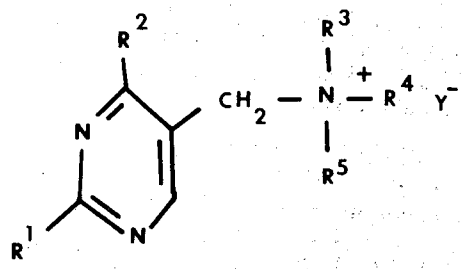
According to a feature of the present invention there are provided new compounds of the Formula:



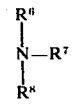
R^1 is an alkyl group having at least 2 carbon atoms;
R^2 is hydrogen, halogen, hydroxy, alkoxy or amino;
R^3, R^4 and R^5 each can be aryl, aralkyl, heteroaralkyl or alkyl, whereby in the latter case two alkyl groups and the nitrogen atom, to which they are attached, may form a ring;
Y^- stands for an organic or inorganic acid residue or a hydroxyl anion,
and acid addition salts of the compounds of that formula.

The term "alkyl group" relates to straight or branched chain radicals (preferably methyl, ethyl or propyl). The symbols R^3, R^4 and R^5 may stand for identical or different alkyl groups. Two alkyl groups may form a heterocyclic ring with the nitrogen atom, to which they are attached (e.g. a pyrrole, pyridine, piperidine or preferably a pyrrolidine ring). R^3, R^4 and R^5 may also be identical or different aryl groups (preferably phenyl), aralkyl (e.g. benzyl) or heteroalkyl.

According to a further feature of the present invention there is provided a process for the preparation of quaternary ammonium compounds of the general Formula:



wherein R^1 is an alkyl group and R^2, R^3, R^4, R^5 and Y^- have the same meaning as stated above, and acid addition salts thereof, which comprises reacting a compound of the Formula II:



(II)

wherein R^6, R^7 and R^8 can be an aryl, aralkyl, heteroaralkyl or alkyl group, whereby in the latter case two alkyl groups and the nitrogen atom, to which they are attached, may form a ring, with a compound of the Formula: R^9-x wherein R^9 stands for an alkyl, aralkyl or heteroaralkyl group, with the proviso that R^6 and/or R^9 stand for a group of the Formula: and if R^1 is methyl, the compound of the general Formula III is other than methyl iodide; X is an electron-attracting atom or atom group, and if desired replacing in the product thus obtained the anion by an other anion and if desired converting the compound thus obtained into an acid addition salt.

The group of the Formula IV (wherein R^1 and R^2 have the definitions stated above) may be present either in the starting materials of the Formula II or in the compounds of the general Formula III or in both of them. X is an atom or group of atoms which makes the R^9 group suitable for electrophilic attack by the electron attracting effect. Thus X can be halogen, a sulphonic acid radical or a group, which contains a quaternary nitrogen atom.

Preferably a N-(2-alkyl-4-amino-5-pyrimidylmethyl)-N,N-dialkylamine, N-(2-alkyl-4-amino-5-pyrimidly-methyl)-pyrrolidine or a N-(2-alkyl-4-amino-5-pyrimidyl-methyl)-N-alkyl-aniline is reacted with an alkyl halide, alkyl sulphate, aralkyl halide or 2-alkyl-4-amino-5-pyrimidyl-methyl-halide.

One may also proceed by using starting materials in which R^2 stands for hydrogen, halogen, hydroxy or alkoxy rather than for an amino group.

The reaction can be carried out in the presence of a solvent or without a solvent. Organic or inorganic solvents may be used, such as aliphatic or aromatic hydrocarbons (e.g. various petroleum-distillate fractions, benzene and homologues thereof), alcohols (e.g. methanol, ethanol, propanol), aldehydes or ketones (e.g. acetone, methyl-ethyl-ketone), ethers (e.g. diethyl-ether, diisopropylether, tetrahydrofurane, dioxane), acids (e.g. acetic acid, propionic acid), esters (e.g. ethyl acetate, butyl acetate) or acid derivatives (e.g. dimethyl formamide). One may also proceed by using an excess of one of the reaction partners as a solvent or by carrying out the reaction without a solvent. The reaction temperature depends on the reactivity of the starting materials of the Formulae II and III. If X is a group having a strong reactivity, the reaction may be carried out at 10°–25°C. If X is less reactive or the groups R^6, R^7 and R^8 decrease the reactivity of the tertiary amine due to a steric hindrance or an electron attracting effect, the reaction mixture should be heated to 50°–150°C. The quaternary ammonium compounds thus obtained may be isolated preferably by filtering the product, which may be purified by crystallization, if necessary.

One may be also proceed by removing the solvent and isolating the desired product by means of crystallization. The products obtained may be converted into any suitable salts by dissolving the same in an excess of the desired acid and adding a solvent, in which the desired salt is insoluble or only slightly soluble (e.g. dioxane, acetone, tetrahydrofurane). Both the crude and

the purified product may be used for salt formation. When iodide salts are to be prepared, an aqueous potassium iodide solution is added to the aqueous solution of the product.

In the product obtained, the anion may be replaced by an other halide anion or a sulphate, nitrate, phosphate or organic anion. These compounds may also be converted into their acid addition salts.

The starting materials used by the process of the present invention may be prepared according to the method described in J. Pharm. Soc. Jap., 76, 230–233 (1956).

As already mentioned above, the compounds of the present invention are useful starting materials in the preparation of known coccidiostatic and bactericidal agents and they also possess valuable therapeutic, and particulary coccidiostatic, activity. A particular advantage of the compounds is that they are also active against strains which are resistant against known coccidiostatic agents.

Further details of the present invention are disclosed in the following Examples.

EXAMPLE 1

3.88 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethylamine are dissolved in 17 ml of acetone, whereupon 1.24 ml of methyl iodide are added. After 10 minutes the temperature rises to about 40°C. The reaction mixture is allowed to stand overnight, whereupon the precipitated crystals are filtered and washed with acetone. Thus 5.13 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium iodide are obtained. M.p. 161°– 162°C. On acidifying the ethanolic solution of the above product with concentrated hydroiodic acid, the iodide-hydroiodide salt is obtained. M.p. 213°–215°C.

EXAMPLE 2

35.4 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethylamine are dissolved in 120 ml of acetone and 45.6 g of an acetonic methyl bromide solution are added (the solution contains 17.4 g of methyl bromide). The reaction mixture is allowed to stand for some minutes, whereafter the temperature rises to 40°C and the precipitation of a crystalline product begins. The reaction-mixture is allowed to stand overnight, whereupon the precipitated product is filtered off and washed with acetone. Thus 47.5 g of N-(2-propyl-4-amino-5-pyrimidylmethyl)-N,N,N-trimethyl-ammonium bromide are obtained. M.p. 244°–245°C. The product is dissolved in anhydrous ethanol and the solution is acidified with 48% hydrobromic acid. The melting point of the bromide-hydrobromide salt thus obtained is 225°–228°C.

EXAMPLE 3

38.8 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethylamine are dissolved in 194 ml of acetone containing 10.1 g of methyl chloride and the solution is allowed to stand in a sealed bomb tube for 65 hours at 25°C, whereupon it is allowed to stand in a water bath having a temperature of 50°C for 4 hours. After cooling, the bomb tube is opened, the crystals are filtered off and washed with acetone. 29.45 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium chloride are obtained, which melts at 199°–201°C. On evaporation the mother liquor 15.58 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethylamine are recovered. The product is dissolved in anhydrous ethanol and the solution is acidified with ethanol containing hydrochloric acid to yield the chloride-hydrochloride salt, which melts at 208°–211°C with decomposition.

EXAMPLE 4

1.5 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethylamine are dissolved in 7 ml of acetone and 0.71 ml of dimethyl sulphate are added. The temperature of the reaction mixture rises gradually to 48°–50°C. The reaction mixture is allowed to stand overnight, the precipitated white crystals are filtered off and washed with acetone. Thus N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-methosulphate are obtained, m.p. 158°163°C. The product is converted into the chloride-hydrochloride salt as described in Example 3. M.p. 208°–211°C.

EXAMPLE 5

11 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-pyrrolidine are dissolved in 75 ml of acetone and 12.5 g of an acetonous methyl bromide solution are added. (The solution contains 4.75 g of methyl bromide). The reaction mixture is allowed to stand in a sealed bombe tube at room temperature overnight; an oily phase separated, which becomes crystalline on scratching. The melting point of the N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N-methyl-pyrrolidinium-bromide thus obtained is 129°–133°C. The product is converted into the bromide hydrobromide salt as described in Example 2. M.p. 216°–218°C.

EXAMPLE 6

9.6 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-pyrrolidine are dissolved in 16.2 ml of acetone and 2,2 g of methylene chloride are introduced into the solution from a bomb. The reaction mixture is allowed to stand in a sealed bomb tube over night, whereupon a yellow product precipitates, which recrystallizes on scratching. The melting point of the N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N-methyl-pyrrolidinium-chloride amounts to 128°–131°C. The product is converted into the chloride-hydrochloride salt as described in Example 3. Melting point: 195°–196°C.

EXAMPLE 7

2.56 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N-methyl-aniline are dissolved in 30 ml of acetone and 1.2 ml of benzyl chloride are added. The reaction mixture is allowed to stand in a sealed bomb tube over night. The precipitated white crystals are filtered off and washed with acetone. The melting point of the N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N-methyl-N-benzyl-aniliniumchloride is 170°–172°C.

EXAMPLE 8

1 g of 2-propyl-4-amino-5-bromomethyl-pyrimidine-dihydro-bromide and 1.48 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethylamine are dissolved in 10 ml of dimethylformamide at room temperature. After standing for 2 hours, the precipitation of crystals begins. The crystals are filtered off and washed with benzene. The melting point of the N,N-bis-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethyl-ammonium bromide amounts to 183°–184°C. On recrystallization from anyydrous ethanol a product having a melting point of 184°–185°C is obtained.

EXAMPLE 9

0.5 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium iodide are dissolved in 4 ml of concentrated hydrochloric acid and 600 ml of acetone are added. The precipitated crystals are filtered off. The melting point of the chloride-hydrochloride salt thus obtained is 208°–211°C.

EXAMPLE 10

2 g of N-(2propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium bromide are dissolved in 15 ml of concentrated hydrochloric acid and 600 ml of acetone are added. The precipitated crystals are filtered off. The melting point of the chloride-hydrochloride salt thus obtained is 208°–211°C.

EXAMPLE 11

2.5 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium bromide-hydrobromide are dissolved in 5 ml of water, whereupon a solution of 2.5 g of potassium iodide and 2.5 ml of water is added. The precipitated crystals are filtered off. The melting point of the iodide-hydroiodide salt thus obtained is 213°–215°C.

EXAMPLE 12

2.13 g of N-(2-propyl-4-chloro-5-pyrimidyl-methyl)-N,N-dimethylamine are reacted in 8 ml of acetone containing 0.95 g of methyl bromide at room temperature. The reaction mixture is allowed to stand for 24 hours, whereupon the precipitated crystals are filtered off and washed with acetone. Thus N-(2-propyl-4-chloro-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium bromide are obtained.

EXAMPLE 13

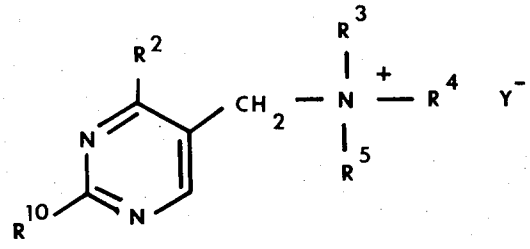
1.66 g of N-(2-methyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethyl amine are reacted in 8 ml of acetone containing 0.95 g of methyl bromide at room temperature, whereupon the reaction mixture is allowed to stand for 16 hours. The precipitated crystals are filtered off and washed with acetone. Thus N-(2-methyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium bromide is obtained.

EXAMPLE 14

1 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium bromide-hydrobromide is heated with 2.1 g of N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethylamine for 4 hours at 135°–140°C. The reaction mixture is cooled and 5 ml of acetone are added. The precipitated crystals are filtered off, washed with anhydrous acetone and recrystallized from ethanol. The melting point of the N,N-bis-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethyl-ammonium bromide is 184°–185°C.

What we claim is:

1. A quaternary ammonium compound of the formula



wherein

R^{10} is propyl

R^2 is amino or chloro,

R^3, R^4 and R^5 are methyl, ethyl, propyl, or benzyl;

Y is an iodide, bromide or chloride anion, or the hydrogen iodide, hydrogen bromide or hydrogen chloride acid addition salt of said formula.

2. A compound selected from the following group:

N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-iodide;

N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-bromide;

N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-chloride;

N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-sulphate;

N,N-bis-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N-dimethyl-ammonium-bromide;

N-(2-propyl-4-chloro-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-bromide;

N-(2-methyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-bromide and;

N,N-bis-(2-propyl-4-amino-5-pyrimidyl-methyl)-N.N-dimethyl-ammonium chloride.

3. The compound defined in claim **1** which consists of:

N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-iodide.

4. The compound defined in claim **1** which consists of:

N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-bromide.

5. The compound defined in claim **1** which consists of:

N-(2-propyl-4-amino-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-chloride.

6. The compound defined in claim **1** which consists of:

N-(2-propyl-4-chloro-5-pyrimidyl-methyl)-N,N,N-trimethyl-ammonium-bromide.

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