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3-QUINOLYL-GUANIDINES

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The present invention relates to new quinoline compounds which contain a guanido group in the 3-position, their acyl derivatives, quaternary ammonium compounds and their salts and a process for the manufacture thereof.

The quinoline nucleus of these compounds may contain one or more identical or different substituents. Such substituents are, for example lower alkyl, such as methyl, ethyl, n-propyl or iso-propyl, n-butyl, secondary or tertiary butyl, the hydroxyl group etherified hydroxyl, such as lower alkoxy, for example methoxy, ethoxy, n-propoxy, n-butoxy, lower alkylenedioxy, such as methylenedioxy, esterified hydroxyl, such as lower alkoxy-carbonyloxy, for example methoxy or ethoxy-carbonyloxy, lower alkanoyloxy, such as acetoxy or propionyloxy, mercapto, etherified mercapto, especially lower alkylmercapto, such as methyl or ethyl mercapto, carboxy, esterified carboxy, such as carbo-lower alkoxy, for example carbomethoxy or carbethoxy, nitro, free amino, mono-substituted amino, for example lower alkylamino, such as methyl- or ethylamino, particularly disubstituted amino, for example di-lower alkylamino, such as dimethylamino or diethylamino, halogen, such as fluorine, chlorine or bromine, or halogen-lower alkyl, such as trifluoromethyl.

In the new compounds the guanido group is preferably unsubstituted. It can also however be substituted by hydrocarbon radicals, especially lower alkyl groups, such as methyl or ethyl, and/or an ethylene radical and/or an acyl radical. When the substituent is an ethylene radical, the guanido group is a 4:5-dihydro-imidazolyl-(2)-amino group. Acyl substituents of the guanido group are more particularly those of lower aliphatic or monocyclic aromatic, heterocyclic, araliphatic or heterocyclic-aliphatic carboxylic acids, for example lower alkoxy-carbonic acids, such as methoxy or ethoxy-carbonic acid, carbamic acids, for example N:N-di-lower alkyl-carbamic acids, such as N:N-dimethyl-carbamic acid, or N-aryl-carbamic acids, for example N-phenyl-carbamic acid, lower alkane-carboxylic acids, such as acetic, propionic or pivalic acid, lower alkene-carboxylic acids, such as acrylic acid, lower alkine-carboxylic acids, such as propiolic acid, substituted aliphatic carboxylic acids, for example β-cyclopentyl-propionic acid, monochloracetic acid or monobromacetic acid, trifluoracetic acid or methoxyacetic acid, dimethylaminoacetic acid, β-diethylamine-propionic acid, β-piperidino-propionic acid or benzoic acid, para-methoxy-benzoic acid, 3:4:5-trimethoxy-benzoic acid, 4-O-ethoxy-carbonyl-syringic acid, 3,4-dichloro-benzoic acid, 3-nitrobenzoic acid, 3-dimethylamino-benzoic acid or nicotinic acid, isonicotinic acid, 2-furan-carboxylic acid, 2-thiophene-carboxylic acid or phenylacetic acid, diphenylacetic acid, β-phenyl-propionic acid, para-methoxy-phenylacetic acid, cinnamic acid, para-chloro-cinnamic acid, 3:4:5-trimethoxy-cinnamic acid or pyridyl-(2)-acetic acid or thienyl-(2)-acetic acid.

Salts of the new compounds are above all those with therapeutically useful acids, such as inorganic acids, such as hydrochloric acid or hydrobromic acid, or perchloric acid, nitric acid or thiocyanic acid, sulfuric or phosphoric acids, or organic acids such as formic acid, acetic acid, propionic acid, glycollic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, ascorbic acid, hydroxymaleic acid, dihydroxymaleic acid, benzoic acid, phenylacetic acid, 4-aminobenzoic acid, 4-hydroxybenzoic acid, anthranilic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxy-benzoic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, benzenesulfonic acid, para-toluene-sulfonic acid, naphthalenesulfonic acid or sulfamyl acids, or methionine, tryptophane, lysine or arginine.

Quaternary ammonium compounds are especially those which are formed by reaction with reactive esters of lower alkanols or aralkanols, for example lower alkyl-halides or aralkyl-halides, such as methyl, ethyl or benzyl chloride, bromide or iodide. From these addition products the ammonium hydroxides can be liberated which can be reacted with the other, above-described therapeutically useful inorganic or organic acids to form other quaternary ammonium salts.

The new quinoline compounds and their salts have a strong and long-lasting antihypertensive effect; they can therefore be used in cases of high blood pressure, particularly in neurogenic, renal or essential hypertension.

An outstanding effect is shown, for example, by 3-guanido-quinoline or 3-[N:N'-ethylene-guanido-(N'')]-quinoline and their physiologically tolerable acid addition salts.

The new compounds are intended to be used as medicaments in the form of pharmaceutical preparations which contain said compounds in admixture with an organic or inorganic, solid or liquid pharmaceutical excipient suitable for enteral, for example oral or parenteral, administration. Suitable excipients are substances that do not react with the new compounds such, for example, as water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, white petroleum jelly, cholesterol and other known medicinal excipients. The pharmaceutical preparations may be, for example, tablets, dragees, capsules or in liquid form solutions, suspensions or emulsions. They may be sterilized and/or contain assistants such as preserving stabilizing, wetting or emulsifying agents, salts for regulating the osmotic pressure or buffers. They may further contain other therapeutically useful substances.

The new compounds can be obtained by reacting in a manner known per se a 3-amino-quinoline or its salts with an S-lower alkyl-isothiourea or a cyanamide or a salt thereof, and if desired, in a resulting quinolyl-(3)-guanidine whose imino and/or amino groups are unsubstituted the latter are substituted by hydrocarbon radicals or acyl radicals and/or resulting salts are converted into the free compounds or resulting free compounds into salts. The S-lower alkyl-isothioureas or the cyanamides may be N-unsubstituted or substiuted, for example by aliphatic hydrocarbon radicals, especially lower alkyl groups, such as methyl or ethyl, or an ethylene radical and/or an acyl radical of an acid mentioned above. Such compounds may be in free form or in the form of salts thereof, particularly salts of mineral acids, for example hydrochloric acid, hydrobromic acid, nitric acid or sulfuric acid may be used. In the 3-amino-quinoline used as starting material the amino group represents more especially a primary amino group, but also a secondary amino group, for example a lower alkylamino group, such as a methyl or ethylamino group.

The reaction of the 3-amino-quinolines or their salts with the etherified isothioureas or its salts is performed preferably in the presence of a diluent, the choice of which depends on the solubilities of the reactants. Diluents or solvents are, for example, water, alkanols, such as methanol, ethanol, n-propanol or iso-propanol or tertiary butanol, ethers, such as dioxane or tetrahydrofuran, ketones such as acetone or methyl-ethyl-ketone, lower alkane-carboxylic acids, such as acetic or propionic acid,

or formamides, such as dimethylformamide. The reaction can be carried out at room temperature or, if necessary, at a raised temperature, for example at the boiling temperature of the reaction mixture, under atmospheric or superatmospheric pressure or in the presence of an inert gas, for example nitrogen.

The reaction with cyanamides is carried out, for example, by heating the mixture of the 3-amino-quinoline, especially an addition salt thereof, with a mineral acid, such as hydrochloric acid, hydrobromic acid or sulfuric acid, and the cyanamide, preferably in the presence of a solvent or diluent, for example a lower alkanol, such as ethanol, or an aqueous acid, such as hydrochloric acid, to the melting or boiling point of the reaction mixture. The acid addition salt of the amine may also be formed intermediarily during this procedure; the cyanamide too when sodium cyanamide or 1-nitroso-3-methyl-guanidine is used.

The starting materials used for these reactions may contain the substituents required for the above defined end products. They are known or can be prepared by a method known per se.

In resulting quinolyl-(3)-guanidines whose imino and/or amino groups are unsubstituted the latter may be converted, if desired, into substituted imino and/or amino groups. For example the resulting quinolyl-(3)-guanidines or their salts can be converted in a manner known per se with an amine substituted by a hydrocarbon radical, such as methyl, ethyl or propylamine, or with ethylenediamine, whereby with the latter, guanidines, cyclicized through the ethylene chain, i.e. 2-amino-4:5-dihydro-imidazoles are obtained. The guanido group can also be acylated, for example by treating the guanidine compound with a reactive functional derivative of a carboxylic acid, for example a halide, such as chloride, or the anhydride. The reactants can be reacted in the presence of an inert diluent, for example a hydrocarbon, such as pentane, hexane, toluene or xylene, or a tertiary organic base, for example a liquid pyridine, such as pyridine or collidine, or in the absence of such, for example by heating with an acylating agent, advantageously acetic anhydride, alone, in an open or closed vessel under pressure.

Depending on the reaction conditions employed, the new guanidines are obtained in the form of the free bases or of their salts. The salts can be converted into the free bases in the known manner, for example by treatment with a strongly basic agent, such as an alkali metal hydroxide, for example lithium hydroxide, sodium hydroxide or potassium hydroxide, or with a strong anion exchange resin, such as a quaternary ammonium exchange resin. The free bases, on the other hand, can be converted into acid addition salts, for example by reaction with an inorganic or organic acid, for example one of the acids mentioned above; if desired, this can be carried out in the presence of a solvent, such as an alcohol, for example methanol, ethanol, propanol or isopropanol, or of an ether, for example diethyl ether or a para-dioxane, or of an alkylalkanoate, for example ethyl acetate, or in a mixture of two or more such solvents, if desired in the presence of water. Basic, neutral, acid or mixed salts may be obtained.

The new guanidines or salts thereof may also be converted into quaternary ammonium compounds, for example by reaction with reactive esters of lower alkanols or aralkanols, such as lower alkyl or aralkyl halides, for example methyl, ethyl or benzyl chloride, bromide or iodide, di-lower alkyl sulfates, such as dimethyl or diethyl sulfate, or lower alkyl esters of alkane or aryl sulfonic acids, such as methane, ethane or para-toluene-sulfonic acid methyl or ethyl ester.

Quaternization is advantageously carried out in the presence of a diluent, for example in a lower alkanol, such as methanol, ethanol, n-propanol or tertiary butanol, a lower alkanone, such as acetone or methyl-ethyl-ketone, or an acid amide, such as formamide or dimethyl-formamide.

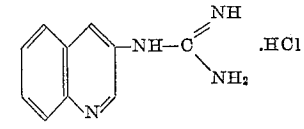
Resulting quaternary ammonium salts may be converted into the corresponding ammonium hydroxides, for example by treatment with an ion exchanger, by reacting the ammonium halide with moist silver oxide, the ammonium sulfate with barium hydroxide, or by electrodialysis. From the quaternary ammonium hydroxides other therapeutically useful ammonium salts may be prepared with the previously mentioned acids.

The present invention further includes any variant of the process in which an intermediate obtained at any stage of the process is used as starting material and the remaining step or steps are carried out, or in which the starting materials are formed in the course of the reaction, or are present in the form of their salts or quaternary ammonium derivatives or acyl compounds.

The following examples illustrate the invention.

Example 1

A solution of 18 grams of 3-aminoquinoline hydrochloride in 20 cc. of ethanol is refluxed at the boil for 3 hours with 4.2 grams of cyanamide. Another 4.2 grams of cyanamide are then added, and the whole is heated for a further 4 hours. When the solution is allowed to cool, 3-guanido-quinoline hydrochloride of the formula



separates from it in colorless crystals. After having been recrystallized from ethanol or methanol, the compound melts at 228–230° C. It is readily soluble in water.

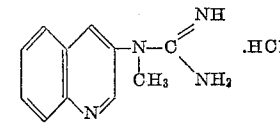
Instead of cyanamide, a filtered ethanolic suspension of an appropriate proportion of sodium cyanamide, treated while cooling with a calculated amount of concentrated hydrochloride, may be used.

When methyl cyanamide is used instead of cyanamide, N-[quinolyl-(3)]-N′-methyl-guanidine hydrochloride is obtained. Other N′-substituted compounds can be prepared in an identical manner.

The above 3-aminoquinoline hydrochloride can be replaced by a substituted 3-aminoquinoline hydrochloride whose benzene or pyridine nucleus contains for example an alkyl, such as methyl group, or alkoxy such as a methoxy group.

Example 2

9.7 grams of 3-methylamino-quinoline hydrochloride (obtained by heating an ethanolic solution of 3-bromoquinoline and methylamine in a tube at 150° C. in the presence of copper and converting the resulting base of M.P. 80° C. into the hydrochloride), 5 grams of cyanamide and 20 cc. of ethanol are heated at the boil for 10 hours. The resulting solution is evaporated to dryness, and the residue is triturated with acetone. The remaining, undissolved portion is recrystallized from ethanol, to yield N-[quinolyl-(3)]-N-methyl-guanidine hydrochloride of the formula



in colorless crystals melting at 237–239° C., which is readily soluble in water. The corresponding nitrate on the other hand, is sparingly soluble in water.

When the cyanamide is replaced by a substituted cyanamide, such as methyl cyanamide, N′-substituted compounds are obtained, such as N-[quinolyl-(3)]-N:N′-dimethyl-guanidine hydrochloride.

Other N-substituted or N′-substituted 3-guanido-quinolines can be prepared in a similar manner.

Example 3

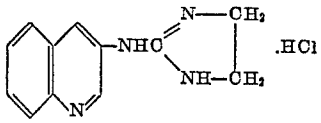
A mixture of 7.2 grams of 3-aminoquinoline, 10 grams of S-ethyl-isothiourea hydrobromide and 25 cc. of butanol is heated at the boil for several hours. After cooling, the separated crystals are suctioned off and washed with butanol. The mother liquor is evaporated and the residue treated with acetone, to yield a further amount of the same crystals, which are recrystallized from a small amount of hot water. In this manner 3-guanido-quinoline hydrobromide, decomposing at 218–220° C., is obtained, when it is treated with sodium nitrate it yields the corresponding nitrate melting at 238–240° C.

The S-ethyl-isothiourea hydrobromide may be replaced by another salt, such as the hydrochloride or hydriodide or another isothiourea ether.

3-aminoquinoline can also be reacted with S-ethyl-N-methyl-isothiourea hydrobromide, to yield N-[quinolyl-(3)]-N'-methyl guanidine hydrobromide.

Example 4

A solution of 22.2 grams of 3-guanido-quinoline hydrochloride and 7.0 grams of ethylenediamine in 100 cc. of n-butanol is refluxed at the boil for 18 hours. On completion of the reaction the solution is cooled in ice. The separated crystals are suctioned off and washed with butanol. Recrystallization from water or methanol yields 3-[N:N'-ethylene-guanido-(N'')]-quinoline hydrochloride of the formula



in colorless crystals melting at 270–271° C. with decomposition. (For the melting point test the product is introduced into the apparatus at 250° C.) The new compound is water-soluble.

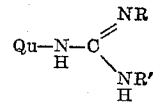
Example 5

A mixture of 16.0 grams of 3-aminoquinoline, 24.4 grams of S-methyl-ethylene isothiourea hydriodide and 10 cc. of n-amyl alcohol is refluxed for 8–12 hours in an oil bath at 135–150° C., whereby methyl mercaptan is

developed. The resulting crystalline magma is treated with ethanol, and the crystals are suctioned off and washed with ethanol and ether on the filter. Recrystallization from boiling water yields 3-[N:N'-ethylene-guanido-(N'')]-quinoline hydriodide as colorless crystals melting at 282–286° C. The residue of the evaporated alcoholic mother liquor yields a further amount of this compound by distribution between water and toluene at an elevated temperature.

What is claimed is:

1. A member selected from the group consisting of guanidines of the formula:



their quaternary lower alkyl ammonium halides and hydroxides, their quaternary benzyl ammonium halides and hydroxides and their therapeutically acceptable acid addition salts, in which formula Qu stands for a member selected from the group consisting of quinolyl-(3), lower alkyl-quinolyl-(3), lower alkoxy-quinolyl-(3), and R and R' stand for a member selected from the group consisting of lower alkyl and hydrogen.

2. 3-guanido-quinoline.

3. A therapeutically acceptable acid addition salt of 3-guanido-quinoline.

4. 3-[N'-methyl-guanido-(N)]-quinoline.

5. A therapeutically acceptable acid addition salt of 3-[N'-methyl-guanido-(N)]-quinoline.

6. 3-[N-methyl-guanido-(N)]-quinoline.

7. A therapeutically acceptable acid addition salt of 3-[N-methyl-guanido-(N)]-quinoline.

8. 3-[N:N'-dimethyl-guanido-(N)]-quinoline.

9. A therapeutically acceptable acid addition salt of 3-[N:N'-dimethyl-guanido-(N)]-quinoline.

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