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3,291,829

(N-CYCLOALKYLAMINE)ALKYL GUANIDINES
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8 Claims. (Cl. 260—564)

The present invention concerns guanidino derivatives. More particularly, it relates to N-R₁-N-R₂-amino-lower alkyl-guanidines, in which R₁ represents a cycloaliphatic radical containing from three to eight, more particularly from five to seven, ring carbon atoms, and R₂ stands for hydrogen, an aliphatic radical, a cycloaliphatic radical, a carbocyclic aryl radical, a carbocyclic aryl-aliphatic radical, a heterocyclic aryl radical or a heterocyclic aryl-aliphatic radical, salts or quaternary ammonium compounds thereof, as well as process for manufacturing such compounds.

A cycloaliphatic radical R₁ containing from three to eight ring carbon atoms stands more especially for cycloalkyl, containing from three to eight, especially from five to seven, ring carbon atoms, e.g. cyclopentyl, cyclohexyl or cycloheptyl, as well as cyclopropyl, cyclobutyl, cyclooctyl and the like. It may also represent cycloalkenyl containing from five to eight, especially six, ring carbon atoms, e.g. 2-cyclohexenyl, 3-cyclohexenyl and the like, as well as 2-cyclopentenyl, 3-cycloheptenyl and the like. These cycloaliphatic radicals are unsubstituted or may contain as substituents lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl and the like, or analogous groups, or functional substituents, such as halogeno, e.g. fluoro, chloro and the like, lower alkoxy, e.g. methoxy, ethoxy and the like.

The group R₂, which may also represent hydrogen, may stand for an aliphatic group, such as lower alkyl, containing preferably from one to four carbon atoms, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, secondary butyl and the like, as well as n-pentyl, neopentyl, n-hexyl, isohexyl, n-heptyl and the like, or any other aliphatic group, as well as a cycloaliphatic group, such as described hereinbefore, particularly cycloalkyl, containing from three to eight, preferably from five to six, ring carbon atoms, e.g. cyclopentyl, cyclohexyl and the like.

The group R₂ may also represent carbocyclic aryl, primarily monocyclic carbocyclic aryl, e.g. phenyl, or bicyclic carbocyclic aryl, e.g. 1-naphthyl or 2-naphthyl. Such radicals may be unsubstituted or may contain substituents; one or more than one of the same or different substituents may be attached to any of the available carbon atoms. Substituents are, for example, lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary butyl and the like, hydroxyl, etherified hydroxyl, such as lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropoxy, n-butoxy and the like, or lower alkylenedioxy, e.g. methylenedioxy, esterified hydroxy, such as lower alkoxy-carbonyloxy, e.g. methoxy-carbonyloxy, ethoxy-carbonyloxy and the like, lower alkanoyloxy, e.g. acetyloxy, n-propionyloxy and the like, or halogeno, e.g. fluoro, chloro, bromo and the like, mercapto, etherified mercapto, particularly lower alkyl-mercapto, e.g. methyl-mercapto, ethylmercapto and the like, carboxy, esterified carboxy, such as carbo-lower alkoxy, e.g. carbomethoxy, carbethoxy and the like, nitro, amino, such as N-unsubstituted amino, N-monosubstituted amino, for example, N-lower alkyl-amino, e.g. N-methyl-amino, N-ethyl-amino and the like, or particularly N,N-disubstituted amino, for example, N,N-di-lower alkyl-amino, e.g. N,N-dimethylamino, N,N-diethylamino and the like, or halogeno-lower alkyl, e.g. trifluoromethyl and the like, or any other analogous substituents.

R₂ may also stand for a carbocyclic aryl-aliphatic

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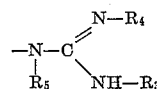
radical, such as a monocyclic carbocyclic aryl-lower alkyl, particularly phenyl-lower alkyl, e.g. benzyl, 1-phenylethyl, 2-phenylethyl and the like, and phenyl-lower alkyl, in which phenyl is substituted as shown hereinabove.

Heterocyclic aryl radicals R₂ are primarily monocyclic or bicyclic heterocyclic aryl radicals, which contain one or more than one sulfur, oxygen and/or nitrogen atom as ring members, and which are preferably pentacyclic or hexacyclic heterocyclic radicals. Such radicals are represented, for example, by monocyclic mono-azacyclic aryl, for example, pyridyl, e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl and the like, bicyclic mono-azacyclic aryl, for example, quinolyl, e.g. 2-quinolyl, 4-quinolyl and the like, monocyclic di-azacyclic aryl, for example, pyridazinyl, e.g. 3-pyridazinyl and the like, pyrimidyl, e.g. 2-pyrimidyl, 4-pyrimidyl and the like, pyrazinyl, e.g. 2-pyrazinyl, pyrrol, e.g. 2-pyrrol and the like, monocyclic thiacyclic aryl, for example, thienyl, e.g. 2-thienyl and the like, or monocyclic oxacyclic aryl, for example, furyl, e.g. 2-furyl and the like. The above described heterocyclic radicals are unsubstituted or may contain as substituents one of those previously described as being attached to a carbocyclic aryl radical.

Also included are heterocyclic aryl-aliphatic radicals representing R₂, such as monocyclic heterocyclic aryl-lower alkyl, in which the heterocyclic aryl radical has the previously given meaning; pyridyl-lower alkyl, e.g. 2-pyridylmethyl, 4-pyridylmethyl and the like, represent heterocyclic aryl-aliphatic radicals.

The lower alkyl portion, linking the N-R₁-N-R₂-amino group with the guanidino group, is represented by lower alkylene containing from one to seven carbon atoms. Preferably, lower alkylene contains from two to three carbon atoms, which separate the N-R₁-N-R₂-amino portion from the guanidino group by the same number of carbon atoms; such radicals are 1,2-ethylene, 1-methyl-1,2-ethylene, 2-methyl-1,2-ethylene or 1,3-propylene. Other lower alkylene radicals are, for example, methylene, 1,1-ethylene, 2,3-butylene, 1,3-butylene, 1,4-butylene, 1,4-pentylene or 1,5-pentylene and the like.

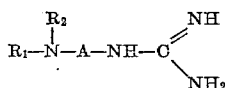
The guanidino group may be represented by the formula:



in which each of the radicals R₃, R₄ and R₅ stands primarily for hydrogen. They may also represent a hydrocarbon, particularly an aliphatic hydrocarbon, radical, such as lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl and the like. One of the radicals R₃ and R₄ may also be an acyl radical; an acyl radical may be, for example, the radical of a lower aliphatic carboxylic acid, for example, a lower alkanic acid, e.g. acetic, propionic, pivalic acid and the like, a substituted lower alkanic acid, e.g. chloroacetic, dichloroacetic, hydroxyacetic, methoxyacetic, cyclopentylpropionic acid and the like, or a lower alkenic acid, e.g. 3-butenic acid and the like, a carbocyclic aryl carboxylic acid, for example, a monocyclic carbocyclic aryl carboxylic acid, e.g. benzoic, 4-hydroxybenzoic, 4-methoxy-benzoic, 3,4-dimethoxybenzoic, 3,4,5-trimethoxy-benzoic, 4-O-ethoxycarbonyl-syringic, 3,4-dichlorobenzoic, 3-N,N-dimethylaminobenzoic, 4-nitrobenzoic acid and the like or a bicyclic carbocyclic aryl carboxylic acid, e.g. 1-naphthoic, 2-naphthoic acid and the like, or a heterocyclic aryl carboxylic acid, for example, monocyclic heterocyclic aryl carboxylic acids, e.g. nicotinic, isonicotinic, 2-furoic acid and the like.

Salts of the new compounds of this invention are particularly therapeutically acceptable, non-toxic acid addition salts, such as those with inorganic acids, for example,

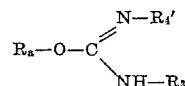
Particularly outstanding pharmacological effects are exhibited by the compounds of the formula:



The new guanidine compounds of this invention may 75

$$\text{R}_a\text{--S--C} \begin{array}{l} \text{=N--R}_4' \\ \text{--NH--R}_3' \end{array}$$

Similar reagents capable of converting an amino group containing at least one hydrogen atom into a guanidino group are the O-lower alkyl-isoureas of the formula:

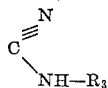


The above-described reagents are known, or, if new, may be prepared according to procedures described in the prior art and used for the manufacture of known analogs. For example, the S-lower alkyl-isothioureas or O-lower alkyl-isoureas may be obtained by alkylating thioureas or ureas, with a lower alkyl halide, e.g. methyl or ethyl chloride, bromide or iodide and the like, or with a di-

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lower alkyl-sulfate, e.g. dimethyl sulfate, diethyl sulfate and the like.

Other reagents capable of transforming the amino group containing at least one hydrogen atom of an N-R₁-N-R₂-lower alkylene diamine, in which R₁ and R₂ have the previously given meaning, and in which the second amino group contains at least one hydrogen atom, particularly of an acid addition salt of such compound, into a guanidino group, are cyanamides having the formula:



in which R₃ has the previously given meaning. The reaction may be carried out, for example, by heating a mixture of the cyanamide compound with the

N-R₁-N-R₂-amino-lower

alkylene-diamine, preferably in the form of a salt, particularly of a mineral acid addition salt, thereof, such as the hydrochloride, hydrobromide, sulfate and the like. A resulting melt may then be dissolved in a solvent, such as a lower alkanolic acid, e.g. acetic acid, and the like, and the desired product may be isolated, for example, by crystallization and the like. The reaction may also be performed in the presence of a suitable solvent, such as a lower alkanol, e.g. ethanol and the like. The salt used as the starting material may also be formed at the site of the reaction by performing the latter in the presence of an acid, particularly of a concentrated aqueous mineral acid, e.g. hydrochloric acid and the like. The cyanamide reagent may also be formed in situ; for example, 1-nitroso-3-methyl-guanidine furnishes the N-methyl-cyanamide during the reaction, and the latter then reacts with the amine to form the desired guanidino compound. The reaction may proceed exothermically, and, if necessary, may be maintained by heating, for example, to from about 80° to about 200°; the atmosphere of an inert gas, e.g. nitrogen, may be advantageous.

A third modification of the general procedure for the manufacture of the compounds of this invention comprises reacting an R₁-N-R₂-amino-lower alkylene-diamine, in which R₁ and R₂ have the previously given meaning, and in which the second amino group contains at least one hydrogen atom with a salt of a 1-guanyl-pyrazole. A salt of a 1-guanyl-pyrazole is primarily a salt with a mineral acid, such as, for example, nitric acid; the pyrazole nucleus of such reagent may contain additional substituents, particularly lower alkyl, e.g. methyl, ethyl and the like. 1-guanyl-3,5-dimethyl-pyrazole salts, particularly the nitrate thereof, represent the preferred reagents. The reaction may be carried out in the absence of a solvent, for example, by fusing the two reactants, or in the presence of a diluent, such as, for example, a lower alkanol, e.g. ethanol and the like; advantageously, contact with carbon dioxide should be avoided, for example, by performing the reaction in the atmosphere of an inert gas, e.g. nitrogen. The reaction mixture is preferably heated, for example, to the melting point of the mixture or to the boiling point of the solvent.

The N-R₁-N-R₂-lower alkyl-diamines, in which R₁ and R₂ have the previously given meaning, and in which the second amino group contains at least one hydrogen atom and the salts thereof, used as the starting materials, are known, or, if new, may be prepared according to known methods. They may be prepared by reacting an

N-R₁-N-R₂-amine

with a halogeno-lower alkyl-nitrile, in which halogeno represents, for example, chloro, bromo and the like, or with a lower alkene-nitrile, in which the double bond is activated by the nitrile group in such fashion, that it adds to the secondary amino group, and converting in a

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resulting N-R₁-N-R₂-amino-lower alkyl-nitrile, the nitrile group to a methylene-amino group by reduction. The latter may be carried out, for example, by catalytic hydrogenation, such as, treatment with hydrogen in the presence of a catalyst containing a metal of the eighth group of the Periodic System, e.g. palladium on charcoal or Raney nickel, or, preferably, by treatment with a light metal hydride, for example, an aluminum hydride, such as lithium aluminum hydride, sodium aluminum hydride, magnesium aluminum hydride, aluminum borohydride, aluminum hydride and the like, which hydrides may be used, if desired, in the presence of an activator, such as aluminum chloride.

The compounds of the present invention may also be prepared by converting in an N-R₁-N-R₂-N'-R_b-lower alkylene-diamines, in which R₁ and R₂ have the previously given meaning, and R_b represents a substituent capable of being converted into an amidino group, or a salt thereof, the substituent R_b into an amidino group, and, if desired, carrying out the optional steps.

Depending on the character of the substituent R_b, its conversion into an amidino group may be carried out according to different modifications.

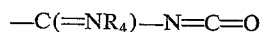
For example, the substituent R_b may contain a carbon atom, which is attached to the nitrogen atom of the amino group in the starting material; to this carbon atom may be connected a nitrogen atom. Said carbon atom may carry an additional nitrogen atom, as well as other hetero atoms, such as, for example, oxygen or sulfur. The substituents R_b may be represented, for example, by cyano of the formula —C≡N, carbamyl of the formula



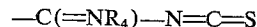
thiocarbamyl of the formula —CSNH—R₄, lower alkoxy-(imino)methyl of the formula —C(=NR₄)—OR_c, in which R_c represents lower alkyl, primarily methyl, as well as ethyl and the like, lower alkylmercapto-(imino)methyl of the formula —C(=NR₄)—SR_c, in which R_c has the above-given meaning, cyano-amidino of the formula —C(=NR₄)—NH—C≡N, guanidino-(imino)methyl of the formula



isocyano-(imino)methyl of the formula



or isothiocyano-(imino)methyl of the formula



and the like, in which R₄ has the previously given meaning, but stands particularly for hydrogen.

Together with the N-R₁-N-R₂-lower alkylene-diamino portion these substituents R_b form cyanamide, urea, thiourea, O-lower alkyl-isourea, S-lower alkyl-isothioureia, cyanoguanidine, biguanide, cyanourea or cyanothioureia derivatives and the like. All of these compounds have the above-given characteristics, i.e., to the amino group in the N-R₁-N-R₂-lower alkylene-diamine is attached a carbon atom, which carries at least one nitrogen atom, apart from other nitrogen or hetero atoms.

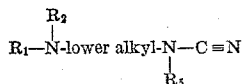
The greater part of these starting materials may be converted to the desired guanidino derivatives by ammonolysis or aminolysis.

For example, a cyanamide may be converted into a guanidino derivative by treatment with ammonia or an ammonia-furnishing reagent, as well as with an amine, such as an N-lower alkyl-amine. This reaction may be carried out, for example, by treating the cyanamide compound with liquid ammonia under pressure and at an elevated temperature, if desired, in the presence of an anion capable of forming a stable salt with a resulting guanidine; ammonium acetate, ammonium sulfate, ammonium chloride and the like may be used as anion sources. Ammonia may be replaced by ammonia furnishing ammonium salts; such salts are, for example, ammonium monohydrogen

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phosphate, which may be used under pressure and at an elevated temperature, or ammonium nitrate, whereby a salt, such as, for example, an alkaline earth metal, e.g. calcium and the like, salt or an alkali metal, e.g. sodium, potassium and the like, salt of the cyanamide starting material is preferably used, which may be reacted with the ammonium nitrate in the presence of catalytic amounts of water.

The cyanamide compounds used as intermediates and having the formula:

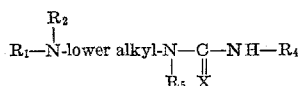


in which R_1 , R_2 and R_5 have the previously given meaning, and salts thereof, may be prepared, for example, by treating an $N-R_1-N-R_2$ -lower alkylene-diamine, in which the second amino group contains a hydrogen atom, with a cyanogen halide, e.g. cyanogen chloride, cyanogen bromide and the like, advantageously in equivalent amounts and preferably in an inert solvent, such as, for example, diethylether and the like.

A carbamyl substituent R_b in an $N-R_1-N-R_2-N'-R_5$ -lower alkylene-diamine may be converted into the desired amidino group by treatment with ammonia, preferably, in the presence of a dehydrating agent, such as, for example, phosphorous pentoxide and the like. This reaction may be carried out at an elevated temperature in a closed vessel; temperature and pressure may be reduced in the presence of a non-aqueous solvent and/or of a reaction accelerator, such as finely dispersed nickel, aluminum, aluminum oxide and the like. Ammonia may be replaced by an amine, such as an N -lower alkyl-amine, to form in the final product a substituted guanidino group.

Furthermore, a thiocarbamyl group R_b , which together with the amino group in an $N-R_1-N-R_2-N'-R_5$ -lower alkylene-diamine forms a thiourea group, may be converted into an amidino group by treatment with ammonia, for example, in the presence of water, and/or of a non-hydrolytic solvent, such as, for example, toluene and the like, and in the presence of a desulfurizing agent. The latter is selected advantageously from basic oxides, basic carbonates and the like, of heavy metals, such as lead, zinc, cadmium, tin, mercury and the like; desulfurizing compounds are, for example, lead oxide, mercuric oxide, lead hydrogen carbonate and the like. Mercuric chloride may also be used. This ammonolysis procedure, is preferably carried out at an elevated temperature, and, if necessary, in a closed vessel, primarily to avoid loss of ammonia. An amine, such as an N -lower alkyl-amine, may replace ammonia, and N -substituted guanidino derivatives may be formed.

Ureas and thioureas, used as the starting material in the above-mentioned modification of the procedure and having the formula:

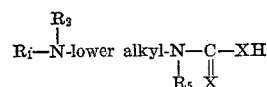


in which R_1 , R_2 , R_4 and R_5 have the previously given meaning, and X stands for oxygen or sulfur, and salts thereof may be obtained, for example, from $N-R_1-N-R_2$ -lower alkyl-diamines, in which the second amino group contains at least one hydrogen atom, by treating the latter with ammonium or metal cyanates or thiocyanates, such as alkali metal, e.g. sodium, potassium and the like, cyanates or thiocyanates. These reagents are preferably used in the presence of a solvent, for example, water, if desired, containing a small amount of an acid, such as a mineral acid, e.g. hydrochloric, sulfuric acid and the like. This procedure furnishes ureas or thioureas of the above-given formula, in which R_4 stands for hydrogen. A lower alkyl isocyanate or a lower alkyl isothiocyanate, when reacted with the $N-R_1-N-R_2$ -lower alkylene-diamine, yields

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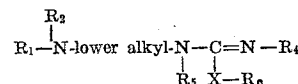
ureas or thioureas, in which R_4 represents lower alkyl. These lower alkyl isocyanates and lower alkyl isothiocyanates are reacted with the amino compound in a solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol and the like.

The above-mentioned urea or thiourea compounds, used as starting materials, may also be obtained by ammonolysis or aminolysis of reactive functional derivatives of $N-(N-R_1-N-R_2\text{-amino-lower alkyl})$ -carbamic acids, as well as $N-(N-R_1-N-R_2\text{-amino-lower alkyl})$ -thiocarbamic acid having the general formula:



in which R_1 , R_2 , R_5 and X have the previously given meaning. Such reactive functional derivatives are primarily esters, for example, lower alkyl, e.g. methyl, ethyl and the like, esters or halides, e.g. chlorides and the like. Upon ammonolysis, for example, by treatment with ammonia, if necessary, at an elevated temperature in a closed vessel, these carbamic and thiocarbamic acids yield the desired urea or thiourea derivatives, respectively. Ammonia may also be replaced by an amine, such as an N -lower alkylamine.

The group of O -lower alkyl-isoureas and S -lower alkyl-isothioureas of the formula:



in which R_1 , R_2 , R_4 , R_5 and X have the previously given meaning and R_6 stands for lower alkyl, primarily methyl, and salts thereof, are compounds containing the previously mentioned O -lower alkoxy-(imino)methyl group of the formula $-C(=NR_4)-OR_6$ and S -lower alkyl-mercapto-(imino)methyl group of the formula



respectively, in which R_4 and R_6 have the previously given meaning; these compounds are, therefore, useful as starting materials in the preparation of the compounds of this invention. They may be converted into the latter, for example, by ammonolysis or aminolysis. Ammonolysis may be carried out by treatment with ammonia, either in its liquid form or as a solution, such as an aqueous solution, thereof, whereby an elevated temperature and/or a closed vessel, as well as the presence of an ammonium salt, such as ammonium chloride and the like, may be required. If necessary, dehydrating agents or desulfurizing agents, such as those previously described, may be present in the reaction medium, depending on the type of starting material used. An amine, such as an N -lower alkyl-amine, may also be used for the conversion of the isoureas and isothioureas into guanidino derivatives containing substituted guanidino groups.

The isourea and isothiourea compounds used as the starting material in the above reaction may be obtained, for example, from the previously mentioned urea and thiourea derivatives by treatment of the latter, or of a metal salt thereof, such as an alkali metal, e.g. sodium, potassium and the like, salt thereof, with a lower alkyl halide, e.g. methyl or ethyl chloride, bromide or iodide and the like, or with a di-lower alkyl sulfate, e.g. dimethyl sulfate, diethyl sulfate and the like. Such reaction may be carried out in the presence of a solvent, the selection of which depends on the type of reagents used; a free urea or thiourea compound may be used in the presence of water or a lower alkanol, e.g. methanol, ethanol and the like, whereas an alkali metal salt of a urea or thiourea compound may be reacted in the presence of a hydrocarbon, e.g. toluene and the like, solution.

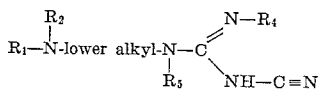
A cyanamidino substituent R_b , which forms a cyanoguanidino group with the amino group of an $N-R_1-N-R_2$ -lower alkylene-diamine, in which the second amino group

contains at least one hydrogen atom, may be converted into an amidino group by ammonolysis or aminolysis. This reaction may be carried out by treatment with ammonia, as well as with an ammonium salt, e.g. ammonium chloride, ammonium nitrate, ammonium sulfate and the like, whereby these salts may also promote ammonolysis with ammonia itself. Aminolysis of the starting materials may be carried out by treatment with an amine, such as an N-lower alkyl-amine, and N-substituted guanidine derivatives may be obtained.

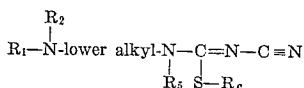
In the ammonolysis procedure of a cyanoguanidino to a guanidino derivative as described hereinabove, a biguanido group may be formed intermediately, which, upon further treatment with the ammonolysis reagent, may be converted to the desired guanidino group. Such biguanido derivatives may be accessible through different procedures (as will be shown hereinbelow) and are, therefore, also useful as starting material for the formation of the desired guanidino compounds by treatment with one of the ammonolysis or aminolysis reagents described hereinbefore.

A cyano-guanidino derivative, as mentioned hereinabove, may also be converted into the desired guanidino compound by reductive cleavage of the cyano group. Such cleavage may be carried out, for example, by electrolytic reduction on a cathode, such as, for example, a lead cathode.

The cyanoguanidino derivatives of the formula:



in which R_1 , R_2 , R_4 and R_5 have the previously given meaning, and their salts, which compounds may be converted to the desired guanidino groups by the above-described ammonolysis, aminolysis or reduction, may be prepared by treatment of S-lower alkyl-cyano-isothioureas of the formula:



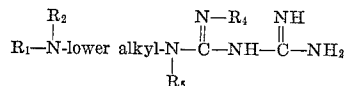
in which R_1 , R_2 , R_5 and R_6 have the previously given meaning, with ammonia, for example, in the presence of a lower alkanol, e.g. ethanol and the like, preferably in a sealed tube, or with an amine, such as an N-lower alkyl-amine.

Since the previously described cyano-guanidine derivatives are obtained by ammonolysis or aminolysis from S-lower alkyl-cyanisothiourea compounds having the above-given formula, the latter compounds may, therefore, directly serve as starting materials for the preparation of the guanidino compounds of this invention. Ammonolysis or aminolysis of the cyanisothiourea compounds to the latter may be carried out by treatment with ammonia or an amine in the presence of an anion of a strong acid, such as a halide, a nitrate, a sulfate ion and the like, for example, by the respective ammonium salts.

The S-lower alkyl-cyanisothioureas of the above formula or their salts may be obtained, for example, by treating an N- R_1 -N- R_2 -amino-lower alkyl-isothiocyanate with an alkali metal, e.g. sodium, cyanamide and alkylating a resulting 1-[(N- R_1 -N- R_2 -amino)-lower alkyl]-3-cyano-2-thiourea, preferably a salt thereof, with a lower alkyl halide, e.g. methyl or ethyl chloride, bromide or iodide and the like, or with a di-lower alkyl sulfate, e.g. dimethyl sulfate, diethyl sulfate and the like, as previously described in the preparation of the S-lower alkyl-isothioureas used as starting material for the preparation of the desired guanidines.

As has been shown, ammonolysis of cyano-guanidines

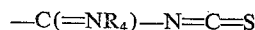
may give rise to the formation of biguanido compounds of the formula:



in which R_1 , R_2 , R_4 and R_5 have the previously given meaning, and salts thereof. These compounds may also be prepared, for example, by reacting an N- R_1 -N- R_2 -amino-lower alkyl-amine, in which the second amino group carries at least one hydrogen atom, with dicyanodiamide, preferably in the presence of a complex metal-forming salt, e.g. copper sulfate and the like. A resulting biguanido complex metal salt, such as the copper complex salt thereof, may be liberated to form the free compounds by treatment with an acid, such as a mineral acid, e.g. sulfuric acid and the like, to form the free compound. As previously described, ammonolysis and aminolysis of these biguanido derivatives give rise to the formation of the desired guanidines of this invention.

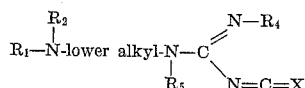
As mentioned hereinbefore, ammonolysis with ammonia or ammonia-furnishing reagents may be replaced by aminolysis with amines, particularly N-lower alkylamines, e.g. N-methylamine, N-ethylamine and the like. Such aminolysis reactions provide for the formation of substituted guanidino groups mentioned hereinabove.

In addition to ammonolysis and aminolysis, the guanidino compounds may also be obtained by hydrolysis of an N- R_1 -N- R_2 -N'- R_5 -lower alkylene-diamine, in which R_1 and R_2 have the previously given meaning, and R_5 represents a substituent capable of being hydrolyzed to an amidino group. For example, such substituent forms together with the amino group of the N- R_1 -N- R_2 -lower alkylene diamine, which carries at least one hydrogen atom, a cyanourea or a cyanothiurea group of the formulae $-C(=NR_4)-N=C=O$ and



respectively, in which R_4 has the previously given meaning. Compounds containing such groups yield upon treatment with a hydrolytic reagent, particularly with a dilute mineral acid, such as aqueous sulfuric acid and the like, the desired guanidino compounds. In such a hydrolysis reaction, the desired guanidine derivative may be formed simultaneously with a biuret derivative as the by-product.

Cyanourea or cyanothiurea compounds of the formula:

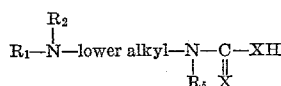


in which R_1 , R_2 , R_4 and R_5 have the above-given meaning, and X represents oxygen or sulfur, and salts thereof, which may be converted to the desired guanidino compounds by hydrolysis, may be obtained, for example, by reacting an N- R_1 -N- R_2 -amino-lower alkylcyanamide with a metal cyanate or thiocyanate, particularly an alkali metal, e.g. sodium or potassium, cyanate or thiocyanate in a neutral medium, for example, in the presence of water.

Apart from N- R_1 -N- R_2 -N'- R_5 -lower alkylene-diamines, in which a carbon atom with a substituting nitrogen atom of the group R_5 is attached to the second amino group, other N- R_1 -N- R_2 -N'- R_5 -lower alkylene-diamines, in which the R_5 represents a substituent convertible into an amidino group, may be useful in the conversion into the desired N- R_1 -N- R_2 -amino-lower alkyl-guanidines. In such a conversion intermediates may be formed, which may have the previously given characteristics, i.e. the carbon atom of the group R_5 carries a nitrogen atom. Such groups are, for example, ester groups, formed by a carboxyl, a thionocarboxyl, a thiocarboxyl or a dithiocarboxyl group with a lower alkanol, as well as halo-

geno-carbonyl or halogeno-thionocarbonyl groups, in which halogeno represents primarily chloro.

Particularly useful starting materials are, for example, the reactive functional derivatives of carbamic acids and thiocarbamic acids, having the formulae:



in which R_1 , R_2 and R_3 have the previously given meaning, and X represents oxygen or sulfur, or salts thereof. As shown hereinabove, esters, for example, lower alkyl, e.g. methyl, ethyl and the like, esters, or halides, e.g. chlorides, of such acids yield upon ammonolysis the corresponding urea and thiourea derivatives. However, if, for example, the ammonolysis of a carbamic acid ester is carried out in the presence of a dehydrating agent, such as, for example, previously shown in the conversion of urea derivatives to guanidines, an N-(N- R_1 -N- R_2 -amino-lower alkyl)-carbamic acid ester may be converted directly to the desired guanidino compound. Or, an ester of an N-(N- R_1 -N- R_2 -amino-lower alkyl)-thiocarbamic acid may be subjected to ammonolysis to yield directly the desired guanidino compound, for example, in the presence of a desulfurizing reagent, such as one of those previously shown in the conversion of a thiourea derivative into the desired guanidino compounds, e.g. lead oxide and the like.

The carbamic and thiocarbamic acid derivatives used as the starting materials may be prepared according to procedures used for the manufacture of known analogs. For example, upon treatment of an N- R_1 -N- R_2 -lower alkylene-diamine, in which the second amino group contains at least one hydrogen atom with phosgene or thiophosgene, which reagents may be used in a slight excess over the amines, the (N- R_1 -N- R_2 -amino)-lower alkyl-isocyanates and (N- R_1 -N- R_2 -amino)-lower alkyl-isothiocyanates, respectively, may be formed. Such cyanate and isothiocyanate compounds may then be converted into esters of carbamic or thiocarbamic acids by treatment with an alcohol, for example, a lower alkanol, e.g. methanol, ethanol and the like, or into the corresponding thioesters, by treatment with a mercaptan, such as a lower alkyl-mercaptan, e.g., methylmercaptan, ethylmercaptan and the like. The above derivatives may also be obtained by reacting an N- R_1 -N- R_2 -lower alkylene-diamine, in which the second amino group contains at least one hydrogen atom, with a carbonic acid lower alkyl ester, or, particularly a dithiocarbonic acid lower alkyl ester, as well as with a lower alkyl ester of a halogeno-formic acid, such as chloroformic acid, or, primarily, of a halogeno-thioformic acid, such as chloro-thioformic acid.

Or, a salt of an N- R_1 -N- R_2 -lower alkylene-diamine, in which the second amino group contains at least one hydrogen atom, particularly a hydrohalide, e.g. hydrochloride, thereof, when reacted with phosgene or thiophosgene at an elevated temperature, preferably in a closed vessel, yields the desired N-(N- R_1 -N- R_2 -amino-lower alkyl)-carbamic acid chloride and N-(N- R_1 -N- R_2 -amino-lower alkyl)-thiocarbamic acid chloride, respectively.

An additional general procedure for the preparation of the compounds of this invention comprises converting in an N- R_1 -N- R_2 -amino-lower alkane carboxylic acid guanide or a guanidino-lower alkane carboxylic acid N- R_1 -N- R_2 -amide, the carbonyl group of the amide portion to a methylene group, and, if desired, carrying out the optional steps.

The reduction of the carbonyl portion of the amide groups may be carried out according to known methods, for example, by treatment with an aluminum hydride, particularly an alkali metal aluminum hydride, e.g. lithium aluminum hydride, sodium aluminum hydride and the like, or an alkaline earth metal aluminum hydride, e.g.

magnesium aluminum hydride and the like, or aluminum hydride. If necessary, activators such as, for example, aluminum chloride, may be used together with the hydride reduction reagent. The reduction with these reagents is preferably performed in the presence of an inert solvent, particularly an ether, such as a di-lower alkyl ether, e.g. diethyl ether, diisopropyl ether and the like, a carbocyclic aryl lower ether, e.g. anisole and the like, a cyclic ether, e.g. tetrahydrofuran, p-dioxane and the like, or any other suitable solvent, and, if desired, at an elevated temperature and/or in the atmosphere of an inert gas, e.g. nitrogen.

Replacement of the oxygen atom of a carbonyl group by two hydrogen atoms in an amide compound may also be accomplished by treatment with hydrogen in the presence of certain catalysts, such as, for example, a copper-chromium catalyst and the like; hydrogenation may be carried out in the presence of an inert solvent and, if necessary, under increased pressure, as well as by electrolytically reducing the amido derivatives according to known methods, for example, on a cathode of a high overpotential such as, for example, mercury, lead amalgam, lead cathode and the like.

The starting materials used in the above reduction procedure may be prepared, for example, by treating a reactive functional derivative of an N- R_1 -N- R_2 -amino-lower alkane carboxylic acid with a guanidine, or a reactive functional derivative of a guanidino-lower alkane carboxylic acid with an N- R_1 -N- R_2 -amine to form the desired amide compounds. Reactive functional derivatives of carboxylic acids are, for example, esters, such as lower alkyl, e.g. methyl, ethyl and the like, esters, or activated esters, which are particularly useful for the formation of amide bonds, such as esters with reactive mercaptan compounds, e.g. mercapto-acetic acid and the like, or with reactive hydroxyl compounds, e.g. hydroxy-acetonitrile and the like. Such esters may be prepared according to methods which are used for the manufacture of analogous esters. Other reactive functional derivatives of acids are the acid addition salts of acid halides, particularly the hydrochloride of an acid chloride, which may be prepared according to standard methods.

The treatment of these reactive functional derivatives of carboxylic acids with the amino compounds may be carried out, for example, by reacting a salt of acid halide, particularly the hydrochloride of an acid chloride with the amine, preferably in a polar, but non-hydroxylated solvent, such as, for example, N,N-dimethylformamide, diethyleneglycol dimethylether, p-dioxane, tetrahydrofuran and the like.

A modification of the above procedure comprises converting in an N- R_1 -N- R_2 -amino-lower alkane thiocarbonyl acid guanide or a guanidino-lower alkane thiocarbonyl acid N- R_1 -N- R_2 -amide, the thiocarbonyl group of the thioamide portion into a methylene group, and, if desired, carrying out the optional steps.

Replacement of the sulfur in the above-mentioned thioamides by two hydrogens may be achieved by desulfurization, for example, with a freshly prepared hydrogenation catalyst, such as Raney nickel, in an alcohol solvent, e.g. methanol, ethanol and the like, if desired, in the presence of hydrogen, or electrolytic reduction as outlined hereinabove for the reduction of the amides.

The thioamides used as the starting materials in this modification may be prepared from the corresponding, previously described amides, for example, by treatment with phosphorus trisulfide, phosphorus pentasulfide and the like. A modification may consist in electrolytically reducing the amide in the presence of an alkali metal sulfide, e.g. sodium sulfide and the like, thereby forming the thioamide as a non-isolated intermediate.

Compounds of the present invention may also be prepared by treating an N- R_1 -N- R_2 -amine, in which R_1 and R_2 have the above-given meaning, or a salt thereof, with a reactive ester of a guanidino lower alkanol, in which the

lower alkanol portion contains at least two carbon atoms, which separate the hydroxyl from the guanidino group by at least two carbon atoms, or a salt thereof, and, if desired, carrying out the optional steps.

A reactive ester of a guanidino-lower alkanol is particularly an ester with a strong inorganic acid, such as a mineral acid, particularly a hydrohalic acid, e.g. hydrochloric, hydrobromic, hydriodic acid and the like, or with a strong organic acid, particularly a strong organic sulfonic acid, such as monocyclic carbocyclic aryl sulfonic acid, e.g. p-toluene sulfonic acid and the like. Such esters are, therefore, primarily guanidino-lower alkyl halides, e.g. chlorides, bromides and the like, or especially salts with hydrohalic acids, e.g. hydrochloric, hydrobromic acid and the like, thereof. The salts may be liberated at the site of the reaction by treating the salt with the necessary amount of an alkaline reagent.

This reaction may be carried out, for example, by adding a basic reagent, such as, for example, an alkali metal, e.g. sodium or potassium, in liquid ammonia, or an alkali metal, e.g. sodium or potassium, carbonate. It is preferably performed in the presence of a solvent, the selection of which depends on the properties of the reagents; a lower alkanol, e.g. methanol, ethanol and the like, may be used with the salt of an ester of the guanidino-lower alkanol, whereas the free base may be reacted in the presence of a non-hydroxylic solvent, such as, for example, an ether, e.g. p-dioxane and the like, or a hydrocarbon, such as a monocyclic carbocyclic aryl hydrocarbon, e.g. benzene, toluene and the like. It may be performed under cooling, or more preferably, at an elevated temperature, if desired, in a closed vessel under pressure, or in the atmosphere of an inert gas.

The reactive esters of guanidino-lower alkanols, in which the lower alkanol portion contains at least two carbon atoms and separates the guanidino group from the hydroxyl group by at least two carbon atoms, and in which the nitrogen atoms of the guanidino group may be substituted as previously shown, and the salts thereof, which reagents are used as the starting materials in the above reaction, may be prepared by esterifying guanidino-lower alkanols. For example, a guanidino-lower alkanol may be converted into a guanidino-lower alkyl halide by treatment with a thionyl halide, particularly thionyl chloride; such reaction may be carried out in the presence of an inert solvent, for example, a hydrocarbon, such as a monocyclic carbocyclic aryl hydrocarbon, e.g. benzene, toluene and the like, or in any other suitable solvent. This procedure yields preferably the acid addition salt with a hydrohalic, e.g. hydrochloric, acid. A guanidino-lower alkyl sulfonate, particularly a p-toluene-sulfonate, may be prepared, for example, by treatment of the guanidino-lower alkanol with a sulfonyl halide, such as p-toluene-sulfonyl chloride, in the presence of a solvent, such as pyridine and the like.

A modification of the above procedure comprises treating a reactive ester of an N-R₁-N-R₂-amino-lower alkanol, in which R₁ and R₂ have the previously given meaning, or a salt thereof with a guanidine, and, if desired, carrying out the optional steps.

A reactive ester of an N-R₁-N-R₂-amino-lower alkanol is an ester with a strong inorganic or organic acid; N-R₁-N-R₂-amino-lower alkyl halides, e.g. chlorides and the like, or N-R₁-N-R₂-amino-lower alkyl monocyclic carbocyclic aryl sulfonates, e.g. p-toluene sulfonates and the like, or salts thereof are the preferred reagents. The guanidines, such as guanidine itself, as well as guanidines containing additional substituents which do not interfere with the reaction, may also be used in the form of their salts. The reaction is performed along the general procedure outlined hereinbefore.

The starting materials, i.e. reactive esters of N-R₁-N-R₂-amino-lower alkanols are known and may be prepared according to standard procedure, used for analogous compounds.

In the products obtained according to the above-described methods, additional groups may be introduced or groups may be exchanged for other substituents. For example, resulting guanidines may be acylated; this reaction may be carried out, for example, by treating the guanidine compound with the reactive derivative of a carboxylic acid, for example, with the halide, e.g. chloride and the like, or the anhydride of a carboxylic acid. The acylation may be performed in the presence of an inert solvent, for example, a hydrocarbon, such as a lower alkane, e.g. hexane and the like, a monocyclic carbocyclic aryl hydrocarbon, e.g. benzene, toluene, xylene and the like, or in a tertiary organic base, such as a liquid pyridine compound, e.g. pyridine, collidine and the like, or any other suitable diluent. Acylation may also be achieved in the absence of a solvent, for example, by heating the guanidine compound or a salt thereof with the acylating reagent, for example, acetic acid anhydride and the like, in a sealed tube.

The new guanidine compounds may be obtained in the form of the free compounds or as the salts thereof. A salt may be converted into the free compound in the customary way, for example, by treatment with a strong alkaline reagent, such as aqueous alkali metal hydroxide, e.g. lithium, sodium, potassium hydroxide and the like, a strong quaternary ammonium anion (hydroxyl ion) exchange resin and the like. A free base may be transformed into its therapeutically useful acid addition salts by reacting the latter with an appropriate inorganic or organic acid, such as one of the above-mentioned acids. The reaction may be carried out, for example, in a solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol, propanol, isopropanol and the like, an ether, e.g. diethylether, p-dioxane and the like, a lower alkyl lower alkanoate, e.g. ethyl acetate and the like, a halogenated hydrocarbon, e.g. methylene chloride and the like, or a mixture of such solvents, and isolating the desired salt. Mono- or poly-salts may be formed, as well as mixed salts; for example, a resulting half-sulfate salt, when treated with hydrogen chloride, yields the hydrochloride half-sulfate salt.

The new guanidine compounds of this invention may also form quaternary ammonium compounds, particularly those with lower alkyl halides, e.g. methyl, ethyl, n-propyl or isopropyl chloride, bromide or iodide and the like, with di-lower alkyl-sulfates, e.g. dimethyl sulfate, diethyl sulfate and the like, or with lower alkyl lower alkane sulfonates, e.g. methyl or ethyl methane or ethane sulfonate, and the like, as well as the corresponding quaternary ammonium hydroxides and the salts which may be formed from the quaternary ammonium hydroxides by the reaction with inorganic acids other than the hydrohalic acids or with organic acids, such as those outlined above for the preparation of the acid addition salts.

The quaternary ammonium compounds may be obtained by reacting a resulting free base with a lower alkyl halide, e.g. methyl, ethyl, n-propyl, isopropyl chloride, bromide or iodide and the like, with a di-lower alkyl-sulfate, e.g. dimethyl sulfate, diethyl sulfate and the like, or with a lower alkyl lower alkane sulfonate, e.g. methyl or ethyl methane or ethane sulfonate and the like. The quaternizing reaction may be performed in the absence or in the presence of a solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol, propanol, isopropanol, tertiary butanol and the like, a lower alkanone, e.g. acetone, ethyl methyl ketone and the like, an organic acid amide, e.g. formamide, N,N-dimethyl-formamide and the like, or a halogenated hydrocarbon, e.g. methylene chloride and the like. Resulting quaternary ammonium compounds may be converted into the corresponding quaternary ammonium hydroxides, for example, by reacting resulting quaternary ammonium halides with silver oxide, by treating quaternary ammonium sulfates with barium hydroxide, or quaternary ammonium salts

with an anion exchanger, or by electrodialysis. From a resulting quaternary ammonium hydroxide there may be formed therapeutically suitable quaternary ammonium salts by treating the quaternary ammonium hydroxide with acids, for example, with those outlined hereinbefore as being useful for the preparation of acid addition salts.

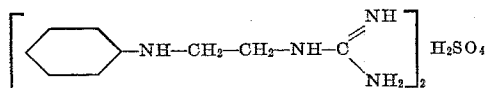
The invention also comprises any modification of the general process, wherein a compound obtainable as an intermediate at any stage of the process is used as the starting material and the remaining step(s) of the process is (are) carried out; also included within the scope of the invention are any new intermediates.

In the process of this invention such starting materials are preferably used which lead to final products mentioned in the beginning as preferred embodiments of the invention.

The following examples illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade.

Example 1

A solution of 10.0 g. of N-cyclohexyl-ethylenediamine and 9.8 g. of S-methyl-isothiurea sulfate in 20 ml. of water is refluxed for four hours and is then concentrated under reduced pressure. The solid residue is recrystallized from a mixture of n-butanol and water (or ethanol and water) to yield the desired 2-(N-cyclohexylamino)-ethyl-guanidine sulfate of the formula:

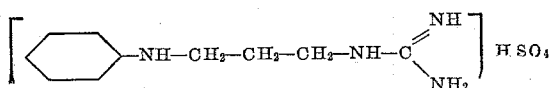


which melts at 240–243° (with decomposition).

The 2-(N-cyclopentylamino)-ethyl-guanidine sulfate is prepared according to the above procedure by reacting N-cyclopentyl-ethylenediamine with S-methyl-isothiurea sulfate in water.

Example 2

A mixture of 5.0 g. of N-cyclohexyl-1,3-propylenediamine and 4.5 g. of S-methyl-isothiurea sulfate in 30 ml. of water is refluxed for six hours and is then evaporated to dryness under reduced pressure. The desired 3-(N-cyclohexylamino)-propylguanidine sulfate of the formula:

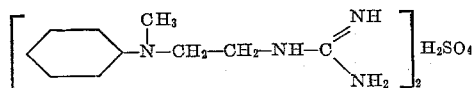


is obtained by recrystallizing the resulting residue from ethanol, M.P. 283–284° (with decomposition).

The 3-(N-cycloheptylamino)-propyl-guanidine sulfate and 3-(N-cyclopentylamino)-propyl-guanidine sulfate can be prepared according to the above procedure by reacting N-cycloheptyl-1,3-propylenediamine and N-cyclopentyl-1,3-propylenediamine with S-methyl-isothiurea sulfate in water.

Example 3

A mixture of 2.5 g. of N-cyclohexyl-N-methyl-ethylenediamine and 2.2 g. of S-methyl-isothiurea sulfate in 25 ml. of water is refluxed for six hours. The reaction mixture is concentrated under reduced pressure and the residue is recrystallized from ethanol to yield 2-(N-cyclohexyl-N-methyl-amino)-ethyl-guanidine sulfate of the formula:



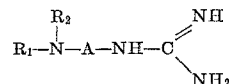
which melts at 239–240° (with decomposition).

The above sulfate salt is suspended in water, an excess of sodium hydroxide is added while cooling and the free base is extracted immediately with chloroform. The chloroform solution is dried, filtered and evaporated. The free base is converted into the dihydrochloride by treating a concentrated solution of the free base in ethanol with a solution of hydrogen chloride in ethanol and diluting the reaction mixture with diethylether, whereupon the salt precipitates.

- Upon reacting N-cyclohexyl-N-methyl-1,3-propylenediamine, N-cyclohexyl-N-ethyl-ethylenediamine, N-cyclopentyl-N-methyl-ethylenediamine, N-cyclopentyl-N-methyl-1,3-propylenediamine, N-cyclopentyl-N-isopropyl-ethylenediamine, N-cycloheptyl-N-methyl-ethylenediamine and the like, with S-methyl-isothiurea sulfate according to the above procedure, the 3-(N-cyclohexyl-N-methyl-amino)-propyl-guanidine sulfate, 2-(N-cyclohexyl-N-ethyl-amino)-ethyl-guanidine sulfate, 2-(N-cyclopentyl-N-methyl-amino)-ethyl-guanidine sulfate, 3-(N-cyclopentyl-N-methyl-amino)-propyl-guanidine sulfate, 2-(N-cyclopentyl-N-isopropyl-amino)-ethyl-guanidine sulfate, 2-(N-cycloheptyl-N-methyl-amino)-ethyl-guanidine sulfate and the like, can be formed.

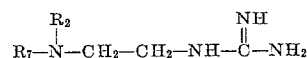
What is claimed is:

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



- in which R₁ is cycloalkyl having 3 to 6 ring carbon atoms, R₂ stands for a member selected from the group consisting of hydrogen and lower alkyl, and A is lower alkylene having from two to three carbon atoms and separating the guanidino from the amino group by from two to three carbon atoms, and an addition salt thereof with a therapeutically acceptable acid.

2. A compound of the formula



- in which R₁ is cycloalkyl having 3 to 6 ring carbon atoms and R₂ is selected from the group consisting of hydrogen and lower alkyl.

3. 2-(N-cyclohexylamino)-ethyl-guanidine.
4. 2-(N-cyclohexylamino)-ethyl-guanidine sulfate.
5. 3-(N-cyclohexylamino)-n-propyl-guanidine.
6. 3-(N-cyclohexylamino)-n-propyl-guanidine sulfate.
7. 2-(N-cyclohexyl-N-methyl-amino)-ethyl-guanidine.
8. 2-(N-cyclohexyl-N-methyl-amino)-ethyl-guanidine sulfate.

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