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PROCESS FOR PREPARING (N,N-ALKYLENE-IMINO)-LOWER ALKYL-GUANIDINES

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The present invention concerns a process for the preparation of guanidino compounds. More particularly, the procedure of the invention relates to the maufacture of (N,N-alkylene-imino)-lower alkyl-guanidines, in which alkylene contains from four to ten carbon atoms as ring members, and the salts thereof. Also anticipated are quaternary ammonium compounds and acyl derivatives of these compounds, whenever prepared according to the procedure of the invention.

N,N-alkylene-imino radicals, containing from four to ten carbon atoms, primarily from six to eight carbon atoms, are unsubstituted, or may contain as further substituents of carbon atoms lower hydrocarbon radicals, such as lower alkyl, e.g. methyl or ethyl. They may be represented by N,N-tetramethylene-imino (1-pyrrolidino), N,N-pentamethylene-imino (1-piperidino), N,N-hexamethylene-imino (1-hexahydro-azepino), N,N-heptamethylene-imino (1-octahydro-azocino), N,N-octamethylene-imino (1-octahydro-azonino), N,N-nonamethylene-imino (1-decahydro-azecino) or N,N-decamethylene-imino radicals.

The lower alkyl radical, linking the alkyleneimino ring with the guanidino group, contains from one to seven carbon atoms and is represented by a lower alkylene radical, which may also be branched. Such alkylene radicals contain preferably from two to three carbon atoms and are represented, for example, by 1,2-ethylene, 1-methyl-1,2-ethylene, 2-methyl-1,2-ethylene or 1,3-propylene; additional alkylene radicals are, for example, methylene, 1,1-ethylene, 2,3-butylene, 1,3-butylene, 1,4-butylene, 1,4-pentylene, 1,5-pentylene and the like.

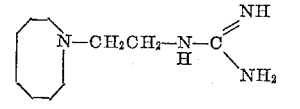
The guanidino group is preferably unsubstituted. However the amino, as well as the imino groups of the guanidino portion may be substituted by lower hydrocarbon radicals, such as lower alkyl, e.g. methyl or ethyl. Such substituted guanidino groups are, for example, N-monomethyl-, N-polymethyl-, N-monoethyl- or N-polyethyl-guanidino groups.

Salts of the compounds prepared according to the process of this invention are particularly therapeutically useful acid addition salts, such as those with inorganic acids, for example, hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric or phosphoric acids, or those with organic acids, such as formic, acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, ascorbic, hydroxymaleic, dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranilic, cinnamic, mandelic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxy-benzoic, methane sulfonic, ethane sulfonic, hydroxyethane sulfonic acid and the like.

The guanidine compounds may also form quaternary ammonium compounds, particularly those with lower alkyl halides, e.g. methyl, ethyl, propyl or isopropyl chloride, bromide or iodide, or lower alkyl lower alkane sulfonates, e.g. methyl or ethyl methane or ethane sulfonate, 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 hydrohalic acids or with organic acids, such as those outlined above for the preparation of the acid addition salts.

Acyl derivatives of the guanidine compounds prepared according to the procedure of this invention are those formed with organic acids, particularly with carboxylic acids, such as lower aliphatic carboxylic acids, for example, lower alkanoic acids, e.g. acetic, propionic or pivalic acid and the like, substituted lower alkanoic acids, e.g. trichloroacetic, hydroxyacetic or cyclopentylpropionic acid and the like, or lower alkenoic acids, e.g. acrylic acid and the like, with aromatic carboxylic acids, for example, monocyclic aromatic carboxylic acids, e.g. benzoic hydroxybenzoic or aminobenzoic acid and the like, or bicyclic aromatic carboxylic acids, e.g. 1-naphthoic or 2-naphthoic acid and the like, with carbocyclic aryl-lower aliphatic acids, such as monocyclic carbocyclic aryl-lower alkanoic acids, e.g. phenylacetic acid or β-phenylpropionic acid and the like, or with heterocyclic carboxylic acids, for example, monocyclic heterocyclic carboxylic acids, e.g. nicotinic, isonicotinic or 2-furoic acid and the like.

The above-mentioned guanidine derivatives and salts thereof have antihypertensive properties and can be used as antihypertensive agents to relieve hypertensive conditions, particularly neurogenic or renal hypertension. A particular characteristic of this antihypertensive effect is its long duration, which property is especially desirable in the treatment of chronic hyperensive states. Particularly valuable with respect to their long-lasting antihypertensive activity are the (N,N-alkylene-imino)-lower alkyl-guanidines, in which the N,N-alkylene-imino portion contains from six to eight, primarily seven, carbon atoms, and carries no additional substituents or only methyl groups, and in which lower alkyl, containing from two to three carbon atoms, separates the N,N-alkylene-imino portion from the guanidino group by two to three carbon atoms, and their salts with inorganic acids, such as mineral acids, e.g. hydrochloric or sulfuric acid, or with organic acids, such as hydroxy-substituted aliphatic acids, e.g. tartaric or citric acid, or unsaturated aliphatic acids, e.g. maleic acid. This group is represented by the (N,N-heptamethylene-imino)-lower alkyl guanidines, particularly the guanidine compound of the formula:



and their therapeutically useful inorganic acid addition salts, particularly their sulfates.

The procedure of the present invention, which concerns the preparation of the above-described guanidine compounds, comprises converting in an (N,N-alkylene-imino)-lower alkyl-amine, in which the amino group carries a substituent capable of being converted into an amidino group, or a salt thereof, such substituent into an amidino group, and, if desired, converting a resulting salt into the free base, and/or, if desired, converting a resulting compound into a salt or an acyl derivative or a quaternary ammonium compound thereof.

Depending on the character of the substituent which is capable of being converted to an amidino group and attached to the amino group of the (N,N-alkylene-imino)-lower alkyl-amine, the procedure outlined hereinabove may be carried out according to different modifications.

For example, the substituent attached to the amino group may comprise a carbon atom, which is attached to the amino group of the (N,N-alkylene-imino)-lower alkyl-amine. To this carbon atoms may be connected at least one nitrogen atom. The carbon atom may also carry an additional nitrogen atom, as well as other hetero atoms, such as, for example, oxygen or sulfur. Such groups may be, for example, cyano of the formula

N≡C—, carbamyl of the formula H_2NOC—, thiocarbamyl of the formula H_2NSC—, lower alkoxy-(imino)-methyl of the formula RO—(NH=)C—, in which R represents lower alkyl, primarily for methyl, as well as ethyl and the like, lower alkyl-mercapto-(imino)methyl of the formula RS—(NH=)C—, in which R has the above-given meaning, cyanoamidino of the formula N≡C—NH—(NH=)C—, guanidino-(imino)methyl of the formula $[H_2N—(NH=)C—NH]—NH=)C—$, isocyano-(imino)methyl of the formula

O=C=N—(NH=)C—

or isothiocyano-(imino)methyl of the formula

S=C=N—(NH=)C—

and the like.

Together with the (N,N-alkylene-imino)-lower alkyl-amino portion these substituents form cyanamide, urea, thiourea, O-lower alkyl-isourea, S-lower alkyl-isothiourea, cyanoguanidine, biguanide, cyanourea or cyanothiourea derivatives and the like. All of these compounds have the above-given characteristic, i.e. to the amino group 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.

Thus, a cyanamide may be converted into the guanidino derivative by treatment with ammonia or an ammonia-furishing reagent. This reaction may be carried out, for example, by treatment of the cyanamide compound with liquid ammonia under pressure and at an elevated temperature, if desired in the presence of an anion capable of combining with a resulting guanidine to form a stable salt; ammonium acetate, ammonium sulfate or ammonium chloride may be used as an anion source. Ammonia may be replaced by ammonia furnishing ammonium salts; such salts are, for example, ammonium monohydrogen 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, or alkali metal, e.g. sodium or potassium, salt of the cyanamide is preferably used, which may be reacted with the ammonium nitrate in the presence of catalytic amounts of water.

Or, a carbamyl group attached to the amino group of the (N,N-alkylene-imino)-lower alkyl-amine may be converted to the desired amidino group by treatment with ammonia, preferably, in the presence of a dehydrating agent, such as, for example, phosphorous pentoxide. This treatment may be carried out at an elevated temperature in a closed vessel; temperature and pressure may be reduced by the presence of a non-aqueous solvent and/or of a reaction accelerator, such as finely dispersed nickel, aluminum, aluminum oxide and the like.

Furthermore, a thiocarbamyl group, which together with the amino group of a (N,N-alkylene-imino)-lower alkyl-amine 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 in the presence of a desulfurizing agent, which is advantageously selected from salts, such as basic salts, particularly basic oxides, carbonates and the like, of heavy metals, such as lead, zinc, cadmium, tin, mercury and the like; such basic salts may be, for example, lead oxide, mercuric oxide or lead hydrogen carbonate. 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 any loss of ammonia.

O-lower alkoxy-(imino)methyl or S-lower alkyl-mercapto-(imino)methyl groups of the formulae

RO—(NH=)C—

and RS—(NH=)C—, respectively, in which R has the

aforementioned meaning, form together with the amino group of the (N,N-alkylene-imino)-lower alkyl-amine N-substituted O-lower alkyl-isourea or N-substituted S-lower alkyl-isothiourea derivatives. These compounds may be converted into the desired (N,N-alkylene-imino)-lower alkyl-guanidines by treatment with ammonia, either as liquid in its form or as an aqueous solution, whereby an elevated temperature and/or a closed vessel, as well as the presence of an ammonium salt, such as ammonium chloride, may be required. If necessary, dehydrating agents or desulfurizing agents, such as those described hereinbefore, may be present, depending on the starting material.

A cyanamidino group, which, connected to the amino group, forms together with the (N,N-alkylene-imino)-lower alkyl-amine a cyanoguanidino derivative, may be converted to the amidino group by ammonolysis. This reaction may be carried out by treatment with ammonia, as well as with an ammonium salt, such as ammonium chloride, ammonium nitrate or ammonium sulfate, whereby these salts may also promote the ammonolysis with ammonia itself.

In the ammonolysis procedure of a cyanoguanidino to a guanidino derivative as described hereinabove, a biguanido group may be formed intermediarily, which, upon further treatment with the ammonolysis reagent, may be converted to the desired guanidino group.

Such biguanido derivatives may also be accessible through different procedures (as will be shown hereinbelow) and may, therefore, also be used as a starting material for the formation of the desired guanidino compounds by treatment with one of the ammonolysis reagents described hereinbefore.

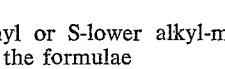
The aforementioned reactions involving ammonolysis with ammonia or ammonia-furnishing reagents may be replaced by aminolysis with amines, particularly lower alkyl-amines, e.g. methylamine or ethylamine. Such aminolysis reactions provide for the formation of the substituted guanidino groups mentioned hereinabove.

In addition to the ammonolysis and aminolysis, the guanidino compounds may also be obtained by hydrolysis of an (N,N-alkylene-imino)-lower alkyl-amines, in which the amino group contains a substituent, which may be hydrolyzed to an amidino group. Such a substituent may form together with the amino group of the (N,N-alkylene-imino)-lower alkyl-amine a cyanourea or a cyanothiourea group of the formulae O=C=N—(NH=)C— and S=C=N—(NH=)C—, respectively. Compounds containing such groups yield upon treatment with a hydrolytic reagent, particularly a dilute mineral acid, such as aqueous sulfuric acid, the desired guanidino compounds. In this hydrolysis reaction, the desired guanidine derivative may be formed simultaneously with a biuret derivative as the by-product.

A cyano-guanidino derivative, as, for example, previously mentioned in the ammonolysis and aminolysis procedure, may also be converted to 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 starting materials used in the above-described procedure are new and are intended to be included within the scope of this invention. The selection of procedures to prepare these starting materials depends primarily on the nature of the group, which is attached to the amino group of the (N,N-alkylene-imino)-lower alkyl-amine and which is converted to the amidino group in the above-described procedures.

For example, cyanamide compounds of the formula



in which R_1 represents the N,N-alkylene-imino portion defined hereinabove, R_2 stands primarily for hydrogen, but may also be lower alkyl, and A represents the lower

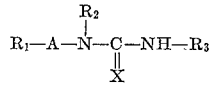
alkylene radical, which in the products of the procedure of the invention connects the N,N-alkylene-imino portion with the guanidino group, and salts thereof may be prepared, for example, by treating the (N,N-alkylene-imino)-lower alkyl-amine with a cyanogen halide, such as cyanogen chloride or cyanogen bromide, advantageously in equivalent amounts and preferably in an inert solvent, such as, for example, ether. As previously shown, these cyanamides may be converted to the guanidines by ammonolysis or aminolysis.

A preferred group of such cyanamides are, for example, the compounds of the formula:

$$R_1'—A'—NH—CN$$

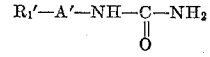
in which R_1' represents an N,N-alkylene-imino radical, the alkylene chain of which contains from six to eight carbon atoms, and A stands for a lower alkylene radical, containing from two to three carbon atoms, and separating the group R_1' from the cyanamide group by two to three carbon atoms. This group may be illustrated, for example, by the 2-(1-N,N-heptamethylene-imino)-ethyl-cyanamide.

Ureas and thioureas of the formula:

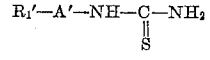


in which R_1, R_2 and A have the previously given meaning, R_3 stands primarily for hydrogen, but may also represent lower alkyl, and X stands for oxygen or sulfur, and salts thereof may be obtained, for example, from the (N,N-alkylene-imino)-lower alkyl-amines by treatment of the latter with metal cyanates or thiocyanates, particularly alkali metal, e.g. sodium or potassium, cyanates or thiocynates. These reagents are preferably used in the presence of a solvent, such as, for example, water, if desired, by adding an acid, such as a mineral acid, e.g. hydrochloric or sulfuric acid. This procedure furnishes ureas or thioureas of the above-given formula, in which R_3 stands for hydrogen. A lower alkyl isocyanate or a lower alkyl isothiocyanate, when reacted with the (N,N-alkylene-imino)-lower alkyl-amine, yields ureas or thioureas, in which R_3 represents lower alkyl. These lower alkyl isocyanates and isothiocyanates are reacted with the (N,N-alkylene-imino)-lower alkyl-amines in a solvent, such as, for example, a lower alkanol, e.g. methanol or ethanol.

This group of urea and thiourea compounds may be represented by the compounds of the formula

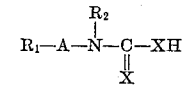


and



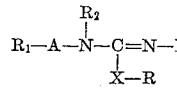
in which R_1' stands for an N,N-alkylene-imino radical, in which alkylene contains from six to eight carbon atoms, and A', representing an alkylene radical having from two to three carbon atoms, separates the N,N-alkylene-imino portion from the urea or thiourea group by two to three carbon atoms. For example, 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-2-urea and 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-2-thiourea are members of this preferred group of urea and thiourea derivatives. As shown hereinabove, ammonolysis or aminolysis of the above urea derivatives in the presence of a dehydrating reagent or of the thiourea compounds in the presence of a desulfurizing reagent, yields the desired guanidino compounds, described hereinabove as having antihypertensive properties.

The above-mentioned urea or thiourea compounds may also be obtained by an ammonolysis procedure from reactive functional derivatives of N-(N,N-alkylene-imino)-lower alkyl carbamic acids or N-(N,N-alkylene-imino)-lower alkyl thiocarbamic acid having the general formula:



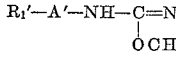
in which R_1, R_2, A and X have the previously-given meaning. Such reactive functional derivatives are primarily esters, for example, lower alkyl, e.g. methyl or ethyl, esters or halides, e.g. chlorides. Upon ammonolysis, for example, by treatment with ammonia, if necessary, at an elevated temperature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

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

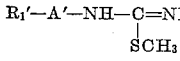


in which R_1, R_2, R_3, A and X have the previously-given meaning and R stands for lower alkyl, e.g. ethyl, or primarily methyl, and their salts, may be converted to the desired guanidino compounds by ammonolysis or aminolysis as has been shown hereinabove. These compounds may be prepared from the previously-mentioned urea and thiourea derivatives by treatment of the latter, or of a metal salt, such as an alkali metal, e.g. sodium or potassium, salt thereof, with a lower alkyl halide, such as a methyl or ethyl chloride, bromide or iodide, or a lower alkyl sulfate, e.g. dimethyl sulfate or diethyl sulfate. 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. ethanol, whereas an alkali metal salt of a urea or thiourea compound may be reacted in a hydrocarbon, e.g. toluene, solution.

A preferred group of the above-shown isourea and isothiourea derivatives are the compounds of the formulae

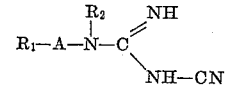


and

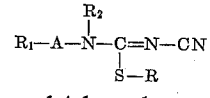


in which R_1' stands for N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, and A' represents an alkylene radical containing from two to three carbon atoms and separating the N,N-alkylene-imino portion from the iosurea or isothiourea group by two to three carbon atoms; 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-O-bethyl-isourea and 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-S-methyl-isothiourea are members of this preferred group.

The cyanoguanidino derivatives of the formula:



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



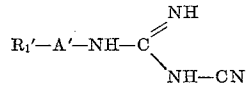
in which R, R_1, R_2 and A have the previously-given meaning, with ammonia in a lower alkanol, e.g. ethanol, preferably in a sealed tube.

The S-lower alkyl-cyanoisothiourea derivatives of the

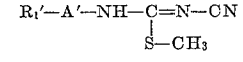
above formula may, therefore, also serve as starting materials in the process for the preparation of the guanidino compounds, inasmuch as the ammonolysis and aminolysis thereof may yield the desired guanidino derivatives directly, if the treatment with ammonia is carried out, for example, in the presence of anions of strong acids, such as halide, nitrate or sulfate ions, furnished, for example, by the respective ammonium salts.

The S-lower alkyl-cyanoisothioureas of the above formula or their salts may be obtained, for example, by treating a (N,N-alkylene-imino)-lower alkyl-isothiocyanate with an alkali metal, e.g. sodium, cyanamide and alkylating a resulting 1-(N,N-alkylene-imino)-3-cyano-2-thiourea, preferably a salt thereof, with a lower alkyl halide, e.g. methyl or ethyl chloride, bromide, or particularly iodide, or with a lower alkyl sulfate, e.g. dimethyl sulfate or diethyl sulfate, as shown hereinbefore for the preparation of S-lower alkyl-isothiourea used as starting materials in the ammonolysis to the desired guanidines.

A preferred group of cyano-guanidine compounds, which may be used as intermediates, are the compounds of the formula:

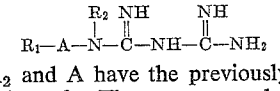


in which R_1' stands for N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, and A' represents an alkylene radical containing from two to three carbon atoms and separating the N,N-alkylene-imino portion from the cyanoguanidino group by two to three carbon atoms. These intermediates may be obtained by ammonolysis of the S-methyl-cyanoisothioureas of the formula:

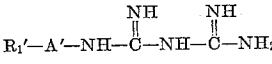


in which R_1' stands for N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, and A' represents an alkylene radical containing from two to three carbon atoms and separating the N,N-alkylene-imino portion from the S-methyl-cyanoisothiourea group by two to three carbon atoms. Ammonolysis or aminolysis of the latter may furnish directly the desired guanidines without isolating any intermediarily formed cyanoguanidine derivatives. The above group of cyanoguanidino derivatives may be illustrated by 1-[2-(1-N,N-heptamethyleneimino)-ethyl]-3-cyano-guanidine, which may be obtained from the 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-3-cyano-S-methylisothiourea by controlled ammonolysis as previously shown.

As has been previously shown, the ammonolysis of cyanoguanidines may give rise to the formation of biguanido compounds of the formula:



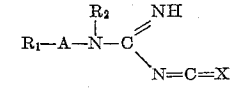
in which R_1, R_2 and A have the previously-given meaning, and salts thereof. These compounds may also be prepared, for example, by reacting an (N,N-alkylene-imino)-lower alkyl-amine with dicyanodiamide, preferably in the presence of a complex metal-forming salt, such as copper sulfate. A resulting biguanido complex metal salt, such as the copper complex salt thereof, may be liberated to the free compound by treatment with an acid, such as a mineral acid, e.g. sulfuric acid. A preferred group of such biguanido compounds are those of the formula:



in which R_1' stands for N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, and A' represents an alkylene radical containing from two to three carbon atoms and separating the N,N-alkylene-imino portion from the biguanido group by two to three

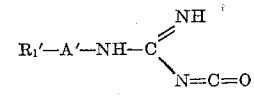
carbon atoms; the 2-(1-N,N-heptamethylene-imino)-ethyl-biguanide is a member of this preferred group.

Furthermore, a cyanourea or cyanothiourea compound of the formula

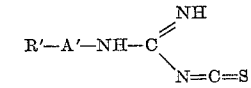


in which R_1, R_2 and A have the above-given meaning, and X represents oxygen or sulfur, and salts thereof, which may be converted to the desired guanidino compounds by hydrolysis, may be obtained, for example, by reacting an (N,N-alkylene-imino)-lower alkyl-cyanamide with a metal cyanate or thiocyanate,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

A preferred group of such cyanoureas and cyanothioureas is represented by the compounds of the formulae



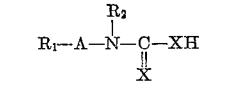
and



in which R_1' stands for N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, and A' represents an alkylene radical containing from two to three carbon atoms and separating the N,N-alkylene-imino portion from the cyanourea or thiocyanourea portion; the 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-cyanourea and the 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-cyanothiourea illustrate this preferred group of intermediates.

Apart from (N,N-alkylene-imino)-lower alkyl-amines, in which the amino group is substituted by a carbon atom carrying a nitrogen atom, other (N,N-alkylene-imino)-lower alkyl-amines, in which the amino group carries a substituent convertible into an amidino group, may be useful for a conversion into the desired (N,N-alkylene-imino)-lower alkyl-guanidines. In such a conversion intermediates may be formed, which may have the previously-given characteristics, i.e. the amino group carries a carbon with a nitrogen atom attached thereto. Such groups are lower alkyl carboxy, lower alkyl thionocarboxy, lower alkyl-thiolocarboxy or lower alkyl-dithiocarboxy, as well as halogeno-carbonyl or halogeno-thionocarbonyl.

Therefore, these (N,N-alkylene-imino)-lower alkyl-amines are, for example, the previously-described reactive functional derivatives of carbamic acids and thiocarbamic acids, having the formula:



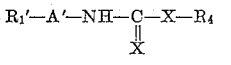
in which R_1, R_2, and A have the previously-given meaning, and X represents oxygen or sulfur. As shown hereinabove, esters, for example, lower alkyl, e.g. methyl or ethyl, esters or halides, e.g. chlorides, of such acids yield upon ammonolysis the corresponding urea and thiourea derivatives. However,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

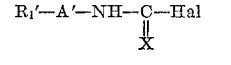
These carbamic and thiocarbamic acid compounds may be prepared according to procedures used for the manufacture of known analogs. For example, upon treatment of an (N,N-alkylene-imino)-lower alkyl-amine with phosgene or thiophosgene, which reagents may be used in a slight excess over the amines, the (N,N-alkylene-imino)-lower alkyl-isocyanates and (N,N-lower alkylene-imino)-lower alkyl-isothiocyanates, respectively, may be formed. These cyanates and isothiocyanates may be converted to esters of carbamic acid or thiocarbamic acid derivatives by treatment with an alcohol, for example, a lower alkanol, e.g. methanol or ethanol, or thiol-esters, by treatment with a mercaptan, such as a lower alkyl-mercaptan, e.g. methylmercaptan or ethylmercaptan. They may also be obtained by reacting the (N,N-alkylene-imino)-lower alkyl-amine with a lower alkyl carbonic acid ester, or, particularly, a lower alkyl dithiocarbonic acid ester, as well as with a lower alkyl ester of a halogeno-formic acid, such as chloro-formic acid, or, primarily, of a halogeno-thioformic acid, such as chloro-thioformic acid.

Or, an (N,N-alkylene-imino)-lower alkyl amine, salt, particularly a hydrohalide, e.g. hydrochloride, when reacted with phosgene or thiophosgene at an elevated temperature, preferably in a closed vessel, may yield the desired N-(N,N-alkylene-imino)-lower alkyl-carbamic acid chloride and N-(N,N-alkylene-imino)-lower alkyl-thiocarbamic acid chloride.

A preferred group of carbamic and thiocarbamic acid derivatives are those of the formulae:



and



in which R_1' and A' have the previously-given meaning, X represents oxygen, or more particularly sulfur, R^4 represents lower alkyl and Hal stands for halogen, particularly chloride. This group may be illustrated, for example, by N-[2-(1-N,N-heptamethylene-imino)-ethyl]-carbamic acid lower alkyl, e.g. methyl or ethyl, ester, N-[2-(1-N,N-heptamethylene-imino)-ethyl]-thiocarbamic acid lower alkyl, e.g. methyl or ethyl, ester, N-[2-(1-N,N-heptamethylene-imino)-ethyl]-carbamic acid esters wtih lower alkyl-mercaptanes, e.g. methylmercaptan or ethylmercaptan, lower alkyl, e.g. methyl or ethyl, esters of N-[2-(1-N,N-heptamethylene-imino)-ethyl]-dithiocarbamic acid, N-[2-(1-N,N-heptamethylene-imino)-ethyl]-carbamic acid chloride or N-[2-(1-N,N-heptamethylene-imino)-ethyl]-thiocarbamic acid chloride. As shown hereinabove, these compounds may be converted to the guanidines by ammonolysis or aminolysis, either directly or by intermediarily forming urea or thiourea derivatives.

The (N,N-alkylene-imino)-lower alkyl-amines which are used in many of the above instances to manufacture the above-described starting materials may be prepared, for example, by treating N,N-alkyleneimines with halogeno-lower alkyl-nitriles, in which halogeno stands for chlorine or bromine, or with lower alkene-nitriles, in which the double bond is activated by the nitrile group in such manner that it adds to a seconday amino group, and converting in the resulting (N,N-alkylene-imino)-lower alkyl-nitriles the nitrile group to a methyleneamino group by catalytic hydrogenation, such as, by 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 or aluminum hydride, which hydrides may be used, if desired, in the presence of an activator, such as aluminum chloride.

Depending on the conditions used, the guanidine compounds are 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 an alkaline reagent, such as an aqueous alkali metal hydroxide, e.g. lithium, sodium or potassium hydroxide, an aqueous alkali metal carbonate, e.g. lithium, sodium or potassium carbonate or hydrogen carbonate or aqueous ammonia. A free base may be transformed into its therapeutically useful acid addition salts by reaction with an appropriate inorganic or organic acid, such as one of those outlined hereinabove; if desired, in this reaction may be carried out in a solution, such as a lower alkanol, e.g. methanol, ethanol, propanol or isopropanol, solution or an ether, e.g. diethylether or p-dioxane, solution and the like or a mixture of solvents.

The guanidine compounds may be converted into the quaternary ammonium compounds by reacting the tertiary bases with an ester formed by a hydroxylated lower hydrocarbon compound with a strong inorganic or organic acid. Hydroxylated lower hydrocarbon compounds contain from one to seven carbon atoms and the esters thereof are more especially those with mineral acids, e.g. hydrochloric, hydrobromic, hydriodic, or sulfuric acid. Such esters are specifically lower alkyl halides, e.g. methyl, ethyl, or n-propyl chloride bromide or iodide, alkyl alkane sulfonates, e.g. methyl or ethyl methane or ethane sulfonate. The quaternizing reaction may be performed in the presence or absence of a solvent; suitable solvents are, for example, lower alkanols, e.g. methanol, ethanol, propanol, isopropanol, tertiary butanol or pentanol, lower alkanones, e.g. acetone or ethyl methyl ketone, or organic acid amides, e.g. formamide or dimethylformamide. The reaction may be carried out under pressure, and/or, if desired, under cooling or at an elevated temperature.

Acyl derivatives of the guanidine compounds may be prepared, for example, by treating a resulting guanidine compound with the reactive derivative of a carboxylic acid, for example, with a halide, e.g. chloride, or with the anhydride or a carboxylic acid. The reaction is preferably carried out in an inert solvent, for example, in a hydrocarbon, such as an aliphatic hydrocarbon, e.g. hexane, or an aromatic hydrocarbon, e.g. benzene, toluene or xylene; or in a tertiary organic base, such as a liquid pyridine compound, e.g. pyridine or collidine.

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 starting material and the remaining steps(s) of the process is(are) carried out, as well as 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 mixture of 23.4 g. of 2-(1-N,N-heptamethylene-imino)-ethylamine and 16 g. of cyanogen bromide in ether yields the 2-(1-N,N-heptamethylene-imino)-ethyl-cyanamide hydrobromide, which may be converted to the free compound by treatment with a stoichiometric amount of an alkaline reagent or may be used in the subsequent ammonolysis by employing an excess of ammonia.

16.7 g. of 2-(1-N,N-heptamethylene-imino)-ethyl-cyanamide and 13.2 g. of ammonium sulfate are dissolved in 100 ml. of a 15 percent aqueous ammonium hydroxide solution. The solution is heated for about three hours in an autoclave to about 100° to about 150°, while agitating. Upon cooling the reaction mixture yields the solid

2-(1-N,N-heptamethylene-imino)-ethyl-guanidine sulfate, M.P. 276–281° (with decomposition).

Example 2

A solution of 15.6 g. of 2-(1-N,N-heptamethylene-imino)-ethylamine in water is treated with 8.1 g. of sodium thiocyanate; the reaction mixture is warmed up for about one hour. The crystalline 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-2-thiourea is obtained upon concentrating the solution under reduced pressure.

A solution of the above 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-2-thiourea in aqueous ammonium hydroxide is heated while stirring in the presence of a suspension of freshly precipitated mercuric oxide as a desulfurizing reagent. The reaction mixture is filtered, the filtrate is made acidic with sulfuric acid, whereupon the 2-(1-N,N-heptamethylene-imino)-ethyl - guanidine sulfate precipitates and is recrystallized from a mixture of ethanol and water. The compound is identical with the product obtained according to the procedure of Example 1.

Example 3

43 g. of the 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-2-thiourea described in Example 2 is dissolved in water and treated with 13.8 g. of dimethyl sulfate. The reaction mixture is allowed to proceed spontaneously, with occasional cooling to control the reaction. The desired 1 - [2 - (1 - N,N-heptamethylene-imino)-ethyl]-2-S-methyl-isothiourea sulfate precipitates from the cold solution.

27.8 g. of 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-2-S-methyl-isothiourea in aqueous methanol is treated with ammonia and mercuric chloride. After several hours the solution is filtered to remove the metallic precipitate. The filtrate is made acidic with sulfuric acid and the desired 2-(1-N,N-heptamethylene-imino)-ethyl-guanidine sulfate can be recovered.

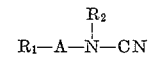
Example 4

16.7 g. of the 2-(1-N,N-heptamethylene-imino)-ethyl-cyanamide, described in Example 1, and 16.2 g. of potassium cyanate are dissolved in water, and the solution is allowed to stand for twenty-four hours. The excess cyanate is destroyed with nitric acid and the silver salt of the resulting 1-[2-(1-N,N-heptamethylene-imino)-ethyl]-cyanourea is precipitated by treatment with silver nitrate. The silver salt is suspended in warm water, decomposed with hydrochloric acid, and the precipitated silver chloride is filtered off.

The resulting 1 - [2 - (1 - N,N-heptamethylene-imino)-ethyl]-cyanourea is heated for three hours to about 50° to 80° with 6 N aqueous sulfuric acid; after cooling the crystalline 2 - (1-N,N-heptamethylene-imino)-ethyl-guanidine sulfate can be recovered and recrystallized from aqueous ethanol.

What is claimed is:

1. A member of the group consisting of compounds of the formula:



in which R_1 represents 1-N,N-alkylene-imino, in which alkylene contains from four to ten carbon atoms, A stands for lower alkylene and R_2 represents a member of the group consisting of hydrogen and lower alkyl, and acid addition salts thereof.

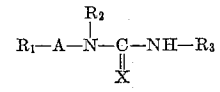
2. Compounds of the formula:

$$R_1—A'—NH—CN$$

in which R_1 represents N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, A' stands for lower alkylene, containing from two to three carbon atoms and separating the group R_1 from the cyanamide group by two to three carbon atoms.

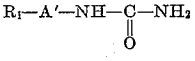
3. 2 - (1 - N,N - heptamethylene - imino) - ethyl - cyanamide.

4. A member of the group consisting of compounds of the formula:



in which R_1 represents 1-N,N-alkylene-imino, in which alkylene contains from four to ten carbon atoms, A stands for lower alkylene, R_2 represents a member of the group consisting of hydrogen and lower alkyl, X stands for a member of the group consisting of oxygen and sulfur, and R_3 stands for a member of the group consisting of hydrogen and lower alkyl, and acid addition salts thereof.

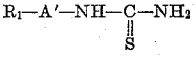
5. Compounds of the formula:



in which R_1 represents N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, A' stands for lower alkylene, containing from two to three carbon atoms and separating the group R_1 from the cyanamide group by two to three carbon atoms.

6. 1-[2-(1 - N,N - heptamethylene - imino) - ethyl] - 2-urea.

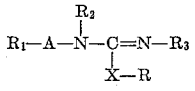
7. Compounds of the formula:



in which R_1 represents N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, A' stands for lower alkylene, containing from two to three carbon atoms and separating the group R_1 from the cyanamide group by two to three carbon atoms.

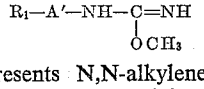
8. 1-[2-(1 - N,N - heptamethylene - imino) - ethyl] - 2-thiourea.

9. A member of the group consisting of compounds of the formula:



in which R_1 represents 1-N,N-alkylene-imino, in which alkylene contains from four to ten carbon atoms, A stands for lower alkylene, R_2 represents a member of the group consisting of hydrogen and lower alkyl, X stands for a member of the group consisting of oxygen and sulfur, R_3 stands for a member of the group consisting of hydrogen and lower alkyl and R stands for lower alkyl, and acid addition salts thereof.

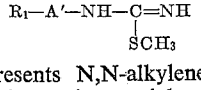
10. Compounds of the formula:



in which R_1 represents N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, A' stands for lower alkylene, containing from two to three carbon atoms and separating the group R_1 from the cyanamide group by two to three carbon atoms.

11. 1-[2-(1-N,N-heptamethylene-imino) - ethyl] - O-methyl-isourea.

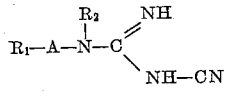
12. Compounds of the formula:



in which R_1 represents N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, A' stands for lower alkylene, containing from two to three carbon atoms and separating the group R_1 from the cyanamide group by two to three carbon atoms.

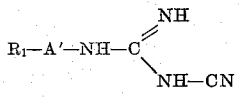
13. 1-[2-(1-N,N - heptamethylene - imino) - ethyl] - S-methyl-isothiourea.

14. A member of the group consisting of compounds of the formula:



in which R_1 represents 1-N,N-alkylene-imino, in which alkylene contains from four to ten carbon atoms, A stands for lower alkylene and R_2 represents a member of the group consisting of hydrogen and lower alkyl, and acid addition salts thereof.

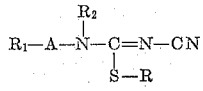
15. Compounds of the formula:



in which R_1 represents N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, A' stands for lower alkylene, containing from two to three carbon atoms and separating the group R_1 from the cyanamide group by two to three carbon atoms.

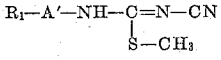
16. 1-[2-(1-N,N-heptamethylene-imino) - ethyl] - 3-cyano-guanidine.

17. A member of the group consisting of compounds of the formula:



in which R_1 represents 1-N,N-alkylene-imino, in which alkylene contains from four to ten carbon atoms, A stands for lower alkylene, R_2 represents a member of the group consisting of hydrogen and lower alkyl, and R stands for lower alkyl, and acid addition salts thereof.

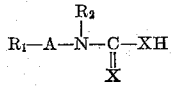
18. Compounds of the formula:



in which R_1 represents N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, A' stands for lower alkylene, containing from two to three carbon atoms and separating the group R_1 from the cyanamide group by two to three carbon atoms.

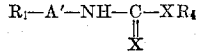
19. 1 - [2 - (1 - N,N-heptamethylene-imino)-ethyl]-3-cyano-S-methyl-isothiourea.

20. A member of the group consisting of lower alkyl esters of acids of the formula:



in which R_1 represents 1-N,N-alkylene-imino, in which alkylene contains from four to ten carbon atoms, A stands for lower alkylene, R_2 represents a member of the group consisting of hydrogen and lower alkyl and X stands for a member of the group consisting of oxygen and sulfur, and acid addition salts thereof.

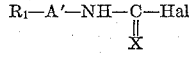
21. Compounds of the formula:



in which R_1 represents N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, A' stands for lower alkylene, containing from two to three carbon atoms and separating the group R_1 from the cyanamide group by two to three carbon atoms, X stands for sulfur and R_4 represents lower alkyl.

22. N - [2 - (1-N,N-heptamethylene-imino)-ethyl]-dithiocarbamic acid lower alkyl ester.

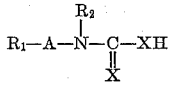
23. Compounds of the formula:



in which R_1 represents N,N-alkylene-imino, in which alkylene contains from six to eight carbon atoms, A' stands for lower alkylene, containing from two to three carbon atoms and separating the group R_1 from the cyanamide group by two to three carbon atoms, X stands for sulfur and Hal for halogen.

24. N - [2-(1-N,N-heptamethylene-imino)-ethyl]-thiocarbamic acid chloride.

25. A member of the group consisting of halides of acids of the formula



in which R_1 represents 1-N,N-alkylene-imino, in which alkylene contains from four to ten carbon atoms, A stands for lower alkylene, R_2 represents a member of the group consisting of hydrogen and lower alkyl and X stands for a member of the group consisting of oxygen and sulfur, and acid addition salts thereof.

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