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3,055,883

BENZO-ALKYLENIMINO-LOWER GUANIDINES

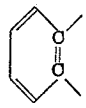
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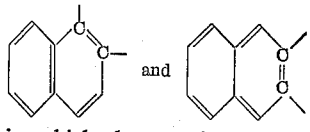
The present invention concerns guanidino compounds. More particularly, it relates to (N,N-alkylene-imino)-lower alkyl-guanidines, in which the alkylene radical contains from four to nine carbon atoms, and in which at least one pair of two neighboring carbon atoms of the alkylene portion are part of an aryl nucleus, and the salts of such compounds. Also included within the scope of the invention are the quaternary ammonium derivatives thereof, as well as process for manufacturing such compounds.

The above-described N,N-alkylene-imino radical may be represented, for example, 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) or N,N-nonamethylene-imino (1-decahydro-azecino) radicals. The carbon atoms of the alkylene portion are preferably unsubstituted or may contain hydrocarbon radicals, such as lower alkyl, e.g. methyl, ethyl and the like, as substituents.

As previously-stated, at least one pair of two neighboring carbon atoms of the alkylene chain, are incorporated into and form part of an aryl nucleus. Such aryl nucleus is above all a carbocyclic aryl nucleus, primarily a monocyclic carbocyclic aryl nucleus, i.e. a benz nucleus of the formula:



in which the two indicated carbon atoms are also part of the alkylene portion, or a bicyclic carbocyclic aryl nucleus, e.g. a naph[1,2] or a naph[2,3] nucleus of the formulae:



and

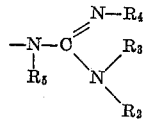
respectively, in which the two indicated carbon atoms are also part of the alkylene portion. The fused-on aryl nucleus may also be represented by a heterocyclic aryl, such as a monocyclic azacyclic aryl nucleus, for example, a pyrido nucleus. The carbon atoms of the above mentioned carbocyclic nuclei may contain additional groups, such as lower alkyl, e.g. methyl, and the like, or functional groups, such as hydroxy, etherified hydroxy, particularly lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and the like, lower alkylenedioxy, e.g. methylenedioxy, or carbocyclic aryl-lower alkoxy, e.g. benzyloxy and the like, esterified hydroxy, such as lower alkoxy-carbonyloxy, e.g. methoxycarbonyloxy, and the like, lower alkanoyloxy, e.g. acetoxy, propionyloxy and the like, or halogen, e.g. fluoro, chloro, bromo and the like, lower alkyl-mercapto, e.g. methylmercapto, ethylmercapto and the like, lower alkanoyl, e.g. acetyl, propionyl and the like, nitro, amino, such as N-unsubstituted amino, N-mono-substituted amino, particularly N-lower alkylamino, e.g. N-methylamino, N-ethylamino and the like, or primarily N,N-di-substituted amino, such as N,N-di-lower alkyl-amino, e.g. N,N-dimethylamino, N-ethyl-N-methylamino, N,N-diethylamino and the like, or 1-N,N-lower alkylene-imino,

1-N,N-lower oxa-alkylene-imino, or 1-N,N-lower aza-alkylene-imino, in which radicals lower alkylene contains from four to six carbon atoms as ring members, e.g. 1-pyrrolidino, 1-piperidino, 2-methyl-1-piperidino, 1-N,N-hexamethylene-imino, 1-morpholino, 4-methyl-1-piperazino, 4-(2-hydroxy-ethyl)-1-piperazino and the like, or halogeno-lower alkyl, e.g. trifluoromethyl, or analogous functional groups, as substituents.

The N,N-alkylene-imino radicals in the (N,N-alkylene-imino)-lower alkyl-guanidine compounds of the present invention may, therefore, be represented, for example, by 2-isoindolinyl, 1-indolinyl, 1-tetrahydroquinolyl, 2-tetrahydroisoquinolinyl, 1 - N,N-benz[b]hexamethylene-imino, 1-N,N-benz[c]hexamethylene-imino, 1-N,N-benz[d]hexamethylene-imino, 1-N,N-benz[b]heptamethylene-imino, 1-N,N-benz[c]heptamethylene-imino, 1-N,N-benz[d]heptamethylene-imino, 1-N,N-dibenz[b,f]hexamethylene-imino, 1-N,N-dibenz[c]heptamethylene-imino and the like, as well as these groups, in which the fused-on aryl portion, particularly benz-nucleus, is substituted, whereby one or more than one of the same or of different substituents selected from the afore-mentioned class may be attached to any of the positions available for substitution.

The lower alkyl radical connecting the guanidino group with the imino-nitrogen atom may be represented by a lower alkylene radical, which contains from one to five, preferably from two to three, carbon atoms. Such lower alkylene radical separates the guanidino group from the imino-nitrogen by from one to five, advantageously by from two to three, carbon atoms. 1,2-ethylene, 1-methyl-1,2-ethylene, 2-methyl-1,2-ethylene or 1,3-propylene represent the preferred group of lower alkylene radicals, which may also include methylene, 1-methyl-1,3-propylene, 1,4-butylene, 1,5-pentylene and the like.

The guanidino group may be represented by:



in each of the radicals R_2, R_3, R_4 and R_5 stands primarily for hydrogen. They may also represent an aliphatic hydrocarbon radical, particularly lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl and the like, with the proviso that at least one of the radicals R_2, R_3 and R_4 stands for hydrogen. One of the radicals R_2 and R_4 may also be an acyl radical of an organic carboxylic acid; such acyl radical may be, for example, the acyl radical of a lower aliphatic carboxylic acid, for example, a lower alkanoic acid, e.g. acetic, propionic, pivalic acid and the like, a substituted lower alkanoid acid, e.g. chloroacetic, dichloroacetic, hydroxyacetic, methoxy-acetic, cyclopentyl-propionic acid and the like, or a lower alkenoic acid, e.g. 3-butenoic acid and the like, a carbocyclic aryl carboxylic acid, for example, a monocyclic carbocyclic aryl carboxylic acid, e.g. benzoic, hydroxybenzoic, 4-methoxy-benzoic, 3,4-dimethoxy-benzoic, 3,4,5-trimethoxy-benzoic, 4-O-ethoxycarbonyl-syringic, 3,4-dichlorobenzoic, 3-N,N-dimethylamino-benzoic, 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, a monocyclic heterocyclic aryl carboxylic acid, e.g. nicotinic, isonicotinic, 2-furoic acid and the like.

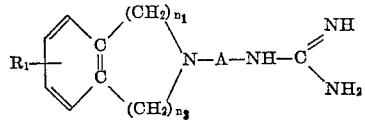
Salts of the new compounds of this invention are particularly therapeutically acceptable, non-toxic acid addition salts, such as those with inorganic acids, for example, mineral acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric acids and the like, or those with organic acids, such as organic carboxylic acids, e.g. 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-acetoxybenzoic and the like, or organic sulfonic acids, e.g. methane sulfonic, ethane sulfonic, 2-hydroxyethane sulfonic, p-toluene sulfonic acid and the like. Mono- or poly-salts may be formed.

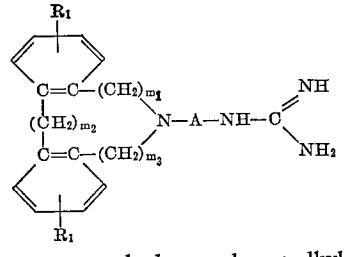
The new compounds of the present invention block the hypertensive, i.e. blood pressure raising, effect of amphetamine or similar sympathomimetic drugs without affecting the stimulating properties of amphetamine or analogs. The compounds of this invention can, therefore, be used, for example, in combination with sympathomimetic drugs of the amphetamine-type to offset the hypertensive side effects of such drugs, without affecting the very valuable stimulation caused by such compounds.

In addition, guanidino derivatives of this invention have antihypertensive properties and can, therefore, be used as antihypertensive agents to relieve hypertensive conditions, particularly those of neurogenic, renal or essential nature. An additional characteristic feature of the guanidino compounds exhibiting antihypertensive effects is the long duration of such properties, which is especially desirable in the treatment of chronic hypertensive states. In addition, compounds of this invention cause an increase in peripheral blood flow and can, therefore, be used in functional peripheral vascular diseases, such as Raynaud's disease.

Particularly outstanding pharmacological effects of the above nature are exerted by compounds of the formulae:

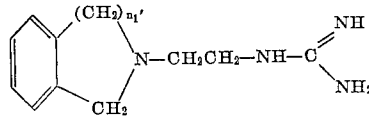


and



in which R_1 represents hydrogen, lower alkyl containing from one to four carbon atoms, e.g. methyl, ethyl and the like, lower alkoxy, containing from one to four carbon atoms, e.g. methoxy, ethoxy and the like, or halogeno, with an atomic weight of below 80, e.g. fluoro, chloro or bromo, each of the symbols n_1 and n_2 stands for one of the numbers 0, 1, 2, 3, 4 or 5, with the proviso that the total of n_1+n_2 represents one of the numbers 2, 3, 4 and 5, each of the symbols m_1, m_2 and m_3 represents one of the numbers 0, 1 and 2, with the proviso, that the total of $m_1+m_2+m_3$ represents one of the numbers 0, 1, 2, 3 and 4, A represent lower alkylene containing from two to three carbon atoms and separating the guanidino group from the iminonitrogen atom by from two to three carbon atoms, and addition salts of such compounds with therapeutically acceptable acids.

This group of compounds may be illustrated by the compounds of the formula:



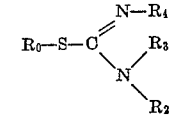
in which n_1' represents one of the numbers 2, 3 or 4, and acid addition salts thereof with therapeutically acceptable acids, particularly mineral acids.

The new guanidine derivatives may be used as medicaments in the form of pharmaceutical preparations, which contain the new compounds or the salts thereof in admixture with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral or parenteral administration. For making up the preparations there can be employed substances which do not react with the new compounds, such as water, gelatine, lactose, starches, stearic acid, magnesium stearate, stearyl alcohol, talc, vegetable oils, benzyl alcohols, gums, propylene glycol, polyalkylene glycols, petroleum jelly or any other known carrier for medicaments. The pharmaceutical preparations may be in solid form, for example, as tablets, dragees, capsules and the like, or in liquid form, for example, as solutions, suspensions, emulsions and the like. If desired, they may contain auxiliary substances, such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers and the like. They may also contain, in combination, other therapeutically useful substances.

The compounds of the present invention may also be used as intermediates for the preparation of other useful compounds.

The new guanidine compounds of this invention may be prepared by converting in an (N,N-alkylene-imino)-lower alkylamine, in which the alkylene group contains from four to nine carbon atoms, and in which at least one pair of two neighboring carbon atoms of the alkylene radical are part of an aryl nucleus, or a salt thereof, the amino group into a guanidino group and, if desired, converting a resulting salt into the free compound, and/or, if desired, converting a resulting compound into its acyl derivative, and/or, if desired, converting a free compound into a salt or a quaternary ammonium compound thereof.

The reagents of choice for the conversion of an amino group into a guanidino group are S-lower alkyl-isothioureas, in which lower alkyl stands primarily for methyl, as well as ethyl, n-propyl, isopropyl and the like, or acid addition salts thereof. The latter are employed in preference over the free base and are primarily those with mineral acids, such as hydrochloric, hydrobromic, or particularly sulfuric acid, and the like. The isothiourea reagents used in the reaction may be depicted by the formula:

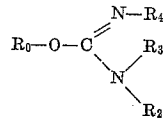


in which R_2, R_3 and R_4 have the previously given meaning, and R_0 stands for lower alkyl, e.g. ethyl, n-propyl or particularly methyl and the like, and mineral acid addition salts thereof. The preferred reagents to form a guanidino group is S-methyl-isothiourea and the mineral acid addition salts thereof; S-methyl-isthiourea sulfate is primarily used to form guanidine compounds, which contain an unsubstituted guanidino group. The (N,N-alkylene-imino)-lower alkyl-amine starting material, in which the amino group is above all a primary amino group, but may also represent a secondary amino group, such as an N-lower alkyl-amino group, e.g. methylamino, ethylamino and the like, is generally used in the form of its free base.

The reaction is carried out by contacting the starting material with the reagent, preferably in the presence of a solvent, the choice of which depends primarily on the solubility of the reactants. Water or water-miscible organic solvents, such as lower alkanols, e.g. methanol, ethanol, propanol, isopropanol, tertiary butanol and the like, cyclic ethers, e.g. p-dioxane, tetrahydrofuran and the like, ketones, e.g. acetone, ethyl methyl ketone and the like, lower alkanoic acids, e.g. acetic acid and the like, formamides, e.g. formamide, N,N-dimethylformamide and the like, or aqueous mixtures of such diluents may

be used as solvents. The reaction may be carried out at room temperature, or, if necessary, at an elevated temperature, for example, at the boiling temperature of the solvent. An absence of oxygen may be achieved by performing the reaction in the atmosphere of an inert gas, e.g. nitrogen, and, if necessary, it may be carried out under pressure in a closed vessel.

Similar reagents capable of converting an amino into a guanidino group are O-lower alkyl-isoureas of the formula:



in which R_2, R_3, R_4 and R_0 have the previously given meaning, or their salts with mineral acids. These isourea derivatives are used in the same way as the above-described, corresponding isothiourea reagents; O-methyl-isourea sulfate represents a preferred reagent.

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, in which at least one of the nitrogen atoms carries a hydrogen atom, 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.

Other reagents capable of transforming the amino group of an (N,N-alkylene-amino)-lower alkyl-amine, in which alkylene has the previously given meaning, particularly of an acid addition salt of such compound, are cyanamides having the formula:



The reaction may be carried out, for example, by heating the mixture of an (N,N-alkylene-imino)-lower alkyl-amine compound, particularly a salt thereof, such as a mineral acid addition salt, e.g. the hydrochloride, hydrobromide, sulfate and the like, thereof and the cyanamide. The resulting melt may then be dissolved in a solvent, such as a lower alkanoic 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 carried out in the presence of a solvent such as a lower alkanol, e.g. methanol, ethanol and the like. The salt of a free base 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 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, which 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°; an atmosphere of an inert gas, e.g. nitrogen, may be advantageous.

A third modification of the procedure for the manufacture of the products of this invention comprises reacting the (N,N-alkylene-imino)-lower alkyl-amine, in which alkylene has the previously given meaning, 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; a 1-guanyl-pyrazole may contain additional substituents in the pyrazole nucleus, particularly lower alkyl, e.g. methyl, ethyl and the like. Salts of 1-guanyl-3,5-dimethyl-pyrazole, particularly the salt with nitric acid, 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, and advantageously, by excluding the presence of carbon dioxide, 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,N-alkylene-imino)-lower alkyl-amines, in which alkylene has the previously given meaning, and the salts thereof, are known, or, if new, may be prepared according to known procedures. They may, for example, be prepared by treating an N,N-alkylene-imine, in which at least one pair of two neighboring carbon atoms of the alkylene portion are part of an aryl nucleus, with a halogeno-lower alkano-nitrile, in which halogeno represents, for example, chloro, bromo and the like, or with a lower alkeno-nitrile, in which the double bond is activated by the nitrile group in such fashion, that it adds to the imino group. In a resulting (N,N-alkylene-imino)-lower alkano-nitrile, the cyano group is converted to a methyleneamino group by reduction, 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, Raney nickel and the like, or, preferably, by treatment with a light metal hydride capable of reducing a nitrile to a methyleneamino group, for example, an aluminum hydride, e.g. 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,N-alkylene-imino)-lower alkylamine, in which alkylene has the previously given meaning and at least one pair of neighboring carbon atoms of the alkylene portion are part of an aryl nucleus, and 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, carrying out the optional steps.

Depending on the properties of the above-mentioned substituent, which is capable of being converted into 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 of the amino group of an (N,N-alkylene-imino)-lower alkyl-amine may comprise a carbon atom, which is attached to the amino group. To such carbon atom, there 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, or other substituents. Such groups may be, for example, cyano of the formula —C≡N, carbamyl of the formula —CONH—R_4, thiocarbamyl of the formula —CS—NH—R_4, lower alkoxy-(imino)methyl of the formula —C(=NH)—OR_0, in which R_0 represents lower alkyl, primarily methyl, as well as ethyl, n-propyl, isopropyl and the like, lower alkyl-mercapto-(imino)methyl of the formula

—C(=NR_4)—SR_0

in which R_0 has the above-given meaning, cyanoamidino of the formula —C(=NR_4)—NH—C≡N, guanidino-(imino)methyl of the formula

—C(=NR_4)—[NH—C(=NH)—NH_2]

isocyano-(imino)methyl of the formula

—C(=NR_4)—N=C=O

or isothiocyano—(imino)methyl of the formula

—C(=NR_4)—N=C=S

and the like, in which R_4 has the previously given meaning, but stands particularly for hydrogen.

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 common characteristic, i.e. to the amino group is attached a carbon atom, which carries at least a nitrogen atom.

The greater part of these starting materials may be converted into 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 a 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 and the like, salt or an alkali metal, e.g. sodium, potassium and the like, salt of the cyanamide is preferably used, which may be reacted with the ammonium nitrate in the presence of catalytic amounts of water.

The cyanamide compounds, used as the starting materials and having the formula

(N,N-alkylene-imino)-lower alkyl-N(R_5)—C≡N

in which R_5 stands primarily for hydrogen, but may also be lower alkyl, and alkylene has the previously-given meaning, and salts thereof may be prepared, for example, by treating an (N,N-alkylene-imino)-lower alkyl-amine, in which alkylene has the above-given meaning, with a cyanogen halide, such as cyanogen chloride, cyanogen bromide and the like, advantageously in equivalent amounts and preferably in an inert solvent, such as, for example, ether.

A carbamyl group attached to the amino group of the (N,N-alkylene-imino)-lower alkyl-amine, in which alkylene has the previously given meaning, 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. This reaction may be carried out at an elevated temperature in a closed vessel; temperature and pressure may be reduced by the presence of an 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, and (N,N-alkylene-imino)-lower alkyl-guanidino compounds with substituted guanidino groups can be formed.

Furthermore, a thiocarbamyl group, which together with the amino group of a (N,N-alkylene-imino)-lower alkyl-amine, in which alkylene has the previously given meaning, 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 nonhydrolytic 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; such 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:

(N, N-alkylene-imino)-lower alkyl-N(R_5)—C(=X)—NH—R_4

in which R_4, R_5 and alkylene have the previously given meaning, R_4 and R_5 representing primarily hydrogen, and X stands for oxygen or sulfur, and salts thereof may be obtained, for example, from (N,N-alkylene-imino)-lower alkyl-amines, in which alkylene has the previously-given meaning, by treating the latter with ammonium or metal cyanates or thiocyanates, particularly alkali metal, e.g. sodium or potassium, 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,N-alkylene-imino)-lower alkyl-amine compound, yields a urea or a thiourea, in which R_4 represents a lower alkyl. The lower alkyl isocyanates and isothiocyanates are used in the presence of an organic solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol and the like.

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

(N,N-alkylene-imino)-lower alkyl-N(R_5)—C(=X)—XH

in which R_5, X and alkylene have the previously-given meaning. Reactive functional derivatives of such acids 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 acid derivatives 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:

(N, N-alkylene-imino)-lower alkyl-N(R_5)—C(=N—R_4)—X—R_0

in which R_4, R_5, X and alkylene have the previously-given meaning, and R_0 stands for lower alkyl, primarily methyl, as well as ethyl, n-propyl, isopropyl and the like, and salts thereof, are compounds containing the previously-mentioned O-lower alkoxy-(imino)methyl group of the formula —C(=NR_4)—OR_0 and S-lower alkyl-mercapto-(imino)methyl group of the formula

—C(=NR_4)—SR_0

respectively, in which R_4 and R_0 have the above-given meaning; these compounds are, therefore, useful as starting materials for 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 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 described previously, 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 isourea and isothiourea into guanidino derivatives containing substituted guanidino groups.

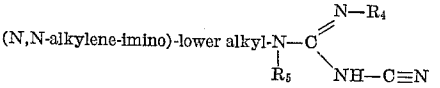
The isourea and isothiourea compounds used as starting materials, may be obtained, for example, from the previously mentioned urea and thiourea derivatives by treatment of the latter, or of a metal salt thereof, such as an alkali metal, e.g. sodium, potassium and the like, salt thereof, with a lower 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 reagent used; a free urea or thiourea compound may be used in the presence of water or a lower alkanol, e.g. 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 group, which forms a cyanoguanidino group with the amino group of a (N,N-alkylene-imino)-lower alkyl-amine, in which alkylene has the previously given meaning, 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.

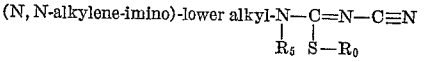
In the ammonolysis procedure of a cyanoguanidino to a guanidino derivative as described hereinabove, a biguanido group may be formed as an intermediate, which, upon further treatment with the ammonolysis reagent, may be converted to the desired guanidino group. Such biguanido derivatives may be accessible through different procedures (as will be shown hereinbelow) and are, therefore, also useful as starting materials 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_4, R_5 and alkylene have the previously given meaning, and their salts, which compounds represent the starting materials used in the above ammonolysis, aminolysis or reduction procedure, may be prepared, for example, by treatment of the S-lower alkyl-cyano-isothioureas of the formula:

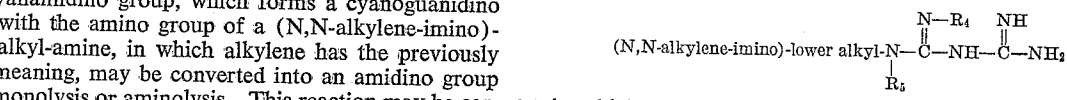


in which R_5, R_0 and alkylene have the previously given meaning, with ammonia in a lower alkanol, e.g. ethanol and the like, or with an amine, such as an N-lower alkyl-amine, preferably in a sealed tube.

In view of this ammonolysis procedure, the S-lower alkyl-cyanoisothiourea derivatives, which are used as the intermediates for the preparation of cyano-guanidine compounds, and which have the previously-given formula, may, therefore, serve themselves as starting materials in the process for the preparation of the guanidino compounds, inasmuch as ammonolysis or aminolysis thereof may yield the desired guanidino derivatives directly, whenever the treatment with ammonia is carried out, for example, in the presence of an anion of a strong acid, such as a halide, a nitrate, a sulfate ion and the like, furnished, for example, by the respective ammonium salts.

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

As has been shown, ammonolysis of cyano-guanidines may give rise to the formation of biguanido compounds of the formula:

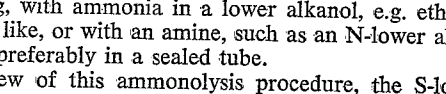


in which R_4, R_5 and alkylene have the previously given meaning, and salts thereof. These compounds may also be prepared, for example, by reacting an (N,N-alkylene-imino)-lower alkyl-amine, in which alkylene has the above-given meaning, with a dicyano-diamide, preferably in the presence of a complex metal-forming salt, such as copper sulfate and the like. A resulting biguanido complex metal salt, such as the copper complex salt thereof, may then be liberated by treatment with an acid, such as a mineral acid, e.g. sulfuric acid and the like, to form the free compound. Ammonolysis or aminolysis of such biguanido compounds, as has been previously shown, gives rise to the formation of the desired (N,N-alkylene-imino)-lower alkyl-guanidines of the invention.

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

In addition to ammonolysis and aminolysis reactions, the guanidino compounds may also be obtained, for example, by hydrolysis of an (N,N-alkylene-imino)-lower alkyl-amine, in which alkylene has the above-given meaning, and in which the amino group carries a substituent capable of being hydrolyzed to an amidino group. For example, such substituent forms together with the amino group of the (N,N-alkylene-imino)-lower alkyl-amine a cyanourea or a cyanothiourea group of the formulae —C(=NR_4)—N=C=O and —C(=NR_4)—N=C=S, respectively, in which R_4 has the previously given meaning, but stands primarily for hydrogen. Compounds containing such groups yield upon treatment with a hydrolytic reagent, particularly with dilute aqueous mineral acid, e.g. aqueous sulfuric acid and the like, the desired guanidino compounds. In such hydrolysis, the desired guanidino derivative may be formed simultaneously with a biuret derivative as the by-product.

A cyanourea or cyanothiourea compound of the formula:

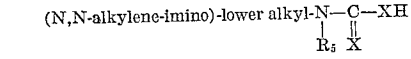


in which R_4, R_5 and alkylene have the above-given meaning, and X represents oxygen or sulfur, or salts thereof, which compounds may be converted to the desired guanidino compounds by hydrolysis, may be prepared for example, by reacting an (N,N-alkylene-imino)-lower alkyl-cyanamide with an ammonium or 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.

Apart from (N,N-alkylene-imino)-lower alkyl-amines, in which the amino group is substituted by a carbon atom carrying at least one 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-guanidino compounds of this invention. In such a conversion, intermediate may be formed, which may have the previously given characteristics, i.e. the amino group carries a carbon with at least one nitrogen atom attached thereto. Such groups are ester groups formed by carboxyl, thionocarboxyl, thiolocarboxyl or dithiocarboxy groups with lower alkanols, as well as halogeno-carbonyl or halogeno-thiocarbonyl groups, in which halogeno represents primarily chloro.

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



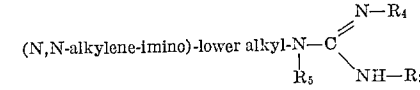
in which R_5 and alkylene have the previously given meaning, and X represents oxygen or sulfur. As shown hereinabove, esters, for example, lower alkyl, e.g. methyl, ethyl and the like, esters or acid halides, e.g. chlorides and the like, of the above-given acids yields upon ammonolysis the corresponding 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 as, for example, previously shown in the conversion of a urea derivative to the desired guanidino compound, an N-(N,N-alkylene-imino)-lower alkyl carbamic acid ester may be converted directly into 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, if such ammonolysis is carried out 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,N-alkylene-imino)-lower alkylamine, in which alkylene has the previously-given meaning, with phosgene or thiophosgene, which reagents may be used in a slight excess over the amine, an (N,N-alkylene-imino)-lower alkyl-isocyanate and an (N,N-lower alkylene-imino)-lower alkylisothiocyanate, respectively, may be formed. Such cyanate and isothiocyanate derivative may then be converted into an ester of a carbamic acid or a thiocarbamic acid derivative by treatment with an alcohol, for example, with a lower alkanol, e.g. methanol, ethanol and the like, or to a thiolester, for example, by treatment with a mercaptan, such as a lower alkylmercaptan, e.g. methylmercaptan, ethylmercaptan and the like. The above derivatives may also be obtained by reacting an (N,N-alkylene-imino)-lower alkyl-amine with a lower alkyl carbonic acid ester, or, particularly, with a lower alkyl dithiocarbonic acid 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 chlorothioformic acid.

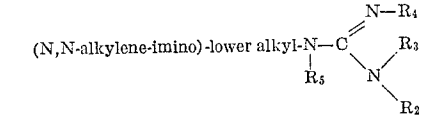
Or, a salt of an (N,N-alkylene-imino)-lower alkyl amine, particularly a hydrohalide, e.g. hydrochloride and the like, thereof, when reacted with phosgene or thiophosgene at an elevated temperature, preferably in a closed vessel, may yield the desired N-(N,N-alkylene-imino)-lower alkyl-carbamic acid chloride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

The (N,N-alkylene-imino)-lower alkyl-amines, in which alkylene has the previously-given meaning, and which are used in many of the above instances for the manufacture of the above-described starting materials, are known or if new may be prepared, for example, according to the previously shown procedure.

In 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, such as, for example, those of the formula:



may be acylated to form compounds of the formula:



in which formulae alkylene, R_3, R_4 and R_5 have the previously given meaning, and R_2 represents an acyl radical. Such 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 thereof. It may be performed in the presence of an inert solvent, for example, in a hydrocarbon, such as a lower alkane, e.g. pentane, hexane and the like, or 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. 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 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 hydroxide, sodium hydroxide, potassium hydroxide and the like, or a strong quaternary ammonium anion (hydroxy 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 those outlined hereinabove; such reaction may be carried out advantageously 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, or a mixture of such solvents, and isolating the desired salt. A salt may be obtained, in which not all of the basic groups of the free compound participate in the salt-formation. Such salts, when treated with an additional amount of an acid, can form compounds, in which all of the basic groups take part in the salt-formation. Mono- or poly-salts may be formed.

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 bromine or iodide and the like, di-lower alkyl-sulfates, e.g. dimethyl sulfate, diethyl sulfate and the like, lower alkyl, lower alkane sulfonates, e.g. methyl or ethyl methane or ethane sulfonate, or lower alkyl monocyclic carbocyclic aryl sulfonates, e.g. methyl p-toluene 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 ob-

tained 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, a di-lower alkyl-sulfate, e.g. dimethyl sulfate, diethyl sulfate and the like, a lower alkyl lower alkane sulfonate, e.g. methyl or ethyl methane or ethane sulfonate and the like, or a lower alkyl monocyclic carbocyclic aryl sulfonate, e.g. methyl p-toluene sulfonate and the like. The quaternizing reaction may be performed 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, or an organic acid amide, e.g. formamide, N,N-dimethylformamide 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 starting material and the remaining step(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.

This is a continuation-in-part application of my application Serial No. 816,667, filed May 29, 1959, now abandoned.

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 2.0 g. of 2-{1-N,N-(benz[b]hexamethylene)-imino}-ethylamine and 1.5 g. of S-methyl-isothiourea sulfate in a small amount of water is refluxed for four hours. The solution is concentrated and the 2-{1-N,N-(benz[b]hexamethylene)-imino}-ethyl-guanidine sulfate is recovered from the residue.

The starting material may be prepared as follows: 14.7 g. of N,N-(benz[b]hexamethylene)-imine and 7.6 g. of chloroacetonitrile are added to a suspension of 5.3 g. of anhydrous sodium carbonate in 75 ml. of benzene. The reaction mixture is refluxed for four hours while vigorously stirring and is cooled and filtered. The filtrate is evaporated to yield the desired 1-N,N-(benz[b]-1,6-hexamethylene-imino-acetonitrile. The latter is dissolved in dry diethyl ether and treated with lithium aluminum hydride while refluxing; the resulting 2-{1-N,N-(benz[b]hexamethylene)-imino}-ethylamine is obtained after evaporating the solvent.

Example 2

A mixture of 2.0 g. of 2-{1-N,N-dibenz[b,f]hexamethylene)-imino}-ethylamine and 1.2 g. of S-methyl-isothiourea sulfate in a small amount is refluxed for four hours; the desired 2-{1-N,N-dibenz[b,f]hexamethylene-imino}-ethyl-guanidine sulfate is obtained after concentrating the solution.

The starting material may be obtained according to the procedure of Example 1, i.e. by reacting 19.5 g. of 1-N,N-(dibenz{b,f}hexamethylene)-imine with 7.6 g. of chloroacetonitrile in the presence of a suspension of 5.3 g. of sodium carbonate in 75 ml. of benzene and reducing the resulting 2-{1-N,N-(dibenz[b,f]hexamethylene)-amino}-ethylamine by treatment with lithium aluminum hydride.

Example 3

A mixture of 1.5 g. of 2-[1-(1,2,3,4-tetrahydroquinolinyl)]-ethylamine and 1.2 g. of S-methyl-isothiourea sulfate in water yields the desired 2-[1-(1,2,3,4-tetrahydroquinolinyl)]-ethyl-guanidine sulfate after refluxing for four hours and concentrating the solution.

The starting material may be obtained by refluxing a mixture of 13.3 g. of 1,2,3,4-tetrahydroquinoline, 7.6 g. of chloroacetonitrile and 5.3 g. of anhydrous sodium carbonate in 75 ml. benzene and reducing the resulting 1-(1,2,3,4-tetrahydroquinolinyl)-acetonitrile with lithium aluminum hydride in an ether solution.

The following compounds may be prepared according to the previously described procedure by selecting the appropriate starting materials: 2-[1-(6-methoxy-1,2,3,4-tetrahydroquinolinyl)] - ethyl-guanidine, 2-[1-(7-chloro-1,2,3,4-tetrahydroquinolinyl)]-ethyl-guanidine, 3-[1-(1,2,-3,4-tetrahydroquinolinyl)]-propyl-guanidine and the like, particularly in the form of their therapeutically acceptable acid addition salts, such as, for example, the sulfates.

Example 4

The 3-(2-isoindolinyl)-propyl-guanidine sulfate is obtained by refluxing a mixture of 2.0 g. of 2-(2-isoindolinyl)-propylamine and 1.8 g. of S-methyl-isothiourea sulfate in 7 ml. of water and concentrating the resulting solution.

The starting material may be obtained by adding 11.9 g. of isoindoline to 21.2 g. of acrylonitrile and a few drops of N-benzyl-N,N,N-trimethyl-ammonium hydroxide. After the initial reaction has subsided the mixture is refluxed for several hours, then cooled and the desired 2-isoindolinyl-propionitrile is recovered by fractionation. The 3-(2-isoindolinyl)-propylamine is obtained by reducing the 2-isoindolinyl-propionitrile with lithium aluminum hydride as shown in Example 1.

Other guanidine derivatives, which may be prepared according to the above described method are, for example, 2-(2-isoindolinyl)-ethyl-guanidine sulfate, 2-(4-methoxy-2-isoindolinyl)-ethyl-guanidine sulfate, 2-{1-N,N-benz[d]-hexamethylene)-amino}-ethyl-guanidine sulfate, 2-{1-N,N-benz[b]heptamethylene) - imino} ethyl - guanidine sulfate and the like.

Example 5

A homogeneous mixture of 9.1 g. of 2-[2-(1,2,3,4-isoquinolinyl)]-ethylamine, 7.2 g. of S-methyl-isothiourea sulfate and 9 ml. of water is refluxed for six hours until the evolution of methylmercaptan ceases. A precipitate is formed on standing overnight, is filtered off and recrystallized from anhydrous ethanol to yield 11.0 g. of 2-[2-(1,2,3,4 - isoquinolinyl)] - ethyl - guanidine sulfate, M.P. 204–207°. The salt, containing two mols of the base per one mol of the acid, crystallizes with half a mole of water.

The starting materials may be prepared as follows: A mixture of 30.6 g. of 1,2,3,4-tetrahydroisoquinoline, 17.3 g. of chloro-acetonitrile, 95.2 g. of anhydrous potassium and 200 ml. of toluene is refluxed while stirring for 4½ hours. The reaction mixture is filtered, the solvent is removed under reduced pressure and the residue is distilled to yield the 2-(1,2,3,4-tetrahydroisoquinolinyl)-acetonitrile B.P. 170–190°/24 mm.; yield; 59 percent.

To a solution of 23.3 g. of 2-(1,2,3,4-tetrahydroisoquinolinyl)-acetonitrile in 100 ml. of diethyl ether is slowly added 6.1 g. of lithium aluminum hydride in 150 ml. of diethyl ether while stirring at room temperature. The addition is complete after one-half hour and the mixture is stirred at room temperature for an additional two hours. The reaction mixture is then treated with 18.5 ml. of ethyl acetate, 6.3 ml. of water, 12.3 ml. of 15 percent aqueous sodium hydroxide and 18.5 ml. of water. The organic

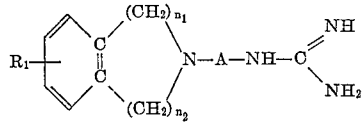
layer is separated, the ether is removed and the residue is distilled to yield 9.1 g. of the colorless 2-[2-(1,2,3,4-tetrahydro-isoquinolinyl)]-ethylamine, B.P. 82–88°/0.1 mm.

The following compounds may also be prepared according to the above described procedure: 3-[2-(1,2,3,4-isoquinolinyl)]-propyl-guanidine, 2-[2-(6-methoxy-1,2,3,4-isoquinolinyl)]-ethyl-guanidine, 2-[2-(6,7-dimethoxy-1,2,3,4-isoquinolinyl)]-ethyl guanidine, 2-[2-(7-chloro-1,2,3,4-isoquinolinyl)]-ethyl-quanidine, 2-[2-(5-methyl-1,2,3,4-isoquinolinyl)]-ethyl-guanidine, 3-methyl-1-{2-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-ethyl}-guanidine and the like, particularly in the form of therapeutically acceptable acid addition salts, such as the sulfate, thereof.

The 3-benzoyl-1-{2-[2-(1,2,3,4-tetrahydro-isoquinolinyl)]-ethyl}-guanidine may be prepared, for example, by treating 2-[2-(1,2,3,4-tetrahydro-isoquinolinyl)]-ethylamine with benzoyl-cyanamide in the presence of a small amount of concentrated hydrochloric acid.

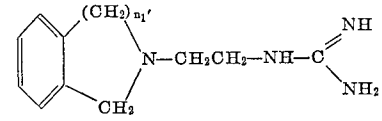
What is claimed is:

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



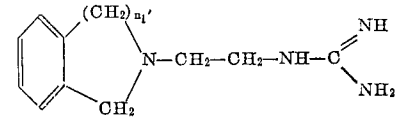
in which R_1 is a member selected from the group consisting of hydrogen, lower alkyl, lower alkoxy and halogeno, each of the symbols n_1, and n_2 stands for an integer from 0 to 5, both inclusive, with the proviso that the total of n_1+n_2 is an integer from 2 to 5, both inclusive, A is lower alkylene having from two to three carbon atoms and separating the guanidino group from the imino-nitrogen by from two to three carbon atoms, and addition salts of such compounds with therapeutically acceptable acids.

2. Compounds of the formula:



in which n_1' is an integer from 2 to 4, both inclusive.

3. Therapeutically acceptable acid addition salts of compounds:



in which n_1' is an integer from 2 to 4, both inclusive.

4. 2-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-ethyl-guanidine.

5. Therapeutically acceptable acid addition salts of 2-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-ethyl-guanidine.

6. 2-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-ethyl-guanidine sulfate.

7. 2-{1-N,N-(benz[b]hexamethylene)-imino}-ethyl-guanidine.

8. 3-(2-isoindolinyl)-propyl-guanidine.

9. 2-(2-isoindolinyl)-ethyl-guanidine.

No references cited.