United States Patent Office 3,093,632 Patented June 11, 1963



3,093,632

# DIBENZPOLYMETHYLENIMINO-ALKYLENE-GUANIDINES

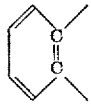
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No Drawing. Filed Feb. 2, 1961, Ser. No. 86,575
2 Claims. (Cl. 260—239)

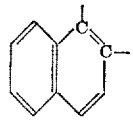
The present invention concerns guanidino compounds. More particularly, it relates to (N,N-alkylene-imino)-lower alkyl-guanidines, in which the alkylene radical contains from four to nine carbon atoms, and in which at least one pair of two neighboring carbon atoms of the alkylene portion are part of an 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-octahydroazocino), 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.

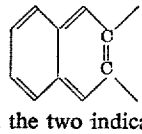
As previously stated, at least one pair of two neighboring carbon atoms of the alkylene chain, are incorporated into and form part of an aryl nucleus. Such aryl nucleus is above all a carbocyclic aryl nucleus, primarily a monocyclic carbocyclic aryl nucleus, i.e. a benz nucleus of the formula:



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

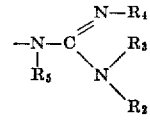


e.g. acetyl, propionyl and the like, nitro, amino, such as N-unsubstituted amino, N-mono-substituted amino, particularly N-lower alkylamino, e.g. N-methylamino, N-ethylamino and the like, or primarily N,N-di-substituted amino, such as N,N-di-lower alkyl-amino, e.g. N,N-dimethylamino, N-ethyl-N-methylamino, 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, 5 - (10,11 - dihydro-dibenz[b,f]azipinyl), 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:



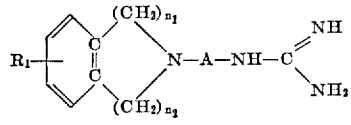
in which each of the radicals $R_2$, $R_3$, $R_4$ and $R_5$ stands primarily for hydrogen. They may also represent an aliphatic hydrocarbon radical, particularly lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl and the like, with the proviso that at least one of the radicals $R_2$, $R_3$ and $R_4$ 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, privalic acid and the like, a substituted lower alkanoic acid, e.g. chloroacetic, dichloroacetic, hydroxyacetic, methoxy-acetic, cyclopentylpropionic 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-aminosalicyclic, 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.

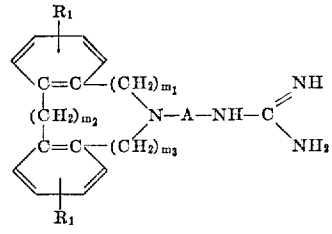
The new compounds of the present invention block the hypertensive, i.e. blood pressure raising, effect of amphetamine or similar sympathominetic drugs without affecting the stimulating properties of amphetamine or analogs. The compounds of this invention can, therefore, be used, for example, in combination with sympathominetic 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 reileve 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:



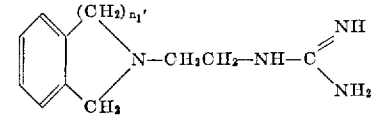
and



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 represents lower alkylene containing from two to three carbon atoms and separating the guanidino group from the imino-nitrogen 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:



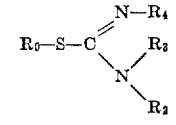
in which $n_1'$ represents one of the numbers 2, 3 or 4, and acid addition salts thereof with therapeutically acceptable acids, particularly mineral acids.

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 alkyl-amine, 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:

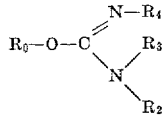


in which $R_2$, $R_3$ and $R_4$ have the previously given meaning, and $R_0$ stands for lower alkyl, e.g. ethyl, n-propyl or particularly methyl and the like, and mineral acid addition salts thereof. The preferred reagents to form a guanidino group are S-methylisothiourea and the mineral acid addition salts thereof; S-methylisothiourea 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, ethyl-

amino 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.

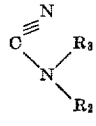
Similar reagents capable of converting an amino into a guanidino group are O-lower alkyl-isoureas of the formula:



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. dimethylsulfate, 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:

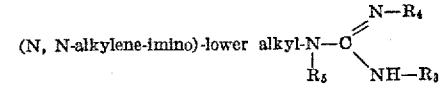


The reaction may be carried out, for example, by heating the mixture of an (N,N-alkylene-imino)-lower alkyl-amine compound, particularly a salt thereof, such as a mineral acid addition salt, e.g. the hydrochloride, hydrobromide, sulfate and the like, thereof and the cyanamide. The resulting melt may 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.

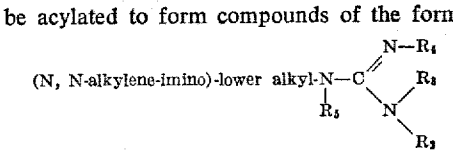
A third modification of the procedure for the manufacture of the products of this invention comprises reacting the (N,N-alkylene-imino)-lower alkyl-amine, in which alkylene has the previously given meaning, with a salt of a 1-guanyl-pyrazole. A salt of a 1-guanyl-pyrazole is primarily a salt with a mineral 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 hydrogentation, 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.

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 thel ike, 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 bromide 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 obtained by reacting a resulting free base with a lower alkyl halide, e.g. methyl, ethyl, n-propyl, isopropyl chloride, bromide or iodide and the like, 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 stages 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



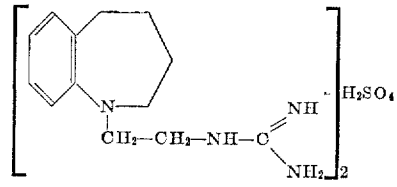
are preferably used which lead to final products mentioned in the beginning as preferred embodiments of the invention.

This is a continuation-in-part application of my application Serial No. 13,997, filed March 10, 1960, now U.S. Patent 3,055,883, which in turn 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 of the formula:

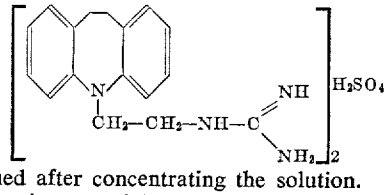


is recovered from the residue.

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]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-{5-(10,11-dihydro-dibenz-[b,f]azepinyl)}-ethylamine and 1.2 g. of S-methyl-isothiourea sulfate in a small amount is refluxed for four hours; the desired 2-{5-(10,11-dihydro-dibenz[b,f]azepinyl)}-ethyl-guanidine sulfate of the formula:

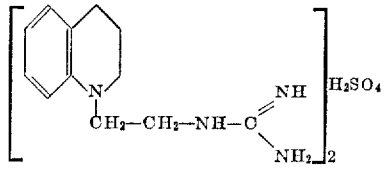


is obtained after concentrating the solution.

The starting material may be obtained according to the procedure of Example 1, i.e. by reacting 19.5 g. of 10,11-dihydro-5H-dibenz[b,f]azepine 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 - {5 - (10,11 - dihydro - dibenz[b,f]azepinyl)}-ethylamine by treatment with lithium aluminum hydride.

*Example 3*

A mixture of 1.5 g. of 2-[1-(1,2,3,4-tetrahydro-quinolinyl)]-ethylamine and 1.2 g. of S-methyl-isothiourea sulfate in water yields the desired 2-[1-(1,2,3,4-tetrahydro-quinolinyl)]-ethyl-guanidine sulfate of the formula:



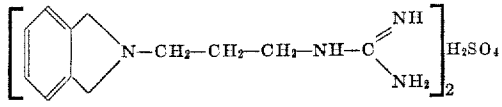
after refluxing for four hours and concentrating the solution.

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 guandine sulfate of the formula:



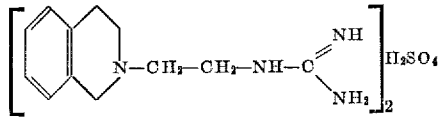
is obtained by refluxing a mixture of 2.0 g. of 2-(2-isoindolinyl)-propylamine and 1.8 g. of S-methyl-isothiourea sulfate in 7 ml. of water and concentrating the resulting solution.

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 lithum 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-iso-indolinyl) - ethyl - guanidine sulfate, 2-{1-N,N (benz[d]hexamethylene)-imino}-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 of the formula:



The salt, containing two mols of the base per one mol of the acid, crystallizes with half a mol of water and melts at 204–207°.

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-tetrahydroisoquinolinyl)]-ethylamine, B.P. 82–88°/0.1 mm.

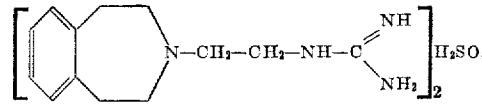


The following compounds may also be prepared according to the above described procedure: 3-[2-(1,2,3,4-isoquinolinyl)]-propyl-guanidine, 2-[2-(6-methoxy-1,2,3,4-isoquinolinyl)]-ethyl-guanidine, 2-[2-(6,7 - dimethoxy-1,2,3,4-isoquinolinyl)] - ethyl-guanidine, 2-[2-(7-chloro-1,2,3,4-isoquinolinyl)]-ethyl-guanidine, 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-isoquinolinyil)]-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.

*Example 6*

A mixture of 6.5 g. of 2-{1-N,N-(benz[d]hexamethylene)-imino}-ethylamine and 4.8 g. of S-methyl-isothiourea sulfate in 8 ml. of water is refluxed for five hours. On cooling the desired 2-{1-N,N-(benz[d]hexamethylene)-imino}-ethyl-guanidine sulfate of the formula:



crystallizes, is filtered off and recrystallized from a mixture of aqueous ethanol and acetone, M.P. 239–242°; yield: 8.5 g.

The starting material used in the above reaction may be prepared as follows: A mixture of 75 g. of α,α'-dicyano-O-xylene and about 10 g. of Raney nickel in 500 ml. of a saturated solution of ammonia in ethanol is hydrogenated; hydrogenation is carried out at 75 atmospheres pressure and at 100° and is interrupted after about five hours. The resulting mixture is filtered, the filtrate is evaporated to dryness and the residue distilled to yield 32.2 g. of N,N-benz[d]hexamethylene-imine, B.P. 123–124/15 mm. ($n_D^{25}$=1.5600), and 14 g. of 1,2-(2-aminoethyl)-benzene, B.P. 90–98°/0.15 mm.; $n_D^{25}$=1.5571.

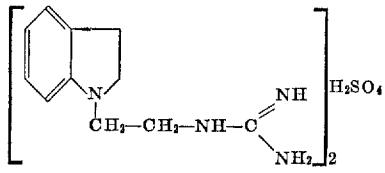
A mixture of 20.4 g. of N,N-benz[d]hexamethylene-imine, 11.6 g. of chloroacetonitrile, 59.5 g. of anhydrous sodium carbonate and 0.5 ml. of water in 70 ml. of toluene is heated while stirring for twelve hours. The hot solution is filtered, the solvent is removed under reduced pressure and the crystalline residue is recrystallized from ethanol to yield 19.2 g. of {1-N,N-(benz[d]hexamethylene)-imino}acetonitrile, M.P. 113–116°.

A solution of 19.2 g. of {1-N,N-(benz[d]hexamethylene)-imino}-acetonitrile in 100 ml. of diethyl ether and 35 ml. of tetrahydro furan is added to a suspension of 8.0 g. of lithium aluminum hydride in 300 ml. of diethyl ether over a period of one hour. The reaction mixture is stirred for an additional two hours and then allowed to stand at room temperature overnight. 24 ml. of ethyl acetate, 8 ml. of water, 16 ml. of 15 percent aqueous sodium hydroxide and 24 ml. of water are added successively; the mixture is filtered, the filtrate is evaporated and the residue is distilled to yield the desired 2-{1-N,N-(benz[d]hexamethylene)-imino}ethylamine, B.P. 117–140°/0.05 mm.

*Example 7*

A solution of 4.5 g. of 2-(1-indolinyl)-ethylamine and 3.9 g. of S-methyl-isothiourea sulfate in 2 ml. of water

is refluxed for five hours. After cooling, the mixture is triturated repeatedly with acetone, the resulting white solid is filtered off and recrystallized from a mixture of water, ethanol and acetone to yield 4.4 g. of 2-(1-indolinyl)-ethyl-guanidine sulfate of the formula:



which melts at 178° (with decomposition), and contains one mol of ethanol. It is converted into the dihydrochloride as follows: A solution of 2.5 g. of 2-(1-indolinyl)-ethyl-guanidine sulfate in water is made basic with concentrated aqueous sodium hydroxide while cooling. The separated oil is extracted with chloroform, the organic solution is dried and evaporated to dryness. The remaining oil is dissolved in ethanol, and the solution is made acidic with a saturated solution of hydrogen chloride in ethanol. The desired 2-(1-indolinyl)-ethyl-guanidine dihydrochloride crystallizes upon trituration with diethyl ether and is recrystallized from a mixture of ethanol and diethyl ether, M.P. 174° (decomposition).

The starting material is prepared as follows: A mixture of 23.8 g. of indoline, 16.7 g. of chloroacetonitrile, 42.4 g. of anhydrous sodium carbonate, 0.25 ml. of water and 250 ml. of toluene is refluxed while stirring for eleven hours. The resulting mixture is filtered, the solid material is washed with toluene and the combined filtrates are evaporated. The desired (1-indolinyl)-acetonitrile is purified by distilling the residue, B.P. 152–172°/15 mm., $n_D^{25}=1.5710$; yield: 8.6 g.

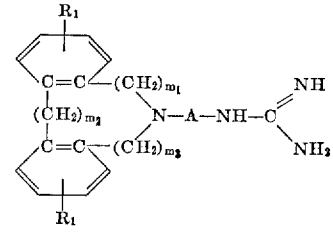
A solution of 8.5 g. of (1-indolinyl)-acetonitrile in 50 ml. of diethyl ether is added over a period of 1½ hours to a stirred solution of 4.3 g. of lithium aluminum hydride in 150 ml. of diethyl ether in an atmosphere of



nitrogen. After standing overnight at room temperature, there are added in succession 12 ml. of ethyl acetate, 4 ml. of water, 8 ml. of 15 percent aqueous sodium hydroxide and 2 ml. of water to destroy the excess of hydride reagent and complex compounds. After standing for twenty minutes, the mixture is filtered, the solid material is washed with diethyl ether and the filtrate is evaporated to dryness. The residue is distilled to yield 4.5 g. of 2-(1-indolinyl)-ethylamine, B.P. 154–160°/17 mm.

What is claimed is:

1. A member selected from 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 $m_1$, $m_2$ and $m_3$ is one of the numbers selected from the group consisting of 0, 1 and 2, with the proviso that the total of $m_1+m_2+_3$ is one of the numbers selected from the group consisting of 2 and 3, A stands for 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 compound with therapeutically acceptable acids.

2. 2{5-(10,11-dihydro-dibenz[b,f]azepinyl)}-ethyl guanidine.

No references cited.