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1-[2-(N,N-ALKYLENE-IMINO)-ALKYL]-3-AMINO-GUANIDINES AND INTERMEDIATES THEREFOR

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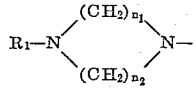
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11 Claims. (Cl. 260—239)

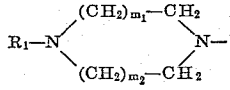
The present invention concerns amino-guanidines. More especially, it relates to 1-R-lower alkyl-3-amino-guanidines, in which R represents N,N-alkylene-imino having from four to ten carbon atoms as chain members, N,N-(N-R_1-aza-alkylene)-imino having from four to six carbon atoms as chain members, and R_1 representing an organic radical, N,N-bicycloalkylene-imino, in which bicycloalkylene has from five to sixteen carbon atoms as chain and bridge members, and N,N-bicycloalkylene-imino, in which bicycloalkylene has from five to sixteen carbon atoms as chain and bridge members, and N,N-(R_1-aza-bicycloalkylene)-imino having in the bicycloalkylene portion from four to fourteen carbon atoms as chain and bridge members and R_1 standing for an organic radical, salts or acyl derivatives of such compounds, as well as to process for the preparation of these compounds.

An N,N-alkylene-imino radical, in which alkylene has from four to ten, preferably from six to eight, chain carbon atoms, may be represented, for example, by N,N-tetramethylene-imino (or 1-pyrrolidino), N,N-pentamethyleneimino (or 1-piperidino), N,N-hexamethyleneimino (or 1-hexahydroazepino), N,N-heptamethyleneimino (or 1-octahydroazocino), N,N-octamethyleneimino (or 1-octahydroazonino), N,N-nonamethyleneimino (or 1-decahydroazecino), N,N-decamethylene-imino and the like.

An N,N-(N-R_1-aza-alkylene)-imino group may be represented by the formula:



in which each of the letters n_1 and n_2 represents one of the numbers 2, 3 and 4, with the proviso that the total of n_1+n_2 is one of the numbers 4, 5 and 6, and R_1 stands for an organic radical. A more preferred group of N,N-(N-R_1-aza-alkylene)-imino radicals may be represented by the formula:



in which each of the letters m_1 and m_2 represents one of the numbers 1 and 2, and R_1 has the previously-given meaning. Such N,N-(N-R_1-aza-alkylene)-imino radicals are represented, for example, by 4-R_1-1-piperazino, 1-N,N-(3-R_1-3-aza-1,6-hexylene)-imino, 1-N,N-(4-R_1-4-aza-1,7-heptylene)-imino, 1-N,N-(3-R_1-3-aza-1,7-heptylene)-imino and the like, in which R_1 has the previously-given meaning, and analogous radicals.

Attached to the aza-nitrogen atom of an N,N-(N-R_1-aza-alkylene)-imino group, is an organic radical R_1, which represents primarily an aliphatic radical, and especially lower alkyl having from one to seven, preferably from one to four, carbon atoms, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secondary butyl, tertiary butyl and the like, as well as n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, n-heptyl and the like, as well as lower alkenyl, preferably allylic lower alkenyl having from three to five carbon atoms, e.g., 2-propenyl (or allyl), 2-methyl-2-propenyl (or 2-methyl-allyl), 2-butenyl (or 3-methyl-allyl) and the like, lower alkynyl, e.g., ethynyl, 1-propynyl and the like, a cycloaliphatic radical, particularly cycloalkyl having from three to seven, particularly from five to six, ring carbon atoms, e.g., cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, cycloalkenyl having from five to seven ring carbon atoms, e.g., 2-cyclopentenyl, 3-cyclohexenyl and the like, or any other suitable aliphatic radical.

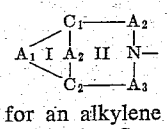
The above-mentioned aliphatic, particularly lower alkyl, groups representing R_1 in the above formulae may be substituted, for example, by other aliphatic radicals, such as cycloaliphatic groups, primarily cycloalkyl and cycloalkenyl as defined hereinabove, carbocyclic aryl, particularly monocyclic or bicyclic carbocyclic aryl, e.g., phenyl, 1-naphthyl or 2-naphthyl, as well as substituted phenyl, substituted 1-naphthyl or substituted 2-naphthyl. Substituents attached to the carbocyclic radicals are, for example, lower alkyl, e.g., methyl, ethyl and the like, lower alkoxy, e.g., methoxy, ethoxy and the like, lower alkylenedioxy, e.g., methylenedioxy and the like, lower alkylmercapto, e.g., methylmercapto, ethyl-mercapto and the like, nitro, amino, particularly N,N-di-substituted amino, such as N,N-di-lower alkyl-amino, e.g., N,N-dimethylamino, N,N-diethylamino and the like, halogeno, e.g., fluoro, chloro, bromo and the like, trifluoromethyl or any other suitable substituent. Groups attached to carbocyclic portions may be in any of the available positions, whereby one or more than one of the same or of different substituents may be present. Other substituents attached to an aliphatic, particularly a lower alkyl, group are heterocyclic aryl radicals, such as monocyclic azacyclic aryl, for example, pyridyl, e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl and the like, bicyclic monocyclic azacyclic aryl, for example, quinolyl, e.g., 2-quinolyl and the like, monocyclic diazacyclic aryl, e.g., 3-pyridazinyl, 2-pyrimidyl, 4-pyrimidyl, 2-pyrazinyl and the like, monocyclic thiacyclic aryl, for example, thienyl, e.g., 2-thienyl and the like, monocyclic oxacyclic aryl, for example, furyl, e.g., 2-furyl and the like. These heterocyclic aryl radicals may also have additional substituents, such as, for example, those attached to the above-described carbocyclic radicals.

An aliphatic radial R_1 in the above formulae, particularly a lower alkyl radical may also be substituted by functional groups, such as, for example, hydroxyl, etherified hydroxy, such as lower alkoxy, e.g., methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy and the like, polyalkylenedioxy, e.g., polyethylenedioxy, polypropylenedioxy and the like, which polyalkyleneoxy radicals may have from two to twenty lower alkyleneoxy portions and may have a free terminal hydroxyl group or an etherified terminal hydroxyl group, such as a terminal lower alkoxy, e.g., methoxy, ethoxy and the like, group, carbocyclic aryloxy, such as monocyclic carbocyclic aryloxy, e.g., phenyloxy and the like, or carbocyclic aryl-lower alkoxy, such as monocyclic carbocyclic aryl-lower alkoxy, e.g., benzyloxy, diphenylmethoxy, (4-chlorophenyl)-phenyl-methoxy and the like, or esterified hydroxyl, such as lower alkoxy-carbonyloxy, e.g., methoxy-carbonyloxy, ethoxy-carbonyloxy and the like, carbamyloxy, such as carbamyloxy, or N-lower alkyl-carbamyloxy, e.g., N-methyl-carbamyloxy and the like, N,N-di-lower alkyl-carbamyloxy, e.g., N,N-dimethyl-carbamyloxy and the like, or N-carbocyclic aryl-carbamyloxy, particularly N-monocyclic carbocyclic aryl-carbamyloxy, e.g., N-phenyl-carbamyloxy and the like, or lower alkanoyloxy, e.g., acetoxy, propionyloxy and the like, or acyl groups, such as lower alkanoyl, e.g., acetyl and the like, amino, for example, unsubstituted amino, N-mono-substituted amino, for example, N-lower alkylamino, e.g., N-methylamino, N-ethylamino and the like, N-carbocyclic

aryl-amino, particularly N-monocyclic carbocyclic aryl-amino, e.g., N-phenylamino and the like, N-carbocyclic aryl-lower aliphatic hydrocarbon amino, particularly N-monocyclic carbocyclic-lower alkyl-amino, such as N-phenyl-lower alkyl-amino, e.g., N-benzyl-amino, N-(2-phenylethyl)-amino and the like, or primarily N,N-disubstituted amino, such as N,N-di-lower alkyl-amino, in which lower alkyl has from one to four carbon atoms, e.g., N,N-dimethylamino, N-ethyl-N-methyl-amino, N,N-diethylamino, N,N-di-n-propylamino, N,N-di-isopropyl-amino and the like, N-cycloalkyl-N-lower alkylamino, e.g., N-cyclopentyl-N-methylamino, N-cyclohexyl-N-ethyl-amino and the like, N-lower alkyl-N-monocyclic carbocyclic aryl-amino, particularly N-lower alkyl-N-phenyl-lower alkylamino, e.g., N-benzyl-N-methylamino, N-methyl-N-(2-phenylethyl)- amino and the like, or N,N-alkyleneimino, N,N-oxa-alkyleneimino or N,N-aza-alkyl-eneimino, in which alkylene has from four to six carbon atoms as ring members, such as, for example, 1-pyrrolidino groups, e.g., 1-pyrrolidino, 2-methyl-1-pyrrolidino and the like, 1-piperidino radicals, e.g., 1-piperidino, 2-methyl-1-piperidino, 3 - methyl-1-piperidino, 4-methyl-1-piperidino, 3-hydroxy-1-piperidino, 3-acetoxy-1-piperidino, 3-hydroxymethyl-1-piperidino and the like, 1-N,N-(1,6-hexylene)-imino, 4-morpholino, or 1-piperazino radicals, particularly 4-lower alkyl-1-piperazino, e.g., 4-methyl-1-piperazino, 4-ethyl-1-piperazino, 4-(2-hydroxy-ethyl)-1-piperazino, 4-(2-acetoxyethyl)-1-piperazino, 4-[2-(ω-methoxy-polyethyleneoxy)-ethyl]-1-piperazino and the like, mercapto, etherified mercapto, especially lower alkyl-mercapto, e.g., methyl-mercapto, ethyl-mercapto and the like, halogeno atoms, e.g., fluoro, chloro, bromo and the like, whereby one or more than one functional group may be attached to one or more than one carbon atom of an aliphatic, particularly lower alkyl, radical.

The group R_1 in the above formulae may also represent carbocyclic aryl, primarily monocyclic carbocyclic aryl, e.g., phenyl, or bicyclic carbocyclic aryl, e.g., 1-naphthyl or 2-naphthyl, which radicals may have one or more than one of the same or different substituents attached to any of the available carbon atoms; substituents are, for example, those previously-described as being attached to a carbocyclic aryl radical. It also represents heterocyclic aryl, primarily monocyclic or bicyclic heterocyclic aryl, which have one or more than one sulfur, oxygen and/or nitrogen atom as ring members, such as, for example, monocyclic mono-azacyclic aryl, for example, pyridyl, e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl and the like, bicyclic mono-azacyclic aryl, for example, quinolyl, e.g., 2-quinolyl, 4-quinolyl and the like, monocyclic di-azacyclic aryl, for example, pyridazinyl, e.g., 3-pyridazinyl and the like, pyrimidyl, e.g., 2-pyrimidyl, 4-pyrimidyl and the like, pyrazinyl, e.g., 2-pyrazinyl and the like, pyrryl, e.g., 2-pyrryl and the like, monocyclic thiacyclic aryl, for example, thienyl, e.g., 2-thienyl and the like, or monocyclic oxacyclic aryl, for example, furyl, e.g., 2-furyl and the like, and these heterocyclic radicals substituted by substituents, such as, for example, those mentioned hereinbefore.

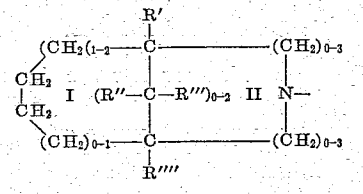
An N,N-bicycloalkyleneimino radical may be represented by the formula:



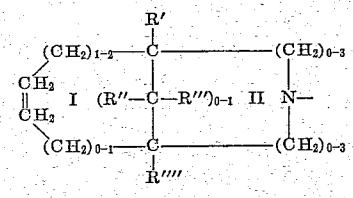
in which A_1 stands for an alkylene radical, which links the C_1-carbon atom with the C_2-carbon atom and has from one to five carbon atoms, or an alkenylene radical, which links the C_1-carbon atom with the C_2-carbon atom and has from two to five carbon atoms, A_2 represents a direct bond between the C_1-carbon atom and the C_2-carbon atom, or any alkylene radical, which separates the C_1-carbon atom from the C_2-carbon atom by from one to two carbon atoms and has a total of from one to six carbon atoms, and each of the groups A_3 represents a

direct bond between the imino-nitrogen atom and one of the bridge carbon atoms C_1 and C_2, or an alkylene radical which links the C_1-carbon atom or the C_2-carbon atom with the imino-nitrogen atom and has from one to three carbon atoms, with the proviso that whenever the carbocyclic ring I has from three to five atoms as ring members, the azacyclic ring II has at least five atoms as ring members.

An N,N-bicycloalkylene-imino radical stands primarily for one of the formulae:



and



in which formulae each of the groups R', R'', R''' and R'''' stands for hydrogen or methyl, and with the proviso that whenever the carbocyclic ring I has five atoms as ring members, the azacyclic ring II has at least five atoms as ring members.

Such N,N-bicycloalkylene-imino radicals are represented for example, by

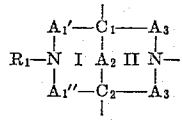
3-aza-3-bicyclo[3,2,0]heptyl,
7-aza-7-bicyclo[4,1,0]heptyl,
2-aza-2-bicyclo[2,2,1]heptyl,
6-aza-6-bicyclo[3,1,1]heptyl,
7-aza-7-bicyclo[2,2,1]heptyl,
3-aza-3-bicyclo[3,3,0]octyl,
2-aza-2-bicyclo[3,2,1]octyl,
3-aza-3-bicyclo[3,2,1]octyl
(or 1,2,3,4,5,6,7,8-octahydro-2-cyclopenta[c]pyrryl),
1,8,8-trimethyl-3-aza-3-bicyclo[3,2,1]octyl,
7-aza-7-bicyclo[3,2,1]octyl,
2-aza-2-bicyclo[2,2,2]octyl,
2-aza-2-bicyclo[4,3,0]nonyl,
3-aza-3-bicyclo[4,3,0]nonyl,
7-aza-7-bicyclo[4,3,0]nonyl
(or 4,5,6,7,8,9-hexahydro-1-indolinyl),
8-aza-8-bicyclo[4,3,0]nonyl
(or 4,5,6,7,8,9-hexahydro-2-isoindolinyl),
2-aza-2-bicyclo[3,3,1]nonyl,
3-aza-3-bicyclo[3,3,1]nonyl,
2-aza-2-bicyclo[3,2,2]nonyl,
3-aza-3-bicyclo[3,2,2]nonyl,
7-aza-7-bicyclo[4,4,0]decyl
(or 1,2,3,4,5,6,7,8,9,10-decahydro-1-quinolinyl),
8-aza-8-bicyclo[4,4,0]decyl
(or 1,2,3,4,5,6,7,8,9,10-decahydro-2-isoquinolinyl),
10-aza-10-bicyclo[4,3,1]decyl,
8-aza-8-bicyclo[4,3,1]decyl,
2-aza-2-bicyclo[5,4,0]undecyl,
4-aza-4-bicyclo[5,4,0]undecyl
(or 2,3,4,6,7,8,9,10,11-decahydro-1H-3-benzazepinyl),

and the like as well as

7-aza-7-bicyclo[4,3,0]non-3-enyl
(or 4,7,8,9-tetrahydro-1-indolinyl),
8-aza-8-bicyclo[4,3,0]non-3-enyl
(or 4,7,8,9-tetrahydro-2-isoindolinyl),
7-aza-7-bicyclo[4,4,0]dec-3-enyl
(or 1,2,3,4,5,8,9,10-octahydro-1-quinolinyl),

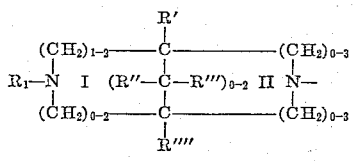
8-aza-8-bicyclo[4,4,0]dec-3-enyl
(or 1,2,3,4,5,8,9,10-octahydro-2-isoquinolinyl),
3-aza-3-bicyclo[3,2,1]oct-6-enyl
and the like.

An N,N-aza-bicycloalkylene-imino radical is primarily a radical of the formula:



in which R_1, A_2 and A_3 have the previously-given meaning, each of the group A_1' represents a direct bond between the C_1-carbon atom and the C_2-carbon atom, respectively, and the aza-nitrogen atom carrying the group R_1 or an alkylene radical, which connects the C_1-carbon atom and the C_2-carbon atom, respectively, with the aza-nitrogen atom carrying the group R_1, and has from one to two carbon atoms, with the proviso that at least one of the groups A_1' and A_1'' represents an alkylene radical having from one to two carbon atoms, and with the further proviso that whenever the azacyclic ring having as the ring member the nitrogen atom carrying the group R_1, i.e., ring I, has four ring members, the azacyclic ring having as the ring member the nitrogen atom carrying the amino-guanidino-lower alkyl group, i.e., ring II, has at least four ring members.

An N,N-aza-bicycloalkylene-imino portion is more especially a group of the formula:



in which each of the groups R', R'', R''', R'''' and R_1 have the previously-given meaning, and with the proviso that whenever the azacyclic ring having as the ring member the nitrogen atom carrying the group R_1, i.e., ring I, has four atoms as ring members the azacyclic ring having as the ring member the nitrogen atom carrying the amino-guanidino-lower alkyl group, i.e., ring II, has at least four ring members.

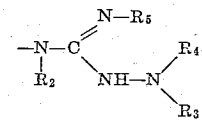
Specific examples of N,N-aza-bicycloalkylene-imino radicals are, for example, 2,5-diaza-5-R_1-2-bicyclo[2,2,0]hexyl, 4,8-diaza-4-R_1-9-bicyclo[4,3,0]nonyl (or 5-R_1-2,3,4,5,6,7,8,9-octahydro-1H-pyrrolo[3,4-c]pyridyl), 2,7-diaza-7-R_1-2-bicyclo[4,4,0]decyl (or 5-R_1-1,2,3,4,5,6,7,8,9,10-decahydro-1-isonaphthyridyl), 3,7-diaza-7-R_1-3-bicyclo[3,3,1]nonyl (or 7-R_1-3-bispidinyl) and the like.

The carbon atoms of an N,N-alkylene-imino, an N,N-(N-R_1-azaalkylene)-imino, an N,N-bicycloalkylene-imino, or an N,N-(N-R_1-aza-bicycloalkylene)-imino may be substituted by aliphatic radicals, such as lower alkyl, particularly, methyl, as well as ethyl, n-propyl, isopropyl and the like. Furthermore, one or more than one pair of neighboring carbon atoms of an alkylene portion in any of the above imino groupings may be part of a monocyclic carbocyclic aryl, particularly phenyl, nucleus, which may have additional substituents, such as those described hereinabove. Such carbocyclic aryl nuclei are preferably fused-on to the N,N-alkylene-imino groups, and resulting bicyclic groupings may be illustrated, for example, by 2-isoindolinyl, 1-indolinyl, 1-tetrahydroquinoyl, 2-tetrahydrosioquinolinyl, 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 arly portion, particularly benz-nucleus, is substituted, whereby one or more than one of the same or of different substituents

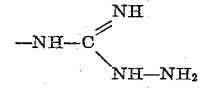
selected from the afore-mentioned class may be attached to any of the positions available for substitution.

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

The 1-amino-guandino group may be represented by the formula:



in which each of the groups R_2, R_3, R_4 and R_5 stands primarily for hydrogen, but may also represent an organic substituent, such as, for example, an aliphatic group, particularly lower alkyl, e.g., methyl, ethyl, n-propyl, isopropyl and the like, as well as a carbocyclic aryl radical, particularly monocyclic carbocyclic aryl, e.g., phenyl, or phenyl substituted by one of the previously-mentioned substituents, or a carbocyclic aryl-aliphatic radical, such as monocyclic carbocyclic aryl-lower alkyl, particularly phenyl-lower alkyl, e.g., benzyl, 1-phenylethyl, 2-phenylethyl, diphenylmethyl and the like, and analogous radicals, in which the phenyl portion is substituted by any of the previously-described substituents. One of the groups R_3 and R_5 may also represent an acyl radical, particularly the acyl radical of an organic carboxylic acid, such as a lower aliphatic carboxylic acid, for example, a lower alkanoic acid, e.g., acetic propionic, pivalic acid and the like, a substituted lower alkanoic 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-methoxybenzoic, 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. The amino-guandino group is more especially the group of the formula:

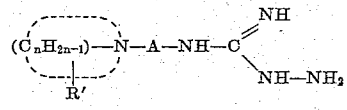


Salts of the new compounds of this invention are particularly pharmacologically and therapeutically acceptable, non-toxic acid addition salts, such as those with inorganic acids, e.g., hydrochloric, hydrobromic, sulfuric, phosphoric acids and the like, with organic carboxylic acids, e.g., acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, dihydroxymaleic, fumaric, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranilic, cinnamic, mandelic, salicyclic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic acid 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 this invention and the salts thereof cause in the anesthetized, normotensive dog an inhibition of the carotid occlusion reflux pressor response and antagonize pressor responses elicited by high doses

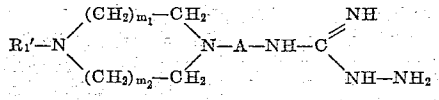
of amphetamine, and lower the arterial pressure in the unanesthetized renal or neurogenic hypertensive dog. These effects appear to be due to an inhibition of the release and/or distribution of transmitter substances from sympathetic nerve terminals. In view of the fact that the compounds of this invention block the hypertensive effects of these pressor substances, they can, therefore, be used as antihypertensive agents to relieve hypertensive conditions, particularly those of neurogenic, renal or essential nature. 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 and the like.

A preferred group of compounds of this invention are represented by the compounds of the formula:



in which R' has the previously-given meaning, the latter *n* stands for 6, 7 and 8, and A represents lower alkylene having from two to three carbon atoms and separating the amino-guanidino group form the N,N-alkylene-imino group by from two to three carbon atoms, and pharmacologically acceptable acid addition salts thereof. Specific members of this group are, for example, 3-amino-1-[2-(N,N-hexamethylene-imino)-ethyl]-guanidine, 3-amino-1-[3-(1-N,N-hexamethylene-imino)-propyl]-guanidine, 3-amino - 1 - {2-[1-N,N-(3-methyl-hexamethylene)-imino]-ethyl}-guanidine, 3 - amino-1-[3-(1-N,N-heptamethylene-imino)-ethyl]-guanidine, 3 - amino - 1-[2-(1-N,N-heptamethylene-imino)-propyl]-guanidine, 3-amino-1-[3-(1-N,N-heptamethylene-imino)-propyl]-guanidine, 3 - amino-1-[-(1-N,N-octamethylene-imino)-ethyl]-guanidine and the like, and pharmacologically acceptable acid addition salts thereof, particularly those with suitable mineral acids.

Another group of preferred compounds of this invention may be illustrated by the formula:



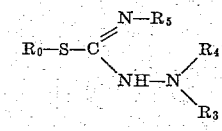
in which A and each of the letters m_1 and m_2 have the previous-given meaning, and R_1' stands for lower alkyl having preferably from one to four carbon atoms, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl and the like, and pharmacologically acceptable acid addition salts thereof. Specific compounds of this group are, for example, 3 - amino-1-[2-(4-methyl-1-piperazino)-ethyl]-guanidine, 3 - amino - 1-[3-(4-methyl-1-piperazino)-propyl]-guanidine, 3amino-1-[2-4-ethyl-1-piperazino)-ethyl]-guanidine, 3 - amino - 1-[2-(4-isopropyl-1-piperazino)-ethyl]-guanidine, 3-amino-1-{2-[1-N,N-(3-aza-3-methyl-hexamethylene)-imino]-ethyl}-guanidine, 3-amino-1-{2-[1-N,N-1-(4-aza - 4-methyl-heptamethylene)-imino]-ethyl}-guanidine and the like, and pharmacologically acceptable acid addition salts thereof, particularly with suitable mineral acids.

The compounds of this invention may be used in the form of pharmaceutical preparations, which contain the new amino-guanidine compounds or the pharmacologically acceptable acid addition salts thereof in admixture with an organic or inorganic, solid or liquid carrier suitable for external or parenteral administration. For making up the preparations there may be employed substances which do not react with the new compounds, such as water, gelatine, lacetose, starches, stearic acid, magnesium stearate, stearyl alcohol, talc, vegetable oils, benzyl alcohols, gums, propylene glycol, polyakylene glycols or any other known carrier used for such preparations. The latter may be in the solid form for example, as capsules, tablets, dragees 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 emulsifying agents and the like,

salts for varying the osmotic pressure, buffers, etc. They may also contain, in combination, other pharmacologically acitve substances.

The amino-guanidine compounds of this invention may be prepared, for example, by converting in an R-lower alkyl-amine, in which R has the above-given meaning, or a salt thereof, the amino group into an amino-guanidino group and, if desired, converting a resulting salt into the free compound, and/or, if desired, converting a resulting compound into a salt or an acyl derivative thereof.

The reagents of choice for the conversion of an amino group into an amino-guanidino group are S-lower alkyl-2-isothiosemicarbazides particularly those of the formula:

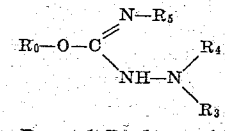


in which R_3, R_4 and R_5 have the previously-given meaning, and R_0 stands for lower alkyl, particularly methyl, as well as ethyl, n-propyl, isopropyl and the like, and acid addition salts thereof. The salts, which are employed in preference over the free base, are primarily those with mineral acids, e.g., hydrochloric, hydrobromic, hydriodic, sulfuric acid and the like. The preferred reagents are acid addition salts of S-methyl-2-isothiosemicarbazide with mineral acids, such as the hydriodide, sulfate and the like. The starting material, in which the group is above all an unsubstituted amino group, but may also represent a substituted amino group having R_2 as the substituent, 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 an inert 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, ethers, e.g., diethyleneglycol dimethyl-ether, 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 solvents represent the preferred diluents.

The reaction may be carried out at room temperature, or, if necessary, at an elevated temperature. Furthermore, it may be performed in the atmosphere of an inert gas, e.g., nitrogen, and/or in a closed vessel.

Analogous reagents capable of converting an amino group into an amino-guanidino group are the O-lower alkyl - 2 - isosemicarbazides, particularly those of the formula:



in which R_3, R_4, R_5 and R_0 have the previously-given meaning, or salts thereof with mineral acids. These semicarbazide derivatives are used in the same way as the above-described, corresponding 1-amino-2-isothiourea reagents; an acid addition salt of O-methyl-2-isosemicarbazide with a mineral acid, e.g., hydriodic, sulfuric acid and the like, 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-2-isothiosemicarbazides or O-lower alkyl-2-isosemicarbazides may be manufactured by alkylating thiosemicarbazides or semicarbazides 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.

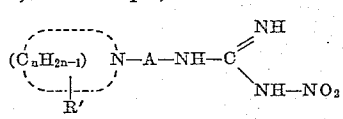
The starting materials, i.e., the R-lower alkyl-amines, in which R has the previously-given meaning, used in the above procedure are known or may be prepared according to known procedures. They may, for example, be obtained by treating a compound of the formula R—H, in which R has the previously-given meaning, with a halogeno-lower alkano-nitrile, in which halogen 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 R-lower alkano-nitrile, the cyano group is then converted into 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 suitable light metal hydride, 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 necessary, in the presence of an activator, such as aluminum chloride and the like.

The compounds of the present invention may also be prepared, for example, by converting in a 1-R-lower alkyl-3-X-guanidine, in which R has the previously-given meaning, and X stands for nitro or nitroso, or a salt thereof, the grouping X into an amino group, and, if desired, carrying out the optional steps.

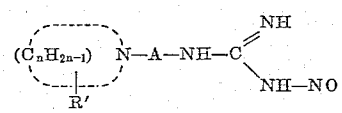
The conversion of a nitro or a nitroso group into an amino group may be carried out by per se conventional reduction methods. For example, reduction may be achieved by treatment with nascent hydrogen; the latter may be generated by contacting a suitable metal or metal compound with a hydrogen donor, for example, a suitable metal, e.g., zinc or any other analogous metal, with an acid, e.g., acetic acid and the like, zinc acetate or any analogous metal compound with water or a moist solvent, or any other equivalent metal-hydrogen donor combination, such as, for example, an alkali metal, e.g., sodium and the like, in the presence of liquid ammonia and an ammonium compound, e.g., ammonium chloride and the like. Treatment with hydrogen in the presence of a catalyst, e.g., nickel and the like, may also be used in the above conversion of a nitro or a nitroso group into an amino group; reduction of a nitro-guanidino group in neutral or basic medium leads first in the formation of a nitroso-guanidino group, whereas reduction in an acidic medium yields directly the desired amino-guanidino group. The reduction procedure may also be carried out electrolytically.

The starting materials, which are new and intended to be included within the scope of this invention, may be prepared, for example, by reacting an R-lower alkyl-amine with an S-lower alkyl-1-nitro-2-isothiourea or an S-lower alkyl-2-nitroso-2-isothiourea or acid addition salts of such reagents; the reaction may be carried out according to the previously-described treatment of an amine with a 1-amino-S-lower alkyl-2-isothiourea. The corresponding O-lower alkyl-1-nitro-2-isoureas or O-lower alkyl-1-nitroso-2-isoureas may replace the 2-isothiourea reagents.

Preferred 1-(R-lower alkyl)-3-nitro-guanidines and 1-(R-lower alkyl)-3-nitroso-guanidines used as the starting materials are, for example, those of the formula:



and

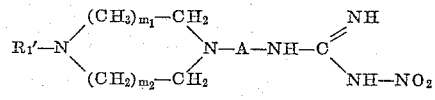


in which R', A and the letter n have the previously-given meaning, and acid addition salts thereof. Such compounds are, for example,

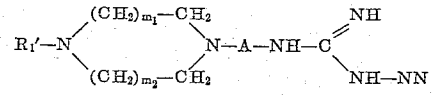
1-[2-(1-N,N-hexamethylene-imino)-ethyl]-3-nitro-guanidine,
1-[3-(N,N-hexamethylene-imino)-propyl]-3-nitro-guanidine,
1-{-2-[1-N,N,-(3-methyl-hexamethylene)-imino]-ethyl}-3-nitro-guanidine,
1-[2-(1-N,N-heptamethylene-imino)-ethyl]-3-nitro-guanidine,
1-[2-(1-N,N-heptamethylene-imino)-propyl]-3-nitro-guanidine,
1-[3-(1-N,N-heptamethylene-imino)-propyl]-3-nitro-guanidine,
1-[2-(1-N,N-octamethylene-imino)-ethyl]-3-nitro-guanidine and the like, and
1-[2-(1-N,N-hexamethylene-imino)-ethyl]-3-nitroso-guanidine,
1-[3-(1-N,N-hexamethylene-imino)-propyl]-3-nitroso-guanidine,
1-{2-[1-N,N-(3-methyl-hexamethylene)-imino]-ethyl}-3-nitroso-guanidine,
1-[2-(1-N,N-heptamethylene-imino)-ethyl]-3-nitro-guanidine,
1-[2-(1-N,N-heptamethylene-imino)-propyl]-3-nitroso-guanidine,
1-[3-(1-N,N-heptamethylene-imino)-propyl]-3-nitroso-guanidine,
1-[2-(1-N,N-octamethylene-imino)-ethyl]-3-nitroso-guanidine

and the like, and acid addition salts of such compounds.

Another group of preferred starting materials are those having the formulae:



and



in which R_1', A and the letters m_1 and m_2 have the previously-given meaning, and acid addition salts thereof. Specific starting materials are, for example,

1-[2-(4-methyl-1-piperazino)-ethyl]-3-nitro-guanidine,
1-[3-(4-methyl-1-piperazino)-propyl]-3-nitro-guanidine,
1-[2-(4-ethyl-1-piperazino)-ethyl]-3-guanidine,
1-[2-(4-isopropyl-1-piperazino)-ethyl]-3-nitro-guanidine,
1-{2-[1-N,N-(3-aza-3-methyl-hexamethylene)-imino]-ethyl}-3-nitro-guanidine,
1-{2-[1-N,N-(4-aza-4-methyl-heptamethylene)-imino]-ethyl}-3-nitro-guanidine and the like, and
1-[2-(4-methyl-1-piperazino)-ethyl]-3-nitroso-guanidine,
1-[3-(4-methyl-1-piperazino)-propyl]-3-nitroso-guanidine,
1-[2-(4-ethyl-1-piperazino)-ethyl]-3-nitroso-guanidine,
1-[2-(4-isopropyl-1-piperazino)-ethyl]-3-nitroso-guanidine,
1-{2-[1-N,N-(3-aza-3-methyl-hexamethylene)-imino]-ethyl}-3-nitroso-guanidine,
1-{2-[1-N,N-(4-aza-4-methyl-heptamethylene)-imino]-ethyl}-3-nitroso-guanidine and the like, and acid addition salts of such compounds.

The new 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 a pharmacologically useful acid addition salt thereof by reacting the latter with an appropriate inorganic or organic acid, such as one of those outlined hereinabove; such reaction may be carried out, for example, by treating a solution of the base in a suitable solvent or solvent mixture with the acid or a solution thereof and isolating the desired salt. Salts of the polybasic compounds of this invention may be obtained, in which not all of the salt-forming basic groups participate in the salt formation. Such salts may then be treated with an acid in order to form compounds, in which all or a greater number of the basic groups take part in the salt formation.

Acyl derivatives of the compound of this invention, i.e., compounds of the previous formula, in which one of the groups R_3 and R_5, may be prepared, for example, by treating the amino-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 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 treating the amine-guanidine compound or a salt thereof with the acylating reagent, for example, acetic acid anhydride in a sealed tube.

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.

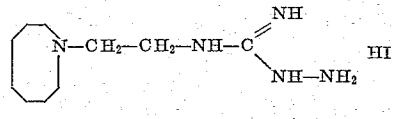
In the process of this invention such starting materials are preferably used which lead to final products mentioned in the beginning as preferred embodiments of the invention.

This is a continuation-in-part application of my application Serial No. 76,480, filed December 19, 1960, and 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 3.12 g. (0.02 mol) of 2-(N,N-heptamethylene-imino)-ethyl-amine and 4.66 g. (0.02 mol) of S-methyl-2-isothiosemicarbazide hydriodide in 10 ml. water is refluxed for four hours and is then cooled. The solid material is filtered off and the resulting 3-amino-1-[2-(N,N-heptamethylene-imino)-ethyl]-guanidine hydriodide of the formula:



is recrystallized from a mixture of ethanol and diethyl-ether, M.P. 129–131°; yield: 3 g.

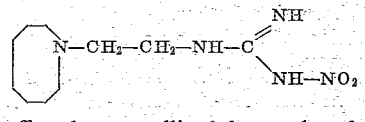
The starting material used in the above reaction may be prepared as follows: To a solution of 73 g. of chloroacetonitrile in 500 ml. of benzene are added 51.5 g. of anhydrous sodium carbonate and a solution of 109.2 g. of N,N-heptamethyleneimine in 250 ml. of benzene. The reaction mixture is refluxed for four hours while stirring. After cooling, filtering and concentrating under reduced pressure, the oily residue is distilled to yield the colorless (1-N,N-heptamethyleneimino)-acetonitrile, B.P. 114–118°/14 mm.; yield: 127.5 g.

To a suspension of 44.5 g. of lithium aluminum hydride in 2000 ml. of ether is added a solution of 127.5 g. of (1-N,N-heptamethyleneimino)-acetonitrile in 300 ml. of ether while cooling. After completing the addition, the solution is refluxed for three hours and stirring is continued overnight. In succession, 40 ml. of water, 50 ml. of 20% aqueous sodium hydroxide and 125 ml. of water are added while cooling. The reaction mixture is filtered, the filtrate is concentrated under reduced pressure, and the desired 2-(1-N,N-heptamethyleneimino)-ethylamine is distilled, B.P. 108–111°/14 mm.; yield: 115.7 g.

Example 2

12 g. of 1-[2-(N,N-heptamethylene-imino)-ethyl]-3-nitro-guanidine and 17 g. of zinc dust are mixed in a mortar with water to form a thick paste, which is then added to 5 ml. of acetic acid while stirring. The temperature is held between 0° and 10° during the mixing of the reagents and is then allowed to slowly rise to room temperature. The reaction mixture is then warmed to 40° on the steam bath and held at that temperature for fifteen minutes. The solid material is filtered off, the filtrate is concentrated under reduced pressure to yield an acetate salt of 3-amino-1-[2-(N,N-heptamethylene-imino)-ethyl]-guanidine, which is converted to the product of Example 1 by treatment with 6 N hydriodic acid.

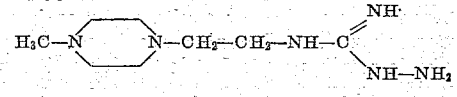
The starting material is prepared as follows: A mixture of 5.2 g. (0.033 mol) of 2-(N,N-heptamethylene-imino)-ethylamine and 3.6 g. (0.027 mol) of S-methyl-1-nitro-2-isothiourea in 100 ml. of ethanol is refluxed for four hours. After cooling 5.2 g. of 1-[2-(N,N-heptamethylene-imino)-ethyl]-3-nitro-guanidine of the formula:



is filtered off and recrystallized from ethanol, M.P. 181–183°.

Example 3

A mixture of 10 g. of 2-(4-methyl-1-piperazino)-ethyl-amine and 16.3 g. of S-methyl-2-isothiosemicarbazide hydriodide in 25 ml. of water is refluxed for four hours and then concentrated to dryness. The residue is recrystallized from a mixture of ethanol and diethyl ether yields the 3-amino-1-[2-(4-methyl-1-piperazino)-ethyl]-guanidine hydriodide of the formula:



which melts at 169–172°.

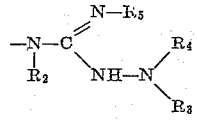
The starting material may be prepared as follows: 50.4 g. of chloroacetonitrile is added dropwise to a solution of 133 g. of 4-methyl-piperazine in 100 ml. of ethanol. The mixture is refluxed, stirred for two hours and allowed to stand overnight. The solution is concentrated under reduced pressure, the residue is treated with 270 ml. of 30 percent aqueous sodium hydroxide while cooling and then extracted with ether. The ether phase is dried over solid sodium hydroxide, the solvent is removed, and the residue fractionated to yield the 4-methyl-piperazino-acetonitrile, B.P. 120–125°/12 mm. The product solidifies upon standing, M.P. 53–56°.

A solution of 50 g. of 4-methyl-piperazino-acetonitrile in 400 ml. of anhydrous ether is added to 1000 ml. of anhydrous ether containing 19 g. of lithium aluminum hydride while cooling and stirring. The reaction mixture is then refluxed for 6 hours, allowed to stand overnight and decomposed by successive addition of 17 ml. of water, 20 ml. of 20 percent aqueous sodium hydroxide and 53 ml. of water. The mixture is filtrated, the filtrate is evaporated and the residue is distilled to yield the desired 2-(4-methyl-1-piperazino)-ethylamine, B.P. 90–92°/16 mm.

What is claimed is:

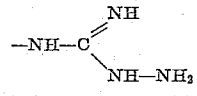
1. A member selected from the group consisting of a 1-R-lower alkyl-3-amino-guanidine, in which R is N,N-

alkylene-imino, in which alkylene has from four to ten chain carbon atoms, and the amino-guanidino group has the formula

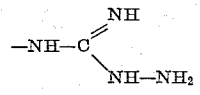


in which each of the groups R_2 and R_4 is a member selected from the group consisting of hydrogen, lower alkyl-phenyl and phenyl-lower alkyl, and each of the groups R_3 and R_5 stands for a member selected from the group consisting of hydrogen, lower alkyl, phenyl, phenyl-lower alkyl, and the acyl group of a lower alkanoic acid, and an acid addition salt of such compound.

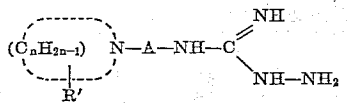
2. 1-R-lower alkyl-3-amino-guanidine, in which R is N,N-alkylene-imino having from six to eight chain carbon atoms, and in which the amino-guanidino group has the formula



3. A pharmacologically acceptable acid addition salt of 1-R-lower alkyl-3-amino-guanidine, in which R is N,N-alkylene-imino having from six to eight chain carbon atoms, and in which the amino-guanidino group has the formula

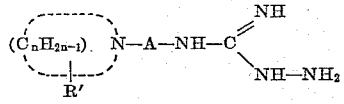


4. A pharmacologically acceptable acid addition salt of a compound of the formula



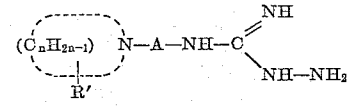
in which R′ is hydrogen, the letter *n* stands for one of the whole numbers 6, 7 and 8, and A is lower alkylene having from two to three carbon atoms and separating the amino-guanidino group from the N,N-alkylene-imino group by from two to three carbon atoms.

5. A compound of the formula



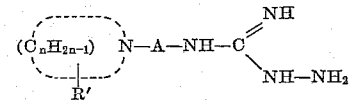
in which R′ is methyl, the letter *n* stands for one of the whole numbers 6, 7 and 8, and A is lower alkylene having from two to three carbon atoms and separating the amino-guanidino group from the N,N-alkylene-imino group by from two two three carbon atoms.

6. A pharmacologically acceptable acid addition salt of a compound of the formula



in which R′ is methyl, the letter *n* stands for one of the whole numbers 6, 7 and 8, and A is lower alkylene having from two to three carbon atoms and separating the amino-guanidino group from the N,N,-alkylene-imino group by from two to three carbon atoms.

7. A compound of the formula:

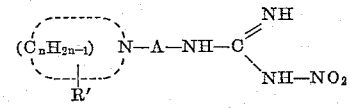


in which R′ is hydrogen, the letter *n* stands for one of the whole numbers 6, 7 and 8, and A is lower alkylene having from two to three carbon atoms and separating the amino-guanidino group from the N,N-alkylene-imino group by from two to three carbon atoms.

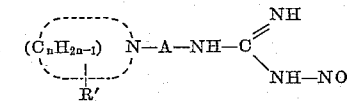
8. 3 - amino - 1 - [2 - (N,N - heptamethylene-imino)-ethyl]-guanidine.

9. 3 - amino - 1 - [2 - (N,N-heptamethylene-imino)-ethyl]-guanidine hydriodide.

10. A member selected from the group consisting of compound having one of the formulae:



and



in which R′ is a member selected from the group consisting of hydrogen and methyl, the letter *n* stands for one of the whole numbers 6, 7 and 8, and A is lower alkylene having from two to three carbon atoms and separating the nitro-guanidine and nitroso-guanidine groups from the N,N-alkylene-imino group by from two to three carbon atoms, and acid addition salts thereof.

11. 1 - [2 - (N,N - heptamethylene - imino) - ethyl]-3-nitro-guanidine.

No references cited.

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