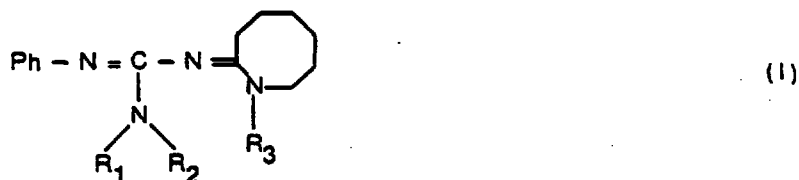


The present invention relates to new guanidine compounds substituted by an N-heterocycle containing an 8-membered ring.

In Belgian Patent Application No. 852,565, guanidines are described which have an N-heterocyclic substituent containing 5, 6 or 7 ring members and which are hypoglycaemically active. The guanidines according to the invention have the advantage that, combined with approximately equivalent hypoglycaemic activity, they have a shorter half life and also no undesired gluconeogenesis-inhibiting action. Shorter half lives in hypoglycaemic activity and the absence of a gluconeogenesis-inhibiting action are nowadays considered as desirable advantages in the world of the specialist.

The invention relates to new guanidine derivatives of the formula I



wherein Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, hydroxyl, mercapto, lower alkoxy, lower alkenyloxy, lower alkylendioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, dilower alkylamino, sulfamoyl, lower alkylsulfamoyl, dilower alkylsulfamoyl, carboxyl or lower alkoxycarbonyl, R_1 and R_2 independently of one another denote lower alkyl or cycloalkyl having at most 10 carbon atoms or both taken together denote a bivalent hydrocarbon radical of aliphatic character optionally substituted by lower alkyl or phenyl, having 4-7 carbon atoms in the chain, in which the carbon atoms of the chain can be interrupted by oxygen, sulfur or nitrogen, R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts.

In connection with the present description, the radicals and compounds designated with "lower" preferably contain up to 7, primarily up to 4 carbon atoms.

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In the preceding as in the following, the general terms may have the following meaning:

R_1 , R_2 and R_3 as lower alkyl radicals, for example, denote straightchain or branched lower alkyl radicals and can be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl and also n-heptyl radicals.

A cycloalkyl group is primarily a monocyclic radical having 3-10 carbon atoms, preferably having 5-7 carbon atoms and is, for example, a cyclopropyl, cyclobutyl, preferably a cyclopentyl, cyclohexyl and also cycloheptyl group.

The two substituents R_1 and R_2 taken together can denote a substituted bivalent aliphatic hydrocarbon radical having 4-7 carbon atoms in the chain and optionally substituted by a substituent from the series comprising lower alkyl or optionally substituted phenyl. The $-NR_1R_2$ group is, for example, lower alkyleneamino, in which the lower alkylene chain can be interrupted, for example, by a heteroatom, such as, for example, oxygen, sulfur or nitrogen which is optionally substituted by a substituent from the series comprising lower alkyl, optionally substituted phenyl, benzyl, phenylethyl or alkoxycarbonyl, such as, for example, methoxycarbonyl or ethoxycarbonyl, and represents, for example, lower alkyleneamino, for example pyrrolidino, 2,5-dimethylpyrrolidino, piperidino, 2-methyl-, 4-methyl- or 4-phenylpiperidino, hexahydroazepino or octahydroazocino, oxalower alkyleneamino, for example morpholino, 2,6-dimethylmorpholino, thialower alkyleneamino, for example thiomorpholino or 2,6-dimethylthiomorpholino and azalower alkyleneamino, for example piperazino, N-methyl-, N-phenyl-, N-benzyl-, N-methoxycarbonyl or N-ethoxycarbonylpiperazine.

Ph or a previously mentioned optionally substituted phenyl radical can be substituted by one, two or more identical or different substituents.

Such substituents are as mentioned for Ph under formula I, for example lower alkyl, hydroxyl or mercapto, lower alkoxy, lower alkenyloxy or

lower alkylenedioxy, furthermore lower alkylthio or halogen, trifluoromethyl, nitro, amino, lower alkylamino or dilower alkylamino, sulfamoyl, lower alkylsulfamoyl or diloweralkylsulfamoyl, carboxy or lower alkoxy-carbonyl.

The lower alkyl radicals suitable as substituents are previously defined for R_1 , R_2 and R_3 .

Lower alkoxy is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy or n-pentyloxy, and lower alkenyloxy for example vinyloxy or allyloxy.

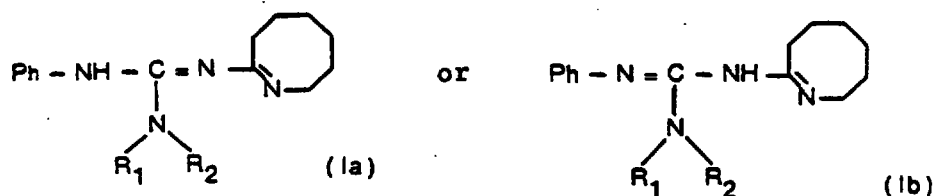
Halogen atoms are primarily fluorine, chlorine or bromine atoms, but can also be iodine atoms.

Lower alkylthio is in particular methylthio, furthermore also ethylthio, isopropylthio, n-propylthio and also straight or branched butylthio.

Lower alkylamino or dilower alkylamino is, for example, methylamino, dimethylamino, ethylamino, diethylamino, n-propylamino, di-n-propylamino, isopropylamino, di-isopropylamino or n-butylamino or di-n-butylamino.

Lower alkylsulfamoyl or dilower alkylsulfamoyl is, for example, methylsulfamoyl, dimethylsulfamoyl, ethylsulfamoyl, diethylsulfamoyl, n-propylsulfamoyl, di-n-propylsulfamoyl, isopropylsulfamoyl, diisopropylsulfamoyl, n-butylsulfamoyl or di-n-butylsulfamoyl.

The new compounds according to the present invention can be present as tautomers, based on the present tautomerism in the case of the meaning of R_3 = hydrogen. The tautomers can be represented by the formulae



The new compounds of the general formula I and their addition salts with inorganic or organic acids possess valuable pharmacological properties, in particular hypoglycaemic activity, as can be detected in metabolically normal rats after oral administration of doses from 10 mg/kg and also in rats which have been converted into a diabetes-like metabolic state by injection of streptozotocin [compare A. Junod et al., Proc. Soc. Exp. Biol. Med. 126, 201-205 (1967)]. The lowering of the blood sugar level is not accompanied by hyperlactataemia. Analogous actions can also be detected in guinea pigs, hamsters and rhesus monkeys. The pharmacological findings characterize the new compounds of the general formula I and their pharmaceutically acceptable acid addition salts as antidiabetics which can be used for the oral treatment of hyperglycaemia, in particular Diabetes mellitus, in mammals.

The invention relates primarily to compounds of the formula I in which Ph denotes an optionally substituted phenyl radical, R_1 and R_2 independently of one another denote a lower alkyl radical, for example methyl or ethyl or cycloalkyl, such as, for example, cyclopentyl, cyclohexyl or cycloheptyl, or both taken together denote a bivalent hydrocarbon radical of aliphatic character having 4 - 7 carbon atoms in the chain and optionally substituted by a substituent from the series comprising lower alkyl or phenyl, in which the carbon atoms of the chain can be interrupted by a heteroatom, R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts.

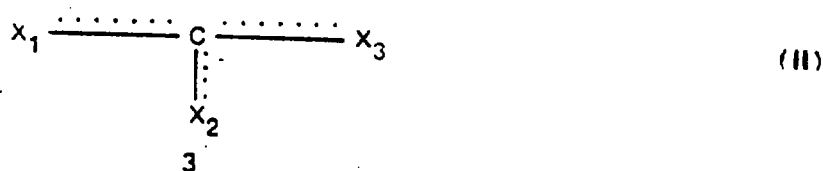
In particular, the invention relates to those compounds of the formula I in which Ph denotes phenyl which is optionally substituted by a substituent from the series comprising lower alkyl, lower alkoxy, halogen or trifluoromethyl, R_1 and R_2 both taken together denote a lower alkylene chain which is optionally substituted by a substituent from the series comprising lower alkyl or phenyl, in which the carbon atoms of the chain can be interrupted by a heteroatom, such as, for example, oxygen, sulfur or nitrogen which is optionally substituted by lower alkyl, phenyl, benzyl, phenylethyl and also alkoxycarbonyl, and R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts.

Of particular interest are compounds of the formula I in which Ph denotes phenyl which is optionally substituted by a substituent from the series comprising lower alkyl, lower alkoxy, halogen or trifluoromethyl, the $-NR_1R_2$ group for example denoting a lower alkyleneamino substituted by a substituent from the series comprising lower alkyl or phenyl, in which the lower alkylene chain can be optionally interrupted by oxygen, sulfur or nitrogen which is optionally substituted by a substituent from the series comprising lower alkyl, phenyl or alkoxycarbonyl, and can be, for example, pyrrolidino, 2,5-dimethylpyrrolidino, piperidino, 2-methyl-, 4-methyl- or 4-phenylpiperidino, hexahydroazepino, morpholino, 2,6-dimethylmorpholino, thiomorpholino, 2,6-dimethylthiomorpholino, piperazino, N-methyl-, N-phenyl-, N-benzyl-, N-methoxy- or N-ethoxycarbonylpiperazine, and R_3 denotes hydrogen and also lower alkyl, and their tautomeric compounds and salts.

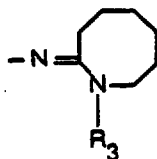
Of very particular interest are compounds of the formula I in which Ph denotes phenyl which is optionally substituted by a substituent from the series comprising lower alkyl, such as, for example, methyl or ethyl, lower alkoxy, such as, for example, methoxy or ethoxy, halogen, such as, for example, chlorine or bromine or trifluoromethyl, the $-NR_1R_2$ group denotes, for example, lower alkyleneamino which is substituted by a substituent from the series comprising lower alkyl, such as, for example, methyl or ethyl, or phenyl, in which the lower alkylene chain can optionally be interrupted by oxygen or nitrogen which is optionally substituted by a substituent from the series comprising lower alkyl, such as, for example, methyl or ethyl, alkoxycarbonyl, such as, for example, methoxycarbonyl or ethoxycarbonyl, and can be, for example, pyrrolidino, piperidino, 4-methyl- or 4-phenylpiperidino, morpholino, 2,6-dimethylmorpholino, piperazino, N-methyl or N-methoxycarbonylpiperazine, and R_3 denotes hydrogen and also lower alkyl, such as, for example, methyl or ethyl, and their tautomeric compounds and salts.

The new guanidines of the formula I are obtained by methods known per se.

Thus, for example, the new compounds of the formula I can be obtained by reacting a compound of the formula II



wherein X_1 denotes the Ph-N= group in which Ph denotes an optionally substituted phenyl radical, or a removable group, X_2 denotes the $-\text{NR}_1\text{R}_2$ group, wherein R_1 and R_2 have the meaning indicated under formula I, or a removable group, and X_3 denotes the group



wherein R_3 has the meaning indicated under formula I, or denotes a removable group, with the proviso that only one of the substituents X_1 , X_2 or X_3 can be a removable group, and wherein one of the groups X_1 , X_2 or X_3 is bonded to the carbon atom by a double bond, with an amine or imine which corresponds to the missing amino or imino groups, which are defined under X_1 , X_2 or X_3 , in order to replace the removable group, and, if desired, carrying out additional process steps, and/or, if desired, converting compounds obtained into a salt, and/or, if desired, converting obtained salts of the compounds of the formula I into the free bases.

Removable groups X_1 , X_2 or X_3 designate, as already indicated above, the groups replaceable by an amino or imino group, and preferably denote lower alkylthio groups, such as, for example, methylthio or ethylthio, lower alkoxy, such as, for example, methoxy or ethoxy, and also halogen, such as, for example, chlorine or bromine.

Compounds of the general formula II are, according to whether X_1 , X_2 or X_3 denotes the removable group, either compounds of the formula IIa



wherein X_1 denotes a removable group, R_1 , R_2 and R_3 have the above-mentioned meanings, or compounds of the formula IIb



wherein X_2 denotes a removable group, Ph, R_3 have the abovementioned meanings, or compounds of the formula IIc



wherein X_3 denotes a removable group, Ph, R_1 and R_2 have the above-mentioned meanings, and their tautomeric forms, or their acid addition salts.

According to whether X_1 , X_2 or X_3 is present in a compound of the formula II as the removable group, a compound of the formula IIb is reacted with amine of the formula HNR_1R_2 , a compound of the formula IIc is reacted with an imino compound of the formula III



or a compound of the formula IIa is reacted with an optionally substituted aniline of the formula Ph-NH_2 . Compounds of the formula IIa, IIb and IIc can also be used as acid addition salts, preferably as hydrohalides. In an analogous manner, the amines, imino compounds and also anilines can be reacted as acid addition salts, preferably as hydrohalides.

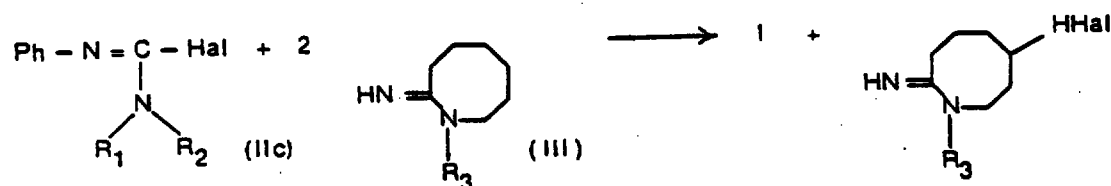
The reaction of a compound of the formula II i.e. in particular a compound of the formula IIa, IIb or IIc for example with a previously mentioned amine or imine as the free base takes place using a stoichiometric excess of the amine or imine, for example in a molar ratio of

1:1.05 to 1:2.0. When using only a small excess of the amine or imine as the free base or when using the amine or imine as the acid addition salt it is expedient to add additionally a stoichiometrically equivalent amount of a tertiary amine, such as, for example, triethylamine or N-ethyldiisopropylamine.

If, for example, an imino compound of the formula (III)



is reacted as the free base with a compound of the formula IIc, in which X₃ denotes a halogen, then 2 molar equivalents or more of the free base of the abovementioned imino compound are preferably used. According to the following equation



one equivalent of the imino compound is formed as the acid addition salt. For this reason, the reaction is preferably carried out in an aprotic solvent in which the compound of the formula I obtained is soluble, whereas the addition salt of the hydrohalic acid precipitates as an insoluble compound according to the above equation. In this manner, the two reaction products obtained can be easily separated from one another.

The acid addition salt of the imino compound obtained is converted into the free base by basic hydrolysis, for example by the addition of alkali metal or alkaline earth metal hydroxide or carbonate and can herewith be recovered as a starting product for further use. Preferably, however, compounds of the formula IIc and III are reacted as acid addition salts, for example as halides, in the presence of an additional tertiary alkylamine as given above, such as, for example, triethylamine or N-ethyldiisopropylamine.

The described reactions of compounds of the formula IIc with an imino compound of the formula III preferably take place, as already mentioned, in aprotic solvents. Examples of preferred utilizable solvents are ethers, such as, for example, diethyl ether and tetrahydrofuran, lower aliphatic ketones and esters, such as, for example, acetone, methyl ethyl ketone and ethyl acetate, aromatic hydrocarbons, such as, for example, benzene, toluene or xylene, and also acetonitrile. However, the reaction is particularly preferably carried out in diethyl ether or acetonitrile. The reactions can be carried out at a temperature between 0-150°C, preferably, however, between room temperature and the reflux temperature of the reaction mixture.

If, however, for example a compound of the formula IIb



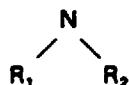
is used as a starting compound of the formula, then X_2 as the removable group preferably has the meaning of a lower alkoxy or lower alkylthio group. Starting compounds of the formula IIb are reacted in the form of their salts, for example in the form of their acid addition salts, with a hydrohalic acid with an amine of the formula HNR_1R_2 as the free base or as the acid addition salt, in which R_1 and R_2 have the previously indicated meaning.

The reactions are carried out, for example, in an alcohol as the solvent, preferably in a lower alcohol, such as, for example, ethanol, isopropanol or tert.-butanol, particularly preferably, however, in an ether, such as, for example, diethyl ether or tetrahydrofuran, or in acetonitrile, at temperatures from room temperature preferably up to the reflux temperature of the reaction mixture. The reactions can be carried out at higher temperatures, however, in a closed reaction vessel under pressure, such as, for example, in a bomb tube or in an autoclave. The guanidine derivatives of the general formula I are obtained in the form of their salts, which, for example, can be converted into the corresponding free bases by

alkaline hydrolysis. When reacting the compounds of the general formula IIb with the amine of the general formula HNR_1R_2 , the amine is preferably used in a stoichiometric excess, for example in a molar ratio of 1:1.05 to 1:2.0 and more. When using only a small excess of the amine or of an acid addition salt, it can be expedient to add an additional stoichiometrically equivalent amount of a tertiary alkylamine, such as, for example, triethylamine or N-ethyldiisopropylamine, in order to increase the rate of reaction.

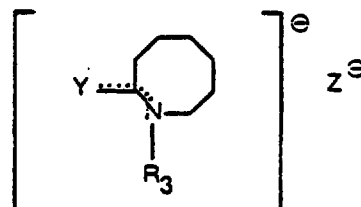
The reactions of compounds of the formula IIa having a removable group X_1 which preferably denotes lower alkoxy or lower alkylthio in addition to the meaning of a halogen atom, or their tautomeric forms with an optionally substituted aniline as the free base take place in a similar manner to that described in the reaction of a compound of the formula IIb with an amine of the formula HNR_1R_2 . The reactions are advantageously also carried out in a stoichiometric excess of the optionally substituted aniline. When using only a small excess of the aniline or of an acid addition salt thereof, it can be expedient to add a stoichiometrically equivalent amount of a tertiary trialkylamine already defined above. The reactions are carried out in solvents analogous to those which have already been described for the reaction of the compounds IIc with compounds of the formula III.

Compounds of the general formula I can also be prepared by reacting a guanidine compound of the general formula IV



(IV).

wherein Ph, R_1 and R_2 have the meanings indicated under formula I, with a compound of the general formula V



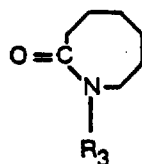
(V).

wherein Y denotes lower alkoxy, lower alkylthio, halogen, or Y denotes two lower alkoxy groups, which are sited on equivalent C atoms, and Z denotes a tetrafluoroborate, a fluorosulfonate, a lower alkyl sulfate, such as, for example, methyl sulfate or lower alkanesulfonate, such as, for example, methanesulfonate anion or a halide, such as, for example, chloride or bromide, in which, when Y has the meaning of two lower alkoxy groups on the equivalent C atom, Z escapes as the anion, or, when R_3 denotes hydrogen, the tautomeric form is present as the free base, and, if desired, by converting compounds of the formula I obtained into a salt, and/or, if desired, converting salts of the compounds of the formula I obtained into the free compounds.

The compounds of the general formula I are expediently prepared by bringing a lactam salt of the previously indicated formula V to reaction with a guanidine derivative of the above-defined formula IV in stoichiometric amounts. The reactions are preferably carried out in a water-free organic solvent. Organic solvents are, for example, lower alcohols, such as, for example, methanol, ethanol, isopropanol, tert.-butanol, ethers, such as, for example, diethyl ether, tetrahydrofuran or dioxane, lower halogenated hydrocarbons, such as, for example, chloroform, methylene chloride or 1,2-dichloroethane, and aromatic hydrocarbons, such as, for example, benzene, toluene or xylene. In general, the reaction is carried out at temperatures which lie between -20°C and $+50^{\circ}\text{C}$, but preferably between 0°C and room temperature.

The reaction product of the general formula I obtained in salt form is converted into the free base by basic hydrolysis, for example by addition of a hydroxide or carbonate of an alkali metal or alkaline earth metal.

The lactam fluoroborates or fluorosulfonates of the general formula V employed according to the process, in which $Z^{\ominus}$ represents, for example, the tetrafluoroborate group of the formula BF_4^- or fluorosulfonate group of the formula $\text{OSO}_2\text{F}^{\ominus}$, can be prepared according to customary processes, by reacting a lactam of the formula Va



(Va)

with a suitable trialkyloxonium fluoroborate or a fluorosulfonic acid lower alkyl ester to give the corresponding lactam salt of the general formula V.

The reaction is carried out, for example, at temperatures of between -20°C and $+50^{\circ}\text{C}$, preferably at temperatures between 0°C and $+25^{\circ}\text{C}$ in an inert gas, such as, for example, nitrogen or argon, and in the presence of an inert, water-free organic solvent, for example in a lower halogenated hydrocarbon, such as, for example, chloroform, 1,2-dichloroethane or preferably methylene chloride. Examples of other utilizable organic solvents are ethers, such as, for example, diethyl ether, dioxane, tetrahydrofuran or 1,2-dimethoxyethane, and also aromatic hydrocarbons, such as, for example benzene, toluene or xylene.

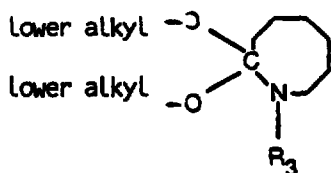
The 2-lower alkyl thiolactim ethers falling under the general formula V can be prepared by reaction of the lactam of the general formula Va with phosphorus pentasulfide in an analogous manner to that described by R. Gomper et al., Org. Syn. Coll., vol. V, pages 780-785. When carrying out this reaction, a thiolactam is initially obtained which by reaction with an alkylating agent yields the 2-alkylthiolactim ether in the form of the corresponding salt. As the alkylating agent, an alkyl halide, for example methyl iodide, a fluorosulfonate alkyl ester, such as, for example, methylfluorosulfonate, a methanesulfonic acid alkyl ester, such as, for example, methyl methanesulfonate, a toluenesulfonic acid alkyl ester, such as, for example, methyl toluenesulfonate, or dimethyl sulfate can be used. The reaction of the lactim ether salts with the guanidine derivative of the general formula IV yields the corresponding salts of the general formula I.

When reacting the previously described lactam fluorosulfonate of the general formula V with the guanidines of the general formula IV,

quaternary ammonium salts of the compounds of the general formula I can also be formed as side reactions.

The methylsulfate salts also falling under the general formula V are obtained from lactams of the general formula Va by reaction with dimethyl sulfate in an analogous manner to that described by H. Brederick et al., Chem. Ber. Vol. 96 (1963), p. 1350 for pyrrolidones. The reaction is preferably carried out in a water-free, inert organic solvent, for example an aromatic hydrocarbon, such as, for example, benzene, toluene or xylene, an ether, such as, for example, diethyl ether, dioxane or tetrahydrofuran, or a halogenated aliphatic hydrocarbon, such as, for example, 1,2-dichloroethane or chloroform. The methosulfate of the general formula V obtained is then converted in the previously described manner to the corresponding lower alkylsulfate salt, such as, for example, methylsulfate salt of the compound of the general formula I with the corresponding guanidine derivative of the general formula IV. The salts obtained can be converted into the corresponding free base of the general formula I by treatment with a hydroxide or carbonate of an alkali metal or alkaline earth metal.

From the lower alkylsulfate salts, such as, for example, methylsulfate salt of the general formula V, the corresponding lactam acetal of the formula Vb



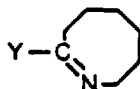
(Vb)

can be prepared, for example, by reaction with a metal alkoxide, preferably an alkali metal alkoxide, such as, for example, sodium methoxide or ethoxide, in a suitable water-free lower alcohol.

From the lactam acetals, as described previously, the free bases of the general formula I can be prepared with the guanidine derivatives of the general formula IV.

The halide, in particular chloride salts of the lactams of the general formula V used according to the process can be prepared in an analogous manner to that described by W. Jentsch and M. Seefelder, Chem. Ber., Vol. 98 (1965), p. 274 for pyrrolidones, by reaction of a lactam of the general formula Va with phosgene or thionyl chloride.

As already mentioned previously, the free bases of the general formula V can also be used for the preparation of the compounds of the general formula I, in which R₃ denotes a hydrogen atom. The reaction of the salts of the general formula V with a base, such as, for example, a hydroxide or carbonate of an alkali metal or alkaline earth metal, preferably in a halogenated aliphatic hydrocarbon as the solvent, such as, for example, methylene chloride or chloroform, yields the free bases of the general formula Vc

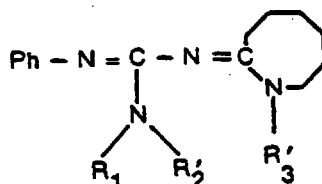


(Vc)

The compounds of the formula I according to the invention, in which R₁ has the above-defined meaning and R₂ and/or R₃ denote hydrogen, can be converted into compounds of the formula I, in which R₂ and/or R₃ in the context of the preceding definition for R₂ and R₃ are other than from hydrogen, by a third process by reaction with a reactive ester of a lower alkanol or, if appropriate, cycloalkanol, and, if desired, additional process steps can be carried out, and/or, if desired, compounds of the formula I obtained can be converted into a salt, and/or, if desired, salts of compounds of the formula I obtained can be converted into the free bases.

As reactive esters, a lower alkyl or cycloalkyl halide, for example, such as, for example, methyl or cyclohexyl iodide, a suitable fluorosulfonic acid alkyl ester, such as, for example, methyl fluorosulfonate, a suitable lower alkanesulfonic acid ester, such as, for example, methyl methanesulfonate, a suitable toluenesulfonic acid alkyl ester, such as, for example, methyl toluenesulfonate, or a dialkyl sulfate, such as, for example, dimethyl or diethyl sulfate, can be used as the so-called alkylating agent.

The compounds of the formula I according to the invention, in which R_2 and/or R_3 denote hydrogen, can be prepared by a fourth process, in compounds of the general formula VI



wherein R_1 and Ph have the meaning indicated under the formula I and one of the substituents R'_2 and R'_3 has the meaning of R_2 or R_3 , and the other denotes an amino-protecting group, or both R'_2 and R'_3 denote an amino-protecting group, by cleaving these off and, if desired, carrying out additional process steps, and/or, if desired, converting compounds of the formula I obtained into a salt, and/or, if desired, converting salts of compounds of the formula I obtained into the free bases.

An amino-protecting group R'_2 or R'_3 is primarily an acyl group, such as acyl of an aliphatic, aromatic or araliphatic carboxylic acid, in particular lower alkanoyl, for example acetyl or propionyl, or aroyl, for example benzoyl or acyl of formic acid or a carbonic acid half derivative, for example of an ester, such as formyl, lower alkoxy-carbonyl, for example ethoxycarbonyl or tert.-butoxycarbonyl, or aryl lower alkoxy-carbonyl, for example benzyloxycarbonyl.

The removal of an acyl radical used as the amino-protecting group R'_2 and/or R'_3 takes place in a manner known per se, for example by solvolysis, primarily by means of alcoholysis, furthermore by means of hydrolysis. The alcoholic removal of an acyl radical R'_2 and/or R'_3 can take place, for example, in the presence of a strongly basic agent, at elevated temperature, for example at about 50°C to about 120°C. In this case, a lower alkanol, for example n-butanol or ethanol is used and an alkali metal lower alkoxide, for example sodium lower alkoxide or potassium lower alkoxide, for example n-butoxide or ethoxide, or an alkali

metal hydroxide, for example sodium hydroxide or potassium hydroxide is used as the strong base.

Amino-protecting groups R'₂ and R'₃, for example lower alkoxycarbonyl groups such as tert.-butoxycarbonyl, can be particularly mildly removed acidolytically, for example by treating with trifluoroacetic acid.

A further, particularly mildly removable amino-protecting group is an ethoxy-carbonyl group which carries a silyl group substituted in the β -position with three hydrocarbon radicals, such as triphenylsilyl, dimethyl-butyl-silyl or, above all, trimethylsilyl groups. Such a β -(trimethylsilyl)-ethoxycarbonyl group forms a corresponding β -trimethylsilyl-ethoxycarbonylamino group with the amino group to be protected, which can be removed under mild conditions by the action of fluoride ions. Suitable fluoride ion-releasing reagents are, for example, fluorides of quaternary organic bases, such as tetraethylammonium fluoride.

It is thus to be observed that, as amino-protecting groups R'₂ and/or R'₃, only those which are selectively removable while maintaining the structure of the compounds of the general formula I are suitable.

The starting materials are known, or if they are new, can be prepared by methods which are known per se. Where it proves appropriate, the starting products used have already been described in connection with the process described.

Compounds of the general formula IIb, in which X₂ denotes a lower alkylthio group, can be prepared, for example, from the corresponding thio-ureas of the general formula VII



by reacting this with a previously enumerated active ester of a lower alkanol.

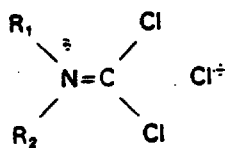


with an amine of the formula HNR_1R_2 , in the presence of a trialkylamine, such as, for example, triethylamine, in an inert aprotic, water-free solvent. Compounds of the formula VIII can also be present as immonium chlorides. An ether, for example diethyl ether, dioxane or tetrahydrofuran, a halogenated aliphatic hydrocarbon, such as, for example, chloroform or methylene chloride, or an aromatic hydrocarbon, such as, for

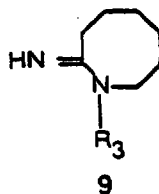
example, benzene, toluene or xylene is used as the solvent. Compounds of the general formula VIII are known and can be prepared in an analogous manner to that described in Angew. Chem., Intern. Ed. vol. 6 (1967), p. 649.

Compounds of the general formula IIc, in which the removable group X_3 denotes halogen, can easily be converted in a known manner into compounds of the formula IIc in which X_3 denotes a lower alkoxy group.

Starting compounds of the general formula IIa, in which the removable group X_1 denotes a halogen, preferably chlorine, can be prepared by reaction of an immonium chloride of the formula



with an imino compound of the formula III



(III)

by the method described by R.G. Glushkow, Khim.-Farmasevt. Zh. 12, No. 6, 59-64/1978.

The reaction takes place in an analogous manner to that described above for the reaction of a compound of the formula VIII.

Compounds of the general formula VI can be prepared by one of the processes described previously for the preparation of compounds of the general formula I, in which, however, R_2 and/or R_3 denote an acyl radical in the starting compounds used. These acyl radicals used as amino-protecting groups are as defined above.

The process described can be carried out in the customary manner at room temperature, with cooling or warming, at normal pressure or elevated pressure and, if necessary, in the presence or absence of a diluent,

catalyst, or condensing agent. If necessary, the reactions can also take place in the atmosphere of an inert gas, such as, for example, nitrogen.

In the context of the definition of the final products, substituents can be introduced, altered, or removed, in the compounds obtained.

Depending on the process conditions and starting materials, the final substance is obtained in free form or, as is also included in the invention, in the form of its salts, in particular acid addition salts. The acid addition salts of the new compounds can be converted into the free compound in a manner known per se, for example with basic agents, such as alkalis or ion exchangers. On the other hand, the free bases obtained can form salts with organic or inorganic acids. For the preparation of acid addition salts, those acids in particular are used which are suitable for the formation of therapeutically utilizable salts. Those acids which may be mentioned as examples are: hydrohalic acids, sulfuric acids, phosphoric acids, nitric acid, perchloric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic or pyruvic acid; phenylacetic, benzoic, p-aminobenzoic, anthranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid, embonic acid, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic acid; halobenzenesulfonic, toluenesulfonic, naphthalenesulfonic acid or sulfanilic acid; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds, such as, for example, the picrates, can also be used for the purification of the free bases obtained, by converting the free bases into salts, separating these off and releasing the bases from the salts again. As a result of the close relations between the new compounds in the free form and in the form of their salts, in the foregoing and the following the free compounds are also analogously and expediently taken to mean, if appropriate, the corresponding salts.

The invention also relates to those embodiments of a process in which a

process is discontinued at any step or in which the starting compound is a compound obtainable as an intermediate at any step and the missing steps are carried out, or a starting material is formed under the reaction conditions or, if appropriate, used in the form of a salt. The invention also comprises new intermediates resulting therefrom.

Therapeutic combinations are also comprised by the invention, which consist of a hypoglycaemically active content of the compounds of the general formula I or an acid addition salt and a pharmacologically acceptable solid excipient or liquid diluent.

The pharmaceutical preparations according to the invention contain at least one compound of the general formula I or a salt thereof as the active compound together with a customary pharmaceutical excipient. The nature of the excipient is substantially dependent on the area of use. The pharmaceutical combinations according to the invention which contain compounds of the formula I as active substances can be administered orally, parenterally or rectally.

For oral treatment of hyperglycaemia, solid dose unit forms are suitable, such as tablets, dragees and capsules which preferably contain between 10 and 90% of an active compound of the general formula I or a salt in order to facilitate the administration of daily doses of between 1.5 and 100 mg/kg to warm-blooded animals. For the preparation of tablets and dragee cores, the compounds of the general formula I are combined with solid, pulverulent excipients, such as lactose, saccharose, sorbitol, maize starch, potato starch or amylopectin, cellulose derivatives or gelatin, preferably with the addition of lubricants, such as magnesium stearate or calcium stearate, or polyethylene glycols of suitable molecular weight. Dragee cores are subsequently coated, for example, with concentrated sugar solutions, which, for example, can also contain gum arabic, talc and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or solvent mixtures. Colorants can be added to these coatings, for example for the identification of different doses of active compounds. Soft gelatin capsules and other sealed capsules consist, for example, of a mixture of gelatin and glycerol and can

contain, for example, mixtures of a compound of the formula I with polyethylene glycol. Cylindrical capsules contain, for example, granules of an active compound with solid, pulverulent excipients, such as, for example, lactose, saccharose, sorbitol, mannitol; starches, such as potato starch, maize starch or amylopectin, cellulose derivatives and also magnesium stearate or stearic acid.

Possible dosage unit forms for rectal use are, for example, suppositories, which consist of a combination of an active compound having a suppository matrix based on natural or synthetic triglycerides (for example cocoa butter), polyethylene glycols or suitable higher fatty alcohols, and gelatin rectal capsules, which contain a combination of the active compound with polyethylene glycols.

Ampoule solutions for parenteral, in particular intramuscular or intravenous administration, contain a compound of the formula I or a salt thereof in a concentration of preferably 0.5 to 5% as an aqueous dispersion prepared with the aid of customary solubilizers and/or emulsifiers, and also if appropriate stabilizers, or preferably contain an aqueous solution of a pharmaceutically acceptable, water-soluble acid addition salt of a compound of the general formula I.

For liquids for oral administration, such as syrups and elixirs, the concentration of the active compound is selected in such a way that an individual dose can easily be measured, for example as the contents of a teaspoon or a measuring spoon of, for example, 5 ml, and also as multiples of this volume.

The examples a) to e) below are intended to illustrate the preparation of some typical administration forms, but in no way represent the only embodiments thereof.

a) 250.0 g of active compound are mixed with 550.0 g of lactose and 292.0 g of potato starch, and the mixture is moistened with an alcoholic solution of 8 g of gelatin and granulated through a sieve. After drying, 60.0 g of talc, 10.0 g of magnesium stearate and 20.0 g of colloidal

silica are admixed and the mixture is compressed to give 10,000 tablets of 125 mg weight each and 25 mg active compound content which can be provided, if desired, with division notches for finer adjustment of the dosage.

b) Granules are produced from 100.0 g of active compound, 379.0 g of lactose and an alcoholic solution of 6.0 g of gelatin which are mixed, after drying, with 10.0 g of colloidal silica, 40.0 g of talc, 60.0 g of potato starch and 5.0 g of magnesium stearate and compressed to give 10,000 dragee cores. These are subsequently coated with a concentrated syrup of 533.5 g of crystalline saccharose, 20.0 g of shellac, 75.0 g of gum arabic, 250.0 g of talc, 20.0 g of colloidal silica and 1.5 g of colorant and dried. The dragees obtained each weigh 150 mg and each contain 10 mg of active compound.

c) 25.0 g of active compound and 1975 g of finely ground suppository matrix (for example cocoa butter) are thoroughly mixed and then melted. 1000 suppositories of 2.0 g are poured from the melt which is kept homogeneous by stirring. They each contain 25 mg of active compound.

d) For the preparation of a syrup having 0.25 % active compound content, 1.5 litres of glycerol, 42 g of methyl p-hydroxybenzoate, 18 g of n-propyl p-hydroxybenzoate and with slight warming 25.0 g of active compound are dissolved in 3 litres of distilled water, 4 litres of 70% strength sorbitol solution, 1000 g of crystalline saccharose, 350 g of glucose and an aromatizing substance, for example 250 g of "orange peel soluble fluid" from Eli Lilly and Co., Indianapolis, or 5 g of natural lemon aroma and 5 g of "half and half" essence, both from the firm of Haarmann and Reimer, Holzminden, Germany, are added, the solution obtained is filtered and the filtrate is made up to 10 litres with distilled water.

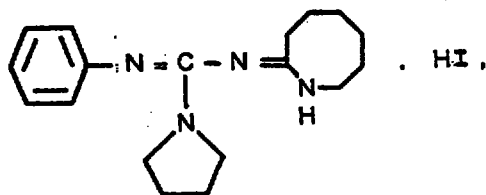
e) For the preparation of a dropping solution having a 1.5% active compound content, 150.0 g of active compound and 30 g of sodium cyclamate are dissolved in a mixture of 4 litres of ethanol (96%) and 1 litre of propylene glycol. On the other hand, 3.5 litres of 70% strength

sorbitol solution are mixed with 1 litre of water and the mixture is added to the above active compound solution. An aromatizing substance, for example 5 g of cough sweet aroma or 30 g of grapefruit essence is added hereto, both from the firm of Haarmann and Reimer, Holzminden, Germany, and the whole is mixed well, filtered and made up to 10 litres with distilled water.

The examples below illustrate the preparation of the new compounds of the general formula I, but are not intended to limit the scope of the invention in any way. The temperatures are indicated in degrees Celcius.

Example 1

4 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine are added to a suspension of 8 g of N-phenyl-1-pyrrolidine-carboximidamide hydroiodide in 30 ml of acetonitrile. The mixture is heated on the water bath for 12 hours with vigorous stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of acetone/ethyl acetate. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-1-pyrrolidinecarboximidamide hydroiodide of the formula



which melts at 242°, is obtained.

The starting material for the above synthesis is prepared as follows: 7 g of pyrrolidine are added to a suspension of 15 g of N-phenyl-S-methyl-isothioureia hydroiodide in 50 ml of acetonitrile. The mixture is heated under reflux for 15 hours with stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of isopropanol/ethyl acetate. N-Phenyl-1-pyrrolidine-carboximidamide hydroiodide, which melts at 165°, is obtained.

Example 2

3 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine are added to a suspension of 6 g of N-phenyl-1-piperidinecarboximidamide hydroiodide in 20 ml of acetonitrile. The mixture is heated under reflux for 12 hours on the water bath and stirred vigorously. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of isopropanol/ ethyl acetate. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-1-piperidinecarboximidamide hydroiodide, which melts at 205°, is obtained.

The starting material is prepared as follows: 8 g of piperidine are added to a suspension of 15 g of N-phenyl-S-methyl-isothioureia hydroiodide in 50 ml of acetonitrile. The mixture is heated under reflux for 15 hours with stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of isopropanol/ ethyl acetate. N-Phenyl-1-piperidinecarboximidamide hydroiodide, which melts at 135°, is obtained.

Example 3

5.6 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine are added to a suspension of 10 g of N-phenyl-4-morpholine-carboximidamide hydroiodide in 15 ml of acetonitrile. The mixture is heated for 12 hours on the water bath with vigorous stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of acetone/ ethyl acetate. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-4-morpholine-carboximidamide hydroiodide, which melts at 260°, is obtained.

The corresponding base and its salts are prepared as follows: 10 ml of 10% strength aqueous sodium hydroxide solution are added to a suspension of 4 g of N-hexahydro-2(1H)-azocinylidene-N'-phenyl-4-morpholine-carboximidamide hydroiodide in 50 ml of methylene chloride with stirring. The organic layer is separated off and evaporated under reduced pressure. The free base is obtained, which melts at 130° after recrystallization from a mixture of methylene chloride/hexane.

Tartrate: 2 g of previously dried and purified d-tartaric acid in acetone are added to a solution of 3.1 g of the free base in 30 ml of acetone. The precipitated product is washed several times with diethyl ether and acetone. The residue is recrystallized from acetone. N-Hexahydro-2(1H)-azocinyllidene-N'-phenyl-4-morpholinecarboximidamide tartrate, which melts at 105°, is obtained.

Sulfate: 10 g of sulfuric acid in methylene chloride are added to a solution of 3 g of the free base in 30 ml of methylene chloride/acetone with stirring. The product precipitates out in the form of white crystals. After recrystallization from a mixture of isopropanol/acetone, N-hexahydro-2(1H)-azocinyllidene-N'-phenyl-4-morpholine-carboximidamide sulfate, which melts at 210°, is obtained.

p-Toluenesulfonate: 1.8 g of p-toluenesulfonic acid are added with stirring to a solution of 3.2 g of the free base in 30 ml of methylene chloride/acetone. The product precipitates out in the form of colorless crystals. After recrystallization from isopropanol, N-hexahydro-2(1H)-azocinyllidene-N'-phenyl-4-morpholine-carboximidamide p-toluenesulfonate, which melts at 198°, is obtained.

Hydrochloride: A solution of 4 g of the free base in 40 ml of isopropanol is acidified with hydrochloric acid in isopropanol. The solvent is evaporated under reduced pressure and the residue is recrystallized from a mixture of isopropanol/acetone. N-Hexahydro-2(1H)-azocinyllidene-N'-phenyl-4-morpholine-carboximidamide hydrochloride, which melts at 210°, is obtained.

Methanesulfonate: 0.5 g of methanesulfonic acid in methylene chloride is added to a solution of 1.6 g of the free base in methylene chloride. The product precipitates out in the form of colorless crystals. After recrystallization from a mixture of methanol/acetone, N-hexahydro-2(1H)-azocinyllidene-N'-phenyl-4-morpholine-carboximidamide methanesulfonate, which melts at 212°, is obtained.

The starting material used in this synthesis is prepared as follows: 11 g

of morpholine are added to a suspension of 29 g of N-phenyl-S-methyl-isothiourea hydroiodide in 90 ml of acetonitrile. The mixture is stirred and heated under reflux for 15 hours. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of methylene chloride/ethyl acetate. 1-(4-Morpholinyl)-N-phenyl-carboximidamide hydroiodide, which melts at 182°, is obtained.

Example 4

2 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine are added with stirring to a suspension of 4 g of 4,N-diphenylpiperidine-carboximidamide hydroiodide in 15 ml of acetonitrile. The mixture is heated for 12 hours on the water bath and vigorously stirred. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of acetone/ethyl acetate. N-Hexahydro-2(1H)-azocinyldene-4,N'-diphenylpiperidinecarboximidamide hydroiodide, which melts at 228-230°, is obtained.

The starting material for this synthesis is prepared as follows: 7 g of 4-phenylpiperidine are added with stirring to a suspension of 10 g of N-phenyl-S-methyl-isothiourea hydroiodide in 30 ml of acetonitrile. The mixture is heated under reflux for 15 hours. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of isopropanol/ethyl acetate. 4,N-Diphenylpiperidinecarboximidamide hydroiodide, which melts at 151°, is obtained.

Example 5

1.5 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine are added with stirring to a suspension of 3.5 g of N-phenyl-2,6-dimethyl-4-morpholinecarboximidamide hydroiodide in 10 ml of acetonitrile. The mixture is heated for 12 hours on the water bath and vigorously stirred. The acetone is evaporated off under reduced pressure and the residue is recrystallized from a mixture of ethyl acetate/acetone. N-Hexahydro-2(1H)-azocinyldene-N'-phenyl-2,6-dimethyl-4-morpholinecarboximidamide hydroiodide, which melts at 235° after recrystallization from a mixture of

isopropanol/ethyl acetate, is obtained.

The starting material for this synthesis is prepared as follows:
9 g of 2,6-dimethyl-morpholine are added to a suspension of 15 g of N-phenyl-S-methyl-isothioureahydroiodide in 50 ml of acetonitrile. The mixture is heated under reflux for 15 hours with stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of methylene chloride/ethyl acetate. N-Phenyl-2,6-dimethyl-4-morpholinecarboximidamide hydroiodide, which melts at 208-210°, is obtained.

Example 6

3 g of morpholine are added to a suspension of 8.2 g of N'-(1-methyl-hexahydro-2(1H)-azocinylidene)-N-phenyl-S-methyl-isothioureahydroiodide in 30 ml of acetonitrile with stirring. The mixture is heated under reflux for 36 hours in an oil bath. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of ethyl acetate/acetone. N'-(1-Methyl-hexahydro-2(1H)-azocinylidene)-N-phenyl-4-morpholinecarboximidamide hydroiodide, which melts at 198° after recrystallization from a mixture of isopropanol/ethyl acetate, is obtained.

The starting material for the above synthesis is prepared as follows:
40 g of triethyloxonium fluoroborate in 50 ml of methylene chloride are added with cooling to a solution of 14 g of 1-methyl-3,4,5,6,7,8-hexahydroazocin-2-one in 50 ml of methylene chloride. The reaction mixture is stirred in a nitrogen atmosphere for 18 hours. Ammonia is then introduced into the mixture for 3 hours. The reaction mixture is allowed to stand at room temperature for 30 hours and the solvent is evaporated off under reduced pressure on a 40° water bath. The crude 1-methyl-2-imino-3,4,5,6,7,8-hexahydroazocine is dissolved in 50 ml of acetonitrile and 12 g of phenyl isothiocyanate in 30 ml of acetonitrile are added with stirring at room temperature. The white crystalline material, which is precipitated in nearly 2 hours, is recrystallized from a mixture of ethyl acetate/isopropanol. N-Phenyl-N'-(1-methyl-hexahydro-2(1H)-

azocynylidene)-thiourea, which melts at 123-125°, is obtained.

10 g of methyl iodide in 30 ml of dioxane are added dropwise with stirring to a solution of 14 g of N-phenyl-N'-(1-methyl-hexahydro-2(1H)-azocynylidene)-thiourea in 50 ml of dioxane. The mixture is heated on the water bath for 3 hours. The dioxane is evaporated off under reduced pressure and the residue is recrystallized from a mixture of ethyl acetate/acetone. N'-(1-Methyl-hexahydro-2(1H)-azocynylidene-N-phenyl-S-methyl-isothiurea hydroiodide, which melts at 135°, is obtained.

Example 7

2.5 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine are added with stirring to a suspension of 3.5 g of N-(p-fluorophenyl)-4-morpholine-carboximidamide hydroiodide in 10 ml of acetonitrile and the mixture is heated on a water bath for 12 hours with vigorous stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of isopropanol/acetone. N-Hexahydro-2(1H)-azocynylidene-N'-(p-fluorophenyl)-4-morpholinecarboximidamide hydroiodide, which melts at 245°, is obtained.

The starting material used in this synthesis is prepared as follows: 3 g of morpholine are added to a suspension of 7.5 g of N-(p-fluorophenyl)-S-methyl-isothiurea hydrochloride in 30 ml of acetonitrile. The mixture is heated under reflux for 15 hours with stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of acetone and ethyl acetate. N-(p-Fluorophenyl)-4-morpholine-carboximidamide hydroiodide, which melts at 210°, is obtained.

Example 8

1.5 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine are added with stirring to a suspension of 2.5 g of N-(m-trifluoromethylphenyl)-4-morpholine-carboximidamide hydroiodide in 15 ml of acetonitrile. The mixture is stirred on the water bath and heated under reflux for 12 hours. The acetonitrile is evaporated off under reduced pressure and the residue is

recrystallized from a mixture of diethyl ether/ethyl acetate. N-Hexahydro-2(1H)-azocinylidene-N'-(m-trifluoromethylphenyl)-4-morpholine-carboximidamide hydroiodide is obtained, which is converted into the free base and this into the p-toluenesulfonate. After recrystallization from acetone, the product melts at 202°.

The starting material for this synthesis is prepared as follows:

8 g of methyl iodide in 20 ml of dioxane are added to a solution of 11 g of N-(m-trifluoromethylphenyl)-thiourea in 30 ml of dioxane. The reaction mixture is heated on the water bath for 3 hours. The dioxane is evaporated off under reduced pressure and the residue is recrystallized from a mixture of isopropanol/ethyl acetate. N-(m-Trifluoromethylphenyl)-S-methyl-isothiourea hydroiodide, which melts at 220°, is obtained.

3 g of morpholine are added to a suspension of 9 g of N-(m-trifluoromethylphenyl)-S-methyl-isothiourea hydroiodide in 30 ml of acetonitrile. The mixture is heated under reflux for 15 hours with stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of acetone/ethyl acetate. (m-Trifluoromethylphenyl)-4-morpholinecarboximidamide hydroiodide, which melts at 220°, is obtained.

Example 9

2 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine are added with stirring to a suspension of 3.5 g of N-p-tolyl-4-morpholinecarboximidamide hydroiodide in 15 ml of acetonitrile. The mixture is heated on the water bath for 12 hours with vigorous stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of acetone/ethyl acetate. N-Hexahydro-2(1H)-azocinylidene-N'-p-tolyl-4-morpholinecarboximidamide hydroiodide is obtained. m.p. 240°.

The starting material for the above synthesis is prepared as follows:

3.5 g of morpholine are added to a suspension of 9 g of N-p-tolyl-S-methyl-isothiourea hydroiodide in 30 ml of acetonitrile. The mixture is

heated under reflux for 15 hours with stirring. The acetonitrile is evaporated off under reduced pressure and the residue is recrystallized from a mixture of isopropanol and ethyl acetate. N-p-Tolyl-4-morpholine-carboximidamide hydroiodide, which melts at 218-220°, is obtained.

Example 10

2.8 g of 1-aza-2-methoxy-1-cyclooctene are added to a suspension of 3 g of N-phenyl-1-(4-carbethoxypiperazine)-carboximidamide hydrochloride in 200 ml of acetonitrile and the mixture is heated under reflux for 12 hours. The solvent is evaporated off under reduced pressure and the residue is triturated with ethyl acetate. N-Hexahydro-2(1H)-azocinyldene-N'-phenyl-1-(4-carbethoxypiperazine)-carboximidamide hydrochloride, which melts at 248-249° after recrystallization from acetonitrile, is obtained as a colourless solid material.

The starting material for the above synthesis is prepared as follows:

9.6 g of N-carbethoxypiperazine in 15 ml of isopropanol are added to a solution of 8.7 g of S-methyl-phenylisothiourea hydroiodide in 30 ml of isopropanol and the solution is heated under reflux for 18 hours. The solvent is evaporated off under reduced pressure and the residue is washed with petroleum ether. N-Phenyl-1-(4-carbethoxypiperazine)-carboximidamide hydroiodide, which melts at 218-219° after recrystallization from a mixture of isopropanol/ethyl acetate, is obtained.

The above product is treated with saturated aqueous potassium carbonate solution and the mixture is extracted with methylene chloride. The extract is dried over water-free sodium sulfate, filtered and the solvent is evaporated off under reduced pressure. The residue obtained is treated with hydrogen chloride in isopropanol. N-Phenyl-1-(4-carbethoxypiperazine)-carboximidamide hydrochloride, which melts at 251-252° after recrystallization from a mixture of methanol and ethyl acetate, is obtained.

Example 11

A mixture of 2.2 g of N-(p-methoxyphenyl)-1-4-carbethoxy-piperazine)-carboximidamide hydroiodide and 1.4 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine is dissolved in 7 ml of acetonitrile and the solution is heated under reflux for 10 hours. The clear solution is cooled and the precipitate obtained is filtered off. N-Hexahydro-2(1H)-azocinylidene-N'-(p-methoxyphenyl)-1-(4-carbethoxypiperazine)-carboximidamide hydroiodide, which melts at 241-242° after recrystallization from a mixture of acetonitrile/ethyl acetate, is obtained.

The starting material for the above product is obtained as follows:

A mixture of 10 g of p-anisidine hydrochloride and 12.25 g of potassium thiocyanate is heated for 16 hours in 100 ml of ethanol. The reaction mixture is cooled and filtered. The residue is washed with water and recrystallized from methanol. A solid material melting at 226°C is obtained, which consists of p-methoxyphenylthiourea. 5.3 g of the latter compound are heated at 50° for 8 hours with 10 ml of methyl iodide in 20 ml of acetone. The reaction mixture is cooled, and the precipitate is filtered off and washed with acetone. S-Methyl-N-(p-methoxyphenyl)-isothioureia hydroiodide, which melts at 165-166°, is obtained.

A mixture of 6.4 g of S-methyl-N-(p-methoxyphenyl)-isothioureia hydroiodide and 6.2 g of N-carbethoxy-piperazine in 50 ml of acetonitrile is heated under reflux for 10 hours. The solvent is evaporated off under reduced pressure and the residue is triturated with ethyl acetate. N-(p-Methoxyphenyl)-1-(4-carbethoxypiperazine)-carboximidamide hydroiodide, which melts at 156-157° after recrystallization from acetonitrile, is obtained.

Example 12

2.3 g of 3,4,5,6,7,8-hexahydro-2-methoxyazocine are added with stirring to a solution of 2.4 g of N-phenyl-1-(4-methyl-piperazine)-carboximidamide hydroiodide in 6 ml of acetonitrile and the mixture is heated under

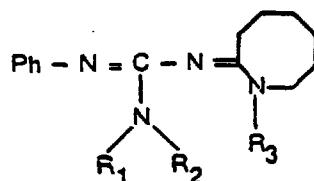
reflux for 12 hours. The reaction mixture is cooled and diluted using 10 ml of ethyl acetate. An amorphous solid material is formed, which becomes crystalline after trituration with acetone. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-1-(4-methylpiperazine)-carboximidamide hydroiodide is obtained, which melts at 222-223° after recrystallization from acetonitrile.

The starting material used for the synthesis of the above product is prepared as follows:

A mixture of 10 g of S-methyl-phenylisothiourea hydroiodide and 7.6 g of N-methylpiperazine is dissolved in 50 ml of isopropanol and the solution is heated under reflux for 10 hours. The solvent is evaporated off under reduced pressure. The residue is treated with petroleum ether. 1-(4-Methylpiperazine)-N-phenyl-carboximidamide hydroiodide is obtained, which melts at 231-232° after recrystallization from a mixture of acetonitrile and ethyl acetate.

Patent claims for the contracting states: BE CH DE FR GB IT LI LU NL SE

1. New guanidine derivatives of the formula I



wherein Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, hydroxyl, mercapto, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, dilower alkylamino, sulfamoyl, lower alkylsulfamoyl, dilower alkylsulfamoyl, carboxyl or lower alkoxy carbonyl, R₁ and R₂ independently of one another denote lower alkyl or cycloalkyl having at most 10 carbon atoms or both taken together denote a bivalent hydrocarbon radical of aliphatic character optionally substituted by lower alkyl or phenyl, having 4-7 carbon atoms



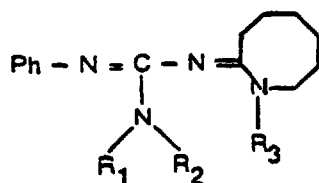
reflux for 12 hours. The reaction mixture is cooled and diluted using 10 ml of ethyl acetate. An amorphous solid material is formed, which becomes crystalline after trituration with acetone. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-1-(4-methylpiperazine)-carboximidamide hydroiodide is obtained, which melts at 222-223° after recrystallization from acetonitrile.

The starting material used for the synthesis of the above product is prepared as follows:

A mixture of 10 g of S-methyl-phenylisothiourea hydroiodide and 7.6 g of N-methylpiperazine is dissolved in 50 ml of isopropanol and the solution is heated under reflux for 10 hours. The solvent is evaporated off under reduced pressure. The residue is treated with petroleum ether. 1-(4-Methylpiperazine)-N-phenyl-carboximidamide hydroiodide is obtained, which melts at 231-232° after recrystallization from a mixture of acetonitrile and ethyl acetate.

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1. New guanidine derivatives of the formula I



(I)

wherein Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, hydroxyl, mercapto, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, dilower alkylamino, sulfamoyl, lower alkylsulfamoyl, dilower alkylsulfamoyl, carboxyl or lower alkoxycarbonyl, R₁ and R₂ independently of one another denote lower alkyl or cycloalkyl having at most 10 carbon atoms or both taken together denote a bivalent hydrocarbon radical of aliphatic character optionally substituted by lower alkyl or phenyl, having 4-7 carbon atoms



in the chain, in which the carbon atoms of the chain can be interrupted by oxygen, sulfur or nitrogen, R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts, where the radicals designated with "lower" have 7 carbon atoms at most.

2. Compounds of the formula I in which Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, hydroxyl, mercapto, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, dilower alkylamino, sulfamoyl, lower alkylsulfamoyl, dilower alkylsulfamoyl, carboxyl or lower alkoxycarbonyl, R_1 and R_2 independently of one another denote a methyl or ethyl, cyclopentyl, cyclohexyl or cycloheptyl radical or both taken together denote a bivalent hydrocarbon radical of aliphatic character having 4 - 7 carbon atoms in the chain, in which the carbon atoms of the chain can be interrupted by an oxygen, sulfur or nitrogen atom and which is optionally substituted by lower alkyl or phenyl, R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts, where the radicals designated with "lower" have 7 carbon atoms at most.

3. Compounds of the formula I, in which Ph denotes phenyl which is optionally substituted by a substituent from the series comprising lower alkyl, lower alkoxy, halogen, or trifluoromethyl, R_1 and R_2 both taken together denote a lower alkylene chain which is optionally substituted by a substituent from the series comprising lower alkyl or phenyl, in which the carbon atoms of the chain can be interrupted by oxygen, sulfur or nitrogen which is optionally substituted by lower alkyl, phenyl, benzyl, phenylethyl or alkoxycarbonyl, and R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts, where the radicals designated with "lower" contain 7 carbon atoms at most.

4. Compounds of the formula I, in which Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, lower alkoxy, halogen or trifluoromethyl, the $-NR_1R_2$ group can be pyrrolidino, 2,5-dimethylpyrrolidino, piperidino, 2-methyl-, 4-methyl- or 4-phenylpiperidino, hexahydroazepino, morpholino, 2,6-di-



methylmorpholino, thiomorpholino, 2,6-dimethylthiomorpholino, piperazino, N-methyl, N-phenyl, N-benzyl, N-methoxy- or N-ethoxycarbonylpiperazine, and R_3 denotes hydrogen and also lower alkyl, and their tautomeric compounds and salts, where the radicals designated with "lower" have 7 carbon atoms at most.

5. Compounds of the formula I, in which Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, such as, for example, methyl or ethyl, lower alkoxy, such as, for example, methoxy or ethoxy, halogen, such as, for example, chlorine or bromine or trifluoromethyl, the $-NR_1R_2$ group can be pyrrolidino, piperidino, 4-methyl- or 4-phenylpiperidino, morpholino, 2,6-dimethylmorpholino, piperazino, N-methyl or N-methoxycarbonylpiperazine, and R_3 denotes hydrogen and also methyl or ethyl, and their tautomeric compounds and salts.

6. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-1-pyrrolidinecarboximidamide.

7. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-1-piperidinecarboximidamide.

8. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-4-morpholinecarboximidamide.

9. N-Hexahydro-2(1H)-azocinylidene-4,N'-diphenylpiperidinecarboximidamide.

10. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-2,6-dimethyl-4-morpholinecarboximidamide.

11. N'-(1-Methylhexahydro-2(1H)-azocinylidene)-N-phenyl-4-morpholinecarboximidamide.

12. N-Hexahydro-2(1H)-azocinylidene-N'-(p-fluorophenyl)-4-morpholinecarboximidamide.

13. N-Hexahydro-2(1H)-azocinylidene-N'-(m-trifluoromethylphenyl)-4-



morpholinecarboximidamide.

14. N-Hexahydro-2(1H)-azocinylidene-N'-p-tolyl-4-morpholinecarboximidamide.

15. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-1-(4-carbethoxypiperazine)-carboximidamide.

16. N-Hexahydro-2(1H)-azocinylidene-N'-(p-methoxyphenyl)-1-(4-carbethoxypiperazine)carboximidamide.

17. N-Hexahydro-2(1H)-azocinylidene-N'-phenyl-(4-methylpiperazine)carboximidamide.

18. Tautomeric compounds of claims 6-17.

19. Salts of compounds of claims 6-18.

20. Pharmaceutically acceptable, non-toxic salts of compounds of claims 6-18.

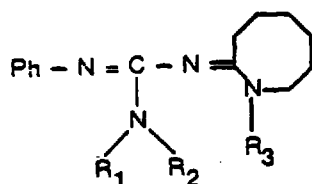
21. Hypoglycaemically active compounds of the formula I and corresponding tautomeric compounds according to claim 1 and salts of such compounds.

22. Pharmaceutical preparations containing one of the compounds of claims 1-17 and 20.

23. The compounds of claims 1-17 and 20, for use as antidiabetics.

24. Use of the compounds of claims 1 to 17 and 20 for the preparation of pharmaceutical compositions.

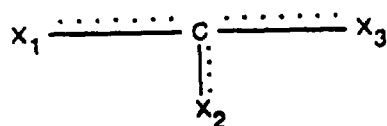
25. A process for the preparation of new guanidine derivatives of the formula I



(I)

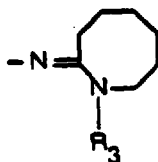
wherein Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, hydroxyl, mercapto, lower alkoxy, lower alkenyloxy, lower alkylendioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, dilower alkylamino, sulfamoyl, lower alkylsulfamoyl, dilower alkylsulfamoyl, carboxyl or lower alkoxycarbonyl, R_1 and R_2 independently of one another denote lower alkyl or cycloalkyl having at most 10 carbon atoms or both taken together denote a bivalent hydrocarbon radical of aliphatic character optionally substituted by lower alkyl or phenyl, having 4-7 carbon atoms in the chain, in which the carbon atoms of the chain can be interrupted by oxygen, sulfur or nitrogen, R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts, where the radicals designated with "lower" have 7 carbon atoms at most, characterized in that

a) a compound of the formula II



(II)

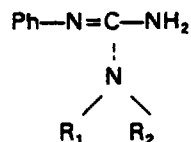
wherein X_1 denotes the $\text{Ph}-\text{N}=\text{C}-$ group, in which Ph denotes an optionally substituted phenyl radical, or a removable group, X_2 denotes the $-\text{NR}_1\text{R}_2$ group, wherein R_1 and R_2 have the meaning indicated under formula I, or denotes a removable group and X_3 denotes the group



wherein R_3 has the meaning indicated under the formula I, or denotes a removable group, with the proviso that only one of the substituents X_1 , X_2 or X_3 can be a removable group, and wherein one of the groups X_1 , X_2



b) a compound of the formula IV



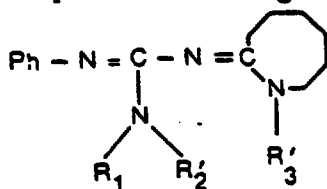
(IV).

$$\left[\begin{array}{c} \text{Y} \cdots \text{N} \text{---} \text{Cyclo-octyl} \\ | \\ \text{R}_3 \end{array} \right]^{\oplus} \text{Z}^{\ominus}$$

(V).

c) compounds of the formula I, in which R_1 has the meaning defined above and R_2 and/or R_3 denotes hydrogen, are converted into compounds of the formula I, in which R_2 and/or R_3 in the context of the previous definitions for R_2 and R_3 are other than hydrogen, by reaction with a reactive ester of a lower alkanol or, if appropriate, of cycloalkanol, or

d) in compounds of the general formula VI



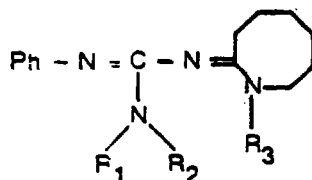
(VI).



wherein R_1 and Ph have the meaning indicated under the formula I, and one of the substituents R'_2 and R'_3 has the meaning of R_2 or R_3 , and the other denotes an amino-protecting group, or both R'_2 and R'_3 denote an amino-protecting group, this is removed and, if desired, additional process steps are carried out, and/or, if desired, compounds of the formula I obtained are converted into a salt, and/or, if desired, salts of compounds of the formula I obtained are converted into the free bases.

Patent claims for the contracting states: AT

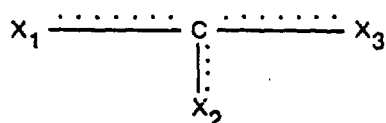
1. A process for the preparation of new guanidine derivatives of the formula I



(I)

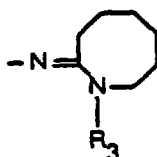
wherein Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, hydroxyl, mercapto, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, dilower alkylamino, sulfamoyl, lower alkylsulfamoyl, dilower alkylsulfamoyl, carboxyl or lower alkoxy carbonyl, R_1 and R_2 independently of one another denote lower alkyl or cycloalkyl having at most 10 carbon atoms or both taken together denote a bivalent hydrocarbon radical of aliphatic character optionally substituted by lower alkyl or phenyl, having 4-7 carbon atoms in the chain, in which the carbon atoms of the chain can be interrupted by oxygen, sulfur or nitrogen, R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts, where the radicals designated with "lower" have 7 carbon atoms at most, characterized in that

a) a compound of the formula II



(II)

wherein X_1 denotes the Ph-N= group, in which Ph denotes an optionally substituted phenyl radical, or a removable group, X_2 denotes the $-\text{NR}_1\text{R}_2$ group, wherein R_1 and R_2 have the meaning indicated under formula I, or denotes a removable group and X_3 denotes the group

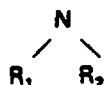


wherein R_3 has the meaning indicated under the formula I, or denotes a removable group, with the proviso that only one of the substituents X_1 , X_2 or X_3 can be a removable group, and wherein one of the groups X_1 , X_2 or X_3 is bonded to the carbon atom by a double bond, is reacted with an amine or imine which corresponds to the missing amino or imino group, which are defined under X_1 , X_2 or X_3 in order to replace the removable group, or

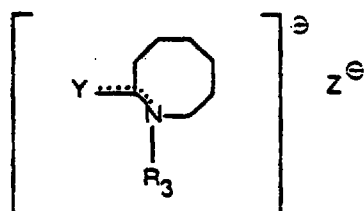
b) a compound of the formula IV



(IV).



wherein Ph, R_1 and R_2 have the meanings indicated under the formula I, is reacted with a compound of the general formula V



(V).

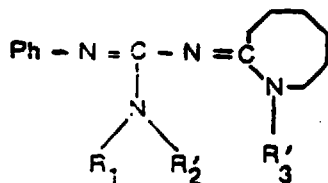
wherein Y denotes lower alkoxy, lower alkylthio, halogen, or Y denotes two lower alkoxy groups which are sited on identical C atoms, and Z



denotes a tetrafluoroborate, a fluorosulfonate, lower alkylsulfate or lower alkanesulfonate anion or a halide, where, if Y has the meaning of two lower alkoxy groups on identical C atoms, Z is not present as the anion, or, if R₃ denotes hydrogen, the tautomeric form is present as the free base, or

c) compounds of the formula I, in which R₁ has the meaning defined above and R₂ and/or R₃ denotes hydrogen, are converted into compounds of the formula I, in which R₂ and/or R₃ in the context of the previous definitions for R₂ and R₃ are other than hydrogen, by reaction with a reactive ester of a lower alkanol or, if appropriate, of cycloalkanol, or

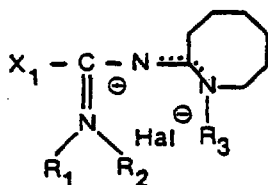
d) in compounds of the general formula VI



(VI).

wherein R₁ and Ph have the meaning indicated under the formula I, and one of the substituents R'₂ and R'₃ has the meaning of R₂ or R₃, and the other denotes an amino-protecting group, or both R'₂ and R'₃ denote an amino-protecting group, this is removed and, if desired, additional process steps are carried out, and/or, if desired, compounds of the formula I obtained are converted into a salt, and/or, if desired, salts of compounds of the formula I obtained are converted into the free bases.

2. Process according to patent claim 1, characterized in that a compound of the formula IIa



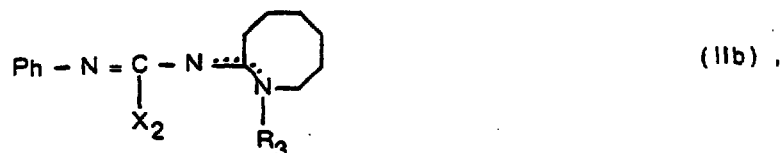
(IIa).

wherein X₁ denotes a removable group and R₁, R₂ and R₃ have the meanings indicated under formula I, is reacted with an optionally substituted aniline of the formula Ph-NH₂.

3. Process according to patent claim 1, characterized in that a compound



of the formula IIb



wherein X_2 denotes a removable group and Ph and R_3 have the meanings indicated under the formula I, is reacted with an amine of the formula HNR_1R_2 .

4. Process according to patent claim 1, characterized in that a compound of the formula IIc



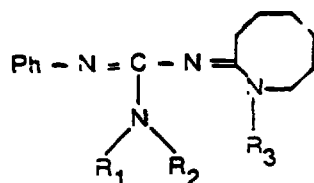
wherein X_3 denotes a removable group and Ph, R_1 and R_2 have the meanings indicated under formula I is reacted with an imino compound of the formula III



5. Process according to patent claims 1-4, characterized in that a removable radical denotes a lower alkylthio group, lower alkoxy group or a halogen atom in the compounds of the formulae II, IIa, IIb and IIc, where the radicals designated with "lower" have 7 carbon atoms at most.

6. Process according to patent claims 1-5, characterized in that a removable radical denotes a methylthio, methoxy or a chlorine or bromine atom in the compounds of the formulae II, IIa, IIb.

7. Process according to patent claim 1, characterized in that new guanidine derivatives of the formula I



(I)

wherein Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, hydroxyl, mercapto, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, dilower alkylamino, sulfamoyl, lower alkylsulfamoyl, dilower alkylsulfamoyl, carboxyl or lower alkoxycarbonyl, R_1 and R_2 independently of one another denote lower alkyl or cycloalkyl having at most 10 carbon atoms or both taken together denote a bivalent hydrocarbon radical of aliphatic character optionally substituted by lower alkyl or phenyl in which the carbon atoms of the chain can be interrupted by oxygen, sulfur or nitrogen, R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts, where the radicals designated with "lower" have 7 carbon atoms at most, are prepared.

8. Process according to patent claim 1, characterized in that compounds of the formula I in which Ph denotes a phenyl radical which is optionally substituted by a substituent from the series comprising lower alkyl, hydroxyl, mercapto, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, dilower alkylamino, sulfamoyl, lower alkylsulfamoyl, dilower alkylsulfamoyl, carboxyl or lower alkoxycarbonyl, R_1 and R_2 independently of one another denote a methyl or ethyl, cyclopentyl, cyclohexyl or cycloheptyl radical of both taken together denote a bivalent hydrocarbon radical of aliphatic character having 4-7 carbon atoms in the chain, in which the hydrocarbon atoms of the chain can be interrupted by oxygen, sulfur or nitrogen, and which is optionally substituted by lower alkyl or phenyl, R_3 denotes hydrogen or lower alkyl, and their tautomeric compounds and salts, where the radicals designated with "lower" have 7 carbon atoms at most, are prepared.



9. Process according to patent claim 1, characterized in that N-hexahydro-2(1H)-azocinylidene-N'-phenyl-1-pyrrolidinecarboximidamide is prepared.

10. Process according to patent claim 1, characterized in that N-hexahydro-2(1H)-azocinylidene-N'-phenyl-1-piperidinecarboximidamide is prepared.

11. Process according to patent claim 1, characterized in that N-hexahydro-2(1H)-azocinylidene-N'-phenyl-4-morpholinecarboximidamide is prepared.

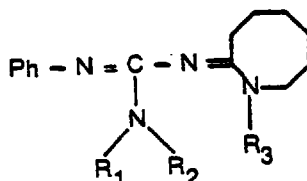
12. Process according to patent claim 1, characterized in that N-hexahydro-2(1H)-azocinylidene-N'-phenyl-2,6-dimethyl-4-morpholinecarboximidamide, is prepared.



As printed.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A novel guanidine derivative of the formula I



(1)

wherein Ph is a phenyl group which is unsubstituted or substituted by lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, di-lower alkylamino, sulfamyl, lower alkylsulfamyl, di-lower alkylsulfamyl, carboxy or lower alkoxycarbonyl, each of R_1 and R_2 independently of the other is lower alkyl or cycloalkyl containing not more than 10 carbon atoms, or both taken together are a bivalent hydrocarbon radical of aliphatic character containing 4 to 7 carbon atoms in the chain, which radical is unsubstituted or substituted by lower alkyl or phenyl, and in which radical the carbon atoms of the chain may be interrupted by oxygen, sulfur or nitrogen, and R_3 is hydrogen or lower alkyl, or a tautomeric compound or a salt thereof, with the radicals qualified by the term "lower" containing not more than 7 carbon atoms.

2. A compound of the formula I, wherein Ph is a phenyl group which is unsubstituted or substituted by lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, di-lower alkylamino, sulfamyl, lower alkylsulfamyl, di-lower alkylsulfamyl, carboxy or lower alkoxycarbonyl, each of R_1 and R_2 independently of the other is a methyl or ethyl, cyclopentyl, cyclohexyl or cycloheptyl radical, or both taken together are a bivalent hydrocarbon radical of aliphatic character containing 4 to 7 carbon atoms in the chain, which radical is unsubstituted or substituted by lower alkyl or phenyl, and in which radical the carbon atoms of the chain may be interrupted by an oxygen, sulfur or nitrogen atom, and R_3 is hydrogen or lower alkyl, or a tautomeric compound or a salt thereof, with the radicals qualified by the term "lower" containing not more than 7 carbon atoms.

3. A compound of the formula I, wherein Ph is a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl, and R_1 and R_2 both taken together are a lower alkylene chain which is unsubstituted or substituted by lower alkyl or phenyl, and in which the carbon atoms of the chain may be interrupted by oxygen or sulfur, or by nitrogen which is unsubstituted or substituted by lower alkyl, phenyl, benzyl, phenylethyl or alkoxycarbonyl, and R_3 is hydrogen or lower alkyl, or a tautomeric compound or a salt thereof, with the radicals qualified by the term "lower" containing not more than 7 carbon atoms.

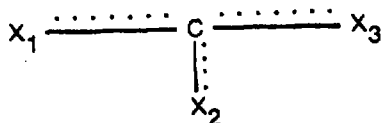
4. A compound of the formula I, wherein Ph is a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl, the group $-NR_1R_2$ may be pyrrolidino, 2,5-dimethylpyrrolidino, piperidino, 2-methyl-, 4-methyl- or 4-phenylpiperidino, hexahydroazepino, morpholino, 2,6-dimethylmorpholino, thiomorpholino, 2,6-dimethylthiomorpholino, piperazino, N-methyl-, N-phenyl-, N-benzyl-, N-methoxy-, N-ethoxycarbonylpiperazine, and R_3 is hydrogen or lower alkyl, or a tautomeric compound or a salt thereof, with the radicals qualified by the term "lower" containing not more than 7 carbon atoms.

5. A compound of the formula I, wherein Ph is a phenyl group which is unsubstituted or substituted by lower alkyl, such as methyl or ethyl, lower alkoxy, such as methoxy or ethoxy, halogen, such as chlorine or bromine, or trifluoromethyl, the group $-NR_1R_2$ may be pyrrolidino, piperidino, 4-methyl- or 4-phenylpiperidino, morpholino, 2,6-dimethylmorpholino, piperazino, N-methyl- or N-methoxycarbonylpiperazine, and R_3 is hydrogen or alternatively methyl or ethyl, or a tautomeric compound or a salt thereof.



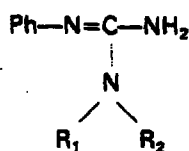
- $$\text{Ph} - \text{N} = \text{C}(\text{N}(\text{R}_1)\text{R}_2) - \text{N}(\text{R}_3) = \text{C}(\text{C}_7\text{H}_{13})$$

a) reacting a compound of the formula II

*N1CCCCC1

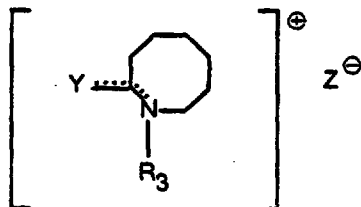
wherein R₃ is as defined for formula I, or a removable group, with the proviso that only one of the substituents X₁, X₂ or X₃ can be a removable group and wherein one of the groups X₁, X₂ or X₃ is attached through a double bond to the carbon atom, with an amine or imine corresponding to the eliminated amino or imino group falling within the definition of X₁, X₂ or X₃, in order to replace the removable group; or

b) reacting a compound of the formula IV



(IV)

wherein Ph, R₁ and R₂ are as defined for formula I, with a compound of the general formula V

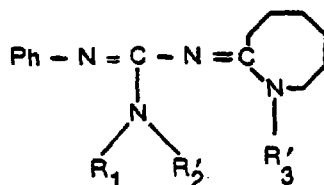


(V)

wherein Y is lower alkoxy, lower alkylthio, halogen, or Y is two lower alkoxy groups which are located on the same C atom, and Z is a tetrafluoroborate anion, a fluorosulfonate anion, a lower alkylsulfate anion, a lower alkanesulfonate anion, or a halide, with the proviso that, if Y is two lower alkoxy groups on the same C atom, Z as anion is not present, or, if R₃ is hydrogen, the tautomeric form is obtained as a free base; or

c) converting a compound of the formula I, in which R₁ is as defined above, and R₂ and/or R₃ are hydrogen, by reaction with a reactive ester of a lower alkanol or optionally of a cycloalkanol, into a compound of the formula I, in which R₂ and/or R₃, within the scope of the definitions for R₂ and R₃ given in the foregoing, are other than hydrogen; or

d) in a compound of the general formula VI

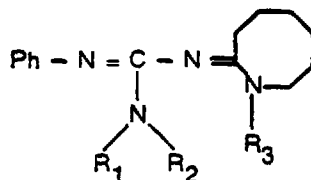


(VI)

wherein R₁ and Ph are as defined for formula I, and one of the substituents R₂' and R₃' has the meaning of R₂ or R₃, and the other is an amino protecting group, or both R₂' and R₃' are an amino protecting group, removing said group; and, if desired, carrying out additional process steps; and/or, if desired, converting a resultant compound of the formula I into a salt; and/or, if desired, converting a salt of a compound of the formula I into a free base.

Claims for the Contracting State: AT

1. A process for the preparation of a novel guanidine derivative of the formula I

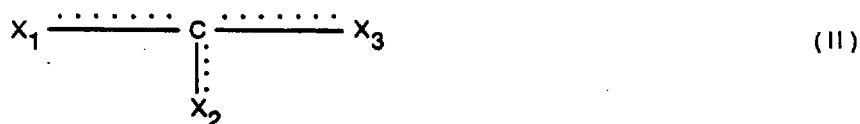


(I)

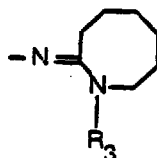
wherein Ph is a phenyl group which is unsubstituted or substituted by lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkylamino, di-lower alkylamino, sulfamyl, lower alkylsulfamyl, di-lower alkylsulfamyl, carboxy or lower alkoxy carbonyl, each of R₁ and R₂ independently of the other is lower alkyl or cycloalkyl containing not more than 10 carbon atoms, or both taken together are a bivalent hydrocarbon radical of aliphatic character, which radical is unsubstituted or substituted by lower alkyl or phenyl, and in which radical the carbon atoms of the chain may be interrupted by oxygen, sulfur or nitrogen, and R₃ is hydrogen or lower alkyl, or a tautomeric compound or a salt thereof, with the radicals qualified by the term "lower" containing not more than 7 carbon atoms, which process comprises



a) reacting a compound of the formula II



wherein X_1 is the group $\text{Ph}-\text{N}=\text{}$, in which Ph is a substituted or unsubstituted phenyl group, or a removable group, X_2 is the group $-\text{NR}_1\text{R}_2$, wherein R_1 and R_2 are as defined for formula I, or a removable group, and X_3 is the group

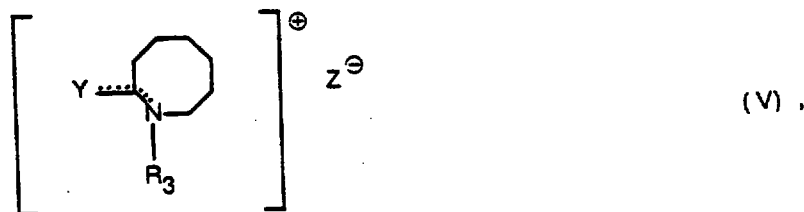


wherein R_3 is as defined for formula I, or a removable group, with the proviso that only one of the substituents X_1 , X_2 or X_3 can be a removable group and wherein one of the groups X_1 , X_2 or X_3 is attached through a double bond to the carbon atom, with an amine or imine corresponding to the eliminated amino or imino group falling within the definition of X_1 , X_2 or X_3 , in order to replace the removable group; or

b) reacting a compound of the formula IV



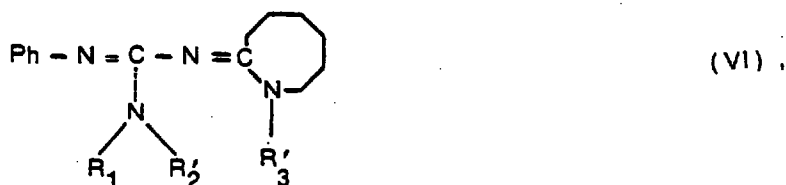
wherein Ph, R_1 and R_2 are as defined for formula I, with a compound of the general formula V



wherein Y is lower alkoxy, lower alkylthio, halogen, or Y is two lower alkoxy groups which are located on the same C atom, and Z is a tetrafluoroborate anion, a fluorosulfonate anion, a lower alkylsulfate anion, a lower alkanesulfonate anion, or a halide, with the proviso that, if Y is two lower alkoxy groups on the same C atom, Z as anion is not present, or, if R_3 is hydrogen, the tautomeric form is obtained as a free base; or

c) converting a compound of the formula I, in which R_1 is as defined above, and R_2 and/or R_3 are hydrogen, by reaction with a reactive ester of a lower alkanol or optionally of a cycloalkanol, into a compound of the formula I, in which R_2 and/or R_3 , within the scope of the definitions for R_2 and R_3 given in the foregoing, are other than hydrogen; or

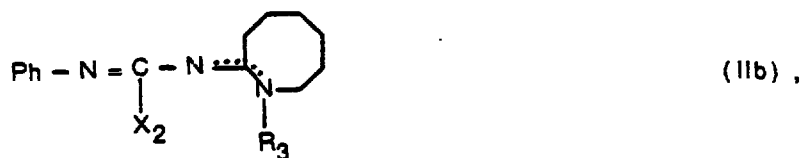
d) in a compound of the general formula VI



wherein R_1 and Ph are as defined for formula I, and one of the substituents R_2' and R_3' has the meaning of R_2 or R_3 , and the other is an amino protecting group, or both R_2' and R_3' are an amino protecting group, removing said group; and, if desired, carrying out additional process steps; and/or, if desired, converting a resultant compound of the formula I into a salt; and/or, if desired, converting a salt of a compound of the formula I into a free base.

$$\begin{array}{c} \text{X}_1 - \text{C} - \text{N} \cdots \text{N} \text{---} \text{Cyclooctyl} \\ \parallel \quad | \\ \text{N}^+ \quad \text{Hal}^- \\ | \quad | \\ \text{R}_1 \quad \text{R}_2 \end{array} \quad \text{(IIa)},$$

3. A process according to claim 1, which comprises reacting a compound of the formula IIb



4. A process according to claim 1, which comprises reacting a compound of the formula IIc


$$\text{HN}=\text{C}(\text{R}_3)\text{C}_6\text{H}_4\text{N} \quad (\text{III})$$

6. A process according to any one of claims 1 to 5, wherein a removable group in a compound of the formula II, IIa, IIb or IIc is a methylthio group, a methoxy group or a chlorine or bromine atom.

$$\text{Ph}-\text{N}=\text{C}(\text{N}(\text{R}_1)\text{R}_2)-\text{N}=\text{N}(\text{R}_3)\text{C}_7\text{H}_{13} \quad (1)$$

8. A process according to claim 1, which comprises preparing a compound of the formula I, wherein Ph is a phenyl group which is unsubstituted or substituted by lower alkyl, hydroxy, mercapto, lower alkoxy,



lower alkenyloxy, lower alkylendioxy, lower alkylthio, halogen, trifluoromethyl, nitro, amino, lower alkyl-amino, di-lower alkylamino, sulfamyl, lower alkylsulfamyl, di-lower alkylsulfamyl, carboxy or lower alkoxy-carbonyl, each of R_1 and R_2 independently of the other is a methyl or ethyl, cyclopentyl, cyclohexyl or cycloheptyl radical, or both taken together are a bivalent hydrocarbon radical of aliphatic character containing 4 to 7 carbon atoms in the chain, which radical is unsubstituted or substituted by lower alkyl or phenyl, and in which radical the carbon atoms of the chain may be interrupted by oxygen, sulfur or nitrogen, and R_3 is hydrogen or lower alkyl, or a tautomeric compound or a salt thereof, with the radicals qualified by the term "lower" containing not more than 7 carbon atoms.

9. A process according to claim 1, which comprises preparing N-hexahydro-2(1H)-azocinylidene-N'-phenyl-1-pyrrolidinecarboximide-amide.

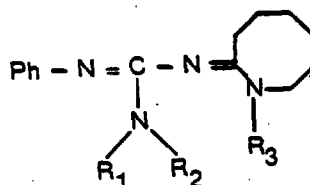
10. A process according to claim 1, which comprises preparing N-hexahydro-2(1H)-azocinylidene-N'-phenyl-1-piperidinecarboximide-amide.

11. A process according to claim 1, which comprises preparing N-hexahydro-2(1H)-azocinylidene-N'-phenyl-4-morpholinecarboximide-amide.

12. A process according to claim 1, which comprises preparing N-hexahydro-2(1H)-azocinylidene-N'-phenyl-2,6-dimethyl-4-morpholinecarboximid-amide.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Nouveaux dérivés de guanidines de formule I



(1)

dans laquelle Ph représente un reste phényle éventuellement substitué par des groupes alkyle inférieurs, hydroxy, mercapto, alcoxy inférieurs, alcényloxy inférieurs, alkylène-dioxy inférieurs, alkylthio inférieurs, des halogènes, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, sulfamyle, alkylsulfamyle inférieurs, di-(alkyle inférieur)-sulfamyle, carboxy ou (alcoxy inférieur)-carbonyle, R_1 et R_2 représentent chacun, indépendamment l'un de l'autre, un groupe alkyle inférieur ou cycloalkyle contenant au maximum 10 atomes de carbone ou forment ensemble un reste hydrocarboné bivalent à caractère aliphatique éventuellement substitué par des groupes alkyle inférieurs ou phényle et contenant 4 à 7 atomes de carbone dans la chaîne, les atomes de carbone de la chaîne pouvant être interrompus par l'oxygène, le soufre ou l'azote, R_3 représente l'hydrogène ou un groupe alkyle inférieur, leurs composés tautomères et leurs sels, les restes qualifiés d'"inférieurs" contenant au maximum 7 atomes de carbone.

2. Composés de formule I dans lesquels Ph représente un reste phényle éventuellement substitué par des groupes alkyle inférieurs, hydroxy, mercapto, alcoxy inférieurs, alcényloxy inférieurs, alkylène-dioxy inférieurs, alkylthio inférieurs, des halogènes, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, sulfamyle, alkylsulfamyle inférieurs, di-(alkyle inférieur)-sulfamyle, carboxy ou (alcoxy inférieur)-carbonyle, R_1 et R_2 représentent chacun, indépendamment l'un de l'autre, un groupe méthyle ou éthyle, cyclopentyle, cyclohexyle ou cycloheptyle ou forment ensemble un reste hydrocarboné bivalent à caractère aliphatique portant éventuellement des substituants alkyle inférieurs ou phényle et contenant 4 à 7 atomes de carbone dans la chaîne, les atomes de carbone de la chaîne pouvant être interrompus par l'oxygène, le soufre ou l'azote, R_3 représente l'hydrogène ou un groupe alkyle inférieur, leurs composés tautomères et leurs sels, les restes qualifiés d'"inférieurs" contenant au maximum 7 atomes de carbone.

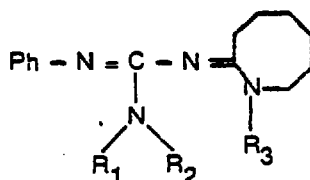
3. Composés de formule I dans lesquels Ph représente un reste phényle éventuellement substitué par des groupes alkyle inférieurs, alcoxy inférieurs, des halogènes ou des groupes trifluorométhyle, R_1 et R_2 forment ensemble une chaîne alkylène inférieur portant éventuellement des substituants alkyle inférieurs ou phényle, les atomes de carbone de la chaîne pouvant être interrompus par l'oxygène, le soufre ou l'azote lui-même éventuellement substitué par des groupes alkyle inférieurs, phényle, benzyle, phényléthyle ou alcoxycarbonyle, et R_3 représente l'hydrogène ou un groupe alkyle inférieur, leurs composés tautomères et leurs sels, les restes qualifiés d'"inférieurs" contenant au maximum 7 atomes de carbone.

4. Composés de formule I dans lesquels Ph représente un reste phényle éventuellement substitué par des groupes alkyle inférieurs, alcoxy inférieurs, des halogènes, ou des groupes trifluorométhyle, le groupe $-NR_1R_2$ peut consister en un groupe pyrrolidino, 2,5-diméthylpyrrolidino, pipéridino, 2-méthyl-, 4-méthyl- ou 4-phénylpipéridino, hexahydroazépino, morpholino, 2,6-diméthylmorpholino, 2,6-diméthylmorpholino, thiomorpholino, 2,6-diméthylthiomorpholino, pipérazino, N-méthyl-, N-phényl-, N-benzyl-, N-méthoxy-, N-éthoxy-carbonylpipérazine, et R_3 représente l'hydrogène ou un groupe alkyle inférieur, leurs composés tautomères et leurs sels, les restes qualifiés d'"inférieurs" contenant au maximum 7 atomes de carbone.



5. Composés de formule I dans lesquels Ph représente un groupe phényle éventuellement substitué par des groupes alkyle inférieurs, par exemple méthyle ou éthyle, alcoxy inférieurs, par exemple méthoxy ou éthoxy, des halogènes, par exemple le chlore ou le brome, ou des groupes trifluorométhyle, le groupe $-NR_1R_2$ peut consister en un groupe pyrrolidino, pipéridino, 4-méthyl- ou 4-phényl-pipéridino, morpholino, 2,6-diméthylmorpholino, pipérazino, N-méthyl-, N-méthoxy-carbonylpipérazine, et R_3 représente l'hydrogène ou un groupe méthyle ou éthyle, leurs composés tautomères et leurs sels.

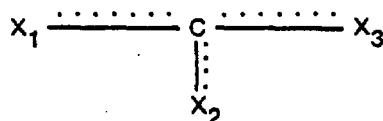
6. Le N-hexahydro-2(1H)-azocinylidène-N'-phényl-1-pyrrolidino-carboximidamide.
7. Le N-hexahydro-2(1H)-azocinylidène-N'-phényl-1-pipéridino-carboximidamide.
8. Le N-hexahydro-2(1H)-azocinylidène-N'-phényl-4-morpholinocarboximidamide.
9. Le N-hexahydro-2(1H)-azocinylidène-4,N'-diphényl-pipéridinocarboximidamide.
10. Le N-hexahydro-2(1H)-azocinylidène-N'-phényl-2,6-diméthyl-4-morpholinocarboximidamide.
11. Le N'-1-méthyl-hexahydro-2(1H)-azocinylidène-N-phényl-4-morpholinocarboximidamide.
12. Le N-hexahydro-2(1H)-azocinylidène-N'-(p-fluorophényl)-4-morpholinocarboximidamide.
13. Le N-hexahydro-2(1H)-azocinylidène-N'-(m-trifluorométhylphényl)-4-morpholinocarboximidamide.
14. Le N-hexahydro-2(1H)-azocinylidène-N'-p-tolyl-4-morpholinocarboximidamide.
15. Le N-hexahydro-2(1H)-azocinylidène-N'-phényl-1-(carbéthoxypipérazino)-carboximidamide.
16. Le N-hexahydro-2(1H)-azocinylidène-N'-(p-méthoxyphényl)-1-(4-carbéthoxypipérazino)-carboximidamide.
17. Le N-hexahydro-2(1H)-azocinylidène-N'-phényl-(4-méthylpipérazino)-carboximidamide.
18. Composés tautomères des rev. 6 à 17.
19. Sels des composés des rev. 6 à 18.
20. Sels non toxiques, acceptables pour l'usage pharmaceutique, des composés des rev. 6 à 18.
21. Composés de formule I possédant une activité hypoglycémique et composés tautomères correspondants selon la rev. 1 et sels de ces composés.
22. Compositions pharmaceutiques contenant l'un des composés des rev. 1 à 17 et 20.
23. Les composés des rev. 1 à 17 et 20, pour l'utilisation en tant qu'antidiabétiques.
24. Utilisation des composés des rev. 1 à 17 et 20 pour la préparation de compositions pharmaceutiques.
25. Procédé de préparation des nouveaux dérivés de guanidines de formula I



(1)

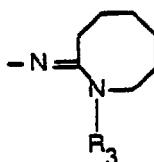
dans laquelle Ph représente un reste phényle éventuellement substitué par des groupes alkyle inférieurs, hydroxy, mercapto, alcoxy inférieurs, alcényloxy inférieurs, alkylène-dioxy inférieurs, alkylthio inférieurs, des halogènes, des groupes tri-fluorométhyle, nitro, amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, sulfamyle, alkylsulfamyle inférieurs, di-(alkyle inférieur)-sulfamyle, carboxy ou (alcoxy inférieur)-carbonyle, R_1 et R_2 représentent, indépendamment l'un de l'autre, un groupe alkyle inférieur ou cycloalkyle contenant au maximum 10 atomes de carbone ou forment ensemble un reste hydrocarboné bivalent à caractère aliphatique éventuellement substitué par des groupes alkyle inférieurs ou phényle et contenant 4 à 7 atomes de carbone dans la chaîne, les atomes de carbone de la chaîne pouvant être interrompus par l'oxygène, le soufre ou l'azote, R_3 représente l'hydrogène ou un groupe alkyle inférieur, de leurs composés tautomères et de leurs sels, les restes qualifiés d'"inférieurs" contenant au maximum 7 atomes de carbone, caractérisé en ce que:

a) on fait réagir un composé de formule II



(11)

dans laquelle X_1 représente le groupe $Ph-N=$ dans lequel Ph est un groupe phényle éventuellement substitué, ou un groupe éliminable, X_2 représente le groupe $-NR_1R_2$ dans lequel R_1 et R_2 ont les significations indiquées en référence à la formule I, ou un groupe éliminable, et X_3 représente le groupe



b) on fait réagir un composé de formule IV


$$\left[\begin{array}{c} \text{Y} \cdots \text{N} \text{---} \text{Cyclooctyl} \\ | \\ \text{R}_3 \end{array} \right]^{\oplus} \text{Z}^{\ominus} \quad (\text{V})$$

d) dans des composés de formule générale VI

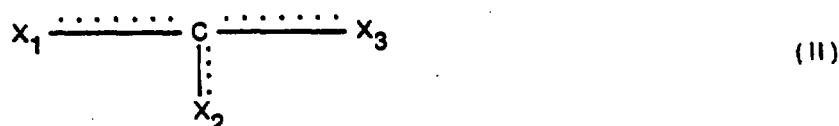

$$\text{Ph}-\text{N}=\text{C}-\text{N}=\text{N} \begin{array}{c} \diagup \\ \text{N} \\ \diagdown \end{array} \begin{array}{c} \text{R}_1 \\ \text{R}_2 \end{array} \quad (1)$$

dans laquelle Ph représente un reste phényle éventuellement substitué par des groupes alkyle inférieurs, hydroxy, mercapto, alcoxy inférieurs, alcényloxy inférieurs, alkylène-dioxy inférieurs, alkylthio inférieurs,

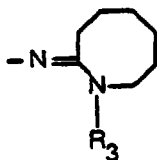


des halogènes, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, sulfamyle, alkylsulfamyle inférieurs, di-(alkyle inférieur)-sulfamyle, carboxy ou (alcoxy inférieur)-carbonyle, R_1 et R_2 représentent chacun, indépendamment l'un de l'autre, un groupe alkyle inférieur ou cycloalkyle contenant au maximum 10 atomes de carbone ou forment ensemble un reste hydrocarboné bivalent à caractère aliphatique éventuellement substitué par des groupes alkyle inférieurs ou phényle et contenant 4 à 7 atomes de carbone dans la chaîne, les atomes de carbone de la chaîne pouvant être interrompus par l'oxygène, le soufre ou l'azote, R_3 représente l'hydrogène ou un groupe alkyle inférieur, leurs composés tautomères et leurs sels, les restes qualifiés d'"inférieurs" contenant au maximum 7 atomes de carbone, caractérisé en ce que:

a) on fait réagir un composé de formule II



dans laquelle X_1 représente le groupe $\text{Ph}-\text{N}=\text{}$ dans lequel Ph est un groupe phényle éventuellement substitué, ou un groupe éliminable, X_2 représente le groupe $-\text{NR}_1\text{R}_2$ dans lequel R_1 et R_2 ont les significations indiquées en référence à la formule I, ou un groupe éliminable, et X_3 représente le groupe

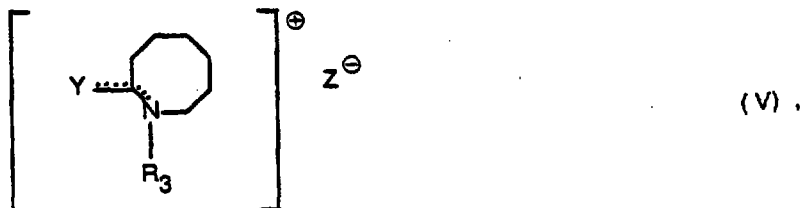


dans lequel R_3 a les significations indiquées en référence à la formule I, ou un groupe éliminable, étant spécifié que l'un seulement des substituants X_1 , X_2 ou X_3 peut consister en un groupe éliminable, et l'un des groupes X_1 , X_2 ou X_3 est relié avec l'atome de carbone par une double liaison, avec une amine ou une imine correspondant au groupe amino ou imino manquant tel que défini en référence à X_1 , X_2 ou X_3 , pour remplacement du groupe éliminable, ou bien

b) on fait réagir un composé de formule IV



dans laquelle Ph, R_1 et R_2 ont les significations indiquées en référence à la formule I, avec un composé de formule générale V

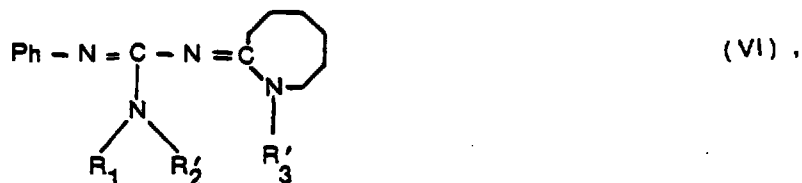


dans laquelle Y représente un groupe alcoxy inférieur, alkylthio inférieur, un halogène ou bien Y représente deux groupes alcoxy inférieurs placés sur le même atome de carbone, et Z représente un anion tétrafluorobate, fluosulfonate, alkylsulfate inférieur ou alcane-sulfonate inférieur ou un halogénure, l'anion Z étant supprimé lorsque Y représente deux groupes alcoxy inférieurs sur le même atome de carbone, ou bien lorsque R_3 représente l'hydrogène, la forme tautomère est à l'état de base libre, ou bien

c) on convertit des composés de formule I dans laquelle R_1 a la signification indiquée ci-dessus et R_2 et/ou R_3 représentent l'hydrogène, par réaction avec un ester réactif d'un alcool inférieur ou le cas échéant d'un cycloalcool, en composés de formule I dans lesquels R_2 et/ou R_3 ont une signification autre que l'hydrogène dans le cadre des définitions données ci-dessous pour R_2 et R_3 , ou bien



d) dans des composés de formule générale VI



dans laquelle R_1 et Ph ont les significations indiquées en référence à la formule I et l'un des substituants R_2 et R_3 a la signification de R_2 ou R_3 , l'autre étant un groupe protecteur du groupe amino, ou bien R_2 et R_3 représentent tous deux des groupes protecteurs du groupe amino, on élimine ces groupes et si on le désire, on exécute des stades opératoires supplémentaires et/ou, si on le désire, on convertit les composés obtenus répondant à la formule I en un sel et/ou, si on le désire, on convertit des sels de composés de formule I ainsi obtenus en les bases libres.

2. Procédé selon la rev. 1, caractérisé en ce que l'on fait réagir un composé de formule IIa



dans laquelle X_1 représente un groupe éliminable et R_1 , R_2 et R_3 ont les significations indiquées en référence à la formule I, avec une aniline éventuellement substituée de formule $\text{Ph}-\text{NH}_2$.

3. Procédé selon la rev. 1, caractérisé en ce que l'on fait réagir un composé de formule IIb



dans laquelle X_2 représente un groupe éliminable et Ph et R_3 ont les significations indiquées en référence à la formule I, avec une amine de formule HNR_1R_2 .

4. Procédé selon la rev. 1, caractérisé en ce que l'on fait réagir un composé de formule IIc



dans laquelle X_3 représente un groupe éliminable et Ph , R_1 et R_2 ont les significations indiquées en référence à la formule I, avec un composé iminé de formule III

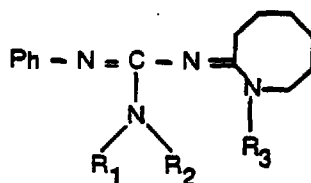


5. Procédé selon les rev. 1 à 4, caractérisé en ce qu'un reste éliminable des composés de formules II, IIa, IIb et IIc consiste en un groupe alkylthio inférieur, alcoxy inférieur ou un halogène, les restes qualifiés d'"inférieurs" contenant au maximum 7 atomes de carbone.

6. Procédé selon les rev. 1 à 5, caractérisé en ce qu'un reste éliminable des composés de formules II, IIa, IIb, consiste en un groupe méthylthio, méthoxy ou un atome de chlore ou de brome.



7. Procédé selon la rev. 1, caractérisé en ce que l'on prépare de nouveaux dérivés de guanidines de formule I



(1)

dans laquelle Ph représente un reste phényle éventuellement substitué par des groupes alkyle inférieurs, hydroxy, mercapto, alcoxy inférieurs, alcényloxy inférieurs, alkylène-dioxy inférieurs, alkylthio inférieurs, des halogènes, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, sulfamyle, alkylsulfamyle inférieurs, di-(alkyle inférieur)-sulfamyle, carboxy ou (alcoxy inférieur)-carbonyle, R₁ et R₂ représentent, indépendamment l'un de l'autre, un groupe alkyle inférieur ou cycloalkyle contenant au maximum 10 atomes de carbone ou forment ensemble un reste hydrocarboné bivalent à caractère aliphatique éventuellement substitué par des groupes alkyle inférieurs ou phényle, les atomes de carbone de la chaîne pouvant être interrompus par l'oxygène, le soufre ou l'azote, R₃ représente l'hydrogène ou un groupe alkyle inférieur, leurs composés tautomères et leurs sels, les restes qualifiés d'"inférieurs" contenant au maximum 7 atomes de carbone.

8. Procédé selon la rev. 1, caractérisé en ce que l'on prépare des composés de formule I dans laquelle Ph représente un reste phényle éventuellement substitué par des groupes alkyle inférieurs, hydroxy, mercapto, alcoxy inférieurs, alcényloxy inférieurs, alkylène-dioxy inférieurs, alkylthio inférieurs, des halogènes, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, sulfamyle, alkylsulfamyle inférieurs, di-(alkyle inférieur)-sulfamyle, carboxy ou (alcoxy inférieur)-carbonyle, R₁ et R₂ représentent chacun, indépendamment l'un de l'autre, un groupe méthyle ou éthyle, cyclopentyle, cyclohexyle ou cycloheptyle ou forment ensemble un reste hydrocarboné bivalent à caractère aliphatique portant éventuellement des substituants alkyle inférieurs ou phényle et contenant 4 à 7 atomes de carbone dans la chaîne, les atomes de carbone de la chaîne pouvant être interrompus par l'oxygène, le soufre ou l'azote, R₃ représente l'hydrogène ou un groupe alkyle inférieur, leurs composés tautomères et leurs sels, les restes qualifiés d'"inférieurs" contenant au maximum 7 atomes de carbone.

9. Procédé selon la rev. 1, caractérisé en ce que l'on prépare le N-hexahydro-2(1H)-azocinylidène-N'-phényl-1-pyrrolidino-carboximidamide.

10. Procédé selon la rev. 1, caractérisé en ce que l'on prépare le N-hexahydro-2(1H)-azocinylidène-N'-phényl-1-pipéridinocarboximidamide.

11. Procédé selon la rev. 1, caractérisé en ce que l'on prépare le N-hexahydro-2(1H)-azocinylidène-N'-phényl-4-morpholinocarboximidamide.

12. Procédé selon la rev. 1, caractérisé en ce que l'on prépare le N-hexahydro-2(1H)-azocinylidène-N'-phényl-2,6-diméthyl-4-morpholinocarboximidamide.