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COMPLETE SPECIFICATION

Novel Hydrazine Derivatives and a Process for the Manufacture Thereof

We, F. HOFFMANN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This application is concerned with novel hydrazine derivatives useful as cytostatic agents and with a process for the manufacture thereof. The invention is also concerned with preparations containing said derivatives.

The novel hydrazine derivatives provided by the invention are compounds of the formula

$$X—CH_2—NH—NH—CH_3$$

I

, wherein X is a mononuclear or polynuclear oxygen-, nitrogen- and/or sulphur-containing heterocyclic residue which may contain one or more of the substituents defined hereinafter (especially alkyl, trifluoro-methyl, cyano, mercapto, alkyl-thio, amino, acyl-amino, ureido, (alkylsulphonyl)-amino, guanidino, amidino, amino-alkyl, carbamoyl, allophanoyl, sulphamoyl, nitro, (2-methyl-hydrazino)-methyl, acyl and phenyl groups or halogen atoms), and acid addition salts thereof. They are active cytostatic agents. They inhibit the growth of transplantable tumours in both mice and rats. Thus, they are active, for example, against WALKER tumours, ERLICH carcinoma and ERLICH ascites carcinoma. They also cause decomposition of macromolecular desoxyribonucleic acid in solution. Both the formulated compounds and their salts can be administered internally in the form of conventional pharmaceutical preparations; for example, they can be administered in conventional enteral or parenteral pharmaceutical preparations containing organic and/or inorganic inert carriers such as water, gelatin, lactose, starch, magnesium stearate, talc, plant oils, gums, alcohol or petroleum jelly. The preparations can be in conventional solid forms such as tablets, dragées, suppositories, capsules or the like, or in conventional liquid forms such as suspensions or emulsions. If desired, they can be sterilized and/or contain conventional pharmaceutical adjuvants such as preservatives, stabilizing agents, wetting agents, emulsifying agents, buffers, or salts used for the adjustment of osmotic pressure. The preparations can also contain other therapeutically active materials.

The acid addition salts of the invention which are required for medicinal purposes are acid addition salts with both pharmaceutically acceptable inorganic and organic acids (for example, hydrohalic acids such as hydrogen chloride, hydrogen bromide and hydrogen iodide, other mineral acids such as sulphuric acid, phosphoric acid and nitric acid, organic acids such as tartaric acid, citric acid, oxalic acid, camphor-sulphonic acid, ethane-sulphonic acid, toluene-sulphonic acid, salicylic acid, ascorbic acid, maleic acid and mandelic acid). The preferred salts are the hydrohalides, especially the hydrochloride. The acid addition salts can suitably be prepared by treatment of the hydrazine derivative in an inert solvent with the corresponding acid.

The following are examples of mononuclear

[*Price* 4*s*. 6*d*.]

or polynuclear heterocyclic residues comprehended by X in formula I: 5-membered heterocyclic residues with one or more hetero atoms such as pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, furanyl, thienyl, oxazolyl, isoxazolyl and isothiazolyl, or 6-membered heterocyclic residues with one or more hetero atoms such as pyridyl, pyridazyl, pyrimidyl, pyrazyl, triazyl, tetrazyl, pyranyl, dioxanyl and oxazyl or a polynuclear radical with a 5-membered heterocyclic component such as indolyl, coumaronyl, thionaphthenyl, dibenzofuranyl, carbazolyl and benzimidazolyl, and a polynuclear radical with a 6-membered heterocyclic component such as quinolyl, cinnolyl, acridyl, xanthyl and thioxanthyl.

The various substituents which can be borne by the substituted heterocyclic residues comprehended by X in the foregoing formula are, for example: 1) lower alkyl groups such as methyl, ethyl and *iso*propyl. 2) trifluoromethyl. 3) halogen atoms such as fluorine, chlorine, bromine and iodine. 4) cyano. 5) mercapto 6) lower alkyl-thio such as methylthio and butyl-thio. 7) amino and substituted amino groups such as lower alkyl-amino (for example, methyl-amino), di(lower alkyl)-amino (for example, dimethyl-amino and diethyl-amino). 8) (a) acyl-amino groups wherein the acylating moiety may be derived from aliphatic, aromatic or heterocyclic acids and the amino group of which may be further substituted (e.g. N-acetyl-N-methyl-amino, acetyl-amino and pivaloyl-amino). 8) (b) acyl-amino groups wherein the acyl moiety is the residue of a naturally occurring α-amino acid (e.g. alanyl-amino). 8) (c) other aliphatic acyl-amino groups (e.g. succinimido). 8) (d) aroyl-amino groups (e.g. benzoylamino and phthalimido). 8) (e) heterocyclic acyl-amino groups wherein the hetero moiety is nitrogen and/or oxygen containing a 5-membered or 6-membered heterocyclic ring containing one or two hetero atoms and optionally bearing further substituents such as lower-alkyl [e.g. nicotinoyl-amino, *iso*nicotinoyl-amino, (methyl-*iso*xazolylcarbonyl)-amino and (methyl-oxazolylcarbonyl)-amino]. 9) ureido groups in which the hydrogen atoms can be partly or completely replaced by saturated or unsaturated aliphatic, *cyclo*aliphatic, araliphatic, aromatic or heterocyclic radicals which themselves can bear further functional groups (e.g. methyl-ureido, *iso*propyl-ureido). 10) (alkyl-sulphonyl)-amino groups [e.g. (methylsulphonyl)-amino]. 11) guanidino groups in which the hydrogen atoms can be partly or completely replaced by saturated or unsaturated aliphatic, *cyclo*aliphatic, araliphatic, aromatic or heterocyclic radicals which themselves can bear further functional groups [e.g. methyl - guanidino, *iso*propylguanidino, (hydroxy-ethyl)-guanidino]. 12) amidino groups in which the hydrogen atoms can be partly or completely replaced by saturated or unsaturated aliphatic, *cyclo*aliphatic, araliphatic, aromatic or heterocyclic radicals which themselves can bear further functional groups [e.g. methyl-amidino, di*iso*propyl-amidino, *cyclo*propyl-amidino, phenyl-amidino, benzyl-amidino, isoxazolyl-amidino and (hydroxyethyl)-amidino]. 13) lower amino-alkyl substituted lower amino-alkyl groups such as amino-methyl, amino-ethyl, amino-propyl, methylamino-methyl, ethylamino-ethyl, methylamino-propyl, dimethylamino-methyl, diethylamino-ethyl and dimethylamino-propyl. 14) carbamoyl groups in which the hydrogen atoms can be replaced by saturated or unsaturated aliphatic or alicyclic radicals which themselves can bear further functional groups or aromatic or heterocyclic radicals (e.g. N-alkyl-carbamoyl, N,N-dialkyl-carbamoyl groups such as N-methyl-carbamoyl, N,N-dimethyl-carbamoyl, N-*iso*propyl-carbamoyl, N-*iso*butyl-carbamoyl, N-(*tert*butyl)-carbamoyl, N,N-di-*iso*propyl-carbamoyl, N-(*tert*amyl)- carbamoyl and N-(*tert*octyl)-carbamoyl, N-alkoxyalkyl-carbamoyl groups such as methoxyethyl-carbamoyl, N-hydroxyalkyl-carbamoyl such as hydroxyethyl - carbamoyl, N - alkylthioalkyl-carbamoyl groups such as methylthioethyl-carbamoyl, N - carbamoylalkyl - carbamoyl groups such as carbamoylmethyl-carbamoyl, N-alkylsulphonylalkyl-carbamoyl groups such as N-methylsulphonylethyl-carbamoyl, N-haloalkyl-carbamoyl groups such as N-(β - chloro - ethyl) - carbamoyl and N-(β,β,β-trifluoro-ethyl)-carbamoyl, N-alkenyl-carbamoyl groups such as N-allyl-carbamoyl, N-aralkyl-carbamoyl groups such as benzyl-carbamoyl, N-furfuryl-carbamoyl, N-*cyclo*alkyl-carbamoyl groups such as N-*cyclo*propyl-carbamoyl, N-alkylaminoalkyl-carbamoyl and N-dialkylaminoalkyl-carbamoyl groups such as N-(β-methylamino-ethyl)-carbamoyl and N-(β-diethylamino-ethyl)-carbamoyl, and N,N-alkylene-carbamoyl groups such as N,N-tetramethylene-carbamoyl and N,N-pentamethylene-carbamoyl). 15) allophanoyl groups in which the hydrogen atoms can be partly or completely replaced by saturated or unsaturated aliphatic *cyclo*aliphatic, araliphatic, aromatic or heterocyclic radicals which themselves can bear further functional groups (e.g. 4-methyl-allphanoyl, 2-*iso*propyl-allophanoyl). 16) sulphamoyl groups in which the hydrogen atoms can be substituted by alkyl groups such as lower-alkyl groups (e.g. N,N-dimethyl-sulphamoyl). 17) nitro. 18) (2-methyl-hydrazino)-methyl. 19) acyl radicals of lower aliphatic carboxylic acids such as formic, acetic and propionic acids and of aromatic carboxylic acids such as benzoic acid. 20) a phenyl radical which may bear any of the foregoing substituents, such as [(2-methyl-hydrazino)-methyl]-phenyl, carbamoyl-phenyl, [{5-methyl - isoxazolyl - (3) - carbonyl} - amino]-phenyl and ureido-phenyl.

Some preferred compounds within the scope

of formula I are A) compounds in which X stands for a pyridyl residue which contains as a substituent a carbamoyl, allophanoyl, acylamino or ureido group—e.g: 1-methyl-2-[5 - *iso*propyl - carbamoyl) - picolyl - (2)]-hydrazine, 1-methyl-2-[5-allophanoyl)-picolyl-2)]-hydrazine, 1-methyl - 2 - [5 - {5 - methyl isoxazolyl - (1) - carbonylamino} - picolyl-(2)]-hydrazine, 1-methyl-2-[(5-ureido-picolyl-(2)]-hydrazine; B) compounds in which X stands for a thenyl residue which contains as a substituent a carbamoyl, allophanoyl, acylamino or ureido group—e.g.: 1-methyl-2-[5-(*iso*propyl - carbamoyl) - thenyl - (2)]-hydrazine, 1-methyl-2-[5-allophanoyl-thenyl-(2)]-hydrazine; 1-methyl-2-[5-{5-methyl-isoxazolyl - (1) - carbonylamino} - thenyl-(2)]-hydrazine, 1-methyl-2-[5-ureido-thenyl-(2)]-hydrazine; and C) compounds in which X stands for an isoxazolyl residue which contains as a substituent a carbamoyl, allophanoyl, acylamino or ureido group—e.g.: 3-*iso*propyl-carbamoyl - 5 - [(2-methyl - hydrazino)-methyl]-isoxazole, 3-allophanoyl-5-[(2-methyl-hydrazino) - methyl] - isoxazole, 3-[5-methyl-isoxazolyl - (1) - carbonylamino] - 5 - [(2-methyl-hydrazino)-methyl]-isoxazole, 3-ureido-5-[(2-methyl-hydrazino)-methyl]-isoxazole.

The novel hydrazine derivatives of the invention are manfactured according to the process of the invention *either* by reacting methyl-hydrazine, or a methyl-hydrazine in which the hydrazine group is partially substituted by protecting groups such as acyl, alkoxycarbonyl, benzyloxycarbonyl or benzyl, with an agent which yields the moiety $X^1—CH_2—$, wherein X^1 has the same meaning as X or is convertible into X, *or* by methylating a hydrazine which contains such a moiety as a substituent, or such a substituted hydrazine which is partially further substituted by protecting groups such as acyl, alkoxycarbonyl, benzyloxycarbonyl or benzyl, *and*, in either case if necessary, converting the moiety X^1 in the product into X and, also if necessary, splitting off any protecting groups present and, if desired, converting the resulting compound of formula I into an acid addition salt.

One embodiment of the invention consists of reacting methyl-hydrazine, or a methyl-hydrazine in which the hydrazine group is partially substituted by protecting groups, with an agent such as one of the following: 2-(chloro-methyl)-thiophene, 2,5 - bis(chloro-methyl)-thiophene, 3-(bromo-methyl)-thiophene, 3,4-bis(chloro-methyl)-2,5-dimethyl-thiophene, 5-(chloro-methyl)-thiophene-(2)-carboxylic acid methyl ester, 5-(chloro-methyl)-2-bromo-thiophene-(3)-carboxylic acid methyl ester, 5-(chloro-methyl)2-chloro-thiophene, 5-(chloro-methyl)2-acetyl-thiophene, 5-(chloro - methyl) - 2 - acetamido - thiophene, 5 - (chloro - methyl) - 2 - cyano-thiophene, 5-(chloro-methyl)-2-nitro-thiophene, 2 - (chloro-methyl) - furan, 2,5 - bis(chloro-methyl)-furan, 5-(chloro-methyl)-furan-(2)-carboxylic acid methyl ester, 5-(chloro-methyl)-2-carbamoyl-furan, 5-(chloro-methyl)-2-cyano-furan, 2-(chloro-methyl)-pyridine, 3-(chloro-methyl)-pyridine, 4-(chloro-methyl)-pyridine, 6-(chloro-methyl)-pyridine-(3)-carboxylic acid ethyl ester, 6-(chloro-methyl)-3-cyano-pyridine, 2-chloro-methyl)-pyrazine, 5-methyl-3-(chloro-methyl)-isoxazole, 3,5 - dimethyl - 4 - (chloro-methyl)-isoxazole, 5-(chloro-methyl)-isoxazole-(3)-carboxylic acid methyl ester and 4-(chloro-methyl)-oxazole-(3)-carboxylic acid methyl ester. When using a dihalo compound as the agent two mols of methyl-hydrazine may be used—thereby forming compounds bearing two methyl-hydrazino groups.

It is convenient to use the methyl-hydrazine starting material in the form of an alkali-metal salt. This salt may be obtained by treating it with an alkali-metal alcoholate in an alcoholic solution. After removal of the alcohol, the resulting salt is advantageously dissolved in an inert solvent (e.g. N,N-dimethyl-formamide) and reacted with the said agent, preferably at an elevated temperature. The reaction product can be purified by conventional methods; for example, by extraction, crystallization or distillation.

According to a process variant in accordance with the invention, the introduction of the $X^1—CH_2—$ moiety can also be effected by reaction of methyl-hydrazine or 'partially protected' methyl-hydrazine (e.g. 1-methyl-1-acetyl-hydrazine) with the appropriate aldehyde and subsequent reduction of the resulting hydrazone (e.g. by catalytic hydrogenation) and splitting off of the protecting groups. This procedure can suitably be effected by heating the reaction components for a short time in a solvent such as ethanol and reducing the resulting hydrazone with hydrogen in the presence of a hydrogenation catalyst such as palladium or platinum.

According to a further process variant in accordance with the invention a 1,2-di(alkoxycarbonyl)-hydrazine is methylated and then reacted with the agent which yields the moiety $X^1—CH_2—$ and the alkoxycarbonyl groups split off from the product. The methylation can be carried out using the usual methylating agents such as methyl iodide or dimethyl sulphate or by condensation with formaldehyde and hydrogenation of the condensation product. Equimolar amounts of the hydrazine compound and formaldehyde are suitably used and the hydrogenation can be carried out at the same time as the condensation or subsequent thereto. Advantageously it is carried out in the presence of a hydrogenation catalyst such as platinum or palladium until a molar amount of hydrogen is taken up. The condensation/hydrogenation mixture can be worked up in a conventional manner; for example, by distillation.

Where necessary, the conversion of the group X^1 into the group X can be effected at any point. It is advantageous, for example, to prepare substituted-carbamoyl compounds from heterocyclic acids such as 5-[{2-methyl-1,2 - di(benzyloxycarbonyl) - hydrazino}-methyl]-thiophene-(2)-carboxylic acid (itself obtained by saponification of corresponding methyl or ethyl esters) by reaction with amines in accord with known methods of amidation. Suitably, the acid is converted into a reactive derivative such as an acid chloride or a mixed anhydride (e.g. with a carbonic acid monoester) or into an activated ester (e.g. a cyanomethylester). The acid can also be amidated directly by use of a condensation agent such as N,N-di*cyclo*hexyl-carbodiimide. The amides can also be obtained in the presence of a strong acid from cyano compounds such as 5[{2-methyl-1,2-di(benzyl-oxycarbonyl) - hydrazino} - methyl] - 2-cyano-thiophene by reaction with olefins (e.g. *iso*butylene) or secondary or tertiary alcohols. Hydrolysis of the nitriles by means of strong acids or with hydrogen peroxide and alkalis produces N-unsubstituted amides. Protecting groups are subsequently removed from carbamoyl compounds obtained according to this method by hydrogenolysis or treatment with a hydrogen bromide/glacial acetic acid solution. The hydrobromides obtained by the latter method can, if desired, be converted into corresponding free bases and/or into other salts.

The acylamino substituted compounds of the invention are preferably prepared by acylation of an appropriate amino compound which can be obtained, for example, by reduction of the corresponding nitro or azo compound. The acylation can be effected, for example, by use of a reactive derivative of the desired carboxylic acid or sulphonic acid or from the free acid by use of a condensation agent such as N,N-di*cyclo*hexyl-carbodiimide. The subsequent removal of the protecting groups can be effected in ways known *per se;* for example, by hydrogenolysis or hydrolysis with hydrogen bromide in glacial acetic acid. The ureido compounds are accessible from the intermediate amino compounds by treatment with cyanates or *iso*-cyanates, and the guanidino compounds are similarly accessible by treatment with cyan-amide or its derivatives (for example, methyl-*iso*thiourea sulphate).

Amidino and substituted-amidino compounds are advantageously prepared from heterocyclic nitriles having methylhydrazino-methyl-substitutes in which the hydrazine group is substituted by protecting groups *via* the corresponding imido ether which can be obtained by reaction of the nitrile with alcohol and mineral acid. By reaction of the imido ether with ammonia or a primary or secondary amine, the desired amidino compound is obtained. Suitably protected heterocyclic nitriles can also be reacted directly with salts of amines such as *iso*propyl amine hydrochloride or *iso*propyl amine tosylate at elevated temperatures and subsequent removal of the protecting groups. One further method consists of converting a monosubstituted heterocyclic methylhydrazinomethyl-amide in which the hydrazine group is substituted by protecting groups into the corresponding imido halides by reaction with a phosphorus halide (e.g. phosphorus pentachloride) and reacting said halides with ammonia or primary or secondary amines and removing the protecting groups, whereupon amidines and monosubstituted or disubstituted amidines are formed.

The following examples are illustrative of the invention.

Example 1.

A solution of 50.8 g of 1-methyl-1,2-dibenzoyl-hydrazine in 100 ml of N,N-dimethyl-formamide was added dropwise, with stirring and slight cooling to 20°—30° C, to a suspension of 4.8 g of sodium hydride in 100 ml of N,N-dimethyl-formamide. A solution of 23.3 g of 2-(chloro-methyl)-furan in 35 ml of N,N-dimethyl-formamide was then added thereto and the resulting solution permitted to stand for 16 hours at *ca.* 20° C. The greater part of the N,N-dimethyl-formamide was then distilled off under reduced pressure and the residue poured into 1-*N* sodium hydroxide solution, extracted with ether, the extract washed with 1-*N* sodium hydroxide and water, dried over sodium sulphate and evaporated, yielding crystals of 1-methyl - 2 - [furfuryl - (2)] - 1,2 - dibenzoyl-hydrazine melting at 92°—95° C.

44 g of this compound in 430 ml of ethanol was boiled under a nitrogen atmosphere for 15 hours with a solution of 70 g of potassium hydroxide in 60 ml of water. The reaction mixture was then concentrated under reduced pressure, the concentrate saturated with potassium hydroxide, diluted with ether and the precipitated potassium benzoate separated. After separation of the aqueous potassium hydroxide solution, the ether phase was dried over potassium hydroxide, filtered and evaporated. The residual 1-methyl-2-[furfuryl-(2)]-hydrazine was purified by distillation, yielding a colourless oil boiling at 67°—68° C/10 mm Hg.

By treatment of this so-obtained base in acetonitrile with an equivalent amount of *para*toluene-sulphonic acid, there was obtained, upon recrystallization from acetonitrile/ether, the tosylate which melted at 76°—77° C.

Example 2.

51 g of 1-methyl-1,2-dibenzoyl-hydrazine were added to a solution of 4.6 g of sodium in 150 ml of absolute ethanol. The solvents were removed under reduced pressure and

residue suspended in 150 ml of N,N-dimethyl-formamide. 17 g of 2,5-bis(chloro-methyl)-furan were added to this suspension with stirring. The reaction mixture was then heated to 30°—45° C. Following a further temperature increase, the temperature of the reaction mixture was held for one hour at 90° C. Then, most of the N,N-dimethyl-formamide was evaporated under reduced pressure, the residue taken up in water and extracted with methylene chloride. The methylene chloride phase was then washed twice with dilute sodium hydroxide, dried over sodium sulphate and evaporated. The residual dark oil was purified by adsorption on aluminium oxide, followed by elution with acetone/ether. By crystallization from ether there was obtained 2,5 - bis[(2 - methyl-1,2-dibenzoyl-hydrazine)-methyl]-furan melting at 115°—120° C.

33 g of this compound were heated under reflux for 8 hours with a solution of 50 g of potassium hydroxide in 50 ml of water and 350 ml of ethanol. The reaction mixture was then concentrated to dryness under reduced pressure, the residue extracted with ether, dried over sodium sulphate and evaporated. The residual 2,5-bis[(2-methyl-hydrazino)-methyl]-furan was purified by distillation under reduced pressure and boiled at 130°—135° C/1.5 mm Hg.

Example 3.

110 g of 1-methyl-1,2-dibenzoyl-hydrazine were added to a solution of 10 g of sodium in 500 ml of absolute ethanol and then, in the course of 0.5 hour and at the boil, 58 g of 2-(chloro-methyl)-thiophene were added to the reaction mixture. The resulting mixture was heated under reflux for 2 hours. After it had cooled down, the precipitated sodium chloride was separated, the filtrate concentrated under reduced pressure and the residue taken up in ether and sodium hydroxide. The ether phase was extracted several times with 1-*N* sodium hydroxide and water and then dried over sodium sulphate. The solvents were then evaporated off, yielding 1-methyl-2-[thenyl-(2)]-1,2-dibenzoyl-hydrazine as crystals melting at 116°—118° C.

A solution of 42 g of this compound in 415 ml of ethanol was heated for 6 hours under a nitrogen atmosphere and under reflux with a solution of 65 g of potassium hydroxide in 58 ml of water. The solvents were distilled off under reduced pressure and the residue treated until saturated with solid potassium chloride, diluted with ether, and the precipitated potassium benzoate separated. After separation of the aqueous potassium hydroxide solution, the ether phase was dried over potassium hydroxide, filtered and the filtrate evaporated. The residual 1-methyl-2-[thenyl-(2)]-hydrazine was purified by distillation and formed a colourless oil which boiled at 96°—98° C/11 mm Hg.

Treatment of this compound with an equivalent amount of *para*toluene-sulphonic acid in acetonitrile followed by recrystallization from acetonitrile/ether yielded the tosylate which melted at 113°—114° C.

Example 4.

A solution of 63.5 g of 1-methyl-1,2-dibenzoyl-hydrazine in 160 ml of N,N-dimethyl-formamide was added, with stirring and slight cooling to 20°—30° C, to a suspension of 6 g of sodium hydride in 100 ml of N,N-dimethyl-formamide. To this mixture was then added a solution of 22.7 g of 2,5-bis(chloro-methyl)-thiophene in 80 ml of N,N-dimethyl-formamide and the resulting mixture was permitted to stand for 12 hours at *ca* 20° C. The greater part of the N,N-dimethyl-formamide was then distilled off under reduced pressure, the residue poured into 1-*N* sodium hydroxide solution, extracted with a mixture of ether and methylene chloride, the extract washed with 1-*N* sodium hydroxide, dried over sodium sulphate, filtered over activated charcoal and evaporated. The residue was recrystallized from (methylene chloride)/ether yielding 2,5 - bis[(2 - methyl-1,2-dibenzoyl-hydrazino)-methyl]-thiophene melting at 178°—179° C.

60 g of this compound in 950 ml of ethanol were boiled for 15 hours under a nitrogen atmosphere with a solution of 100 g of potassium hydroxide in 85 ml of water. The reaction mixture was then concentrated under reduced pressure, the concentrate saturated with solid potassium hydroxide and treated with ether. The aqueous hydroxide was then separated, the ether phase dried over ~~potassium~~ hydroxide, filtered and evaporated. The residual 2,5-bis[(2-methyl-hydrazino)-methyl]-thiophene, a yellowish viscous oil, boiled at 118°—120° C/0.02 mm Hg.

The dihydrochloride was prepared from the foregoing base by treatment with ethanolic hydrogen chloride and, upon recrystallization from methanol/ether, melted at 155° C (decomposition).

Example 5.

31.4 g of 1-methyl-1,2-di(benzyloxy-carbonyl)-hydrazine were added to a solution of 5.4 g of sodium in 300 ml of absolute ethanol and the resulting mixture evaporated under reduced pressure to a syrup. This was then dissolved in 120 ml of N,N-dimethyl-formamide and, after the gradual addition of 22 g of 3-(chloro-methyl)-pyridine hydrochloride, heated for one hour on the steam-bath. The mixture was then poured into 1 litre of water, the resulting oil extracted with ether and the basic part of the ether extract removed by twice extracting with 200 ml of 3-*N* hydrochloric acid. The hydrochloric acid

solution was rendered alkaline with sodium hydroxide, the separated bases extracted with ether, the ether extract dried over potassium charbonate and concentrated under reduced pressure. The so-obtained intermediate was hydrogenolysed without purification. The hydrogenolysis was effected by dissolving the product in 300 ml of methanol and hydrogenating in the presence of palladium/carbon. After the hydrogen absorption had terminated, the catalyst was filtered off, the solution evaporated under reduced pressure and the residue purified by fractional distillation. The so-obtained 1-methyl-2-[pyridyl-(3)-methyl]-hydrazine formed a light yellow oil which boiled at 135°—140° C/10 mm Hg., and was readily soluble in water.

EXAMPLE 6.

The procedure described in Example 5 was followed using 22 g of 4-(chloro-methyl)-pyridine hydrochloride. After termination of the hydrogenation, the solution was evaporated under reduced pressure and the residue treated with ethanolic oxalic acid. The so-obtained 1-methyl-2-[pyridyl-(4) - methyl] - hydrazine oxalate melted at 118°—120° C and was readily soluble in water.

EXAMPLE 7.

The procedure described in Examples 5 and 6 was followed using 22 g of 2-(chloro-methyl)-pyridine hydrochloride. The so-obtained 1-methyl-2-[pyridyl-(2)-methyl]-hydrazine oxalate melted at 129°—130° C.

EXAMPLE 8.

31.5 g of 1-methyl-1,2-di(benzyloxy-carbonyl)-hydrazine were added to a solution of 2.3 g of sodium in 200 ml of absolute ethanol and the resulting solution evaporated under reduced pressure. The residual syrup was dissolved in 150 ml of N,N-dimethyl-formamide and treated with a solution of 14.5 g of 3,5-dimethyl-4-(chloro-methyl)-isoxazole in a small amount of N,N-dimethyl-formamide. The reaction was exothermic and terminated after 0.5 hour. The reaction mixture was then diluted with water, extracted with methylene chloride and the methylene chloride extracts washed twice with water, dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by distillation *in vacuo*, yielding 1-methyl - 2 - [{3,5 - dimethyl - isoxazolyl-(4)} - methyl] - 1,2 - di(benzyloxycarbonyl)-hydrazine as a highly viscous yellowish oil boiling at 230°—240° C/0.1 mm Hg.

32 g of the so-obtained intermediate were poured with stirring into 120 ml of a 33% solution of hydrogen bromide in glacial acetic acid and the resulting mixture stirred for a further 2 hours. The reaction mixture was then evaporated under reduced pressure, the residue taken up in water and the benzyl bromide removed by extraction with ether. The aqueous solution was then concentrated under reduced pressure, the residue dissolved in absolute ethanol and treated until turbidity with ethyl acetate. The precipitated 1-methyl-2 - [{3,4 - dimethyl - isoxazolyl - (4)} - methyl]-hydrazine hydrobromide melted at 147°—148° C.

EXAMPLE 9.

31.5 g of 1-methyl-1,2-di(benzyloxy-carbonyl)-hydrazine, 2.3 g of sodium and 13.1 g of 5-methyl-3-(chloro-methyl)-isoxazole were reacted according to the procedure set forth in Example 8. The condensation product, a thick yellowish oil, boiled at 245°—250° C/0.1 mm Hg. By solvolysis with (hydrogen bromide)/(glacial acetic acid) there was obtained a non-crystallizable hydrobromide which was dissolved in water and the bromine ion exchanged for oxalate ion by the use of a column of a polystyrene quaternary ammonium type anion exchange resin (oxalate form). The eluted aqueous phase was concentrated under reduced pressure and the separated residue was recrystallized from absolute ethanol, yielding 1-methyl-2-[{5-methyl - isoxazolyl - (3)} - methyl] - hydrazine oxalate which melted at 135°—137° C.

EXAMPLE 10.

31 g of 1methyl-1,2-di(benzyloxycarbonyl)-hydrazine with 17.5 g of 3-(dimethylamino-methyl)-indole and a solution of a small amount of pulverized potassium hydroxide in 250 ml of toluene were boiled under reflux for 48 hours. The hot toluene solution was then filtered and the filtrate twice extracted, each time with 100 ml of 3-*N* hydrochloric acid in order to remove excess 3-(dimethyl-amino-methyl)-indole. The toluene solution was then dried over sodium sulphate, filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in 300 ml of methanol and hydrogenated in the presence of palladium/carbon. After termination of the hydrogen absorption, the catalyst was filtered off, the residue dissolved with slight warming in 60 ml of absolute ethanol, and ethanolic hydrochloric acid added thereto to a pH of 5. Then, the solution was slowly diluted with 200 ml of ethyl acetate. After standing for 12 hours in the cold, the product, 1-methyl-2-[{indolyl-(3)}-methyl] - hydrazine hydrochloride separated out and formed crystals melting at 125°—126° C.

EXAMPLE 11.

31.5 g of 1-methyl-1,2-di(benzyloxy-carbonyl)-hydrazine were added to a solution of 2.3 g of sodium in 200 ml of absolute ethanol and, after the addition of 30.3 g of 3 - (dimethylamino - methyl) - dibenzofuran methylsulphonate, the mixture was boiled under reflux for 3 hours. The evolution of

dimethyl amine, which was strong at first, ceased almost completely in the course of this time. The reaction mixture was then diluted with water, extracted with methylene chloride, the extract shaken with 3-*N* hydrochloric acid, dried over sodium sulphate, and evaporated under reduced pressure. The residue was dissolved in 300 ml of methanol and hydrogenated in the presence of palladium/carbon. After termination of the hydrogen absorption, the catalyst was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in absolute ethanol and the solution treated with ethanolic hydrochloric acid. At a pH of 5, a hydrochloride spontaneously precipitated. The mixture was then permitted to stand for 12 hours in the cold, during which time further crystallization occurred. The crystals were filtered off and washed with ether, yielding 1-methyl-2-[{dibenzofuranyl-(3)}-methyl]-hydrazine hydrochloride melting at 205°—207° C.

EXAMPLE 12.

To a suspension of 6 g of sodium hydride in 100 ml of N,N-dimethyl-formamide, there was added dropwise, while stirring and slight cooling at 20°—30° C, a solution of 63.5 g of 1-methyl-1,2-dibenzoyl-hydrazine in 160 ml of N,N-dimethyl-formamide. Then, a solution of 26 g of 3,4-bis(chloro-methyl)-2,5-dimethyl-thiophene in 80 ml of N,N-dimethyl-formamide was added thereto and the mixture allowed to stand for 15 hours at *ca.* 20° C. The major part of the N,N-dimethyl-formamide was eliminated under reduced pressure, the residue was poured into 1-*N* sodium hydroxide solution, extracted with a mixture of ether and methylene chloride, the extract was washed with 1-*N* sodium hydroxide solution and with water and the ether/(methylene chloride) phase dried over sodium sulphate and concentrated. The residue was recrystallized from (methylene chloride)/ether. There was thus obtained 3,4-bis[(2-methyl-1,2 - dibenzoyl - hydrazino) - methyl] - 2,5-dimethyl-thiophene of melting point 198°—200° C. 100 g of this intermediate product were boiled for 14 hours under nitrogen with 1500 ml of ethanol together with a solution of 160 g of potassium hydroxide in 137 ml of water. The reaction mixture was then concentrated under reduced pressure, the concentrate saturated with solid potassium hydroxide and extracted with ether. After elimination of the aqueous potassium hydroxide solution, the ether phase was dried over potassium hydroxide and fractionated *in vacuo*. There was thus obtained 3,4-bis [(2 - methyl - hydrazino) - methyl] - 2,5-dimethyl-thiophene as a yellowish viscous oil of boiling point 130° C/0.1 mm Hg. The dihydrochloride prepared therefrom by means of alcoholic hydrochloric acid melted at 225°—225.5° C after recrystallization from methanol/ether.

EXAMPLE 13.

26 g of 5-[{2-methyl-1,2-di(benzyloxy-carbonyl) - hydrazino} - methyl] - thiophene-(2)-carboxylic acid were heated under reflux for 2 hours with 100 ml of benzene and 15 ml of thionyl chloride. The excess thionyl chloride and the benzene were distilled off *in vacuo* and the residue was again concentrated twice *in vacuo* with 100 ml of absolute benzene each time. The 5-[{2-methyl-1,2-di(benzyloxycarbonyl) - hydrazino} - methyl]-thiophene-(2)-carboxylic acid chloride obtained as a yellowish viscous oil was dissolved in 100 ml of methylene chloride and slowly reacted, while stirring and cooling with ice-water, with a solution of 11 ml of *iso*propyl amine and 50 ml of methylene chloride. Then, the solution was allowed to stand for 15 hours at *ca* 20° C, then poured on to about 200 ml of water. 500 ml of ether were added thereto and the mixture was well shaken. The organic phase was separated, washed with water, 1% sodium carbonate solution and again with water and dried over sodium sulphate. The filtered solution was concentrated *in vacuo* and there was thus obtained 1-methyl-2-[5-{*iso*-propyl - carbamoyl} - thenyl - (2)] - 1,2-di(benzyloxycarbonyl)-hydrazine as a yellow-brown viscous oil. This was dissolved in 20 ml of glacial acetic acid and reacted with 100 ml of a 33% solution of hydrobromic acid in glacial acetic acid. After standing for 3 hours at *ca.* 20° C, 1 litre of absolute ether was added, the solution decanted from the the viscous oil which separated, the latter dissolved in 50 ml of water and the aqueous solution extracted with 500 ml of ether. The aqueous phase was separated, treated with solid potassium carbonate under nitrogen while cooling with ice until completely saturated, and extracted with methylene chloride. The methylene chloride extract was dried with potassium carbonate and concentrated *in vacuo*, the residue dissolved in 50 ml of *iso*propanol and treated with one equivalent of alcoholic hydrochloric acid. The 1-methyl-2 - [5 - {*iso*propyl - carbamoyl} - thenyl-(2)]-hydrazine hydrochloride crystallized from the solution on standing. Melting point= 141°—143° C after recrystallization from methanol/ether.

The acid used as starting material was obtained as follows: To a suspension of 13.5 g of sodium hydride in 50 ml of N,N-dimethyl-formamide were added dropwise, while stirring and slight cooling at 20°—30° C a solution of 177 g of 1-methyl-1,2-di (benzyloxycarbonyl)-hydrazine in 150 ml of N,N-dimethyl-formamide. As soon as the evolution of hydrogen had ceased and the solution was complete, there was added dropwise a solution of 102.5 g of 5-(chloro-

methyl)-thiophene-(2)-carboxylic acid methyl ester in 60 ml of N,N-dimethyl-formamide, whereby the temperature was kept below 30° C by cooling. Stirring was then continued for a further 3 hours at *ca.* 20° C, the reaction mixture poured on to 2 litres of ice-water and extracted with ether. The ether extract was concentrated and the residue dissolved in 400 ml of of dioxan and stirred for 15 hours at *ca.* 20° C with a solution of 22 g of sodium hydroxide in 150 ml of water. The mixture was then poured on to about 2 litres of water and the unsaponifiable substance was extracted with ether. The aqueous phase was made slightly acid to congo red by means of concentrated hydrochloric acid and the acid which precipitated was extracted with ether. The ether extract was washed neutral with water, dried over sodium sulphate and then concentrated. There was thus obtained 5-[{2-methyl-1,2-di(benzyloxycarbonyl) - hydrazino} - methyl] - thiophene-(2)-carboxylic acid as a yellowish viscous oil which was sufficiently pure enough for the next step.

EXAMPLE 14.

6 g of urea, 47.3 g of 5-[{2-methyl-1,2-di(benzyloxycarbonyl) - hydrazino} - methyl]-thiophene-(2)-carboxylic acid chloride, 8 g of pyridine and 200 ml of benzene were mixed and boiled for 8 hours while stirring. The mixture was cooled, poured on to water and extracted with an ether/(methylene chloride) mixture. The extract was washed with water, 1% hydrochloric acid, 1% sodium carbonate solution and again with water, dried over sodium sulphate and the solvent distilled off. The residual 1-methyl-2-[5-allophanoyl-thenyl - (2)] - 1,2 - di(benzyloxycarbonyl)-hydrazine, as a viscous yellow oil, was dissolved in 30 ml of glacial acetic acid and treated with 100 ml of a 33% solution of hydrobromic acid in glacial acetic acid. After standing for 3 hours, the dihydrobromide of 1 - methyl - 2 - [5 - allophanoyl - thenyl-(2)]-hydrazine which crystallized out was filtered off and washed with (glacial acetic acid)/ether (4:1) and with ether.

EXAMPLE 15.

25 g of 5-[{2-methyl-1,2-di(benzyloxycarbonyl) - hydrazino} - methyl] - furan - (2)-carboxylic acid were transformed into the acid chloride in the same way as thiophene-(2)-carboxylic acid (See example 13). The acid chloride obtained was reacted with *iso*propyl amine as described in example 13 to obtain 5 - methyl - 2 - [5 - {*iso*propyl - carbamoyl}-furfuryl - (2)] - 1,2 - di(benzyloxycarbonyl)-hydrazine. The intermediate substance obtained was dissolved in 250 ml of methanol and debenzyloxycarbonylated by shaking in a hydrogen atmosphere in the presence of palladium/carbon. Once the reaction was over, there was added one equivalent of alcoholic hydrochloric acid, the catalyst filtered off and the filtrate concentrated. On treating the concentrate with acetonitrile and ether, there was obtained a crystalline precipitate consisting of 1-methyl-2-[5-{*iso*propyl-carbamoyl}-furfuryl-(2)]-hydrazine hydrochloride melting at 121°—123° C.

The acid used as starting material was obtained in a similar way as thiophene-(2)-carboxylic acid (See example 13) starting from 5 - (chloro-methyl)-furan-(2)-carboxylic acid methyl ester.

EXAMPLE 16.

40 g of 5-[{2-methyl-1,2-di(benzyloxycarbonyl) - hydrazino} - methyl] - thiophene-(2)-carboxylic acid chloride were dissolved in 100 ml of ether and added dropwise during 1 hour, while stirring at 0°—5° C, to 100 ml of concentrated aqueous ammonia. Stirring was continued for a further 15 hours at 0°—5° C, the reaction mixture poured on to 1 litre of ether, the aqueous layer separated and the ether phase washed with water, 1% hydrochloric acid, 1% sodium carbonate solution and again with water. After drying with sodium sulphate, the ether was distilled off and the residue dissolved in 30 ml of glacial acetic acid and reacted with 140 ml of a 33% solution of hydrobromic acid in glacial acetic acid. The solution was allowed to stand for 2 hours, whereupon the crystallized product was filtered off and washed with glacial acetic acid and with ether. There was thus obtained 1-methyl-2-[5-carbamoyl-thenyl-(2)]-hydrazine dihydrobromide.

EXAMPLE 17.

320 g of 5-[{2-methyl-1,2-di(benzyloxycarbonyl) - hydrazino} - methyl] - thiophene-(2)-carboxylic acid were dissolved in 320 ml of absolute benzene and heated under reflux for 2 hours with 76 ml of thionyl chloride. Then, the reaction mixture was concentrated *in vacuo* and twice distilled with 250 ml of benzene each time until all excess thionyl chloride was eliminated. Then the viscous oily residual acid chloride was dissolved in acetone and added dropwise to a solution of ammonium thiocyanate in acetone, whereby ammonium chloride immediately precipitated. Then, the mixture was heated to the boil for 5 minutes. The precipitated salt was filtered off and the filtrate concentrated *in vacuo*. The residue, containing the corresponding acyl isothiocyanate, was dissolved in absolute benzene and saturated with gaseous ammonia. The reaction mixture ws boiled for a short while and again cooled down, washed with water and concentrated *in vacuo*. There was thus obtained about 400 g of 5-[{2-methyl-1,2-di(benzyloxycarbonyl) - hydrazino} - methyl]-thiophene-(2)-carbonyl-thiourea which were dissolved in 700 ml of a 30% solution of hydrobromic acid in glacial acetic acid. The

evolution of carbon dioxide started immediately and after some time a yellow precipitate formed. After standing for 16 hours at *ca.* 20° C, the precipitate was filtered off under suction, washed at first with glacial acetic acid, then with ether and finally recrystallized from *iso*propanol. There was thus obtained 5-[(2-methyl-hydrazino)-methyl]-thiophene-(2)-carbonyl-thiourea as a cream-coloured powder melting at 195°—197° C (decomposition).

The following examples illustrate the manner in which the novel hydrazine derivatives may be made up into pharmaceutical preparations.

EXAMPLE A.

Preparation of capsules containing:

1 - methyl - 2 - [5 - {*iso*propyl-carbamoyl} - thenyl - (2)]-hydrazine hydrochloride - -	50 mg
mannitol - - - - - -	145 mg
talc - - - - - - -	15 mg
	210 mg

The active substance was homogeneously mixed with the other ingredients, sieved through a number 5 sieve (mesh opening about 0.23 mm) and mixed again. The substance was then filled into gelatin capsules (No. 2).

EXAMPLE B.

Preparation of capsules containing:

2,5 - bis[(2 - methyl - hydrazino) - methyl] - furan - -	25 mg
mannitol - - - - - -	90 mg
talc - - - - - - -	5 mg
	120 mg

The active substance was homogeneously mixed with the other ingredients, sieved through a number 5 sieve (mesh opening about 0.23 mm) and mixed again. The substance was then filled into gelatin capsules (No. 4).

EXAMPLE C.

Preparation of 300 mg dragées containing the following ingredients:

a) kernel

1 - methyl - 2 - [5 - {*iso*propyl-carbamoyl} - thenyl - (2)]-hydrazine hydrochloride - -	50 mg
mannitol - - - - - -	80 mg
talc - - - - - - -	5 mg
corn starch - - - - -	15 mg
total weight of the kernel	150 mg

b) coating:

This contained 90% sugar, 5% rice starch and 5% talc to a weight of 150 mg.

The active substance was mixed with mannitol and sieved through a No. 5 sieve (mesh opening about 0.23 mm). The corn starch was boiled with water to form a 10% paste with which the (active substance)/mannitol mixture was mixed until homogeneous. The slightly moist mass was granulated using a No. 3 sieve (mesh opening about 1.0 mm). The granulate was dried and mixed with the talc. The whole mixture was pressed to biconvex kernels of 150 mg and 8.0 mm diameter.

These kernels were coated according to usual methods with sugar syrup until an end weight of 300 mg was attained.

EXAMPLE D

Preparation of 200 mg dragées containing:

a) kernel

1 - methyl - 2 - [pyridyl-(3)-methyl]-hydrazine -	25.0 mg
mannitol - - - - -	60.0 mg
talc - - - - - -	5.0 mg
corn starch - - - -	10.0 mg
weight of kernel	100.0 mg

b) coating

This comprised 90% sugar, 5% rice starch and 5% talc to a weight of 100 mg.

These dragées were prepared in the same manner as described in Example C.

WHAT WE CLAIM IS:—

1) Compounds of the formula

$$X—CH_2—NH—NH—CH_3$$

, wherein X is a mononuclear or polynuclear oxygen-, nitrogen- and/or sulphur-containing heterocyclic residue which may contain one or more of the substituents defined hereinbefore, and acid addition salts thereof.

2) Compounds as formulated in claim 1, wherein the substituents are alkyl, trifluoromethyl, cyano, mercapto, alkyl-thio, amino, acyl-amino, ureido, (alkylsulphonyl)-amino, guanidino, amidino, amino-alkyl, carbamoyl, allophanoyl, sulphamoyl, nitro, (2-methyl-hydrazino)-methyl, acyl or phenyl groups or halogen atoms, and acid addition salts thereof.

3) 1-Methyl-2-[5-{*iso*propyl-carbamoyl}-thenyl-(2)]-hydrazine hydrochloride.

4) 2,5-Bis[(2-methyl-hydrazino)-methyl]-furan.

5) 1 - Methyl - 2 - [pyridyl](3) - methyl]-hydrazine.

6) 1-Methyl-2-[furfuryl-(2)]-hydrazine.

7) 1-Methyl-2-[thenyl-(2)]-hydrazine.

8) 2,5-Bis[(2-methyl-hydrazino)-methyl]-hydrazine.

9) 1 - Methyl - 2 - [pyridyl - (4) - methyl]-hydrazine oxalate.

evolution of carbon dioxide started immediately and after some time a yellow precipitate formed. After standing for 16 hours at *ca.* 20° C, the precipitate was filtered off under suction, washed at first with glacial acetic acid, then with ether and finally recrystallized from *iso*propanol. There was thus obtained 5-[(2-methyl-hydrazino)-methyl]-thiophene-(2)-carbonyl-thiourea as a cream-coloured powder melting at 195°—197° C (decomposition).

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$$X—CH_2—NH—NH—CH_3$$

, wherein X is a mononuclear or polynuclear oxygen-, nitrogen- and/or sulphur-containing heterocyclic residue which may contain one or more of the substituents defined hereinbefore, and acid addition salts thereof.

2) Compounds as formulated in claim 1, wherein the substituents are alkyl, trifluoromethyl, cyano, mercapto, alkyl-thio, amino, acyl-amino, ureido, (alkylsulphonyl)-amino, guanidino, amidino, amino-alkyl, carbamoyl, allophanoyl, sulphamoyl, nitro, (2-methyl-hydrazino)-methyl, acyl or phenyl groups or halogen atoms, and acid addition salts thereof.

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4) 2,5-Bis[(2-methyl-hydrazino)-methyl]-furan.

5) 1 - Methyl - 2 - [pyridyl](3) - methyl]-hydrazine.

6) 1-Methyl-2-[furfuryl-(2)]-hydrazine.

7) 1-Methyl-2-[thenyl-(2)]-hydrazine.

8) 2,5-Bis[(2-methyl-hydrazino)-methyl]-hydrazine.

9) 1 - Methyl - 2 - [pyridyl - (4) - methyl]-hydrazine oxalate.

10) 1 - Methyl - 2 - [pyridyl - (2) - methyl] - hydrazine oxalate.

11) 1 - Methyl - 2 - [{3,4 - dimethyl-isoxazolyl - (4)} - methyl] - hydrazine hydrobromide.

12) 1 - Methyl - 2 - [{5 - methyl-isoxazolyl-(3)}-methyl]-hydrazine oxalate.

13) 1 - Methyl - 2 - [{indolyl-(3)}-methyl]-hydrazine hydrochloride.

14) 1 - Methyl - 2 - [{dibenzofuranyl-(3)}-methyl]-hydrazine hydrochloride.

15) 3,4 - Bis[(2 - methyl - hydrazino)-methyl]-2,5-dimethyl-thiophene and its dihydrochloride.

16) 1 - Methyl - 2 - [5 - allophanoyl-thenyl-(2)]-hydrazine dihydrobromide.

17) 1 - Methyl - 2 - [5 - {*iso*propyl-carbamoyl}-furfuryl-(2)]-hydrazine hydrochloride.

18) 1 - Methyl - 2 - [5 - carbamoyl-thenyl-(2)]-hydrazine dihydrobromide.

19) 5 - [(2 - Methyl-hydrazino) - methyl]-thiophene-(2)-carbonyl-thiourea.

20) A pharmaceutical preparation comprising a derivative as claimed in claim 1 in association with a compatible pharmaceutical carrier.

21) A process for the manufacture of the derivatives claimed in claim 1 which process comprises *either* reacting methyl-hydrazine, or a methyl-hydrazine in which the hydrazine group is partially substituted by protecting groups such as acyl, alkoxycarbonyl, benzyloxycarbonyl or benzyl, with an agent which yields the moiety $X^1—CH_2—$, wherein X^1 has the same meaning as X or is convertible into X, *or* methylating a hydrazine which contains such a moiety as a substituent, or such a substituted hydrazine which is partially further substituted by protecting groups such as acyl, alkoxycarbonyl, benzyloxycarbonyl or benzyl, *and*, in either case if necessary, converting the moiety X^1 in the product into X and, also if necessary, splitting off any protecting groups present and, if desired, converting the resulting compound as formulated in claim 1 into an acid addition salt.

22) A process in accordance with claim 21, wherein the methyl hydrazine starting material is used in the form of an alkali-metal salt.

23) A variation of the process claimed in claim 21, wherein the appropriate aldehyde is used instead of said agent and the hydrazone reaction product reduced by catalytic hydrogenation.

24) A further variation of the process claimed in claim 21, wherein a 1,2-di(alkoxycarbonyl)-hydrazine is methylated and then reacted with the agent which yields the moiety $X^1—CH_2—$ and the alkoxycarbonyl groups split off from the product.

25) A process for the manufacture of the derivatives as claimed in claim 1, substantially as described with reference to the examples given.

26) Compounds of the formula set forth in claim 1, and acid addition salts of same, when manufactured by the process claimed in any one of claims 21 to 25 inclusive.

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