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COMPLETE SPECIFICATION

Novel Hydrazine Derivatives and Salts 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:—

The present invention is concerned with novel hydrazine derivatives and salts and a process for the manufacture thereof.

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

$$A—NH—NH—CH_3 \qquad I$$

, in which 'A' is a saturated or unsaturated aliphatic hydrocarbon radical which, when a saturated chain contains, or which otherwise may contain, one or more substituents of the kind to be described later, and the corresponding compounds in which the fragment —NH—NH— is replaced by the fragment —N=N— or —N(→O)=N—. The salts provided by the invention are acid addition salts of the formulated compounds. Both the compounds and their acid addition salts are active cytostatic agents. They inhibit the growth of transplantable tumours in both mice and rats. Thus, they are active against WALKER tumours, ERLICH carcinoma, ERLICH ascites carcinoma and the like. They also cause decomposition of macromolecule desoxyribonucleic acid in solution. They can be administered internally in the form of conventional pharmaceutical preparations; for example, the bases or their pharmaceutically acceptable acid addition salts can be administered in conventional enteral or parenteral pharmaceutical excipients containing organic and/or inorganic inert carriers such as water, gelatine, lactose, starch, magnesium stearate, talc, plant oils, gums, alcohol and petroleum jelly. The pharmaceutical preparations can be in conventional solid forms (tablets, dragées, suppositories, capsules or the like) or conventional liquid forms (suspensions, emulsions or the like). If desired, the preparations can be sterilized and/or contain conventional pharmaceutical adjuvants such as preservatives, stabilizing agents, wetting agents, emulsifying agents, buffers or salts useful for the adjustment of osmotic pressure. The preparations can also contain other therapeutically active materials.

It will be appreciated that the saturated or unsaturated aliphatic hydrocarbon radicals comprehended by 'A' in the foregoing formula can be alkyl, *cyclo*alkyl, alkenyl or *cyclo*alkenyl radicals. The substituents to which reference has been made are: 1) Halogen atoms such as fluorine and chlorine. 2) Cyano. 3) Carboxy (which may be esterified). 4) Hydroxy-alkyl such as hydroxymethyl and hydroxy-ethyl or esterified hydroxy-alkyl (for example, esterified with lower-alkanoic acids such as acetic acid or aralkanoic acids such as benzoic acid) or etherified hydroxy-alkyl (for example, etherified with lower-alkyl, lower-alkenyl or aralkyl groups—such as acetoxy, benzoyloxy, meth-

oxy, allyloxy and benzyloxy). 5) Lower alkylthio such as methyl-thio and butyl-thio. 6) Amino-alkyl groups, the amino residue of which may be mono- or disubstituted (such as amino-methyl, methylamino-ethyl, dimethylamino-methyl and diethylamino-propyl), and methylhydrazinoalkylamino-alkyl groups (such as 2-methylhydrazino-ethylamino-methyl) in which the remaining hydrogen atom of the amino group may be replaced by the benzyloxycarbonyl radical. 7) Amino-alkoxy groups, the amino moiety of which may be mono- or disubstituted, such as 2-amino-ethoxy, 1-methyl-2-ethyl-amino-ethoxy and 3-dimethylamino-propoxy. 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. acetyl - amino, N - acetyl - N - methyl-amino, N - [2 - (2 - methyl - hydrazino) - ethyl] - acetyl - amino and pivaloyl-amino). 8(b) Acyl-amino groups wherein the acyl moiety is the residue of a naturally occuring α-amino acid (e.g. alanyl-amino). 8(c) Other aliphatic acyl-amino groups (e.g. succinimido). 8(d) Aroyl-amino groups (e.g. benzoyl-amino and phthalimido). 8(e) Heterocyclic acyl-amino groups wherein the hetero residue is a nitrogen and/or oxygen containing 5- or 6-membered heterocyclic ring containing one or two hetero atoms and optionally bearing further substituents such as lower-alkyl groups [e.g. nicotinoyl-amino, *iso*-nicotinoyl - amino, (methyl - *iso*xazolylcar - bonyl)-amino and (methyl-oxazolylcarbonyl)-amino]. 9) Ureido or thioureido 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, hydroxyethyl - ureido, [2 - (2 - methyl - hydrazina) - ethyl] - ureido]. 10) 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*propyl - guanidino, (hydroxy - ethyl) - guanidino. 11) 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 be further functional groups [e.g., methyl-amidino, di-*iso*propyl - amidino, *cyclo*propyl - amidino, phenyl - amidino, benzyl - amidino, iso - xazolyl - amidino and (hydroxy - ethyl) - amidino. 12) Carbamoyl groups in which the hydrogen atoms can be replaced by saturated or unsaturated aliphatic, alicyclic or aromatic 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, N - *tert*octyl - carbamoyl, N - phenyl - carbamoyl, N - hydroxyalkyl - carbamoyl such as hydroxyethyl - carbamoyl, N - alkyl - thioalkyl - carbamoyl groups such as methyl-thioethyl - carbamoyl, N - carbamoylalkyl - carbamoyl groups such as carbamoylmethyl-carbamoyl, N - alkylsulphonylalkyl - carbamoyl groups such as methylsulphonylethyl-carbamoyl, N - (halo - alkyl) - carbamoyl groups such as (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,N - dialkylaminoalkyl - carbamoyl groups such as N - (β - methylamino - ethyl) - carbamoyl and N,N - (diethylamino - ethyl) - carbamoyl, N - methylhydrazinoalkyl - carbamoyl groups such as N-[β-(β-methyl-hydrazino) - ethyl] - carbamoyl and N,N - alkylene-carbamoyl groups such as N,N-tetramethylene - carbamoyl and N,N - pentamethylene-carbamoyl. 13) 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. allophanoyl, 4-methyl-allophanoyl and 2-*iso*propyl-allophanoyl. 14) Lower alkylsulphonyl groups such as methylsulphonyl. 15) (2 - Methyl-hydrazino) - methyl. 16) Acyl radicals of lower-aliphatic carboxylic acid such as formic, acetic and propionic acids and of aromatic carboxylic acids such as benzoic acid. 17) Methylhydrazino-(lower-alkoxy) radicals such as β-(β-methyl-hydrazino)-ethoxy. 18) Methylhydrazino-(lower-alkylcarbonyl) radicals such as β-(β-methyl-hydrazino)-acetyl.

Some preferred compounds within the scope of formula I are: 1,3 - bis(β-methyl-hydrazino) - propane, 1,4 - bis(β - methyl - hydazino) - butane, 1,3 - bis(β - methyl - hydazino) - 2 - methyl - propane, 1,4 - bis (β - methyl - hydrazino) - butene - (2), *cis* 1,2 - bis(β methyl - hydrazino) - *cyclo* - propane, *trans* 1,2-bis(β-methyl-hydrazino)-*cyclo*propane and 1-methyl-2-[3-chloro-buten-(2)-yl]-hydrazine.

According to the process provided by the invention, the novel hydrazine derivatives aforesaid are manufactured *either* by reacting methyl-hydrazine or a methyl-hydrazine in which the hydrazine is partially substituted

by protecting groups such as acyl, alkoxycarbonyl, benzyloxycarbonyl or benzyl, with a compound which yields the radical A^1 (wherein A^1 has the same meaning as A hereinbefore or is a radical (which is convertible into A) *or* by methylating a hydrazine which contains such a radical as a substituent or a hydrazine which not only contains such a radical as a substituent but is also partially further substituted by protecting groups such as acyl, alkoxycarbonyl, benzyloxycarbonyl or benzyl, *and*, in either case if necessary, converting the radical A^1 in the product into A 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—said compound of formula I or acid addition salt being then, if desired, oxidized to the corresponding azo or azoxy compound.

One embodiment of the process provided by the present invention consists in reacting methyl-hydrazine or a methyl-hydrazine in which the hydrazine group is partially substituted by protecting groups with a compound which yields the radical A^1. This embodiment can be carried out using an agent such as one of the following: 1,2-dibromo - ethane, 1,3 - dibromo - propane, 1,3 - dibromo - 2 - methyl - propane, 1,4 - dibromo - butane, 1,5 - dibromo - pentane, 1,3 - dibromo - 2 - methoxy - propane, bis(2 - bromo - ~~methyl~~ ethyl) - ether, ethyl bromoacetate, bromo - acetanilide, N - (β - chloro - ethyl) - chloro - acetamide, chloro - acetonitrile, N,N - bis(β - chloro - ethyl) - ethyl amine, N,N - bis(β - chloro - ethyl) - carbamic acid benzyl ester, N,N-bis(β-chloro - ethyl) - acetamide, 1,1 - bis(β - chloro - ethyl) - urea, 1,3 - bis(β - chloro - ethyl) - urea, chloro - acetone, 1,3 - di - chloro - acetone, 1,4 - dibromo - butene - (2), 1,3 - dichloro - butene - (2), 1,2 - bis (iodo - methyl) - *cyclo*propane or 1,3 - bis (*para*tosyloxymethyl)-*cyclo*hexane.

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 a salt. The salt may be obtained by treating said starting material 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.

Another embodiment of the process of the present invention comprises methylating a hydrazine which contains the radical A^1 as a substituent or a hydrazine which not only contains such a radical as a substituent but is also partially further substituted by protecting groups. The methylation can be carried out, for example, with methylating agents such as methyl iodide or dimethyl sulphate, under the conditions previously described for the introduction of the radical A^1. The introduction of the methyl group can also be effected by condensation of a hydrazine which contains the radical A^1 as a substituent with formaldehyde and subsequent reduction of the ~~hydrazine~~ hydrazone formed, preferably in the presence of a hydrogenation catalyst such as palladium or platinum.

According to a process variant in accordance with the invention, the introduction of the desired radical can also be effected by reaction of methyl-hydrazine or a methyl-hydrazine in which the hydrazine is partially substituted by protecting groups (e.g. 1-methyl-1-acetyl-hydrazine) with the appropriate carbonyl compound and subsequent reduction of the resulting hydrazone and splitting off any 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 in the presence of a hydrogenation catalyst such as palladium or platinum.

Any protecting groups present in the intermediates can be split off according to known procedures.

As stated earlier, the hydrazine compounds obtained may be oxidised. The oxidation products obtained depend on the oxidation agent used. Weak oxidation agents such as mercuric oxide yield azo compounds whereas stronger oxidation agents such as peracids yield azoxy compounds.

Where necessary, the conversion of the radical A^1 into the radical A can be effected at any point. It is advantageous, for example, to prepare substituted carbamoyl compounds from a [2-methyl-1,2-di(benzyloxycarbonyl)-hydrazino]-alkanoic acid such as 2 - [2 - methyl - 1,2 - di(benzyloxycar - bonyl)-hydrazino]-acetic 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, for example, into an acid chloride or a mixed anhydride (e.g. with a carbonic acid monoester) or into an activated ester (e.g. a cyano-methyl ester). The acid can also be amidated directly by use of a condensation agent such as N,N-di*cyclo*hexylcarbodiimide. Protecting groups are subsequently removed from carbonyl compounds obtained according to this method by hydrogenolysis or by 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. 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 same intermediate amino compounds by treatment with cyanates and the guanidino compounds are likewise accessible by treatment with cyanimide or its derivatives (for example, methyl-*iso*thiourea sulphate).

Amidino or substituted-amidino compounds are advantageously prepared from suitable nitriles *via* the corresponding imido ether which can be obtained by reaction of the nitrile with alcohol and mineral acid. The desired amidino compound is then obtained by reaction of the imido ether with ammonia or a primary or secondary amine. The 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.

The hydrazine compounds of formula I form acid addition salts with inorganic acids such as, for example, hydrohalic acids (e.g. hydrochloric acid, hydrobromic acid, hydroiodic acid), sulphuric acid, phosphoric acid and nitric acid, and with 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 hydrochlorides. The acid addition salts can suitably be prepared by treating the bases in an inert solvent with the corresponding acid.

The following examples illustrate the process of the invention.

EXAMPLE 1

26 g of 1-methyl-1,2-diacetyl-hydrazine were added to a solution of 4.6 g of sodium in 150 ml of absolute ethanol. The solution was evaporated to dryness *in vacuo* and the residue heated to 160°—170°C for 14 hours with 19 g of ethylene bromide. The reaction product was poured into ice-water and extracted with methylene chloride. There was thus obtained a thick oil which was recrystallized from (ethyl ether)/(ethyl acetate) and then recrystallized several times from ethyl acetate, yielding 1,2-bis(2-methyl-1,2-diacetyl-hydrazino)ethane melting at 134°C.

2 g of the so-obtained tetraacetate were heated on a steam-bath for 2 hours with 20 ml of concentrated hydrochloric acid. After the addition of a small amount of water, the mixture was extracted with methylene chloride and the aqueous phase concentrated to dryness *in vacuo*. This yielded white crystals which were crystallized from ethanol to give 1,2 - bis(2 - methyl - hydrazino) - ethane dihydrochloride melting at 123°—124°C.

EXAMPLE 2

38 g of 1-methyl-1,2-dibenzoyl-hydrazine and 15 g of 1,3-dibromo-propane were added to a solution of 3.45 g of sodium in 100 ml of absolute ethanol. The resulting solution was heated at reflux for 2 hours, poured into water and extracted with ether. The ether extract was washed twice with dilute sodium hydroxide and then with water, dried with sodium sulphate and evaporated to dryness. 29 g of the so-obtained glassy product were heated for 2 hours with 150 ml of concentrated hydrochloric acid on the steam-bath. The reaction mixture was then diluted with water, extracted with methylene chloride and the aqueous phase evaporated to dryness *in vacuo*, yielding very hygroscopic crystals of 1,3-bis(2-methyl-hydrazino)-propane dihydrochloride which, after recrystallization from ethanol/ether, melted at 92°—95°C.

In an analogous manner the following were prepared: 1,5 - bis(2 - methyl - hydrazino) - pentane dihydrochloride which melted at 100°—120°C and 1,6-bis(2-methyl-hydrazino)-hexane trihydrochloride which melted at 182°—184°C and 1,10-bis(2-methyl-hydrazino)-decane dihydrochloride which melted at 106°—108°C.

EXAMPLE 3

38 g of 1-methyl-1,2-dibenzoyl-hydrazine and 17.5 g of di(β-bromo-ethyl)-ether were added to a solution of 3.45 g of sodium in 100 ml of absolute ethanol. The reaction mixture was heated at reflux for 20 hours. It was then permitted to cool, the ethanol removed *in vacuo* and the residue partitioned between water and (methylene chloride)/(ethyl ether) (1:2). The organic layer was washed with dilute sodium hydroxide and water, dried with sodium sulphate and the solvents evaporated off *in vacuo*. The so-obtained thick oil was heated for 2 hours with 200 ml of concentrated hydrochloric acid on a steam-bath. After the reaction solution had cooled, it was extracted with methylene chloride and the aqueous phase evaporated to dryness *in vacuo*, yielding a very hygroscopic hydrochloride which was dissolved in 100 ml of water and filtered through 300 g of a polystyrene trimethyl

benzyl ammonium type anion exchange resin. The so-obtained aqueous solution of the free base was concentrated *in vacuo* and the residue distilled in a high vacuum. The so-obtained 2,2[1] - bis(2 - methyl - hydrazino) - diethyl ether distilled at 78°—82°C/0.05 mm Hg; $n_D^{25}=1.4736$.

Example 4

71.5 g of 1-methyl-1,2,-di(~~benzoyloxycarbonyl~~)-hydrazine were dissolved in 125 ml of 2-*N* sodium methylate solution. 29.7 g of 1,3-dichloro-butene-(2) were then added thereto and the resulting mixture heated at reflux for one hour. The reaction mixture was then concentrated *in vacuo*, mixed with ice-water and extracted with ethyl ether. The ether layer was washed with diluted sodium hydroxide and water, dried with sodium sulphate and concentrated *in vacuo*. The amorphous residue was dissolved in 250 ml of 33% solution of hydrogen bromide in glacial acetic acid and the resulting solution permitted to stand for 24 hours, whereupon 1-methyl - 2 - [3 - chloro - buten - (2) - yl] - hydrazine dihydrobromide crystallized. After recrystallization from glacial acetic acid it melted at 104°—110°C.

Example 5

39.3 g of 1,4-dibromo-butene-(2) were added to a solution of 113.5 g of 1-methyl-1,2-di(~~benzoyloxycarbonyl~~)hydrazine and 300 ml of N,N-dimethyl-formamide which contained 9 g of sodium hydride. The resulting mixture was heated for one hour at 80° C and worked up as described in Example 4, yielding a thick oil which was permitted to stand for 24 hours in 600 ml of a 33% solution of hydrogen bromide in glacial acetic acid. 1,4 - Bis(2 - methyl - hydrazino)-butene-(2) dihydrobromide precipitated and, after recrystallization from ethanol/water, melted at 192°—194°C.

Example 6

A solution of 63.5 g of 1-methyl-1,2-dibenzoyl-hydrazine in 160 ml of N,N-dimethyl-formamide was added to a solution of 6 g of sodium hydride in 100 ml of N,N-dimethyl-formamide with stirring and slight cooling to 20°—30°C. To the so-obtained mixture there was then added a solution of 34 g of *trans* 1,4-bis(bromo-ethyl)-*cyclo*hexane in 35 ml of N,N-dimethyl-formamide. The resulting mixture was heated for 15 hours at 55°C. Most of the N,N-dimethyl-formamide was then distilled off *in vacuo*, the residue poured into 1-*N* sodium hydroxide and extracted with a mixture of ethyl ether and methylene chloride. The (ethyl ether)/(methylene chloride) extract was washed with 1-*N* sodium hydroxide and with water, dried with sodium sulphate and evaporated. The residue crystallized upon trituration with ethyl ether and the so-obtained crystalline 1,4 bis[(2 - methyl - 1,2 - dibenzoyl - hydrazino)-methyl]-*cyclo*hexane melted at 167°—175°C.

45 g of the so-obtained product in a mixture of 250 ml of acetic acid and 250 ml of concentrated hydrochloric acid was boiled for 2.5 hours in a nitrogen atmosphere. After the mixture had cooled, the precipitated product was filtered off with suction, washed with concentrated hydrochloric acid and ethyl ether and recrystallized from methanol/(ethyl ether). The so-obtained hydrochloride of *trans* 1,4-bis[(2-methyl-hydrazino)-methyl]-*cyclo*hexane melted at 190°—191°C.

Example 7

A solution of 254 g of 1-methyl-1,2-dibenzoyl-hydrazine and 650 ml of N,N-dimethyl-formamide was added to a solution of 24 g of sodium hydride in 400 ml of N,N-dimethyl-formamide with stirring and slight cooling to 20°—30°C. There was then added thereto a solution of 227 g of *cis* 1,2-bis (*para*tolyl-sulphonyl oxymethyl)-*cyclo*hexane in 600 ml of N,N-dimethyl-formamide and the resulting mixture heated at 75°—80°C for 20 hours. Most of the N,N-dimethyl-formamide was then distilled off *in vacuo*, the residue poured into 1-*N* sodium hydroxide, extracted with a mixture of ethyl ether and methylene chloride, the (ethyl ether)/(methylene chloride) extract washed with 1-*N* sodium hydroxide and with water, dried with sodium sulphate and evaporated.

The residual *cis* 1,2-bis[(2-methyl-1,2-benzoyl-hydrazino)-methyl]-*cyclo*hexane (a viscous oil) was poured, without further purification, into 2.7 litres of ethanol and, following the addition of a solution of 530 g of potassium hydroxide and 475 ml of water, boiled for 15 hours under a nitrogen atmosphere. The reaction mixture was then concentrated under reduced pressure, the concentrate saturated with solid potassium hydroxide and mixed with ether. The resulting ether phase was filtered, dried with potassium hydroxide and evaporated. The residual *cis* 1,2-bis[(2-methyl-hydrazino)-methyl]-*cyclo*hexane was purified by fractional distillation. The distillate was a colourless oil which boiled at 91°—93°C/0.02 mm Hg.

Upon treatment of the base in an alcoholic solution with an alcoholic solution of 2 equivalents of oxalic acid, the dioxalate crystallized out. After recrystallization from water/ethanol it melted at 160°—162°C.

In an analogous manner the following were prepared: *trans* 1,2-bis[(2-methyl-hydrazino)-methyl]-*cyclo*hexane of boiling point 89°—90°C/0.04 mm Hg and *cis* 1,3-bis[(2-methyl - hydrazino - methyl] - *cyclo*hexane of boiling point 95°—98°C/0.01 mm Hg.

EXAMPLE 8

A solution of 67 g of 1-methyl-1,2-dibenzoyl-hydrazine in 170 ml of N,N-dimethyl-formamide was added to a solution of 6.3 g of sodium hydride in 100 ml of N,N-dimethyl-formamide with stirring and slight cooling to 20°—30°C. A solution of 40 g of *trans* 1,2-bis(iodo-methyl)-*cyclo*propane in 50 ml of N,N-dimethyl-formamide was then added thereto and the resulting mixture heated for 2 hours at 40°C. Most of the N,N-dimethyl-formamide was then distilled off *in vacuo*, the residue poured into 1-*N* sodium hydroxide and extracted with a mixture of ethyl ether and methylene chloride. The (ethyl ether)/(methylene chloride) extract was washed with 1-*N* sodium hydroxide, water, 5% sodium thiosulphate and water, dried with sodium sulphate and evaporated.

The residual *trans* 1,2-bis[(2-methyl-1,2-dibenzoyl-hydrazino)-methyl]-*cyclo*propane (a viscous oil) was dissolved, without further purification, in 800 ml of ethanol and, following the addition of a solution of 65 g of potassium hydroxide in 60 ml of water, boiled for 16 hours under a nitrogen ~~atmosophere~~. The reaction product was concentrated under reduced pressure, the concentrate saturated with solid potassium hydroxide and treated with ether. The ether phase was filtered, dried with potassium hydroxide and evaporated. The residual *trans* 1,2-bis[(2-methyl-hydrazino)-methyl]-*cyclo*propane was purified by distillation yielding a colourless oil which boiled at 88°C/0.04 mm Hg and which, upon cooling, congealed to a crystalline mass which melted at about 30°C.

EXAMPLE 9

Cis 1,2 - bis[(2 - methyl - hydrazino) - methyl]-*cyclo*propane was prepared according to the procedure described in Example 8 and boiled at 74°C/0.02 mm Hg.

The *trans* or *cis* 1,2-bis(iodo-methyl)-*cyclo*propane starting materials used in examples 8 and 9 were prepared as follows: *Cyclo*propane-1,2-dicarboxylic acid diethyl ester was reduced in ethyl ether with lithium aluminium hydride to form 1,2-*bis*(*p*-hydroxy-methyl)-*cyclo*propane. This was treated in pyridine at −5° to −10°C with *para*toluene-sulphonyl chloride, whereby there was obtained 1,2 - bis(*para*tolyl - sulphonyloxy - methyl)-*cyclo*propane (*trans* form, melting point 76°—76.5°C; *cis* form, melting point 88°—89°C). Upon boiling the toluenesulphonic acid ester with sodium iodide in acetone, there was obtained the corresponding iodide: *trans* 1,2-bis(iodo-methyl)-*cyclo*propane, melting point 10°—11°C; *cis* 1,2-bis (iodo-methyl)-*cyclo*propane, melting point 59°—60°C.

EXAMPLE 10

To a solution of 12.5 g of sodium in 520 ml of absolute methanol cooled to 20°C there was added at one time 71 g of 1-methyl-1,2-diacetyl-hydrazine mixed with 50 ml of absolute ethanol, and directly thereafter 80 g of bromo-acetic acid ethyl ester were added. The mixture was then heated for 2 hours at reflux, cooled to 20°C, neutralized with glacial acetic acid and evaporated *in vacuo*. The oily residue was partitioned twice using 700 ml of chloroform and 300 ml of water. The chloroform layer was separated and the aqueous phase extracted once with 300 ml of chloroform. The combined chloroform extracts were then dried with sodium sulphate and evaporated *in vacuo*. The so-obtained oily residue was distilled and, after a short time, 1-methyl-1,2-diacetyl-2-ethoxy-carbonylmethyl-hydrazine distilled at 116°/~~0.02~~ mm Hg as a nearly colourless oil; $n_D^{24}=1.4652$.

A) 20 g of the foregoing diacetyl compound in 150 ml of concentrated aqueous hydrochloric acid were heated on a steam-bath for 1.5 hours under a nitrogen atmosphere. The yellow solution was then evaporated *in vacuo* and the crystalline residue twice recrystallized from water/methanol yielding 1 - methyl - 2 - (carboxy - methyl)-hydrazine hydrochloride melting at 168°C (decomposition).

B) 73.1 g of 1-methyl,1,2-diacetyl-2-ethoxy-carbonylmethyl-hydrazine in 300 ml of absolute methanol were heated at reflux for 6 hours. In the course of this time hydrogen chloride was introduced into the solution. Then, the solution was evaporated and the oily residue dissolved in 200 ml of concentrated aqueous ammonia solution. The solution was then maintained for 6 hours at 20° C, evaporated *in vacuo* and the crystalline residue recrystallized three times from methanol/water yielding 1-methyl-2-(carbamoyl-methyl)-hydrazine hydrochloride melting at 165°C.

EXAMPLE 11

To a suspension of 4.6 g of sodium in 300 ml of absolute N,N-dimethyl-formamide (cooled to 10°C) there was added at one time, 62.8 g of 1-methyl-1,2-di(benzyloxycarbonyl)-hydrazine in 100 ml of absolute N,N-dimethyl-formamide and, immediately thereafter, 43 g of bromo-acetanilide in 100 ml of absolute N,N-dimethyl-formamide were added.

The mixture was then heated for 4 hours at 100°C, evaporated *in vacuo* and twice partitioned between 300 ml of water and 700 ml of chloroform. The chloroform solution was separated, dried over sodium sulphate and evaporated *in vacuo*. The oily residue crystallized upon treatment with methanol and, after three recrystallizations from methanol, yielded 1-methyl-1,2-di-(benzyloxycarbonyl - 2 - [(phenyl - carb - amoyl)-methyl]-hydrazine melting at 103°—109°C.

44.7 g of the foregoing di(benzyloxycar-

bonyl) compound were hydrogenated in 200 ml of methanol over 5 g of palladium/carbon (5%) under atmospheric pressure and at *ca* 20°C. After termination of the hydrogen absorption, the catalyst was filtered off, the filtrate adjusted to pH 3 by treatment with ethereal hydrochloric acid and then evaporated *in vacuo*. 1-Methyl-2-[(phenyl-carbamoyl)-methyl]-hydrazine hydrochloride was isolated from the oily residue by several recrystallizations from methanol/(methyl ether) and melted at 176°C (decomposition).

EXAMPLE 12

i) 1.4 - bis(2 - methyl - hydrazino) - butane dihydrochloride of melting point 160°—162° C was prepared according to the details given in example 2.

ii) 19.0 g of 1,4-bis(2-methyl-hydrazino)-butane dihydrochloride were suspended in 100 ml of methylene chloride. Following the addition of 80 g of potassium hydroxide in 50 ml of water, the mixture was thoroughly shaken, the methylene chloride layer separated and the aqueous phase extracted twice with methylene chloride. The combined methylene chloride extracts were dried with potassium carbonate and then evaporated *in vacuo*. The residual oil was dissolved in 100 ml of absolute ether. This solution was cooled in an ice-bath and 37 g of yellow mercuric oxide added thereto in portions. The resulting mixture was permitted to stand for 0.5 hour at 25°C, filtered evaporated to dryness, and the residual oil distilled *in vacuo* yielding 1,4 - bis(methyl - azo) - butane boiling at 63°—64°C/15 mm Hg, $n_D^{24}=1.4353$.

iii) 8.5 g of 1,4-bis(methyl-azo)-butane were dissolved in 50 ml of methylene chloride. The solution was cooled to 0°C and, in the course of 2 hours with stirring and ice-cooling, a solution of 18.9 g of perbenzoic acid in 600 ml of methylene chloride added thereto. The mixture was then stirred for a further hour at 0°C. The methylene chloride solution was then rapidly shaken, first with 500 ml of 10% potassium hydroxide and then with 300 ml of saturated sodium thiosulphate solution, then washed with saturated sodium carbonate solution and water, dried over sodium sulphate, the solvent evaporated and the residue distilled *in vacuo* yielding 1,4-bis(methyl-azoxy)-butane boiling at 96°—97°C/0.4 mm Hg, $n_D^{25}=1.4849$.

The following examples illustrate the preparation of pharmaceutical preparations containing the novel derivatives of the invention.

A) Preparation of capsules containing:

1 - methyl - 2 - (carbamoyl - methyl)-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).

B) Preparation of capsules containing:

1,5 - bis(2 - methyl - hydrazino)-pentane dihydrochloride	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).

C) Preparation of 300 mg dragées containing the following ingredients:

A) kernel

1 - methyl - 2 - (carbamoyl - hydrazine hydrochloride	50 mg
mannitol	80 mg
talc	5 mg
corn starch	15 mg
total weight of the kernel	150 mg

B) coating

This consisted of 90% sugar, 5% rice starch and 5% talc to give a total 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 with 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 each of 150 mg and 8.0 mm diameter.

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

D) Preparation of 200 mg dragées containing:

A) kernel

trans 1,2 - bis[(2 - methyl - hydrazino)-methyl]-*cyclo*-propane	25 mg
mannitol	60 mg
talc	5 mg
corn starch	10 mg
weight of the kernel	100 mg

B) coating

This consisted of 90% sugar, 5% rice starch and 5% talc to give a total weight of 100.0 mg.

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

WHAT WE CLAIM IS:—

1) Compounds of the formula

A—NH—NH—CH_3

, in which A is a saturated or unsaturated aliphatic hydrocarbon radical which, when a saturated chain contains, or which otherwise may contain one or more substituents as hereinbefore defined, and the corresponding azo and azoxy compounds and acid addition salts of the formulated compounds.

2) Compounds of the formula given in claim 1, and acid addition salts thereof, wherein the substituents are taken from the series halogen, cyano, carboxy (which may be esterified, hydroxy-alkyl, alkyl-thio, amino-alkyl, amino-alkoxy, acyl-amino, ureido, thioureido, guanidino, amidino, carbamoyl, allophenyl, alkylsulphonyl, acyl, methylhydrazino-methyl, methylhydrazino-alkoxy and methylhydrazino-alkylcarbonyl, and the corresponding azo and azoxy compounds.

3) 1,3 - Bis(2 - methyl - hydrazino) - propane and its dihydrochloride.

4) 1,4 - Bis(2 - methyl - hydrazino) - butane and its dihydrochloride.

5) 1,10 - Bis(2 - methyl - hydrazino) - decane and its dihydrochloride.

6) 1,4 - Bis(2 - methyl - hydrazino) - butene-(2) and its dihydrobromide.

7) *Cis* 1,2 - bis(2 - methyl - hydrazino) - *cyclo*propane.

8) *Trans* 1,2 - bis(2 - methyl - hydrazino) - *cyclo*propane.

9) 1 - Methyl - 2 - [3 - chloro - buten - (2)-yl]-hydrazine and its dihydrobromide.

10) 1,2 - Bis(2 - methyl - hydrazino) - ethane and its dihydrochloride.

11) 1,5 - Bis(2 - methyl - hydrazino) - pentane and its dihydrochloride.

12) 1,6 Bis(2 - methyl - hydrazino) - hexane and its trihydrochloride.

13) $2,2^1$ - Bis(2 - methyl - hydrazino) - diethyl ether.

14) *Trans* 1,4 - bis[(2 - methyl - hydrazino)-methyl]-*cyclo*hexane and its hydrochloride.

15) *Cis* 1,2 - bis[(2 - methyl - hydrazino)-methyl]-*cyclo*hexane and its dioxalate.

16) *Trans* 1,2 - bis[(2 - methyl - hydrazino)-methyl]-*cyclo*hexane.

17) *Cis* 1,3 - bis[(2 - methyl - hydrazino)-methyl]-*cyclo*hexane.

18) 1 - Methyl - 2 - (carboxy - methyl) - hydrazine and its hydrochloride.

19) 1 - Methyl - 2 - (carbamoyl - methyl)-hydrazine and its hydrochloride.

20) 1 - Methyl - 2 - [(phenyl - carb - amoyl)-methyl]hydrazine and its hydrochloride.

21) 1,4-Bis(methyl-azo)-butane.

22) 1,4-Bis(methyl-azoxy)-butane.

23) A composition of matter comprising a compound as formulated in claim 1 (or a salt thereof) or a corresponding azo or azoxy compound in association with a compatible pharmaceutical carrier.

24) A process for the manufacture of the derivatives and salts claimed in claim 1, which process comprises *either* reacting methyl-hydrazine or a methyl-hydrazine in which the hydrazine is partially substituted by protecting groups with a compound which yields the radical A^1 (wherein A^1 has the same meaning as A in claim 1 or is a group which is convertible into A) *or* methylating a hydrazine which contains such a radical as a substituent or a hydrazine which not only contains such a radical as a substituent but is also partially further substituted by protecting groups, *and*, in either case if necessary, converting the radical A^1 in the product into A and, also if necessary, converting the resulting compound of the formula given in claim 1 into an acid addition salt—said formulated compound or acid addition salt being then, if desired, oxidized to the corresponding azo or azoxy compound.

25) A variation of the process set forth in claim 24, which comprises reacting methyl hydrazine or a methyl hydrazine in which the hydrazine is partially substituted by protecting groups with the appropriate carbonyl compound and subsequently reducing the resulting hydrazone and splitting off any protecting group therefrom.

26) A process for the manufacture of the derivatives and salts claimed in claim 1, substantially as described with reference to the Example.

27) Compounds as formulated in claim 1 and the corresponding azo and azoxy compounds and acid addition salts of the formulated compounds, when manufactured by the process claimed in claim 24, claim 25 or claim 26.

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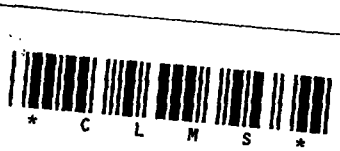
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