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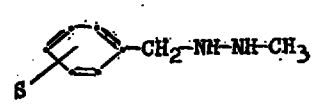
COMPLETE SPECIFICATION

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

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



I

in which S indicates substitution consisting of at least one amino, alkyl-amino, dialkyl-amino, acyl-amino, ureido, substituted-ureido, (alkyl-sulphonyl)-amino, guanidino, substituted-guanidino, amidino, substituted-amidino, amino-alkyl, (alkyl-amino)-alkyl, (dialkyl-amino)-alkyl, carbamoyl, substituted-carbamoyl, allophanoyl, substituted-allophanoyl, sulphamoyl, N-alkyl-sulphamoyl, N,N-dialkyl-sulphamoyl, alkyl-sulphonyl, nitro, (2-methyl-hydrazino)-methyl, alkanoyl, aroyl, phenyl or substituted phenyl group together with, if desired, one or more alkyl, trifluoro-methyl, halogeno, hydroxy, alkoxy, alkylenedioxy, alkenyloxy, aralkoxy, alkanoyloxy, aroyloxy, mercapto or alkyl-thio groups, and acid addition salts thereof. They are active as cytostatic agents. They inhibit the growth of transplantable tumours in both mice and rats. Thus, for example, they are active against WALKER tumours, ERLICH carcinoma and ERLICH ascites carcinoma. Further, they cause decomposition of macromolecular desoxy-ribonucleic acid in solution. They can be administered internally in the form of conventional pharmaceutical preparations; for example, the bases or 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, gelatin, lactose, starch, magnesium stearate, talc, plant oils, gums, alcohol or petroleum jelly. The pharmaceutical preparations can be in conventional solid forms (e.g. tablets, dragees, suppositories or capsules) or conventional liquid forms (e.g. suspensions or emulsions). If desired, they can be sterilized and/or contain conventional pharmaceutical adjuvants such as preservatives, stabilizing agents, wetting agents, emulsifying agents,

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buffers or salts used for the adjustment of osmotic pressure. The preparations can also contain other therapeutically active materials.

The preferred alkyl-amino, dialkyl-amino, (alkyl-sulphonyl)-amino, amino-alkyl, (alkyl-amino)-alkyl, (dialkyl-amino)-alkyl, N-alkyl-sulphamoyl, N,N-dialkyl-sulphamoyl, alkyl, alkoxy, aralkoxy and alkyl-thio groups included among the values of 'S' are those in which the alkyl group is an alkyl group containing up to six carbon atoms (e.g. a methyl, ethyl, propyl or *iso*propyl group).

Examples of substituted ureido, guanidino, amidino and allophanoyl group values of 'S' in the foregoing formula are ureido, guanidino, amidino and allophanoyl groups in which one or more of the hydrogen atoms are replaced by a saturated or unsaturated aliphatic, *cyclo*aliphatic, araliphatic, aromatic or heterocyclic radical which may itself carry a functional group or functional groups. The following are specific examples: methyl-ureido, *iso*propyl-ureido, methyl-guanidino, *iso*propyl-guanidino, (2-hydroxy-ethyl)-guanidino, methyl-amidino, di*iso*propyl-amidino, *cyclo*propyl-amidino, phenyl-amidino, benzyl-amidino, isoxazolyl-amidino, (2-hydroxy-ethyl)-amidino, 4-methyl-allophanoyl and 2-*iso*propyl-allophanoyl.

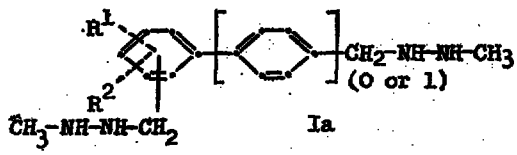
Examples of substituted carbamoyl group values of 'S' are carbamoyl groups in which one or both hydrogen atoms are replaced by a saturated or unsaturated aliphatic or alicyclic radical which may itself carry a functional group or functional groups or one or more aromatic or heterocyclic radicals. The following are specific examples: 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 - methoxyethyl - carbamoyl, N - hydroxyethyl - carbamoyl, N - methylthioethyl - carbamoyl, N - carbamoylmethyl-carbamoyl, N - methylsulphonylethyl - carbamoyl, N - (β - chloro - ethyl) - carbamoyl and N - (β,β,β - trifluoro - ethyl) - carbamoyl, N - allyl - carbamoyl, N - benzyl - carbamoyl, N - furfuryl - carbamoyl, N - *cyclo*propyl - carbamoyl, N - (β - methylamino - ethyl) - carbamoyl and N - (β - diethylamino - ethyl) - carbamoyl, N,N-tetramethylene - carbamoyl and N,N - pentamethylene - carbamoyl.

Suitable acyl-amino group values of 'S' are those wherein the acyl residue is derived from an aliphatic, aromatic or heterocyclic acid and wherein the remaining hydrogen atom attached to the amino-nitrogen may be replaced by, say, an alkyl group. Specific examples are: N - acetyl - N - methyl - amino, acetyl-amino, pivaloyl-amino, alanyl-amino, succinimido, benzoyl-amino, phthalimido, nicotinoyl-amino, *iso*nicotinoyl-amino, (methyl-isoxazolylcarbonyl)-amino. It will be appreciated that the heterocyclic acyl-amino values may be derived from 5-membered or 6-membered nitrogen and/or oxygen containing heterocyclic rings (which may contain substituents).

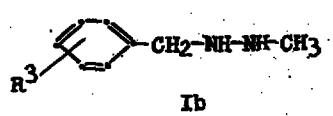
Suitable substituted-phenyl group values of 'S' are phenyl groups which carry one of the groups prior mentioned in the list of values indicated for 'S' immediately after the formula. The following are specific examples: (2-methyl-hydrazino)methyl-phenyl, carbamoyl-phenyl, ureido-phenyl, [5-methyl-isoxazolyl-(3)-carbonylamino]-phenyl.

Suitable alkanoyl and aroyl groups which may be included in the value for 'S' are, on the one hand, formyl, acetyl and propinoyl and, on the other hand, benzoyl.

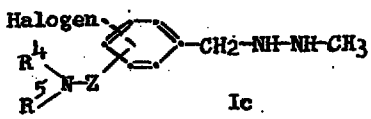
The following set of formulae represent useful sub-genera of the compounds of formula I:



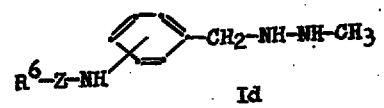
Ia



Ib



Ic

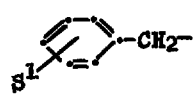


Id

in which set R^1 and R^2 are each an optional phenyl or benzoyl group or an alkanoyl or alkoxy group containing up to six carbon atoms or, together, an alkylenedioxy group containing up to six carbon atoms (the bonds being shown as broken lines), R^3 is a nitro, amidino, guanidino, ureido, allophanoyl benzoyl or amino group or an alkyl-amino or dialkyl-amino group containing up to six carbon atoms, Z is the carbonyl or sulphonyl group, R^4 and R^5 are each a hydrogen atom, an alkyl or *cyclo*alkyl group containing up to six carbon atoms or a hydroxy-alkyl, alkanoyloxy-alkyl, dialkylamino-alkyl, phenyl-alkyl, alkoxy-alkyl, alkyl-carbamoyl or halogeno-alkyl group in which the alkyl moiety contains up to six carbon atoms or the radical of an α-amino acid bereft of its α-amino group or a pyridyl-methyl, furfuryl or carbamoyl group or, together, an alkylene of oxa-alkylene group containing up to six carbon atoms, and R^6 is a phenyl or amino group or an alkyl group containing up to six carbon atoms or an alkyl-amino, dialkyl-amino, (hydroxy-alkyl)-amino group in which the alkyl moiety contains up to six carbon atoms or the residue of an α-amino acid bereft of its carboxyl group or a 5-membered or 6-membered heterocyclic ring containing one or two hetero atoms comprising nitrogen and/or oxygen atoms and carrying an alkyl group containing up to six carbon atoms.

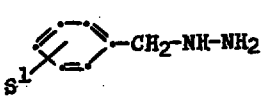
Particularly preferred derivatives are *p* - [(2 - methyl - hydrazino) - methyl] - benzamide, 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid ethyl - amide, 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *iso*propyl - amide, 4 - [(2 - methyl-hydrazino) - methyl] - benzoic acid *sec*butyl - amide, 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *tert*butyl - amide, 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *iso*pentyl - amide, 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2 - hydroxy - ethyl) - amide, 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2 - chloro - ethyl) - amide, 1 - methyl - 2 - [*p* - (alanyl - amino) - benzyl] - hydrazine, 1 - methyl - 2 - [*p* - [5 - methyl - isoxazolyl - (3) - carbonylamino] - benzyl] - hydrazine, 1 - methyl - 2 - (*p* - ureido - benzyl) - hydrazine, 1 - methyl - 2 - (*p* - allophanoyl - benzyl) - hydrazine, 1,2 - bis - [(2 - methyl - hydrazino) - methyl] - benzene, 1,4 - bis - [(2 - methyl - hydrazino) - methyl] - benzene and 3,3¹ - bis - [(2 - methyl - hydrazino) - methyl] - biphenyl and acid addition salts thereof.

According to the process provided by the invention, the aforementioned derivatives are manufactured *either* by benzylation of methyl-hydrazine or of a partially protected methyl-hydrazine with a benzylating agent which yields a substituted benzyl group of the formula



II

wherein S^1 has the same meaning as 'S' or is readily convertible thereinto, and subsequent conversion of said group S^1 in the product into the group 'S' if different *or* by methylation of a compound of the formula



III

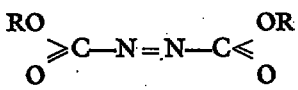
wherein S^1 has the significance already given, or of such a compound which is partially protected at the hydrazino group and subsequent conversion of the group S^1 in the product into the group S if different *and*, in either event, the splitting off of any protecting group present and transformation (if desired) into a salt.

Examples of benzylating agents which may be used are *p*-carbamoyl-benzyl bromide, *p* - cyano - benzyl bromide, *p* - alkoxycarbonyl - benzyl bromide, *o* - cyano - benzyl bromide, *p* - nitro - benzyl bromide, *m* - nitro - benzyl bromide, *p* - carbamoyl-*o* - chloro - benzyl bromide, *p* - acylamino - benzyl bromide, 1,2 - bis(bromo - methyl)-benzene, 4,4¹ - bis(chloro - methyl) - biphenyl, *p* - benzoyl - benzyl bromide and *p* - acetyl-benzyl bromide. When using a dihalogeno compound as the benzylating agent two moles of methyl-hydrazine can be used and compounds bearing two methyl-hydrazino groups are thereby formed.

It is convenient to convert the hydrazine compound into a salt before benzylation, preferably by treatment with an alkali-metal alcoholate in an alcoholic solution. After removal of the alcohol, the resulting salt is advantageously dissolved in an inert solvent such as N,N-dimethyl-formamide and treated with the benzylating agent (preferably at an elevated temperature). The reaction product can be purified by conventional methods, for example, by extraction, crystallization or distillation.

In a variant method, also provided by the invention, the introduction of the substituted benzyl moiety can also be effected by reaction of methyl-hydrazine or partially protected methyl-hydrazine (e.g. 1-methyl-1-acetyl-hydrazine) with a carbonyl compound and subsequent reduction of the so formed hydrazone and removal of the protecting groups. This can suitably be effected by heating of the reaction components for a short time in a solvent (e.g. alcohol) and hydrogenating the resulting hydrazone in the presence of a hydrogenation catalyst such as palladium or platinum.

According to a further variant, also in accordance with the invention, a 1,2-di-(alkoxycarbonyl)-hydrazine or its dehydro-derivative of the formula



IV

(wherein R represents an alkyl group) is methylated and then benzylated in the usual manner. The alkoxycarbonyl groups are then split off.

According to the alternative process of the invention wherein hydrazine compounds of formula III are first methylated, the methylation can be conducted, for example, with methyl iodide or dimethyl sulphate under the conditions previously described for the benzylation reaction.

The introduction of the methyl group can also be effected by condensation of the compound of formula III with formaldehyde and subsequent reduction of the condensation product. The condensation is suitably effected with equimolar amounts of the compound of formula III and the formaldehyde. Reduction of the condensation product by hydrogenation can be carried out simultaneously with the condensation or subsequent thereto. Advantageously, it is carried out in the presence of a hydrogenation catalyst (e.g. platinum or palladium) until the absorption of an equimolar amount of hydrogen. The working up of the reaction mixture can be effected by conventional means; for example, by fractional distillation.

In a variation of this alternative, the required derivatives can be obtained by benzylation of a 1,2-di(alkoxycarbonyl)-hydrazine or dehydro-derivative thereof (see formula IV) and methylation of the product.

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

Many of the products formed by the process of the invention can, if desired, be further substituted in the phenyl ring. Thus, for example, many compounds of formula I hereinbefore can be provided with protecting groups for the hydrazino and other vulnerable moieties and can then be nitrated by, for example, treatment with potassium nitrate in concentrated sulphuric acid at a temperature of from about 0°C. to about 70°C. or halogenated by reaction with chlorine or bromine in the presence of a suitable catalyst (e.g. ferric chloride) at slightly elevated temperatures.

Where necessary, the conversion of substitution S^1 into substitution S can be effected in the foregoing process procedures at any point. Thus, it is advantageous, for example, to prepare substituted carbamoyl compounds from 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid [obtainable by saponification of corresponding methyl or ethyl esters] by reaction with amines in accord with known methods of amidation. Suitably, the said benzoic acid derivative is converted into a reactive derivative (for example, into an acid chloride or a mixed anhydride) or into an activated ester (for example, a cyano-methyl ester). The acid can also be ami-

dated directly in the presence of a condensation agent such as di*cyclo*hexyl - carbodiimide. The foregoing amides can also be obtained in the presence of a strong acid from [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzonitrile by reaction with olefins (for example, *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 benzamides. Protecting groups are subsequently removed from the carbamoyl compounds obtained according to this method by hydrogenolysis or treatment with a (hydrogen bromide)/(glacial acetic acid) solution. The hydrobromides obtained by this latter method can, if desired, be converted into corresponding free bases and/or into other salts.

The acyl-amino substituted compounds of the invention (see formula Id above) are preferably prepared by acylation of, for example, 1 - methyl - 1,2 - dibenzyloxycarbonyl - 2 - (*p* - amino - benzyl) - hydrazine which itself, for example, can be obtained 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 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. Accessible from the same intermediate amino compounds are ureido compounds. These are obtainable by treatment with cyanates or *iso*cyanates. Guanidines can also be obtained by treatment with cyanamide and its derivatives (for example, methyl - *iso*thiourea sulphate).

Amidino or substituted amidino compounds of formula I are advantageously prepared from protected methylhydrazinomethyl-benzonitriles *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. Suitably protected methylhydrazinomethyl-benzonitriles can also be reacted directly with salts of amines (for example, *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 protected monosubstituted methylhydrazinomethyl-benzamide [for example, 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid *iso*propyl-amide] by reaction with a phosphorus halide (for example, phosphorus pentachloride) into the corresponding imido halides and then reacting these with ammonia or a primary or secondary amine and removing the protecting groups. Amidines and monosubstituted and disubstituted amidines are obtained in this way.

The hydrazine compounds of formula I form acid addition salts with inorganic acids such as, for example, hydrohalic acids (e.g. hydrogen chloride, hydrogen bromide, hydrogen iodide), 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, some of which illustrate the preparation of the starting materials, illustrate the process of the invention.

Example 1

A) *Preparation of the starting material*

The starting material was 1,4 - bis[(1,2 - diethoxy - carbonyl - hydrazino) - methyl] - benzene and was prepared as follows: 10.6 g of *para*xylene and 8.7 g of azodicarboxylic acid ethyl ester were heated together under a nitrogen atmosphere at 140°—150°C. for 72 hours. During this time there was thrice added to the reaction mixture, at intervals of 12 hours, three portions of 8.7 g of azodicarboxylic acid ethyl ester. After the heating, the unreacted starting material was distilled off under reduced pressure, the residue which had been distilled over was digested with hot petroleum ether and the precipitated crystals recrystallized four times from benzene, yielding 1,4-bis[(1,2 - diethoxycarbonyl - hydrazino) - methyl] - benzene melting at 149°—151°C.

B) *The process*

To a suspension of 4.8 g of sodium hydride and 200 ml of N,N-dimethyl-formamide were added dropwise in the course of 0.5 hours a solution of 45.4 g of 1,4 - bis[(1,2 - diethoxycarbonyl - hydrazino) - methyl] - benzene in 150 ml of N,N - dimethyl-formamide. The resulting mixture was stirred for a further 3 hours and then 30 g of methyl iodide were added at one time to the turbid solution. The reaction mix-

ture was then heated for 4 hours at 100°C. After cooling, the reaction mixture was distilled under reduced pressure, the residue taken up in 300 ml of chloroform, the resulting solution shaken twice each time with 200 ml of water, the chloroform phase dried over sodium sulphate, filtered and the solvents evaporated yielding 1,4 - bis[(2 - methyl - 1,2 - diethoxycarbonyl - hydrazino) - methyl] - benzene which upon being twice recrystallized from methanol, melted at 102°C.

The so-obtained product was then heated on a steam-bath for 7 hours with 300 ml of aqueous concentrated hydrochloric acid. The resulting clear solution was concentrated and the residue twice recrystallized from methanol, yielding 1,4-bis[(2-methyl-hydrazino)-methyl]-benzene dihydrochloride melting at 212°—214°C.

EXAMPLE 2

A mixture of 26 g of 1-methyl-1,2-diacetyl-hydrazine and 30 ml of absolute ethanol was poured into a solution of 4.6 g of sodium in 120 ml of absolute ethyl alcohol maintained at 20°C. and immediately thereafter 25 g of 1,2-bis(bromo-methyl)-benzene were added to the reaction mixture.

After being heated under reflux for 2 hours, the reaction mixture was cooled down, the solvents evaporated under reduced pressure and the residue partitioned between 75 ml of water and 200 ml of methylene chloride. The aqueous phase was separated and again extracted, this time with 100 ml of methylene chloride. The combined methylene chloride extracts were then washed with 100 ml of water, dried over sodium sulphate, evaporated under reduced pressure and the reaction product isolated by distillation, yielding the tetraacetyl derivative of 1,2 - bis[(2 - methyl - hydrazino) - methyl] - benzene as an almost colourless viscous oil boiling at 246°C./0.08 mm Hg. which congealed in the cold to a glassy material. 30 g of this product were then covered with 150 ml of aqueous concentrated hydrochloric acid and the mixture heated on a steam bath under a nitrogen atmosphere for 1.25 hours. While doing so, the mixture was shaken from time to time. The clear brown solution was then concentrated under reduced pressure and the precipitated crystalline residue recrystallized three times from ethyl alcohol, each time with treatment with animal charcoal. The 1,2 - bis[(2 - methyl-hydrazino) - methyl] - benzene dihydrochloride thus obtained melted at 117°—120°C. The free base obtained in the usual way from the dihydrochloride distilled over as a light brown oil boiling at 125°C./0.08 mm Hg.

In an analogous manner, the following compounds were prepared: 1,4 - bis[(2 - methyl - hydrazino) - methyl] - benzene dihydrochloride which melted at 212°—214°C. (decomposition), 1,3 - bis[(2 - methyl - hydrazino) - methyl] - benzene which boiled at 128°C./0.1 mm Hg, 4,4¹ - bis[(2 - methyl - hydrazino) - methyl - biphenyl-dihydrochloride which melted at 253°—255°C., 2,2¹ - bis[(2 - methyl - hydrazino) - methyl] - biphenyl dihydrochloride which melted at 188°—189°C., 3,3¹ - bis[(2 - methyl - hydrazino) - methyl] - biphenyl dihydrochloride which melted at 172°—174°C., 2,3 - bis[(2 - methyl - hydrazino) - methyl] - biphenyl dihydrochloride which melted at 217°—218°C. (decomposition), 3,4 - bis[(2 - methyl - hydrazino) - methyl] - biphenyl dihydrochloride, which melted at 136°—140°C. (decomposition), 4 - [(2 - methyl - hydrazino) - methyl] - biphenyl hydrochloride which melted at 195°—196°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzophenone hydrochloride which melted at 147°—149°C., 4 - [(2 - methyl - hydrazino) - methyl] - acetophenone hydrochloride which melted at 138°—140°C., 1,2 - bis[(2 - methyl - hydrazino) - methyl] - 4,5 - methylenedioxy - benzene dihydrochloride which melted at 182°—184°C. and 1,2 - bis[(2 - methyl - hydrazino) - methyl] - 4,5 - dimethoxy - benzene dihydrochloride which melted at 182°—184°C.

EXAMPLE 3

A mixture of 44 g of 1 - methyl - 1,2 - diacetyl - hydrazine and 80 ml of absolute ethanol was added to a solution of 7.7 g of sodium in 200 ml of absolute ethyl alcohol. 57 g of 4-nitro-benzyl chloride in 60 ml of N,N-dimethyl-formamide were then added dropwise thereto in the course of 0.5 hours with stirring and heating. The reaction mixture was then heated for 1 hour, cooled to 0°C., the separated precipitate filtered off and washed twice, each time with 100 ml of ethanol. The filtrate was then evaporated *in vacuo* and the residue partitioned between 200 ml of water and 300 ml of methylene chloride. The aqueous phase was separated and again extracted this time with 200 ml of methylene chloride. The methylene chloride extracts were then washed with 200 ml of 2-*N* sodium hydroxide and 200 ml of water, dried over sodium sulphate and concentrated. The residue was recrystallized from chloroform/ethanol yielding 1-methyl-2-(4-nitro-benzyl)-1,2-diacetyl-hydrazine which melted at 141°—142°C.

10 g of this product were dissolved in 50 ml of concentrated hydrochloric acid, the solution diluted with 40 ml of water and warmed on a water-bath under a nitrogen atmosphere for 1.5 hours. The reaction mixture was then concentrated *in vacuo* and the residue recrystallized from methanol yielding 1-methyl-2-(4-nitro-benzyl)-hydrazine hydrochloride melting at 168°—170°C.

EXAMPLE 4

24.7 g of 1-methyl-1,2-diacetyl-hydrazine were added to a solution of 4.38 g of sodium in 150 ml of absolute ethanol and 27.5 g of 2-cyano-benzyl chloride were then added to the resulting mixture which was then heated under reflux for 4 hours. The precipitated salt was filtered off and the filtrate concentrated *in vacuo*. The residue was treated with water and extracted over 15 hours with a mixture of ether and methylene chloride (2:1). Concentration of the extract yielded a residue that was heated under a nitrogen atmosphere for 2 hours with a mixture of 85 ml of concentrated hydrochloric acid and 67 ml of water. The reaction solution was then concentrated and rendered alkaline by addition of sodium hydroxide, whereupon 2 - [(2 - methyl - hydrazino) - methyl] - benzamide separated out. The dihydrobromide prepared therefrom was crystallized from glacial acetic acid and melted at 240°—242°C.

EXAMPLE 5

A solution of 25.4 g of 1-methyl-1,2-dibenzoyl-hydrazine in 50 ml of N,N-dimethyl-formamide was added dropwise, with stirring and cooling at 20°—30°C., to a suspension of 2.4 g of sodium hydride in 50 ml of N,N-dimethyl-formamide. 17.2 g of 3-nitro-benzyl chloride were then added to the reaction mixture and the resulting mixture 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, the residue poured into 1-*N* sodium hydroxide, extracted with ether, the eluate washed with 1-*N* sodium hydroxide and with water and the so-obtained ether phase dried over sodium sulphate and evaporated. The residue was then decanted twice each time with 0.5 litre of low-boiling petroleum ether. The petroleum ether insoluble portion, a viscous yellow oil, consisted of crude 1-methyl-2-(3-nitro-benzyl)-1,2-dibenzoyl-hydrazine. Without further purification, this crude product was dissolved in 200 ml of acetic acid and the resulting solution, after addition of 200 ml of concentrated hydrochloric acid, boiled for 2 hours under a nitrogen atmosphere. The concentrate obtained by evaporation under reduced pressure was then partitioned between water and ether. The aqueous phase was separated, evaporated under reduced pressure and concentrated *in vacuo* and the so-obtained crystals were dried over potassium hydroxide and ~~rercrystallized~~ recrystallized from ethanol/ether, yielding 1-methyl-2-(3-nitro-benzyl)-hydrazine monohydrochloride melting at 153°—155°C.

EXAMPLE 6

First, 2.05 g of sodium and then 28 g of 1-methyl-1,2-dibenzyloxycarbonyl-hydrazine were dissolved in 150 ml of absolute ethanol, and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in 100 ml of N,N-dimethyl-formamide and to this solution were added at one time with stirring 20.5 g of 4-(bromo-methyl)-benzamide. The reaction was exothermic and the temperature of the reaction mixture rose to about 60°C. The reaction mixture was stirred for 2 hours, then poured into 500 ml of water and extracted three times with ether/(methylene chloride) (3:1). The organic extracts were washed 5 times with water, dried with sodium sulphate and evaporated to dryness *in vacuo*. The residual oil was dissolved in 180 ml of a 33% solution of hydrogen bromide in glacial acetic acid, and the resulting solution permitted to stand for 4 hours at *ca* 20°C. The crystals which separated were filtered off, washed with glacial acetic acid and ether, and recrystallized from ethanol, yielding 4 - [(2 - methyl - hydrazino) - methyl] - benzamide hydrobromide melting at 173°—175°C.

In an analogous manner, the following compounds were prepared: 3 - [(2 - methyl - hydrazino) - methyl] - benzamide hydrobromide melting at 142°—143°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid methyl amide hydrobromide melting at 186°—187°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzenesulphonic acid dimethyl amide dihydrobromide melting at 126°—128°C. and 4 - [(2 - methyl - hydrazino) - methyl] - 3 - chloro - benzamide hydrobromide melting at 197°—199°C.

EXAMPLE 7

A solution of 2.3 g of sodium in 150 ml of absolute ethanol was treated with 31.4 g of 1 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazine and then with a solution of

18.3 g of 3-acetamido-benzyl chloride in 50 ml of absolute ethanol. The mixture was then heated to a boil with stirring for 2.5 hours, cooled and evaporated *in vacuo*. The oily residue was partitioned between methylene chloride and water and worked up as usual. The crude 1 - methyl - 2 - (3 - acetamido - benzyl) - 1,2 - dibenzyloxycarbonyl-hydrazine was hydrogenated in 200 ml of methanol with palladium/carbon as the catalyst. After termination of the hydrogen absorption, the solvent was evaporated off, the residue taken up in 50 ml of absolute ethanol and treated with a solution of 12.6 g of oxalic acid and alcohol. The first colloidal precipitate was rendered solid by trituration with methanol and then recrystallized from methanol/ether, yielding 1 - methyl - 2 - (3 - acetamido - benzyl) - hydrazine oxalate melting at 175°C. (decomposition).

In a similar manner 1-methyl-2-(2-acetamido-benzyl)-hydrazine hydrochloride melting at 162°C. was obtained.

Example 8

A mixture of 12 g of methyl-hydrazine, 37.3 g of 4-dimethylamino-benzaldehyde, 200 ml of ethanol and 0.5 ml of acetic acid was heated under a nitrogen atmosphere to the boiling point for 5 minutes. After cooling to 20°C. and without isolation of the intermediate hydrazone, the reaction mixture was hydrogenated under normal conditions in the presence of 2 g of platinum in the form of platinum oxide (ADAMS catalyst). The hydrogenation was interrupted after the uptake of 6.5 litres of hydrogen, the catalyst filtered off, rinsed with 20 ml of ethanol and the purified filtrate along with the rinse ethanol concentrated at 40° (bath temperature)/12 mm Hg. The oily brown coloured residue was purified by fractional distillation under a nitrogen atmosphere, yielding 1-methyl-2-(4-dimethylamino-benzyl)-hydrazine which boiled at 131°C./0.3 mm Hg and formed a colourless oil which was unstable in air.

In a similar manner, there was prepared 1-methyl-2-(4-amino-benzyl)-hydrazine which boiled at 123°—124°C./0.4 mm Hg.

Example 9

A mixture of 37.6 g of 3-nitro-benzaldehyde, 100 ml of methyl alcohol, 50 ml of aqueous methyl-hydrazine solution (obtained from 26 g of methyl-hydrazine) and 1 ml of acetic acid were heated to the boil for 10 minutes. The deep red coloured solution was cooled to 4°C. and permitted to stand for 16 hours. The crystals which separated were filtered off, washed with 90% aqueous ethanol and dried *in vacuo*. The filtrate and wash liquid were concentrated under reduced pressure to about half of their volume. Upon cooling, further substance crystallized out. The crude dried 1-methyl-2-(3-nitro-benzylidene)-hydrazine was twice recrystallized from ether/(petroleum ether) and melted at 66°C.

17.6 g of this product in 100 ml of ethyl acetate were hydrogenated in the presence of 2 g of palladium/carbon (10%) under normal conditions. After the uptake of the calculated amount of hydrogen, the hydrogenation was interrupted, the catalyst filtered off and the filtrate concentrated at 40°C. (bath temperature)/12 mm Hg. The oily residue was purified by distillation under a nitrogen atmosphere, yielding 1-methyl-2-(3-amino-benzyl)-hydrazine as a colourless viscous oil which distilled over at 113°—115°C./0.05 mm Hg practically free of any residue.

In an analogous manner, the following product were prepared: 1 - methyl - 2 - (2 - amino - benzyl) - hydrazine which boiled at 93°C./0.02 mm Hg and 1 - methyl - 2 - (4 - amino - benzyl) - hydrazine which boiled at 123°—124°C./0.4 mm Hg.

Example 10

14.92 g of 4 - dimethylamino - benzaldehyde in 100 ml of ethyl alcohol were added to an aqueous acetic acid solution of 1 - methyl - 1 - acetyl - hydrazine. The reaction mixture was then heated to the boil for 5 minutes, the clear red solution cooled down and the separated crystals of 1 - methyl - 2 - (4 - dimethylamino - benzylidene) - 1 - acetyl - hydrazine filtered off. This intermediate was twice recrystallized from methanol and melted at 127°—129°C.

10.9 g of this hydrazone were dissolved in 250 ml of ethanol and hydrogenated under normal conditions in the presence of 0.5 g of platinum catalyst. Hydrogenation came to a standstill after the absorption of the calculated amount of hydrogen. The catalyst was then filtered off, the filtrate evaporated under reduced pressure and the residue which formed upon cooling of the concentrate recrystallized twice from ether/(petroleum ether), yielding 1 - methyl - 2 - (4 - dimethylamino - benzyl) - 1 - acetyl - hydrazine melting at 73°—74°C.

39 g of this acetyl compound were added to a solution of 40 g of potassium hydroxide in 400 ml of absolute ethanol, and the mixture boiled for 6 hours under

a nitrogen atmosphere. The reaction mixture was then concentrated to about 100 ml, treated with an equal amount of water, saturated with potassium carbonate and extracted three times, each time with 500 ml of ether. The purified ether extracts were dried over potassium carbonate and evaporated to dryness under reduced pressure. The residue was taken up in 500 ml of benzene, dried for 2 hours over sodium sulphate in the presence of animal charcoal, filtered, and the filtrate concentrated under reduced pressure, yielding 1 - methyl - 2 - (4 - dimethylamino - benzyl) - hydrazine as a light yellow coloured oil which boiled at 131°C./0.3 mm Hg; $n_D^{22} = 1.5704$.

EXAMPLE 11

First, 0.62 g of sodium and then 8.8 g of 1 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazine were dissolved in 50 ml of absolute ethanol and the solution evaporated to dryness under reduced pressure. The residue was dissolved in 50 ml of N,N-dimethyl-formamide and treated with a solution of 9.8 g of N - (N - benzyloxycarbonyl - DL - α - alanyl) - 4 - (chloro - methyl) - aniline in 20 ml of N,N-dimethyl-formamide. After 10 minutes, the reaction mixture reacted neutral. It was then poured into water and extracted with methylene chloride, the extract washed with water and dried with sodium sulphate. The methylene chloride was distilled off *in vacuo*, the residual oil dissolved in 300 ml of methanol and hydrogenated in the presence of palladium/carbon until the benzyloxycarbonyl groups were completely split off. After the catalyst had been filtered off, the filtrate was adjusted to a pH of 5 with alcoholic hydrochloric acid, concentrated to a small volume *in vacuo* and treated with ethyl acetate. The precipitated hydrochloride of 1 - methyl - 2 - [4 - (DL - α - alanyl - amino) - benzyl] - hydrazine was an amorphous hygroscopic powder which decomposed at 95°—100°C.

There was obtained in an analogous manner 1 - methyl - 2 - [4 - (L α - alanyl - amino) - benzyl] - hydrazine hydrochloride which decomposed between 100° and 110°C., $[\alpha]_D = +24.5°$ (c = 1 in water).

EXAMPLE 12

31.4 g of 1 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazine were added portionwise, with stirring at 25°—30°C., to a suspension of 2.4 g of sodium hydride in 100 ml of N,N-dimethyl-formamide. The reaction mixture was then stirred until the hydrogen evolution had terminated and all the material had gone into solution. A solution of 23 g of 4-phenylazo-benzyl chloride in 100 ml of N,N-dimethyl-formamide was then added dropwise thereto with stirring in the course of 0.5 hours. After the addition had been terminated, the mixture was stirred for a further 2 hours at 80°C., then cooled and the solvents evaporated off *in vacuo* as far as possible. The deep red oily residue was partitioned between 300 ml of water and 400 ml of methylene chloride. The methylene chloride solution was washed with 200 ml of water, dried over sodium sulphate and concentrated *in vacuo*. The oily residue was taken up in 100 ml of ethyl acetate, the resulting solution evaporated *in vacuo*, the residue dissolved in 300 ml of ethyl acetate and hydrogenated with 5 g of RANEY-nickel under normal conditions. After the absorption of 4.9 litres of hydrogen, the hydrogenation came to a standstill, whereupon the catalyst was filtered off and the colourless filtrate evaporated *in vacuo*. The oily residue was extracted with boiling petroleum ether (boiling point 40°—45°C.) until no more aniline could be detected. The petroleum ether insoluble portion was dissolved in ether and shaken with 100 ml of 3-*N* hydrochloric acid, whereupon there precipitated a heavy water and ether insoluble oil which was separated and stirred with 3-*N* sodium hydroxide until the mixture was strongly alkaline. It was then extracted with ether, the ether solution washed neutral with water and dried with sodium sulphate. By distillation, there was obtained 1 - methyl - 2 - (4 - amino - benzyl) - 1,2 - dibenzyloxycarbonyl - hydrazine as a yellow viscous oil which was sufficiently pure for further reaction. It was then dissolved in 100 ml of a 33% solution of hydrogen bromide in glacial acetic acid and permitted to stand for 4 hours at *ca* 20°C. The precipitated crystals were then filtered off, washed with glacial acetic acid and ether and recrystallized from ethanol/acetonitrile/ether, yielding 1 - methyl - 2 - (4 - amino - benzyl) - hydrazine hydrobromide which melted at 130°—134°C. (decomposition).

EXAMPLE 13

A solution of 8.9 g of 5 - methyl - isoxazolyl - (3) - carbonyl chloride in 30 ml of absolute benzene was added dropwise with stirring so that the temperature did not rise over 40°C. to a solution of 20 g of 1 - methyl - 2 - (4 - amino - benzyl) - 1,2 - dibenzyloxycarbonyl - hydrazine in 30 ml of absolute pyridine. After the addition, the reaction mixture was stirred for 16 hours at *ca* 20°C. and then treated with 200 ml of

water. The aqueous phase was extracted twice, each time with 300 ml of benzene. The benzene extracts were extracted 3 times (in all with 400 ml of 2-*N* hydrochloric acid) then with 200 ml of water and finally twice with a total of 300 ml of saturated sodium bicarbonate solution, then dried over sodium sulphate and evaporated *in vacuo*. The residue crystallized upon digestion with ether and was then recrystallized from absolute ethyl alcohol, yielding 1 - methyl - 2 - [4 - [5 - methyl - isoxazolyl - (3) - carbonyl-amino] - benzyl] - 1,2 - dibenzyloxycarbonyl - hydrazine of melting point 128°—130°C.

12 g of this product were covered with 100 ml of a 33% solution of hydrogen bromide in glacial acetic acid and the resulting mixture kept at *ca* 20°C. with occasional agitation for 5 hours. The separated crystals were then filtered off, washed with glacial acetic acid and ether and recrystallized 3 times from absolute ethanol, yielding 1 - methyl - 2 - 4 - [[5 - methyl - isoxazolyl - (3) - carbonylamino] - benzyl] - hydrazine hydrobromide melting at 211°C. (decomposition).

In an analogous manner the following compounds were prepared: 1 - methyl - 2 - (4 - *iso*nicotinoylamino - benzyl) - hydrazine dihydrobromide of melting point 231°—232°C. (decomposition) (from water/ethanol), 1 - methyl - 2 - (4 - nicotinoylamino - benzyl) - hydrazine hydrobromide of melting point 210°—211°C. (decomposition) (from water/ethanol), 1 - methyl - 2 - (4 - benzamido - benzyl) - hydrazine hydrobromide of melting point 184°—186°C. (from ethanol) and 1 - methyl - 2 - (4 - acetamido-benzyl)-hydrazine hydrobromide of melting point 180°C. (from ethanol/ether).

Example 14

A) *Preparation of the starting material*

The starting material was prepared as follows:

544 g of 4-methyl-benzoic acid were boiled with 550 ml of thionyl chloride until a clear solution was obtained. After the excess thionyl chloride had been distilled off, the residue was fractionated yielding 605 g of 4-methyl-benzoyl chloride; boiling point 91°C./9 mm Hg, $n_D^{24} = 1.5532$. This was dissolved in 550 ml of absolute benzene and the so-formed solution added to a mixture of 248 ml of absolute methanol and 550 ml of absolute benzene. After the exothermic reaction had terminated, the reaction mixture was boiled for a further 20 hours, then concentrated *in vacuo* and the product, 4-methyl-benzoic acid methyl ester, isolated by conventional means. It could be purified by distillation and the purified product boiled at 91°C./9 mm Hg; melting point 32°C.

574 g of this ester were dissolved in 1200 ml of carbon tetrachloride and, while boiling and exposing to an ultraviolet lamp, treated dropwise with a solution of 109 ml of bromine in 400 ml of carbon tetrachloride. After all of the bromine had been dropped in, the mixture was heated for a further hour, concentrated *in vacuo* and the residue crystallized from low boiling petroleum ether, yielding as colourless fine crystals, 4-(bromo-methyl)-benzoic acid methyl ester which melted at 52°C. For the reaction of this ester with 1-methyl-1,2-dibenzyloxycarbonyl-hydrazine, the following procedure was followed: 309 g of a 27% suspension of sodium hydride in an inert solvent were treated with 300 ml of N,N-dimethyl-formamide, and a solution of 1095 g of 1-methyl-1,2-dibenzyloxycarbonyl-hydrazine in N,N-dimethyl-formamide was added thereto. When all the material had been added and the hydrogen evolution had nearly come to a standstill, the mixture was heated for an hour at about 80°C. in order to carry the formation of the sodium salt to completion. A mixture of 759 g of 4-(bromo-methyl)-benzoic acid methyl ester in 700 ml of N,N-dimethyl-formamide was then dropped in and finally the reaction mixture was heated for an hour at 80°C. After cooling, the reaction mixture was poured into 10 litres of ice-water and the condensation products taken up in ether. The thereby obtained crude methyl ester ($n_D^{24} = 1.1558$) was used without further purification for the next step. It was dissolved in about 2200 ml of dioxan, treated with a solution of 133 g of sodium hydroxide in 870 ml of water and the resulting mixture stirred for about 24 hours at *ca* 20°C. It was then poured into about 10 litres of ice-water and neutral materials were extracted with ether. The aqueous phase was rendered acid with concentrated hydrochloric acid (weak congo-red) and the separated acid taken up in ether. The isolated crude acid was recrystallized from dibutyl ether, yielding colourless crystals of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid which melted at 112°C. The so-obtained product was sufficiently pure for the process.

B) *The process*

15 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid were boiled under reflux with an excess of thionyl chloride for 1 hour. The unconverted thionyl chloride was distilled off *in vacuo*, the residue dissolved twice

each time in 75 ml of absolute benzene and then concentrated *in vacuo*. The so-obtained 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride, a viscous light yellow oil, was dissolved in 50 ml of absolute benzene and with stirring mixed with a solution of 4.45 g of *iso*propyl amine in 100 ml of absolute benzene. By cooling, the temperature of the reaction mixture was kept below 30°C. After the mixing had been completed, the reaction mixture was maintained first at *ca* 20°C. for 3 hours and then at 40°C. for 0.5 hours. It was then cooled down and poured into about 100 ml of ice-water. After the addition of a mixture of methylene chloride and ether (40 ml + 200 ml), the organic phase was separated and then washed with water, dilute hydrochloric acid, water, dilute sodium hydroxide and again with water. The solvents were then evaporated, yielding 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid *iso*propyl amide as a yellow oil which crystallized upon triturating with ether; melting point 90°—92°C. This product was then covered with 70 ml of a 33% solution of hydrogen bromide in glacial acetic acid and then permitted to stand for 2 hours with occasional swirling, whereupon a thick slurry of crystals was formed. The precipitate was filtered off, washed with 20 ml of glacial acetic acid and finally with ether, yielding crystals of 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *iso*propyl amide hydrobromide which, after recrystallization from methanol/ether, melted at 216°—217°C. (decomposition).

In a similar way, but using different amines, the following compounds were prepared: 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid methyl amide hydrobromide of melting point 186°—187°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid ethyl amide hydrobromide of melting point 164°—165°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *n* - propyl amide hydrobromide of melting point 177°—178°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *n* - butyl amide hydrobromide of melting point 173°—175°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *sec*butyl amide hydrobromide of melting point 155°—156°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *tert*butyl amide hydrobromide of melting point 200°—201°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *iso*butyl amide hydrobromide of melting point 177°—179°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *iso*pentyl amide hydrobromide of melting point 163°—164°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *n* - pentyl amide hydrobromide of melting point 174°—175°C., 4 - [(2 - methyl - hydrazino) - methyl]-benzoic acid dimethyl amide dihydrobromide of melting point 142°—145°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid di*iso*propyl amide hydrobromide of melting point 202°—203°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid tetramethylene amide dihydrobromide hydrate of melting point 139°—142°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid pentamethylene amide oxalate of melting point 170°—172°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid allyl amide hydrobromide of melting point 158°—159°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2-chloro-ethyl) amide hydrobromide of melting point 168°—169°C., 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2 - methyl - thio - ethyl) amide hydrobromide of melting point 152°—153°C. and 4 - [(2 - methyl-hydrazino) - methyl]benzoic acid (2 - methyl - sulphonyl - ethyl) amide hydrobromide of melting point 126°—218°C.

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Example 15

16.5 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride were added to 100 ml of absolute benzene and treated with 3.1 g of *cyclo*propyl amine hydrochloride. 7.5 g of triethyl amine and 50 ml of benzene were then dropped into the reaction mixture at 20°—30°C. with stirring. The reaction mixture was worked up as in Example 14, yielding 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid *cyclo*propyl amide, the benzyloxycarbonyl groups of which were then removed by treatment with (hydrogen bromide)/(glacial acetic acid). The product, 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *cyclo*propyl amide hydrobromide melted at 180°—182°C.

Example 16

Reaction of 16.5 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride with morpholine according to the process of Example 14 yielded the recation product as a viscous yellow oil. The benzyloxycarbonyl groups were split off by hydrogenation as follows: the so-obtained 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid 3-oxa-tetramethylene amide was dissolved in 210 ml of methanol and, after the addition of 2.1 g of 5% palladium/

carbon, hydrogenated at *ca* 20°C. and atmospheric pressure. After the hydrogen uptake had come to a standstill, the catalyst was filtered off, washed with methanol and the filtrate concentrated *in vacuo*. The residue was taken up in 25 ml of methanol, treated with a solution of 4.54 g of oxalic acid in 20 ml of methanol and ether added thereto until the solution became turbid. Upon cooling, 4-[(2 - methyl - hydrazino) - methyl]-benzoic acid 3-oxa-tetramethylene amide oxalate crystallized out and, after recrystallization from methanol/ether, melted at 142°—144°C.

By the same method and using 2-cyano-ethyl amine, the following compound was prepared: 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2-cyano-ethyl) amide oxalate.

Example 17

14.1 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride in 20 ml of benzene were added to a mixture of 13.2 g of glycine benzyl ester tosylate and 100 ml of absolute pyridine. After the mixture had stood for one hour at *ca* 20°C., it was worked up in the usual manner and the crude condensation product was hydrogenated in methanol with palladium/carbon as the catalyst. The so-obtained N - [4 - [(2 - methyl - hydrazino) - methyl] - benzoyl] - glycine, melted at 209°—120°C. (decomposition) after recrystallization from water/alcohol.

The same product was obtained by a reaction of 4 - [(2 - methyl - 1,2 - dibenzyl-oxycarbonyl - hydrazino) - methyl] - benzoic acid and glycine benzyl ester tosylate in methylene chloride in the presence of triethyl amine and di*cyclo*hexyl-carbodiimide. After removal of the formed di*cyclo*hexyl-urea by filtration under suction, the methylene chloride solution was washed with dilute hydrochloric acid and sodium bicarbonate solution, then concentrated. The product was then hydrogenated as described previously.

Example 18

17 g of L-glutamine 4-nitro-benzyl ester hydrobromide in 120 ml of absolute pyridine were treated with a solution of 22 g of 4 - [(2 - methyl - 1,2 - dibenzyloxy - carbonyl - hydrazino) - methyl] - benzoyl chloride in 50 ml of benzene, and then worked up as in Example 17.

During the hydrogenation both the benzyloxycarbonyl groups, as well as the 4-nitro-benzyl ester group, were split off and the final product N - [4 - [(2 - methyl - hydrazino) - methyl] - benzoyl] - L - glutamine, after recrystallization from aqueous ethanol, melted at 209°—210°C.; $[\alpha]_D = 15.8°$ (c = 1 in water).

By the above procedure, employing glycine amide or serine amide, the following compounds were prepared: N - [4 - [(2 - methyl - hydrazino) - methyl] - benzoyl] - glycine amide hydrochloride of melting point 190°—192°C. and N - [4 - [(2 - methyl-hydrazino) - methyl] - benzoyl] - serine amide hydrochloride of melting point 184°—186°C.

Example 19

5.75 g of sodium and then 79 g of 1-methyl-1,2-dibenzyloxycarbonyl-hydrazine were dissolved in 250 ml of absolute alcohol. The solution was evaporated to dryness *in vacuo* at 40°C. and the residue dissolved in 150 ml of N,N-dimethyl-formamide. Over ten minutes, 46 g of 4-chloromethyl-thioanisole were added to the solution, the temperature of the reaction mixture rising to 60°C. The reaction mixture was then stirred for two hours at *ca* 20°C., poured into 1.5 litres of water and extracted with (methylene chloride)/ether. The extracts were washed several times with water, dried with sodium sulphate and concentrated *in vacuo*. The oily residue was dissolved in 400 ml of glacial acetic acid and, after the addition of 80 ml of 30% hydrogen peroxide, heated on the steam-bath for two hours. The reaction mixture was then evaporated to dryness *in vacuo* and the residue dissolved in 500 ml of a 33% solution of hydrogen bromide in glacial acetic acid. After a short time, the product 1-methyl-2-(4-methyl-sulphonyl-benzyl)-hydrazine hydrobromide crystallized therefrom. It melted at 173°—175°C. (decomposition).

Example 20

10 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride were dissolved in a mixture of 50 ml of benzene and 10 ml of pyridine. While stirring, this solution was treated with 8 g of 1 - methyl - 2 - (4 - amino - benzyl) - 1,2 - dibenzyloxycarbonyl - hydrazine in 30 ml of benzene. After standing for one hour at *ca* 20°C., the reaction mixture was poured into water and extracted

with methylene chloride. The methylene chloride extract was washed with sodium bicarbonate solution, dried with sodium sulphate and then concentrated. The residual viscous oil was debenzyloxycarbonylated with 70 ml of a 33% solution of hydrogen bromide in glacial acetic acid. From this reaction mixture, the dihydrobromide of 4,4[1] - bis - [(2 - methyl - hydrazino) - methyl] - benzanilide crystallized out. After recrystallization from methanol, it melted at 247°—248°C. (decomposition).

EXAMPLE 21

By reaction of 23.4 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino)-methyl]-benzoyl chloride with 4.85 g of furfuryl amine in a mixture of 8 ml of pyridine and 50 ml of benzene according to the procedure of Example 15, followed by hydrogenation of the condensation product with palladium/carbon in methanol, there was obtained 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid furfuryl amide the oxalate of which melted at 170°—171°C. (decomposition).

In an analogous manner, there was obtained 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (3-methoxy-propyl) amide hydrochloride of melting point 135°—136°C.

By employing β-phenyl-ethyl amine in the condensation step, and splitting off the benzyloxycarbonyl groups with (hydrogen bromide)/(glacial acetic acid), there was obtained 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid phenyl-ethyl amide hydrobromide which, after recrystallization from ethanol/ether, melted at 180°—183°C.

In an analogous manner, the following compounds were obtained by using the corresponding amines: 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid [pyridyl - (3) - methyl] amide dihydrobromide of melting point 136°—139°C. and 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid benzyl amide hydrobromide of melting point 175°—177°C.

EXAMPLE 22

23.4 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride were dissolved in 60 ml of benzene and, with stirring and cooling, added dropwise to a solution of 13.4 g of 2-diethylamino-ethyl amine in 20 ml of benzene. The mixture was permitted to stand for 16 hours and then partitioned between a dilute solution of sodium hydroxide and ether. The ether phase was washed thoroughly neutral with water and then extracted with 0.25-*N* hydrochloric acid. The hydrochloric acid extract was rendered strongly alkaline with sodium hydroxide and then again extracted with ether. The ether solution was washed neutral with water, dried with sodium sulphate and evaporated. The residue yellow oil was dissolved in 75 ml of a 33% solution of hydrogen bromide in glacial acetic acid and the resulting mixture permitted to stand for three hours at *ca* 20°C. It was then treated with ether, whereupon a hygroscopic salt separated out. This was separated and then dissolved in the minimum amount of water. The solution was then saturated with potassium carbonate and extracted with methylene chloride. The methylene chloride extracts were dried with potassium carbonate and concentrated. The residue was dissolved in methanol and treated with a methanolic solution of 2 equivalents of picric acid, whereupon the dipicrate of 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid diethylamino-ethyl amide crystallized out. It melted at 137°—139°C.

In an analogous manner there was obtained 4-[(2-methyl-hydrazino)-methyl]-benzoic acid dimethylamino-ethyl amide dihydrobromide of melting point 131°—133°C.

EXAMPLE 23

9 g of ethanol amine were dissolved in a solution of 18.2 g of sodium carbonate in 200 ml of water. Over two hours, a solution of 65 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride in 150 ml of ether was then added thereto dropwise with vigorous stirring at 0°—5°C. The reaction mixture was then stirred for 16 hours at 0°—5°C. It was then extracted with a mixture of methylene chloride and ether and the extract washed with water, 1-*N* hydrochloric acid, potassium bicarbonate solution and water, dried with sodium sulphate and evaporated. The residual 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid (2-hydroxy-ethyl) amide crystallized upon trituration with ether; melting point 74°—76°C. 68 g thereof were dissolved in 210 ml of a 33% solution of hydrogen bromide in glacial acetic acid and the so-formed mixture permitted to stand at *ca* 20°C. for 16 hours. The 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2-acetoxy-

ethyl) amide hydrobromide separated off. This hygroscopic salt melted at 119°—121°C. (decomposition). It was then filtered off, washed with (acetic acid)/ether (4:1), washed with ether and dissolved in the minimum amount of water. This solution was saturated with potassium carbonate and extracted with ether. An etheric picric acid was then added to the ether extract, whereupon the picrate of 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2-acetoxy-ethyl) amide crystallized out. After recrystallization from methanol, it melted at 143°—145°C.

EXAMPLE 24

13.5 g of diethanol amine were dissolved in a solution of 14.5 g of sodium carbonate in 160 ml of water. In the course of 2 hours, a solution of 52 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride in 150 ml of ether was added thereto dropwise with vigorous stirring at 0°—5°C. The mixture was then stirred for 16 hours at 0°—5°C. It was extracted with ethyl acetate and the ethyl acetate solution washed with sodium bicarbonate solution and sodium chloride solution, dried with sodium sulphate and evaporated. The residual viscous yellow oil was dissolved in 500 ml of methanol and shaken with palladium/carbon in a hydrogen atmosphere until the benzyloxycarbonyl groups had been hydrogenated off. The catalyst was then filtered off, and the filtrate evaporated. The residue was dissolved in ethanol and treated with one equivalent of oxalic acid. Upon standing, the oxalate of 4-[(2-methyl-hydrazino)-methyl]-benzoic acid bis(2-hydroxy-ethyl) amide crystallized out. It melted at 145°—146°C.

EXAMPLE 25

20 g of 1-methyl-2-(4-amino-benzyl)-1,2-dibenzyloxycarbonyl-hydrazine were dissolved in 25 ml of pyridine and, with stirring and cooling, 6.4 g of pivaloyl chloride in 10 ml of benzene were added thereto dropwise. The reaction mixture was then permitted to stand for 16 hours at *ca* 20°C., poured into 400 ml of water, taken up in ether and the ether solution washed with water, 3-*N* hydrochloric acid, potassium bicarbonate solution and water, dried with sodium sulphate and evaporated. The residual yellow oil was dissolved in 70 ml of a 33% solution of hydrogen bromide in glacial acetic acid and permitted to stand for 3 hours at *ca* 20°C. The precipitated crystals were filtered off, washed with (acetic acid)/ether (4:1) and ether and recrystallized from ethanol/ether, yielding 1-methyl-2-(4-pivaloylamino-benzyl)-hydrazine hydrobromide melting at 181°—182°C. (decomposition).

EXAMPLE 26

20 g of 1-methyl-2-(4-amino-benzyl)-1,2-dibenzyloxycarbonyl-hydrazine were dissolved in 100 ml of 85% acetic acid. With stirring at 30°—35°C., a solution of 6 g of sodium cyanate in 45 ml of water was then added dropwise to the mixture. The reaction mixture was then stirred for 1.5 hours at 50°C., poured into 850 ml of water, taken up in ether and washed with water, 3-*N* hydrochloric acid, potassium bicarbonate solution and water. After drying with sodium sulphate, the ether was distilled off and the residue viscous oil dissolved in 70 ml of a 33% solution of hydrogen bromide in glacial acetic acid. The so-formed mixture was permitted to stand for 4 hours. The precipitated crystals were filtered off, washed with (acetic acid)/ether (4:1) and ether and recrystallized from ethanol, yielding the hydrobromide of 1-methyl-2-(4-ureido-benzyl)-hydrazine which melted at 140°—142°C.

EXAMPLE 27

18.9 g of 1-methyl-2-(4-amino-benzyl)-1,2-dibenzyloxycarbonyl-hydrazine were dissolved in 50 ml of ethanol, treated with one equivalent of ethanolic hydrochloric acid and 2.7 g of cyanamide, and then boiled under reflux for 18 hours. The reaction mixture was then evaporated *in vacuo*, the residue dissolved in water, rendered alkaline with sodium hydroxide and extracted with ether/(methylene chloride). The extract was washed with water, dried with sodium sulphate and evaporated. The residual yellow oil was shaken for 16 hours at *ca* 20°C. with 60 ml of a 33% solution of hydrogen bromide in glacial acetic acid. The so-formed crystals were filtered off and washed with acetic acid and ether, yielding 1 - methyl - 2 - (4 - guanidino - benzyl) - hydrazine dihydrobromide which melted at 122°—125°C. (decomposition).

EXAMPLE 28

30 g of 1 - methyl - 2 - (4 - amino - benzyl) - 1,2 - dibenzyloxycarbonyl - hydrazine were reacted with 9 g of methylsulphonyl chloride according to the procedure de-

scribed in Example 25. After the reaction mixture had been poured into water, it was extracted with a mixture of ether and methylene chloride. It was then washed with water, 3-*N* hydrochloric acid, potassium bicarbonate solution and water, dried with sodium sulphate and evaporated. The so-obtained residual yellow oil was dissolved in 105 ml of 33% solution of hydrogen bromide in glacial acetic acid, and permitted to stand for 3 hours at *ca* 20°C. The precipitated crystals were isolated and purified as previously described, yielding 1 - methyl - 2 - (4 - methylsulphonylamino - benzyl) - hydrazine hydrobromide melting at 177°—178°C.

EXAMPLE 29

106.5 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride were dissolved in 400 ml of diethyleneglycol dimethyl ether, and, with stirring in the course of 1.5 hours at −75° to −68°C., treated with a suspension of 70 g of tri *tert*butoxy lithium aluminium hydride in 400 ml of diethyleneglycol dimethyl ether. The temperature of reaction mixture was then allowed to rise to 0°C. in the course of 1 hour and then the mixture was treated with 60 ml of water and 25.5 ml of 3-*N* sodium hydroxide. After a further 1.5 hours, the reaction mixture was poured into a large amount of water, acidified with hydrochloric acid and the crude aldehyde taken up in ether. The ether solution was washed three times with 3-*N* hydrochloric acid, twice with water, four times with sodium hydroxide solution and a further three times with water, dried with sodium sulphate and concentrated, yielding crude 4-[(2-methyl-1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzaldehyde. In order to split off the benzyloxycarbonyl groups, this aldehyde was dissolved in about 40 ml of glacial acetic acid and to this solution were added 280 ml of a 33% solution of hydrogen bromide in glacial acetic acid. The reaction mixture was then permitted to stand for 3 hours at *ca* 20°C. The separated crystals were filtered off under suction, washed first with glacial acetic acid and then with absolute ether, and then dried in a desiccator over potassium hydroxide, yielding 4 - [(2 - methyl - hydrazino) - methyl] - benzaldehyde hydrobromide melting at 127°—132°C.

EXAMPLE 30

52 g of the product obtained in Example 21 by the condensation of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride and furfuryl amine were hydrogenated in 300 ml of ethanol in the presence of 6 g of acetic acid and 1 g of platinum until 2 equivalent amounts of hydrogen had been taken up. The catalyst was then filtered off and the solution concentrated, whereupon the residue was dissolved in 150 ml of a 33% solution of hydrobromic acid in glacial acetic acid and allowed to stand for 3 hours. The crystallized product was filtered off, washed with glacial acetic acid and ether and recrystallized from a mixture of methanol, acetonitrile and ether, yielding 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid tetrahydrofurfuryl amide dihydrobromide melting at 124°—125°C.

EXAMPLE 31

23.8 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid (2-hydroxy-ethyl) amide (obtained according to Example 23) were dissolved in 240 ml of methanol and shaken in a hydrogen atmosphere together with 5 g of palladium/carbon until the benzyloxycarbonyl groups were hydrogenated off. The catalyst was then filtered off and the filtrates were concentrated. The residue was dissolved in 20 ml of ethanol and treated with 1 equivalent of 25% alcoholic hydrochloric acid. On diluting with acetonitrile, the 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2-hydroxy-ethyl) amide hydrochloride crystallized. It melted at 150°—152°C. after recrystallization from methanol/acetonitrile.

EXAMPLE 32

87.5 g of 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid *iso*propyl amide hydrobromide (obtained according to Example 14) were dissolved in 550 ml of water To this solution were added 1000 ml of methylene chloride and, while cooling with ice and stirring under a nitrogen atmosphere, 1200 g of potassium carbonate then added portionwise. The methylene chloride layer was separated and the aqueous slurry extracted three times with 500 ml of methylene chloride in a nitrogen atmosphere. The united methylene chloride extracts were concentrated *in vacuo*. The residue was dissolved under nitrogen in 100 ml of methanol and treated, while cooling with ice, with 40 ml of a 45% methanolic hydrochloric solution, which induced immediate crystallization. The crystals were filtered off and recrystallized from methanol, yielding 4-

[(2 - methyl - hydrazino) - methyl] - benzoic acid *iso*propyl amide hydrochloride melting at 223°—226°C.

EXAMPLE 33

A solution of 15.5 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino)-methyl] - benzoyl chloride in 50 ml of methylene chloride was poured while stirring into a solution of 2 - (N - benzyloxycarbonyl - methylamino) - ethyl amine in 50 ml of methylene chloride and 3.5 g of triethyl amine. The mixture was stirred for 3 hours at *ca* 20°C. and for 0.5 hours at 40°C., then poured on to water. The methylene chloride layer was separated and washed with 1-*N* hydrochloric acid and with water. The methylene chloride solution was dried and concentrated and the residue dissolved in 75 ml of a 33% solution of hydrobromic acid in glacial acetic acid and allowed to stand for 3 hours. The crystals formed were filtered off, washed with glacial acetic acid and ether and recrystallized from ethanol, yielding 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2-methylamino-ethyl) amide dihydrobromide melting at 166°—168°C.

The 2-(N-benzyloxycarbonyl-methylamino)-ethyl amine was prepared as follows:

20 g of 2-methylamino-ethyl amine in 100 ml of absolute benzene was stirred with 28.7 g of benzaldehyde. The mixture warmed up somewhat and became yellow. The benzene was evaporated *in vacuo* and the residue distilled under reduced pressure in a HICKMANN flask. After a little forerun, the desired fraction distilled at 106°—107°C./13 mm. The N-benzylidene-N^1-methylethylene diamine was obtained as a colourless oil of $n_D^{22} = 1.5452$ and an ultraviolet-absorption maximum at 245 mμ. 25 g of this product were dissolved in 150 ml of methylene chloride and thereto were added 16.5 g of triethyl amine and while stirring and cooling in an ice-bath, 26.7 g of benzyloxycarbonyl chloride in 100 ml of methylene chloride in such a way that the temperature did not rise over 20°C. The mixture was stirred for 3 hours at *ca* 20°C. and shaken with 100 ml of water. The methylene chloride layer was washed three times with water and concentrated *in vacuo*. The yellow oil obtained was well mixed with 100 ml of ether and 100 ml of 6-*N* sulphuric acid for one hour at *ca* 20°C. The layers were separated, the aqueous layer extracted a further five times with 30 ml of ether each time. To these combined ether extracts were added, while cooling on an ice-bath, 50 g of solid potassium hydroxide. The oily product was extracted with methylene chloride, the extract concentrated and the residue distilled under reduced pressure. The desired product distilled (after a short forerun) at 105°—112°C./0.04 mm as a colourless oil of $n_D^{24} = 1.5355$.

EXAMPLE 34

7.4 g of methyl-urea, 46.7 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride, 8 g of pyridine and 200 ml of benzene were mixed and heated under reflux for 8 hours. After cooling down, the mixture was poured on to water and extracted with an ether/(methylene chloride) mixture. The extract was washed with water, with 1-*N* hydrochloric acid and again with water, dried over sodium sulphate and freed of the solvent by distillation. The residue crystallized upon triturating with methanol. The crystals were filtered off and dried, yielding 1-methyl - 2 - [4 - (4 - methyl - allophanoyl) - benzyl] - 1,2 - dibenzyloxycarbonyl - hydrazine melting at 141°—142°C. 25 g thereof were dissolved in 50 ml of glacial acetic acid and to it were added 100 ml of a 33% solution of hydrobromic acid in glacial acetic acid. After standing for 4 hours, the crystals formed were filtered off, washed with glacial acetic acid and ether and recrystallized from methanol, yielding 1-methyl-[4-(4-methyl-allophanoyl)-benzyl]-hydrazine hydrobromide of melting point 183°—183.5°C.

In an analogous manner, the following products were obtained: 1 - methyl - 2 - (4 - allophanoyl - benzyl) - hydrazine hydrobromide of melting point 203°—204°C., 1 - methyl - 2 - [4 - (4 - ethyl - allophanoyl) - benzyl] - hydrazine hydrobromide of melting point 193°—194°C. and 1 - methyl - 2 - [4 - (4 - butyl - allophanoyl) - benzyl] - hydrazine hydrobromide of melting point 171°—172°C.

EXAMPLE 35

A suspension of 21.5 g of sodium hydride in 80 ml of N,N-dimethyl-formamide was added slowly while stirring to a solution of 281 g of 1-methyl-1,2-dibenzyloxycarbonyl-hydrazine in 300 ml of N,N-dimethyl-formamide. After the evolution of hydrogen had subsided, there was added to the reaction mixture a solution of 167 g of 4-(bromo-methyl)-benzonitrile in 200 ml of N,N-dimethyl-formamide and the mixture

was then heated for one hour at 80°C. The solvent was then almost completely distilled off *in vacuo*, the residue triturated with water and extracted with ether. The ether extract was washed with water, dried and concentrated. By recrystallization from dibutyl ether, there was obtained the 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino)-methyl]-benzonitrile melting at 68°C.

43 g of the foregoing nitrile were mixed with 50 ml of glacial acetic acid and 7.5 g of tertiary butanol. Thereto were added dropwise while stirring and cooling with ice to 0°—5°C., 5.6 ml of concentrated sulphuric acid. The ice-bath was then taken away and the mixture was stirred until homogeneous. It was then allowed to stand for 15 hours at *ca* 20°C., poured on to ice, extracted with ether and the ether extract washed until neutral with water and 5% sodium carbonate solution. After drying over sodium sulphate, the ether was distilled off. The residue, 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid *tert*butyl amide, was dissolved in 150 ml of a 33% solution of hydrogen bromide in glacial acetic acid and allowed to stand for 2 hours at *ca* 20°C. The crystalline salt which separated was filtered off and washed with (glacial acetic acid)/ether (4:1) and with ether. By recrystallization from methanol/acetonitrile/ether, there was obtained the 4 - [(2 - methyl - hydrazino) - methyl]-benzoic acid *tert*butyl amide hydrobromide melting at 200°—201°C.

EXAMPLE 36

21.5 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzonitrile were dissolved in 70 ml of a 33% solution of hydrogen bromide in glacial acetic acid and allowed to stand for 20 hours at *ca* 20°C. The crystallized product was filtered off, washed with ether and recrystallized from alcohol, yielding 4-[(2-methyl-hydrazino)-methyl]-benzamide hydrochloride melting at 173°—175°C.

EXAMPLE 37

15.8 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride were dissolved in 50 ml of methylene chloride and, while stirring, added dropwise to a solution of 6.2 g of 2-amino-butanol-(1) in 50 ml of methylene chloride. Stirring was continued for a further 2 hours at *ca* 20°C. and for 0.5 hours at 40°C., whereupon 50 ml of water were added to the solution which was then worked up according to Example 14. The yellowish glassy material obtained was dissolved in 200 ml of methanol, shaken with 2 g of 5% palladium/carbon in a hydrogen atmosphere, whereby two thirds of the calculated amount of hydrogen had been absorbed after about 6 hours. The solution was then filtered and the filtrate concentrated *in vacuo*. The colourless residue was dissolved in 50 ml of methanol and to it was added a solution of 3.2 g of anhydrous oxalic acid in 25 ml of methanol. Upon addition of some ether a salt precipitated, which was recrystallized from ethanol/acetonitrile, yielding 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (1 - hydroxymethyl - propyl) amide oxalate melting at 141°—143°C. (decomposition).

EXAMPLE 38

15.8 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride were dissolved in 50 ml of dry ether and, within 30 minutes with stirring, added dropwise to a solution of 3.3 g of 2-amino-2-methyl-propanol-(1) and 3.6 g of anhydrous sodium carbonate in 50 ml of water. The solution was stirred for 16 hours at 0°C., the mixture diluted with 100 ml of water and extracted three times with 100 ml of methylene chloride each time. The combined methylene chloride extracts were freed of the solvent *in vacuo* and the residue dissolved in 200 ml of methanol, whereupon it was hydrogenated in the presence of 2 g of 5% palladium/carbon. The colourless glacial material was transformed according to Example 37 into its oxalic acid salt. The crystalline crude material was recrystallized from methanol/acetonitrile, yielding 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (1,1 - dimethyl - 2 - hydroxy - ethyl) amide oxalate as colourless platelets melting at 160°—162°C. (decomposition).

EXAMPLE 39

The condensation product obtained in Example 38 from 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoylchloride and 2 - amino - 2 - methyl - propanol - (1) gave, upon treatment with hydrogen bromide in glacial acetic acid and subsequent precipitation with ether, an amorphous material which was dissolved in 50 ml of water. To this solution were added 300 ml of methylene chloride and, while cooling with ice under nitrogen, 150 g of anhydrous potassium carbonate. The solution was well stirred, the organic phase decanted and the aqueous phase ex-

tracted three times with 300 ml of methylene chloride each time. The united methylene chloride extracts were dried over potassium carbonate and the solvent was evaporated off. The residue was dissolved in 20 ml of ethanol and to the mixture was immediately added a solution of 5 g of anhydrous oxalic acid in 20 ml of ethanol. Upon addition of a small amount of ether the 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (1,1 - dimethyl - 2 - acetoxy - ethyl) amide oxalate formed colourless crystals melting at 116°—126°C. (decomposition) after two recrystallizations from ethanol.

EXAMPLE 40

15.8 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoyl chloride were dissolved in 50 ml of methylene chloride. This solution was added dropwise while stirring to a suspension of 12.6 g of 2-hydroxy-3,3,3-trichloro-propyl amine in 150 ml of methylene chloride. Stirring was continued for 2 hours at *ca* 20°C. and for 0.5 hours at 40°C., whereupon 50 ml of water were added thereto. The product was worked up according to Example 14 and treated with hydrogen bromide in glacial acetic acid. The crystalline crude material was recrystallized from ethanol/acetonitrile/ether, yielding 4 - [(2 - methyl - hydrazino) - methyl] - benzoic acid (2-hydroxy-3,3,3-trichloro-propyl) amide hydrobromide melting at 187°—189°C. (decomposition).

EXAMPLE 41

6.4 g of phosphorus pentachloride were suspended in 100 ml of dry benzene. To this suspension was added, while stirring, a solution of 4 - [(2 - methyl - 1,2 - dibenzyl-oxycarbonyl - hydrazino) - methyl] - benzoic acid *iso*propyl amide in 50 ml of dry benzene. After 0.5 hours, the solution became yellow and was concentrated *in vacuo* at 60°C. The residue was treated with 1.8 g of *iso*propyl amine in 50 ml of dry benzene and the mixture was heated to 60°C. for 2 hours. After evaporating off the solvent, there was obtained a yellow glacial material which was taken up in 80 ml of a 33% solution of hydrogen bromide in glacial acetic acid. The product went into solution after stirring for a short time and after about 0.5 hours crystallization began. After standing for one hour at *ca* 20°C., the solid material was filtered off and recrystallized from glacial acetic acid yielding 1 - methyl - 2 - [4 - (N,N^1 - di*iso*propyl - amidino) - benzyl] - hydrazine dihydrobromide as slightly hygroscopic colourless prisms of melting point 128°—133°C. (decomposition).

EXAMPLE 42

55.5 g of 1-methyl-2-(4-amino-benzyl)-1,2-dibenzyloxycarbonyl-hydrazine were dissolved in 250 ml of absolute benzene. To this solution were added while stirring, 14.5 g of N-butyl-isocyanate and the reaction mixture heated for 5 hours at 55°C., whereupon the benzene was distilled off *in vacuo*. The residue was dissolved in ether and the ether solution washed with 3-*N* hydrochloric acid and with water, dried with sodium sulphate and concentrated. The viscous oily residue was dissolved in 200 ml of a 33% solution of hydrogen bromide in glacial acetic acid, whereupon crystallization soon began. After standing for 2 hours, the crystals were filtered off washed with (glacial acetic acid)/ether (4:1) and with ether and recrystallized from *iso*propanol, yielding 1 - methyl - 2 - [4 - (3 - *n* - butyl - ureido) - benzyl] - hydrazine hydrobromide melting at 168°—169°C.

In an analogous manner, but using *iso*propyl - *iso*cyanate, there was obtained: 1 - methyl - 2 - [4 - (3 - *iso*propyl - ureido) - benzyl] - hydrazine hydrobromide, melting at 171°—173°C.

EXAMPLE 43

42 g of 4 - [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] - benzoic acid azide (which had been prepared in the usual manner from 4 - [(2 - methyl-1,2 - dibenzyloxycarbonyl - hydrazino) - methyl] benzoyl chloride and sodium azide) were heated in 170 ml of toluene to 100°C. until the evolution of nitrogen had subsided. The residue obtained after distilling off the toluene *in vacuo* was recrystallized from dibutyl ether yielding 1 - methyl - 2 - (4 - *iso*cyanato - benzyl) - 1,2 - dibenzyl-oxycarbonyl - hydrazine of melting point 55°—57°C. This product was dissolved in 100 ml of absolute benzene and to this solution was added, while stirring at 0°—10°C., a solution of 2.85 g of 2-hydroxy-ethyl amine in 10 ml of absolute benzene. The reaction mixture was then heated for 5 hours to 55°C., whereupon it was concentrated *in vacuo*. The residue was dissolved in ether/(methylene chloride) (2:1), washed successively with 3-*N* hydrochloric acid, saturated potassium hydrogen carbonate solution

and with water and dried over sodium sulphate. The residue obtained after distilling off the solvents was dissolved in 300 ml of methanol, then shaken with palladium/carbon in a hydrogen atmosphere until the benzyloxycarbonyl group had been split off. One equivalent amount of alcoholic hydrochloric acid was added to the hydrogenation mixture which was then concentrated to a small volume, yielding 1 - methyl - 2 - [4-[3 - (2 - hydroxy - ethyl) - ureido] - benzyl] - hydrazine hydrochloride melting at 160°—162°C.

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

EXAMPLE A

Preparation of capsules containing:

4-[(2-methyl-hydrazino)-methyl]-benzoic acid *iso*propyl amide hydrobromide	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:

1-methyl-2-(4-ureido-benzyl)-hydrazine hydrobromide	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.)

PATENT OFFICE dragées

EXAMPLE C

Preparation of 300 mg dragées containing the following ingredients:

i) kernel:		
4-[(2-methyl-hydrazino)-methyl]-benzoic acid *iso*propyl amide hydrobromide		50 mg
mannitol		80 mg
talc		5 mg
corn starch		15 mg
	total weight of the kernel	150 mg
ii) coating:		
sugar	90%	150 mg
rice starch	5%	
talc	5%	

The active substance was mixed with mannitol and sieved through a No. 5 sieve (mesh opening about 0.23mm). 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 of 150 mg and 8.0 mm diameter.

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

PATENT OFFICE dragées

EXAMPLE D

Preparation of 200 mg dragées containing:

i) kernel:		
1-methyl-2-(4-ureido-benzyl)-hydrazine hydrobromide		25 mg
mannitol		60 mg
talc		5 mg
corn starch		10 mg
	total weight of the kernel	100 mg
ii) coating		
sugar	90%	100 mg
rice starch	5%	
talc	5%	

PATENT OFFICE dragées

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

EXAMPLE E

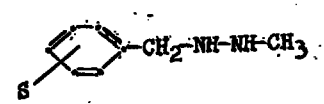
Preparation of dry ampoules:

1,2-bis(2-methyl-hydrazino-methyl)-benzene dihydrochloride		250 mg
dextran		245 mg
sodium pyrosulphite		5 mg
methyl *p*-hydroxy-benzoate		2 mg
propyl *p*-hydroxy-benzoate		0.25 mg
distilled water	ad	2.5 ml

The ingredients were filled in 5 ml ampoules (dark ampoules) and freeze-dried in a carbon dioxide atmosphere.

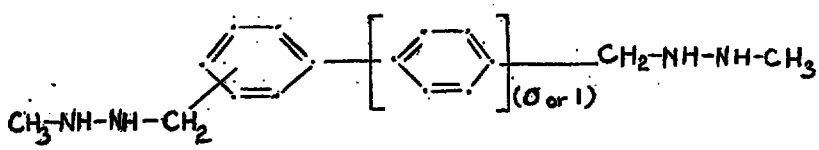
WHAT WE CLAIM IS:—

1) Compounds of the formula

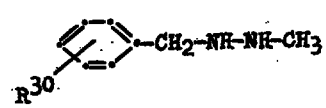


in which S indicates substitution consisting of at least one amino, alkyl-amino, dialkyl-amino, acyl-amino, ureido, substituted-ureido, (alkyl-sulphonyl)-amino, guanidino, substituted-guanidino, amidino, substituted-amidino, amino-alkyl, (alkyl-amino)-alkyl, (dialkyl-amino)-alkyl, carbamoyl, substituted-carbamoyl, allophanoyl, substituted-allophanoyl, sulphamoyl, N-alkyl-sulphamoyl, N,N-dialkyl-sulphamoyl, alkyl-sulphonyl, nitro, (2-methyl-hydrazino)-methyl, alkanoyl, aroyl, phenyl or substituted phenyl group together with, if desired, one or more alkyl, trifluoro-methyl, halogeno, hydroxy, alkoxy alkylenedioxy, alkenyloxy, aralkoxy, alkanoyloxy, aroyloxy, mercapto or alkyl-thio groups, and acid addition salts thereof.

2) Compounds of the formula

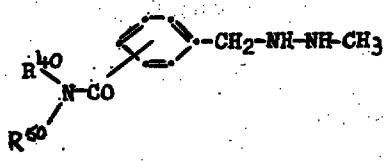


3) 1,2-Bis[(2-methyl-hydrazino)-methyl]-benzene.
4) 1,4-Bis[(2-methyl-hydrazino)-methyl]-benzene.
5) 3,3¹-Bis[(2-methyl-hydrazino)-methyl]-biphenyl.
6) Compounds of the formula



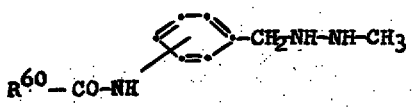
wherein R^{30} stands for ureido or allophanoyl substitution.

7) 1-Methyl-2-(4-ureido-benzyl)-hydrazine.
8) 1-Methyl-2-(4-allophanoyl-benzyl)-hydrazine.
9) Compounds of the formula



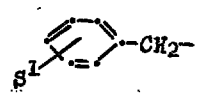
wherein R^{40} and R^{50} are each a hydrogen atom or an alkyl group containing up to six carbon atoms or a hydroxy-alkyl or halogeno-alkyl group in which the alkyl moiety contains up to six carbon atoms.

10) 4-[(2-Methyl-hydrazino)-methyl]-benzamide.
11) 4-[(2-Methyl-hydrazino)-methyl]-benzoic acid ethyl-amide.
12) 4-[(2-Methyl-hydrazino)-methyl]-benzoic acid *iso*propyl-amide.
13) 4-[(2-Methyl-hydrazino)-methyl]-benzoic acid *sec*butyl-amide.
14) 4-[(2-Methyl-hydrazino)-methyl]-benzoic acid *tert*butyl-amide.
15) 4-[(2-Methyl-hydrazino)-methyl]-benzoic acid *iso*pentyl amide.
16) 4-[(2-Methyl-hydrazino)-methyl]-benzoic acid (2-hydroxy-ethyl)-amide.
17) 4-[(2-Methyl-hydrazino)-methyl]-benzoic acid (2-chloro-ethyl)-amide.
18) Compounds of the formula

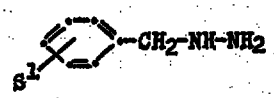


wherein R^{60} is an alkyl group containing up to six carbon atoms or the radical of an α-amino acid bereft of its carboxyl group or an alkyl-substituted oxazolyl-(3) ring.

19) 1-Methyl-2-[4-(alanyl-amino)-benzyl]-hydrazine.
20) 1-Methyl-2-[4-[5-methyl-isoxazolyl-(3)-carbonyl-amino]-benzyl]-hydrazine.
21) A process for the manufacture of the derivatives claimed in claim 1 hereof, which process comprises *either* benzylation of methyl-hydrazine or of a partially protected methyl-hydrazine with a benzylating agent which yields a substituted benzyl group of the formula



wherein S^1 has the same meaning as S or is readily convertible thereinto, and subsequent conversion of said group S^1 in the product into the group S if different *or* methylation of a compound of the formula



wherein S^1 has the significance already given, or of such a compound which is partially protected at the hydrazino group and subsequent conversion of the group S^1 in the product into the group S if different *and*, in either event, the splitting off of any protecting group present and transformation (if desired) into a salt.

22) A process in accordance with claim 21, wherein the substituent S^1 in the benzylating agent used or in the compound to be methylated is a methylhydrazinomethyl substituent.

23) A process in accordance with claim 21, insofar as compounds in which S stands for a ureido substituent are required, wherein the substituent S^1 in the benzylat-

ing agent used or in the compound to be methylated is an amino group, this is then converted into the ureido substituent by treatment with a cyanate or *iso*cyanate and any protecting groups are then removed.

24) A process in accordance with claim 21, wherein the substituent S^1 in the benzylating agent used or in the compound to be methylated is the carbamoyl, N-alkyl-carbamoyl, N-(hydroxy-alkyl)-carbamoyl or N-(halogeno-alkyl)-carbamoyl substituent containing up to six carbon atoms in the alkyl moiety.

25) A process in accordance with claim 21 insofar as compounds in which S stands for a carbamoyl or substituted-carbamoyl substituent are required, which process comprises *either* converting the carboxy substituent of a [(2 - methyl - 1,2 - dibenzyl-oxy - carbonyl - hydrazino) - methyl] - benzoic acid into a carbamoyl or substituted-carbamoyl substituent by reaction with ammonia or primary or secondary amines *or* converting the cyano substituent of a [(2 - methyl - 1,2 - dibenzyloxycarbonyl - hydrazino - methyl] - benzonitrile into a carbamoyl or substituted-carbamoyl substituent by reaction with olefines or secondary or tertiary carbinols in the presence of strong acids and, in either case, removing the benzyloxycarbonyl groups.

26) A process in accordance with claim 21, wherein the substituent S^1 in the benzylating agent or in the compound to be methylated is an alkyl group containing up to six carbon atoms or the radical of an α-amino acid bereft of its carboxyl group or an alkyl-substituted oxazolyl-(3) ring.

27) A process in accordance with claim 21 insofar as compounds in which S stands for a guanidino substituent are required, which process comprises converting the amino substituent of a 1,2 - dibenzyloxycarbonyl - 2 - (amino - benzyl) - hydrazine into a guanidino substituent by reaction with cyanamide and removing the benzyloxy-carbonyl groups.

28) A process in accordance with claim 21 insofar as compounds in which S stands for an amidino substituent are required, which process comprises *either* converting the cyano substituent of a protected methylhydrazinomethyl-benzonitrile into an amidino substituent by reaction with alcohols and mineral acids and treatment of the resulting imino ethers with ammonia or a primary or secondary amine *or* converting the carbamoyl substituent of a protected monosubstituted methylhydrazinomethyl-benzamide into an amidino substituent by reaction with a phosphorus halide, treatment of the resulting imino halide with ammonia or a primary or secondary amine and removal of the protecting groups.

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

30) Compounds as formulated in claim 1 hereof and salts thereof, when manufactured by the process claimed in any one of claims 21 to 29 inclusive.

31) A pharmaceutical preparation which comprises a compound as formulated in claim 1 hereof, or a salt thereof, in association with a compatible pharmaceutical carrier.

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