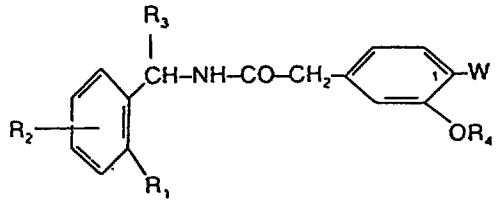
SPECIFICATION

EP-A-0 058 779 and EP-A-0 099 017 have already described phenylacetic acid derivatives which have an effect on the metabolism, but more particularly a hypoglycaemic effect.

It has now been found that the new phenylacetic acid derivatives of general formula



(I)

which differ from the aforementioned phenylacetic acid derivatives by the group $-OR_4$ have valuable properties. Thus, the compounds of general formula I wherein R_4 represents a methyl, ethyl or allyl group have superior pharmacological properties, especially a superior effect on the metabolism, but preferably a better hypoglycaemic effect, and compounds of general formula I wherein R_4 is a hydrogen atom are valuable intermediates for the preparation of the abovementioned compounds.

The present invention thus relates to new phenylacetic acid derivatives of the above general formula I, the enantiomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, pharmaceutical compositions containing these compounds and processes for preparing them.

In general formula I above:

R_1 represents a pyrrolidino, piperidino, hexamethyleneimino, methyl-pyrolidino, dimethyl-pyrrolindino, 2-methyl-piperidino, 3-methyl-piperidino, 4-methyl-piperidino, 3,3-dimethyl-piperidino, cis-3,5-dimehthyl-piperidino or trans-3,5-dimethyl-piperidino group,

R_2 represents a hydrogen or halogen atom or a methyl or methoxy group,

R_3 represents a hydrogen atom, an alkyl group with 1 to 4 carbon atoms, an n-pentyl or 3-methyl-n butyl group or a phenyl group optionally substituted by a halogen atom or by a methyl or methoxy group,

R_4 represents a hydrogen atom, a methyl, ethyl or allyl group and

W represents a methyl, hydroxymethyl, formyl, carboxy or alkoxycarbonyl group with a total of 2 to 5 carbon atoms, whilst the alkyl part of the alkoxy group may be substituted by a phenyl group.

As examples of the definitions of the groups R_2 to R_4 and W mentioned hereinbefore:

R_2 may represent a hydrogen, fluorine, chlorine or bromine atom or a methyl or methoxy group,

R_3 may represent a hydrogen atom, a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, n-pentyl, 3-methyl-n-butyl, phenyl, fluorophenyl, chlorophenyl, bromophenyl, methylphenyl or methoxyphenyl group, and

W may represent a methyl, hydroxymethyl, formyl, carboxy, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, 1-phenylethoxy-carbonyl, 2-phenylethoxycarbonyl or 3-phenylpropoxy-carbonyl group.

However, preferred compounds of general formula I above are those wherein

R_3 and R_4 are defined as hereinbefore, R_1 represents a pyrrolidino, piperidino, 4-methyl-

piperidino, 3-methyl-piperidino, 3,3-dimethyl-piperidino, 3,5-dimethyl-piperidino or hexamethyleneimino group,

R_2 represents a hydrogen, fluorine or chlorine atom or a methyl or methoxy group, and

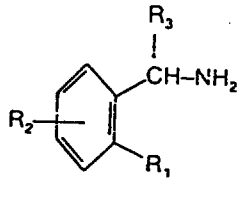
W represents a carboxy, methyl, hydroxymethyl, formyl or benzyloxycarbonyl group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms,
particularly those compounds wherein

R_1 represents a piperidino group,
R_2 represents a hydrogen, fluorine or chlorine atom,
R_3 represents a methyl, ethyl, n-propyl, n-butyl, n-pentyl or phenyl group,
R_4 represents a methyl or ethyl group and
W represents a carboxy, methoxycarbonyl or ethoxycarbonyl group,
the enantiomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Particularly preferred compounds of general formula I above are those wherein W represents a carboxy group.

According to the invention, the new compounds are obtained by the following processes:

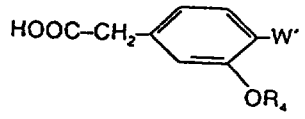
a) reaction of an amine of general formula



(II)

wherein

R_1 to R_3 are as hereinbefore defined, with a carboxylic acid of general formula



(III)

wherein

R_4 is as hereinbefore defined and

W' has the meanings given for W hereinbefore or represents a carboxyl group protected by a protecting group,

or with a reactive derivative thereof, which may optionally be prepared in the reaction mixture, followed where necessary by removal of any protecting group used.

Examples of reactive derivatives of a compound of general formula III include the esters such as the methyl, ethyl or benzyl esters, the thioesters such as the methylthio or ethylthio esters, the halides such as the acid chloride, the anhydrides and imidazolides thereof.

The reaction is appropriately carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethylformamide, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or an agent activating the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, which may simultaneously act as solvent, at temperatures of between -25 and 250°C, but preferably

at temperatures of between -10°C and the boiling temperature of the solvent used. The reaction may also be carried out without a solvent, moreover, any water formed during the reaction may be removed by azeotropic distillation, e.g. by heating with toluene using a water separator or by adding a drying agent such as magnesium sulphate or molecular sieve.

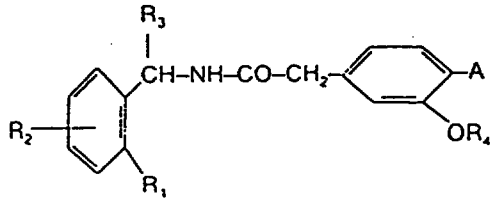
If necessary the subsequent splitting off of a protecting group is preferably carried out hydrolytically, conveniently either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxan at temperatures of between -10 and 120°C, e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

A tert.butyl group used as protecting group may also optionally be split off thermally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxan and preferably in the presence of a catalytic amount of an acid such as p-toluenesulphonic acid, sulphuric, phosphoric or polyphosphoric acid.

Moreover, a benzyl group used as protecting group may also be split off by hydrogenolysis in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide.

b) In order to prepare a compound of general formula I wherein W represents a carboxy group:

Splitting of a compound of general formula



(IV)

wherein

R_1 to R_4 are as hereinbefore defined and

A represents a group which can be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis.

Examples of hydrolysable groups include functional derivatives of the carboxy group such as the unsubstituted or substituted amides, esters, thioesters, orthoesters, iminoethers, amidines or anhydrides thereof, the nitrile group, the tetrazolyl group or an optionally substituted 1,3-oxazol-2-yl or 1,3-oxalin-2-yl group and

examples of thermolytically removable groups include esters with tertiary alcohols, e.g. the tert.butyl ester, and

examples of hydrogenolytically removable groups include aralkyl groups, e.g. the benzyl group.

The hydrolysis is appropriately carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of between -10 and 120°C, e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

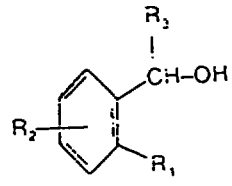
If A in a compound of general formula IV represents a nitrile or aminocarbonyl group, these groups may be converted into a carboxy group by means of 100% phosphoric acid at temperatures of between 100 and 180°C, preferably at temperatures of between 120 and 160°C, or with a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulphuric acid, which is appropriately also used as solvent, at temperatures of between 0 and 50°C.

If A in a compound of general formula IV represents, for example, the tert.butyloxycarbonyl group, the tert.butyl group may also be thermally split off, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxan and preferably in the presence of a catalytic amount of an acid such as p-toluenesulphonic acid, sulphuric, phosphoric or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures of between 40 and 100°C.

If A in a compounds of general formula IV represents, for example, a benzyloxycarbonyl group, the benzyl group may also be split off by hydrogenolysis in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, methanol/water, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide, preferably at temperatures of between 0 and 50°C, e.g. at ambient temperature and under a hydrogen pressure of from 1 to 5 bar. During the hydrogenolysis a halogen-containing compound may simultaneously be dehalogenated.

c) In order to prepare a compound of general formula I wherein R_4 represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms:

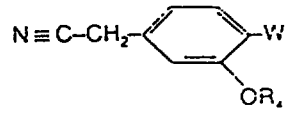
Reaction of a compound of general formula



(V)

wherein

R_1 to R_3 are as hereinbefore defined, with a compound of general formula



(VI)

wherein

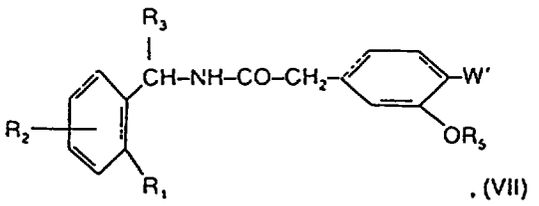
R_4 and W are as hereinbefore defined.

The reaction is carried out in the presence of a strong acid, which may simultaneously serve as solvent, preferably in concentrated sulphuric acid, at temperatures of between 0 and 150°C, preferably at temperatures of between 20 and 100°C.

If in a compound of general formula VI R_4 represents an acyl, allyl or benzyl group, this is split off during the reaction or after the reaction when water is added.

d) In order to prepare compounds of general formula I wherein R_4 represents a hydrogen atom:

Splitting off a protecting group from a compound of general formula



(VII)

. (VII)

wherein

R_1 to R_3 are as hereinbefore defined,

W' has the meanings given for W hereinbefore or represents a group which can be converted into a carboxy group and

R_5 represents a protecting group for a hydroxy group.

Examples of groups which can be converted into carboxy groups, for W', include an alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aminocarbonyl or nitrile group whilst examples of protecting groups for R_5 include alkyl, aralkyl, trialkylsilyl or acyl groups, e.g. the methyl, ethyl, propyl, benzyl, trimethylsilyl, acetyl or propionyl group.

Depending on the protecting group used the protecting groups may be split off either by hydrolysis or by hydrogenolysis, optionally in a suitable solvent, at temperatures of between -78 and 250°C.

Ether splitting may be carried out, for example, in the presence of an acid such as hydrogen chloride, hydrogen bromide, sulphuric acid, boron tribromide, aluminium trichloride or pyridine hydrochloride, conveniently in a suitable solvent such as methylene chloride, glacial acetic acid or water or in mixtures thereof at temperatures of between -78 and 250°C. Ether splitting in the presence of a protic acid is conveniently carried out at temperatures of between 0 and 150°C, preferably at temperatures of between 50 and 150°C, or with a Lewis acid preferably in a solvent such as methylene chloride at temperatures of between -78 and 20°C.

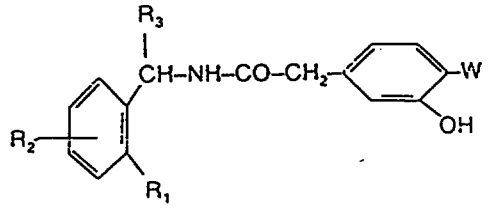
Ester splitting may be carried out, for example, in the presence of a base such as aqueous ammonia,

sodium carbonate, potassium carbonate or sodium or potassium hydroxide in a solvent such as water, water/methanol, water/ethanol, water/tetrahydrofuran or water/dioxan at temperatures of between 50 and 100°C, preferably at the temperature of the solvent used.

Hydrogenolytic splitting off of a protecting group, such as a benzyl group, may be carried out, for example, with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide, preferably at ambient temperature and under a hydrogen pressure of from 1 to 5 bar.

e) In order to prepare compounds of general formula I wherein R_4 represents a methyl, ethyl or allyl group:

Reaction of a compound of general formula



(VIII)

wherein

R_1 to R_3 and W are as hereinbefore defined, with a compound of general formula

$$R_4' - X \qquad \text{(IX)}$$

wherein

R_4' is defined as hereinbefore, with the exception of hydrogen, and

X represents a nucleophilically exchangeable group such as a halogen atom or a sulphonyloxy group, or, together with an adjacent hydrogen atom, a diazo group, if R_4' represents a methyl or ethyl group, followed, if necessary, by hydrolysis.

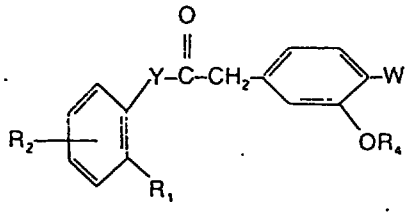
The reaction is appropriately carried out with a corresponding halide, anhydride, sulphonic acid ester, sulphuric acid diester or diazoalkane, e.g. with methyl iodide, dimethyl sulphate, ethyl bromide, diethyl sulphate, propyl bromide, isopropyl bromide, allyl bromide, benzyl chloride, benzyl bromide, acetyl chloride, acetic anhydride, ethyl p-toluenesulphonate, isopropyl methanesulphonate or diazomethane, optionally in the presence of a base such as sodium hydride, potassium carbonate, sodium hydroxide, potassium tert.butoxide or triethylamine or, in the case of acylation, with an anhydride in the presence of an acid such as sulphuric acid, preferably in a suitable solvent such as acetone, diethyl ether, tetrahydrofuran, dioxan, pyridine or dimethylformamide at temperatures of between 0 and 100°C, preferably at temperatures of between 20 and 50°C, whereby an anhydride used as acylating agent may also simultaneously serve as solvent.

If W in a compound of general formula VIII represents a carboxy or hydroxymethyl group, this may be converted into the corresponding ester compound. A compound thus obtained is, if necessary, after the splitting of the ester group, converted into the desired compound of general formula I.

The ester group is preferably split hydrolytically, either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxan at temperatures of between -10 and 120°C, e.g. at temperatures

of between ambient temperature and the boiling temperature of the reaction mixture.

f) Reduction of a compound of general formula



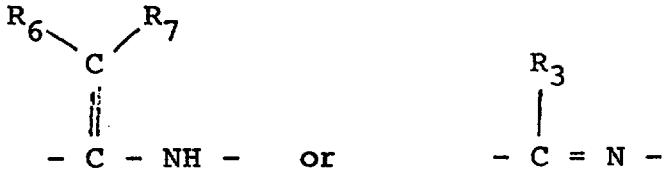
(X)

wherein

R_1, R_2, R_4 and W are as hereinbefore defined

and

Y represents a group of formula



wherein R_3 is as hereinbefore defined and

R_6 and R_7 together with the carbon atom to which they are attached represent an alkylidene group with 1 to 4 carbon atoms.

The reduction is preferably carried out with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal or Raney nickel in a suitable solvent such as methanol, ethanol, isopropanol, ethyl acetate, dioxan, tetrahydrofuran, dimethylformamide, benzene or benzene/ethanol at temperatures of between 0 and 100°C, but preferably at temperatures of between 20°C and 50°C, under a hydrogen pressure of from 1 to 5 bar. If a suitable chiral hydrogenation catalyst is used such as a metal ligand complex, e.g. a complex of μ,μ'-dichloro-bis-[1,5-cyclooctadiene

rhodium] and (+)- or (-) O,O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (= DIOP), the addition of hydrogen occurs enantioselectively. Moreover during the catalytic hydrogenation other groups, e.g. a benzyloxy group on a hydroxy group or a formyl group on a hydroxymethyl group, may also be reduced or be replaced by hydrogen atoms, e.g. a halogen atom may be replaced by a hydrogen atom.

If, according to the invention, a compound of general formula I is obtained wherein R_2 represents a halogen atom and/or R_3 represents a halophenyl group and/or W represents a hydroxymethyl group which has been converted into a halomethyl group, it may if desired be converted by dehalogenation into a corresponding compound of general formula I wherein R_2 represents a hydrogen atom and/or R_3 represents a phenyl group and/or W represents a methyl group, and/or

a compound of general formula I is obtained wherein W represents a carboxy group, this may if desired be converted by esterification into a corresponding compound of general formula I wherein W represents an alkoxycarbonyl or phenylalkoxycarbonyl group, and/or

a compound of general formula I is obtained wherein W represents a carboxy, alkoxycarbonyl or phenylalkoxy-carbonyl group, this may be converted by reduction into a corresponding compound of general formula I wherein W represents a formyl or hydroxymethyl group, and/or

a compound of general formula I is obtained wherein W represents a hydroxymethyl group, this may be converted by oxidation into a corresponding compound of general formula I wherein W represents a formyl or carboxyl group, and/or

a compound of general formula I is obtained wherein W represents a carboxy group, this may be converted, via a sulphonic acid hydrazide and subsequent disproportionation into a corresponding compound of general formula I wherein W represents a formyl group, and/or

a racemic compound of general formula I is obtained wherein R_3 has the meanings given hereinbefore, with the exception of the hydrogen atom, this may be resolved via the diastereoisomeric adducts, complexes or salts thereof into its enantiomers.

The subsequent dehalogenation is appropriately carried out using catalytic hydrogenation, e.g. with palladium/charcoal, in a suitable solvent, e.g. methanol, ethanol, tetrahydrofuran, dioxan, dimethylformamide or ethyl acetate, optionally in the presence of a base such as triethylamine and at temperatures of between 20 and 100°C, preferably at 20 to 50°C.

The subsequent esterification is appropriately carried out in a suitable solvent, e.g. in a corresponding alcohol, pyridine, toluene, methylene chloride, tetrahydrofuran or dioxan, in the presence of an acid-activating and/or dehydrating agent such as thionyl chloride, ethyl chloroformate, carbonyldiimidazole or N,N'-dicyclohexylcarbodiimide or the isourea ethers thereof, optionally in the presence of a reaction accelerator such as copper chloride, or by transesterification, e.g. with a corresponding carbonic acid diester, at temperatures of between 0 and 100°C, but preferably at temperatures of between 20°C and the boiling temperature of the solvent used.

The subsequent reduction is preferably carried out with a metal hydride, e.g. with a complex metal hydride such as lithium aluminium hydride, lithium

borohydride or lithium borohydride/trimethylborate, in a suitable solvent such as diethyl ether, tetrahydrofuran, dioxan or 1,2-dimethoxyethane at temperatures of between 0 and 100°C, but preferably at temperatures of between 20°C and 60°C.

The subsequent oxidation of an alcohol is preferably carried out with an oxidising agent, e.g. with pyridinium chlorochromate or manganese dioxide, in a suitable solvent such as chloroform or methylene chloride at temperatures of between -10 and 50°C, but preferably at temperatures of between 0 and 20°C.

The subsequent disproportionation of a sulphonic acid hydrazide, obtained by reacting a corresponding hydrazine with a suitable reactive carboxylic acid derivative, is carried out in the presence of a base such as sodium carbonate in a solvent such as ethylene glycol at temperatures of between 100°C and 200°C, but preferably at 160-170°C.

The subsequent racemate resolution is preferably carried out using column or HPL chromatography by forming the diastereomeric adducts or complexes in a chiral phase.

The compounds of general formula I obtained may also be converted into their salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases. Suitable acids include, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, lactic, citric, tartaric, succinic, maleic or fumaric acid and suitable bases include sodium hydroxide, potassium hydroxide, calcium hydroxide, cyclohexylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine or lysine.

The compounds of general formulae II to X used as starting materials are in some cases known from the literature or they may be obtained by methods known per se.

Thus, for example, a compound of general formula II may be obtained by reduction of a corresponding nitrile with lithium aluminium hydride or with catalytically activated hydrogen, by reacting a corresponding nitrile with a suitable Grignard or lithium compound and subsequent lithium aluminium hydride reduction or subsequent hydrolysis to form the ketimine, which is subsequently reduced with catalytically activated hydrogen, with a complex metal hydride or with nascent hydrogen, by hydrolysis or hydrazinolysis of a corresponding phthalimido compound, by reacting a corresponding ketone with ammonium formate and subsequent hydrolysis or with an ammonium salt in the presence of sodium cyanoborohydride, by reducing a corresponding oxime with lithium aluminium hydride, with catalytically activated or nascent hydrogen, by reduction of a corresponding N-benzyl or N-1-phenylethyl-Schiff's base, e.g. with a complex metal hydride in ether or tetrahydrofuran at temperatures of between -78°C and the boiling temperature of the solvent used and subsequently splitting of the benzyl or 1-phenylethyl group by catalytic hydrogenation by a Ritter reaction of a corresponding alcohol with potassium cyanide in sulfuric acid, or by a Hofmann, Curtius, Lossen or Schmidt degradation of a corresponding compound.

An amine of general formula II thus obtained with a chiral centre may be resolved into the enantiomers thereof by racemate resolution, e.g. using fractional crystallisation of the diastereoisomeric salts with optically active acids and subsequent decomposing of the salts or by column or HPL chromatography, optionally in the form of the acyl derivative, or by forming diastereoisomeric compounds, then separating them and subsequently splitting them.

Moreover, an optically active amine of general formula II may also be prepared by enantioselective reduction of a corresponding ketimine using complex

boro- or aluminium hydrides in which some of the hydride hydrogen atoms are replaced by optically active alkoxide groups, or using hydrogen in the presence of a suitable chiral hydrogenation catalyst or analogously starting from a corresponding N-benzyl or N-(1-phenethyl)-ketimine or from a corresponding N-acyl-ketimine or enamide and optionally subsequently splitting off the benzyl, 1-phenethyl or acyl group.

Moreover, an optically active amine of general formula II may also be prepared by diastereoselective reduction of a corresponding ketimine or hydrazone chirally substituted at the nitrogen atom by means of complex or non-complex boro- or aluminium hydrides wherein some of the hydride hydrogens may optionally be replaced by corresponding alkoxide, phenoxide or alkyl groups, or means of hydrogen in the presence of a suitable hydrogenation catalyst and optionally subsequently splitting off the chiral auxiliary group by catalytic hydrogenolysis or hydrolysis.

Furthermore, an optically active amine of general formula II may also be prepared by diastereoselective addition of a correspond organometallic compound, preferably a Grignard or lithium compound, to a corresponding aldimine chirally substituted at the nitrogen atom, by subsequent hydrolysis and optionally subsequent splitting off the chiral auxiliary group by catalytic hydrogenolysis or hydrolysis.

The compounds of general formulae IV, VII and VIII used as starting materials may be obtained by reacting a corresponding amine with a corresponding carboxylic acid or a reactive derivative thereof and optionally subsequently splitting off any protecting group used.

A compound of general formula V used as starting material may be obtained by reducing a corresponding carbonyl compound or by reacting a corresponding carbonyl compound with a corresponding Grignard or lithium reagent.

A compound of general formula X used as starting material may be obtained by acylation of a corresponding imino compoud or an organometallic complex thereof with a corresponding carboxylic acid or a reactive derivative thereof and optionally subsequently splitting an ester group.

As already mentioned hereinbefore, the new compounds of general formula I have valuable pharmacological properties, namely an effect on intermediate metabolism, but particularly a hypoglycaemic effect.

The following compounds, for example:

A = 2-methoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid,

B = 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

C = 2-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,

D = 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,

E = (+)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

F = 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid,

G = sodium 2-ethoxy-4-[N-(1-(2-pyrrolidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate,

H = 2-ethoxy-4-[N-(1-(2-hexamethylenimino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

I = 2-methoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

K = 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-pentyl)-aminocarbonylmethyl]-benzoic acid

and

L = 2-ethoxy-4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

were tested for their hypoglycaemic properties as follows:

Hypoglycaemic Effect

The hypoglycaemic effect of the test substances was tested on female rats of a particular strain weighing from 180-220 g which had been fasted for 24 hours before the start of the test. The test substances were suspended in 1.5% methyl cellulose immediately before the start of the test and administered by oesophageal tube.

Blood samples were taken immediately before the administration of the substance and 1, 2, 3 and 4 hours afterwards, in each case from the retroorbital Venous plexus. 50 µl of each sample were deprotenated with 0.5 ml of 0.33 N perchloric acid and centrifuged. The glucose in the supernatant was measured using the hexokinase method with the aid of an analytical photometer. The statistical evaluation was made using the t-test according to Student with p = 0.05 as the limit of significance.

The following table shows the values found in percent compared with the control:

Substance	1 mg/kg 1	2	3	4 h	0.5 mg/kg 1	2	3	4 h
A	-37	-46	-23	-14				
B	-38	-49	-38	-33	-43	-36	-34	-35
C	-38	-41	-38	-34				
D	-42	-54	-37	-34				
E					-40	-39	-36	-36
F	-44	-44	-40	-30				
G					-40	-33	-30	-17
H					-42	-34	-18	n.s.
I					-42	-39	-37	-30
K					-41	-45	-38	-39
L	-44	-41	-35	-27				

n.s. = not statistically significant

In the tests for hypoglycaemic activity of the substances, no toxic side effects were observed even at a dosage of 10 mg/kg p.o.

The new compounds are virtually non-toxic; for example, after a single dose of 2,000 mg/kg p.o. (suspension in 1% methyl cellulose) of substances B and D to 5 male and 5 female mice, only one animal in this group died during the observation period of 14 days.

In the light of their pharmacological properties the compounds of general formula I prepared according to the invention and the physiologically acceptable salts thereof are suitable for the treatment of diabetes mellitus. For this purpose they may be incorporated, optionally together with other active substances, in the usual galenic preparations such as tablets, coated tablets, capsules, powders or suspension. The single dose in adults is from 1-50 mg, preferably 2.5-20 mg, once or twice a day.

The Examples which follow are intended to illustrate the invention:

Example 1

Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)aminocarbonylmethyl]-benzoate

To a solution of 1.84 g (7.9 mmol) of 1-(2-piperidinophenyl)-1-butylamine in 19 ml of acetonitrile, are added 2 g (7.9 mmol) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid, 2.46 g (9.38 mmol) of triphenyl-phosphine, 1.7 ml (12.3 mmol) of triethylamine and 0.76 ml (7.9 mmol) of carbon tetrachloride and the mixture is stirred for two days at ambient temperature. It is then evaporated in vacuo and the residue is distributed between ethyl acetate and water. The organic extract is dried and filtered and evaporated in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 5/1).

Yield: 3g (81% of theory),

Mp: 113-115°C (petroleum ether)

Calculated:	C 72.07	H 8.21	N 6.00
Found:	72.18	8.27	6.16

The following compounds were obtained analogously to Example 1:

a) Methyl 2-methoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-ethylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 78% of theory,

Mp: 82-85°C

Calculated:	C 70.22	H 7.37	N 6.82
Found:	70.54	7.49	6.75

b) Ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 77% of theory,

Mp: 149-151°C

Calculated: C 74.37 H 7.25 N 5.60
Found: 74.69 7.44 5.59

c) Methyl 2-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.
Yield: 65% of theory,
Mp: 189-190°C
Calculated: C 73.70 H 6.83 N 5.93
Found: 73.51 6.75 5.86

d) Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-ethylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.
Yield: 69% of theory,
Mp: 92-93°C
Calculated: C 71.21 H 7.81 N 6.36
Found: 71.29 8.03 6.58

e) Ethyl 2-ethoxy-4-[N-(1-(5-chloro-2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(5-chloro-2-piperidino-phenyl)-1-propylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.
Yield: 80% of theory,
Mp: 110-112°C
Calculated: C 66.58 H 7.24 N 5.75 Cl 7.28
Found: 66.61 7.34 5.86 7.35

f) Ethyl 2-ethoxy-4-[N-(2-piperidino-phenyl)-1-pentyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-pentylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.
Yield: 63% of theory,
Mp: 113-115°C
Calculated: C 72.47 H 8.39 N 5.83
Found: 72.66 8.26 5.99

g) Ethyl 2-ethoxy-4-[N-(1-(2-pyrrolidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-pyrrolidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 50% of theory,

Mp: 85-87°C

Calculated:	C 71.65	H 8.02	N 6.19
Found:	71.90	8.37	6.34

h) Ethyl 2-ethoxy-4-[N-(1-(2-(4-methyl-piperidino)-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-(4-methyl-piperidino)-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 44% of theory,

Mp: 127-128°C

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.20	8.23	5.69

i) Ethyl 2-ethoxy-4-[N-(1-(2-hexamethyleneimino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-hexamethyleneimino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 44% of theory,

Mp: 97-100°C

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.41	8.50	5.66

k) Ethyl 2-ethoxy-4-[N-(1-(4-methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(4-methyl-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 68% of theory,

Mp: 113-114°C

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.36	8.31	5.91

l) Ethyl 2-ethoxy-4-[N-(1-(6-methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(6-methyl-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 62% of theory,

Mp: 20°C

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.30	8.50	5.72

m) Ethyl 2-ethoxy-4-[N-(1-(6-chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(6-chloro-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 85% of theory,

Mp: 20°C

Calculated:	C 67.12	H 7.44	N 5.50	Cl 7.08
Found:	67.60	7.77	5.92	7.24

n) Ethyl 2-ethoxy-4-[N-(1-(4-methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(4-methoxy-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 65% of theory,

Mp: 109-110°C

Calculated: Mol. peak m/e = 496

Found: Mol. peak m/e = 496

o) Ethyl 2-ethoxy-4-[N-(1-(5-methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(5-methoxy-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 31% of theory,

Mp: 117-120°C

Calculated: mol peak m/e = 496
Found: mol peak m/e = 496

p) Ethyl 2-hydroxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 4-ethoxycarbonyl-3-hydroxy-phenylacetic acid.
Yield: 46% of theory,
Mp: 133-134°C

Calculated:	C 71.21	H 7.81	N 6.39
Found:	71.08	7.91	6.45

q) Methyl 2-methoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.
Yield: 67% of theory,
Mp: 128-131°C

Calculated	C 71.21	H 7.81	N 5.39
Found:	71.46	7.80	6.07

r) Ethyl 2-ethoxy-4-[N-(5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from 5-chloro-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.
Yield: 65% of theory,
Mp: 106-108°C

Calculated	C 65.41	H 6.81	N 6.10	Cl 7.73
Found:	65.81	6.89	6.11	7.62

s) Ethyl (-)-2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from (-)-α-phenyl-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.
Yield: 87% of theory,
Mp: 110-111°C
Calculated mol peak m/e = 500

Found: mol peak m/e = 500

Specific rotation: $[\alpha]_D^{20}$ = -6.3° (c = 1, methanol)

t) Ethyl 2-ethoxy-4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from 6-methyl-α-phenyl-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 39% of theory,

Mp: <20°C

Calculated:	C 74.68	H 7.44	N 5.44
Found:	74.81	7.56	5.32

u) Ethyl 2-ethoxy-4-[N-(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-(4-methyl-phenyl)-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 34% of theory,

Mp: 150-152°C

Calculated	C 74.68	H 7.44	N 5.44
Found:	74.71	7.51	5.29

v) Ethyl 2-ethoxy-4-[N-(α-phenyl-2-pyrrolidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-pyrrolidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 45% of theory,

Mp: 85-87°C

Calculated	C 74.05	H 7.04	N 5.76
Found:	73.95	7.07	5.70

w) Methyl 2-methoxy-4-[N-(2-hexamethylenimino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from 2-hexamethyleneimino-α-phenyl-benzylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 45% of theory,

Mp: 181-183°C
Calculated: C 74.05 H 7.04 N 5.74
Found: 74.09 6.62 5.74

x) Ethyl 2-ethoxy-4-[N-(2-hexamethyleneimino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from 2-hexamethyleneimino-α-phenyl-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.
Yield: 41% of theory,
Mp: 140-141°C
Calculated: C 74.68 H 7.44 N 5.44
Found: 74.46 7.62 5.45

y) 2-Ethoxy-4-[N-(1-(2-pyrrolidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-methyl-phenylacetic acid.
Yield: 55% of theory,
Mp: 107-108°C
Calculated: C 76.43 H 8.88 N 6.86
Found: 76.38 8.99 6.97

Example 2

Ethyl (+)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

0.90 g (3.57 mmol) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid and 0.61 g (3.73 mmol) of N,N'-carbonyldiimidazole are refluxed for 5 hours in 9 ml of absolute tetrahydrofuran. Then a solution of 0.85 g (3.67 mmol) of (+)-1-(2-piperidino-phenyl)-1-butylamine (ee = 94.2) in 9 ml of absolute tetrahydrofuran is added and the mixture is refluxed for 3 hours. It is concentrated in vacuo and the evaporation residue is distributed between chloroform and water. The organic phase is dried, filtered and evaporated in vacuo. The evaporated extract is purified by column chromatography on silic gel (toluene/acetone = 10:1).

Yield: 0.85 g (51.2% of theory),
Mp: 118-119°C (petrolum ether/toluene = 50/2)
Calculated: C 72.07 H 8.21 N 6.00
Found: 72.43 8.34 6.00
Specific rotation: $[\alpha]_D^{20}$ = + 7.1° (c = 1.06 in methanol)

The following compounds were obtained analogously to Example 2:

Example 3
Ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

To a mixture of 30 ml of concentrated sulphuric acid and 30 ml of o-dichlorobenzene, a solution of 4.7 g (20 mmol) of ethyl 2-ethoxy-4-cyanomethyl-benzoate and 5.3 g (20 mmol) of α-phenyl-2-piperidino-benzyl alcohol in 30 ml of 0-dichlorobenzene is added dropwise at 32-25°C. The mixture is stirred for 2 hours at ambient temperature. Then the o-dichlorobenzene phase is separated off and the residue is added to ice. After it has been made alkaline with soda solution, it is extracted with chloroform. The extracts are dried over magnesium sulphate and concentrated by evaporation. The residue is trituated with petroleum ether (30-60°), filtered off and purified on silica gel (toluene/ethyl-acetate = 5:1) by column chromatography.
Yield: 5.6 g (56% of theory),
Mp: 150-151°C
Calculated: C 74.37 H 7.25 N 5.60
Found: 74.59 7.41 5.45

The following compounds were obtained analogously to Example 3:

a) Methyl 2-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzyl alcohol and methyl 4-cyanomethyl-2-methoxy-benzoate.
Yield: 34% of theory,
M.p.: 189-191°C

Calculated:	C 73.70	H 6.83	N 5.93
Found:	73.63	7.05	5.95

b) 2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid

Prepared from α-phenyl-2-piperidino-benzyl alcohol and 2-ethoxy-4-cyanomethyl-benzoic acid.
Extraction at pH 5.
Yield: 47% of theory,
M.p.: 154-155°C

Calculated:	C 73.70	H 6.83	N 5.93
Found:	73.61	6.72	5.65

c) 2-Methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from α-phenyl-2-piperidino-benzyl alcohol and 4-cyanomethyl-2-methoxy-benzoic acid.
Extraction at pH 5.
Yield: 30% of theory,
M.p.: 202-204°C

Calculated:	C 73.34	H 6.59	N 6.11
Found:	73.17	6.41	6.05

d) Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butanol and ethyl 2-ethoxy-4-cyanomethyl-benzoate.
Yield: 5% of theory,
M.p.: 112-114°C

Calculated:	C 72.07	H 8.21	N 6.00
Found:	72.29	8.46	6.31

e) Methyl 2-methoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-ethanol and methyl 4-cyanomethyl-2-methoxy-benzoate.
Yield: 18% of theory,
M.p.: 83-85°C
Calculated: C 70.22 H 7.37 N 6.82
Found: 70.60 7.29 6.97

f) 2-Methoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid

Prepared from 1-(2-piperidino-phenyl)-1-ethanol and 4-cyanomethyl-2-methoxy-benzoic acid. Extraction at pH 5.5.
Yield: 21% of theory,
M.p.: 118-120°C
Calculated: m/e = 396
Found: m/e = 396

g) Ethyl 2-ethoxy-4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from 4-methyl-α-phenyl-2-piperidino-benzyl alcohol and ethyl 2-ethoxy-4-cyanomethyl-benzoate.
Yield: 46% of theory,
M.p.: 124-125°C
Calculated: C 74.68 H 7.44 N 5.44
Found: 74.81 7.56 5.32

h) Methyl 2-methoxy-4-[N-(α-(4-chloro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-(4-chlorophenyl)-2-piperidino-benzyl alcohol and methyl 2-methoxy-4-cyanomethyl-benzoate.
Yield: 47% of theory,
M.p.: 176-178°C
Calculated: C 68.70 H 6.17 N 5.53 Cl 6.99
Found: 69.05 5.93 5.76 7.10

i) Ethyl 2-hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzyl alcohol and ethyl 4-cyanomethyl-2-hydroxy-benzoate.
Yield: 78% of theory,
M.p.: 172-174°C

Calculated:	C 73.70	H 6.83	N 5.93
Found:	73.80	6.81	5.83

Example 4

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

A mixture of 2 g (4.3 mmol) of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonyl-methyl]-benzoate and 5.3 ml of 1N sodium hydroxide solution in 20 ml of ethanol is stirred for 3 hours at 60°C, then neutralised with 5.3 ml of 1N hydrochloric acid and the ethanol is evaporated off in vacuo. The residue is distributed between ethyl acetate and water; the organic extract is dried and filtered and evaporated in vacuo. The evaporation residue is crystallised from petroleum ether with the addition of ethanol.
Yield: 1.3 g (69% of theory),
M.p.: 88-90°C

Calculated:	C 71.21	H 7.81	N 6.39
Found:	71.62	7.73	6.54

The following compounds were obtained analogously to Example 4:

a) 2-Methoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid x 0.67 H_2O

Prepared from methyl 2-methoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoate.
Yield: 60% of theory,

M.p.: 116-120°C
Calculated: C 67.62 H 7.07 N 6.85
Found: 67.60 6.87 6.55

b) 2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.
Yield: 89% of theory,
M.p.: 155-156°C
Calculated: C 73.70 H 6.83 N 5.93
Found: 73.60 6.96 6.12

c) 2-Methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.
Yield: 68% of theory,
M.p.: 202-204°C
Calculated: C 73.34 H 6.59 N 6.11
Found: 73.60 6.77 6.20

d) 2-Ethoxy-4-[N-(1-(5-chloro-2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(5-chloro-2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoate.
Yield: 74% of theory,
M.p.: 115-118°C
Calculated: C 65.42 H 6.81 N 6.10 Cl 7.72
Found: 65.54 6.94 5.81 7.89

e) 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoate.
Yield: 73% of theory,
M.p.: 81-83°C

Calculated: C 70.73 H 7.60 N 6.60
Found: 70.90 7.47 6.77

f) 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-pentyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-pentyl)-aminocarbonylmethyl]-benzoate.
Yield: 92% of theory,
M.p.: 82-85°C
Calculated: C 71.65 H 8.02 N 6.19
Found: 71.45 8.01 6.13

g) 2-Ethoxy-4-[N-(1-(2-pyrrolidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-pyrrolidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.
Yield: 77% of theory,
M.p.: 120-123°C
Calculated: C 70.33 H 7.60 N 6.60
Found: 70.71 7.44 6.33

h) 2-Ethoxy-4-[N-(1-(2-(4-methyl-piperidino)-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-(4-methyl-piperidino)-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.
Yield: 71% of theory,
M.p.: 83-85°C
Calculated: C 71.65 H 8.02 N 6.19
Found: 71.60 7.94 6.09

i) 2-Ethoxy-4-[N-(1-(2-hexamethyleneimino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-hexamethyleneimino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.
Yield: 81% of theory,

M.p.: 101-105°C

Calculated:	C 71.65	H 8.02	N 6.19	
Found:	71.31	7.79	6.18	

k) 2-Ethoxy-4-[N-(1-(6-chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(6-chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.

Yield: 82% of theory,

M.p.: 133-136°C

Calculated:	C 66.02	H 7.03	N 5.92	Cl 7.50
Found:	66.48	7.47	5.98	7.88

l) 2-Ethoxy-4-[N-(1-(4-methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(4-methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.

Yield: 81% of theory,

M.p.: 98-100°C

Calculated:	C 69.21	H 7.74	N 5.98
Found:	69.12	7.62	5.78

m) 2-Ethoxy-4-[N-(1-(5-methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(5-methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.

Yield: 74% of theory,

M.p.: 145-148°C

Calculated:	C 69.21	H 7.74	N 5.98
Found:	69.00	7.65	5.89

n) 2-Methoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.
Yield: 86% of theory,
M.p.: 140-143°C

Calculated:	C 70.73	H 7.60	N 6.60
Found:	70.49	7.58	6.31

o) 2-Ethoxy-4-[N-(5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid x 0.5 H_2O

Prepared from ethyl 2-ethoxy-4-[N-(5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl[-benzoate.
Yield: 93% of theory,
M.p.: 153-155°C

Calculated:	C 62.79	H 6.41	N 6.36	Cl 8.06
Found:	63.21	6.34	5.89	8.46

p) 2-Ethoxy-4-[N-(2-piperidino-benzyl)-aminocarbonyl-methyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.
Yield: 77% of theory,
M.p.: 108-109°C

Calculated:	C 69.68	H 7.12	N 7.07
Found:	70.00	7.99	7.31

q) 2-Hydroxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-hydroxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.
Yield: 61% of theory,
M.p.: 136-138°C

Calculated:	C 70.22	H 7.37	N 6.82
Found:	70.40	7.64	6.60

r) 2-Allyloxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-allyloxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.

Yield: 92% of theory,

M.p.: 110-112°C

Calculated: C 71.97 H 7.61 N 6.22

Found: 71.90 7.62 6.21

s) (+)-2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl (+)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.

Yield: 81% of theory,

M.p.: 122-123°C

Calculated: C 71.21 H 7.81 N 6.39

Found: 71.19 7.77 6.29

Specific rotation $[\alpha]_D^{20}$ = + 4.75° (c = 1.03 in methanol)

t) 2-Ethoxy-4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 41% of theory,

M.p.: 127-129°C

Calculated: C 74.05 H 7.04 N 5.76

Found: 73.80 7.09 5.74

u) 2-Ethoxy-4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 40% of theory,

M.p.: 118-121°C

Calculated: C 74.05 H 7.04 N 5.76

Found: 73.71 6.92 5.76

v) 2-Ethoxy-4-[N-(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 94% of theory,

M.p.: 148-151°C

Calculated: C 74.05 H 7.04 N 5.76

Found: 74.20 7.15 5.81

w) 2-Methoxy-4-[N-(α-(4-chloro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-(α-(4-chloro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 77% of theory,

M.p.: 177-180°C

Calculated: C 68.21 H 5.93 N 5.68 Cl 7.19

Found: 68.10 5.78 5.53 7.43

x) 2-Ethoxy-4-[N-(α-phenyl-2-pyrrolidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(α-phenyl-2-pyrrolidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 67% of theory,

M.p.: 141-143°C

Calculated: C 73.34 H 6.59 N 6.11

Found: 73.33 6.74 6.02

y) 2-Methoxy-4-N-(2-hexamethyleneimino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-N-(2-hexamethyleneimino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 90% of theory,

M.p.: 154-156°C

Calculated: C 73.70 H 6.83 N 5.93

Found: 73.70 7.00 5.95

z) 2-Ethoxy-4-[N-(2-hexamethyleneimino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(2-hexamethyleneimino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoate.
Yield: 75% of theory,
M.p.: 139-141°C
Calculated: C 74.05 H 7.04 N 5.76
Found: 73.90 7.14 5.79

aa) 2-Hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate by saponification with 4 equivalents of 1N sodium hydroxide solution in ethanol/dioxan.
Yield: 35% of theory,
M.p.: 222-224°C
Calculated: C 72.95 H 6.35 N 6.30
Found: 73.00 6.64 6.28

ab) 2-Allyloxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-allyloxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.
Yield: 69% of theory,
M.p.: 172-173°C
Calculated: C 74.35 H 6.66 N 5.78
Found: 74.11 6.50 5.74

ac) (-)-2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl (-)-2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.
Yield: 89% of theory,
M.p.: 90-95°C

Calculated: C 73.70 H 6.83 N 5.93
Found: 73.59 6.81 5.83
Specific rotation: $[\alpha]_D^{20}$ = -2.2° (c = 1 in methanol)

Example 5

Sodium salt of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid x 1.5 H_2O

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoate analogously to Example 4. After purification by column chromatography the evaporation residue obtained is dissolved in ethanol and mixed with 1 equivalent of 1N sodium hydroxide solution. By evaporation in vacuo and trituration with acetone, the crystalline sodium salt is obtained.
Yield: 76% of theory,
M.p.: 242-244°C
Calculated: C 62.73 H 7.01 N 6.01
Found: 62.74 7.17 6.05
The following compounds were obtained analogously to Example 5:

a) Sodium salt of 2-ethoxy-4-[N-(1-(4-methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid x 0.5 H_2O

Prepared from ethyl 2-ethoxy-4-[N-(1-(4-methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.
Yield: 72% of theory,
M.p.: 255-260°C
Calculated: C 67.06 H 7.50 N 5.79
Found: 66.94 7.28 5.50

b) Sodium salt of 2-ethoxy-4-[N-(1-(6-methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid x 2.5 H_2O

Prepared from ethyl 2-ethoxy-4-[N-(1-(6-methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.

Yield: 81% of theory,

M.p.: 232-240°C

Calculated:	C 62.39	H 7.75	N 5.39
Found:	62.22	7.46	5.61

c) Sodium salt of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.

Yield: 87% of theory,

M.p.: 250-258°C

Calculated:	C 67.79	H 7.22	N 6.08
Found:	67.60	7.37	6.04

d) Sodium salt of 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 89% of theory,

M.p.: 233-235°C

Calculated:	C 70.42	H 6.32	N 5.67
Found:	70.20	6.41	5.49

Example 6

Ethyl 2-hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

To a stirred solution of 2 g (4 mmol) of ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in 20 ml of 1,2-dichloro-ethane, 1 ml (10.4 mmol) of boron tribromide is added dropwise at -20°C under anhydrous conditions. The mixture is allowed to reach ambient temperature and then stirred for a further 17 hours. It is

then poured into ethanol, evaporated in vacuo, ice is added and the resulting mixture is distributed between chloroform and water. The organic extract is dried and filtered and evaporated in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1).
Yield: 0.37 g (21% of theory),
M.p.: 172-173°C

Calculated:	C 73.70	H 6.83	N 5.93
Found:	73.95	7.05	6.12

The following compounds were obtained analogously to Example 6:

a) 2-Hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid.
Yield: 40% of theory,
M.p.: 221-223°C

Calculated:	C 72.95	H 6.35	N 6.30
Found:	72.68	6.45	6.49

b) Ethyl 2-hydroxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 19% of theory,
M.p.: 132-134°C

Calculated:	C 71.21	H 7.81	N 6.39
Found:	71.43	7.91	6.55

c) 2-Hydroxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 42% of theory,
M.p.: 136-137°C

Calculated:	C 70.22	H 7.37	N 6.82
Found:	70.19	7.39	6.99

Example 7

tert.Butyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

A mixture of 1.98 g (9.6 mmol) of N,N-dicyclohexyl-carbodiimide, 1.06 ml (11.2 mmol) of absolute tert.butanol and 0.020 g (0.20 mmol) of copper(I) chloride is stirred for 60 hours at ambient temperature, then 6.6 ml of methylene chloride are added and the resulting solution is added dropwise to a solution of 0.44 g (1 mmol) of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid in 15 ml of methylene chloride. After 60 hours' stirring at 20°C, the precipitate is filtered off, washed with methylene chloride and the methylene chloride solution is evaporated in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethyl acetate = 9/1).

Yield: 0.30 g (60% of theory),

M.p.: 74-77°C (from petroleum ether)

Calculated:	C 72.84	H 8.56	N 5.66
Found:	73.00	8.65	5.79

Example 8

Ethyl 2-allyloxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

To a solution of 1.1 g (2.3 mmol) of ethyl 2-hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoate in 10 ml of anhydrous dimethylformamide are added 0.10 g (2.3 mmol) of sodium hydride (55% in oil) and the resulting mixture is stirred for 0.5 hours at ambient temperature. Then a solution of 0.27 ml (2.3 mmol) of allyl bromide in 5 ml of anhydrous dimethylformamide is added dropwise and the mixture is stirred for 5 hours at ambient temperature. It is evaporated

in vacuo, the residue is distributed between dilute sodium hydroxide solution and chloroform, the organic extract is dried, filtered and evaporated in vacuo. The evaporation residue is recrystallised from acetonitrile and then from ethanol.
Yield: 0.55 g (46 % of theory),
M.p.: 117-119°C
Calculated: C 74.97 H 7.08 N 5.47
Found: 74.90 7.14 5.38
The following compound was obtained analogously to Example 8:

a) Ethyl 2-allyloxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-hydroxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate using allyl bromide.
Yield: 72% of theory,
M.p.: 105-106°C
Calculated: C 72.77 H 8.00 N 5.85
Found: 72.90 7.90 5.87

Example 9

Ethyl 2-ethoxy-4-[N-(2-piperidino-benzyl)-aminocarbonyl-methyl]-benzoate

1.0 g (2.18 mmol) of ethyl 2-ethoxy-4-[N-(5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate is hydrogenated in 20 ml of ethanol with 0.5 g of 10% palladium/charcoal at 50°C under 1 bar of hydrogen for 45 minutes. It is filtered over kieselguhr, evaporated in vacuo and purified by column chromatography on silica gel (chloroform/methanol = 10/1).
Yield: 0.71 g (77% of theory),
M.p.: 83-84°C (from petroleum ether)
Calculated: C 70.73 H 7.60 N 6.60
Found: 70.89 7.66 6.76

The following compound was obtained analogously to Example 9:

a) Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-ethoxy-4-[N-(1-(5-chloro-2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoate.

Yield: 74% of theory,

M.p.: 115-117°C

Calculated:	C	71.65	H	8.02	N 6.19
Found:		71.47		8.11	6.25

Example 10

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid

i) 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl)-aminocarbonylmethyl]-benzoate

Yield: 85% of theory,

M.p.: 110-113°C

Calculated:	C	71.97	H	7.61	N 6.22
Found:		71.92		7.80	5.98

ii) 0.21 g (0.39 mmol) of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid are hydrogenated in 10 ml of absolute ethanol with 0.10 g of 10% palladium/charcoal at 50°C under 1 bar of hydrogen for 7 hours. The mixture is filtered over kieselguhr, evaporated in vacuo and the residue is purified by column chromatography on silica gel (chloroform/methanol = 10/1).

Yield: 0.10 g (47% of theory),

M.p.: 90-92°C
Calculated: C 71.65 H 8.02 N 6.19
Found: 71.50 8.12 6.45

The following compound was obtained analogously to Example 10:

a) Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl)-aminocarbonylmethyl]-benzoate, melting point 125-126°C [prepared from (2-piperidino-phenyl)-isobutyl-ketimine and 3-ethoxy-4-ethoxycarbonyl-phenyl-acetic acid analogously to Example 1].
Yield: 51% of theory,
M.p.: 139-141°C
Calculated: C 72.47 H 8.39 N 5.83
Found: 72.30 8.20 5.87

Example 11

2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzyl alcohol

To 0.28 g (7.4 mmol) of lithium aluminium hydride in 50 ml of absolute tetrahydrofuran, a solution of 1.8 g (3.6 mmol) of ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in 20 ml of absolute tetrahydrofuran are added dropwise at -5°C and the mixture is stirred for 3 hours at 0°C. It is then diluted with absolute ether and 4N sodium hydroxide solution is added. The mixture is filtered over kieselguhr, the residue is concentrated by evaporation in vacuo and purified by column chromatography on silica gel (toluene/ethyl acetate = 2/1).
Yield: 0.51 g (31% of theory),
M.p.: 133-135°C
Calculated: C 75.95 H 7.47 N 6.11

Found: 75.97 7.55 5.95

The following compound was obtained analogously to Example 11:

a) 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzyl alcohol

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate by reduction with lithium borohydride in boiling tetrahydrofuran with the addition of 10% of trimethyl borate.

Yield: 68% of theory,

M.p.: 112-115°C

Calculated: C 73.55 H 8.55 N 6.60

Found: 73.60 8.38 6.69

Example 12

2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzaldehyde

To a stirred solution of 0.28 g (1.3 mmol) of pyridinium chlorochromate in 5 ml of chloroform, a solution of 0.4 g (0.87 mmol) of 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzyl alcohol is added dropwise at ambient temperature. The mixture is stirred overnight at ambient temperature, evaporated in vacuo, mixed with ether, filtered, evaporated in vacuo and purified by column chromatography on silica gel (toluene/ethyl acetate = 2/1).

Yield: 0.16 g (40% of theory),

M.p.: 154-156°C

Calculated: C 76.29 H 7.06 N 6.14

Found: 76.30 7.15 6.10

The following compound was obtained analogously to Example 12:

a) 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzaldehyde

Prepared from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzyl alcohol.
Yield: 47% of theory,
M.p.: 109-111°C
Calculated: C 73.90 H 8.11 N 6.63
Found: 74.22 8.14 6.73

Example 13

2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzaldehyde

0.67 g (5.6 mmol) of sodium carbonate are heated together with 6 ml of ethylene glycol in a bath at 170°C and then, with rapid stirring, 0.70 g (1.1 mmol) of N^1-[2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoyl]-N^2-tosyl-hydrazine are added thereto within a minute, and a violent evolution of gas is observed. Then the mixture is heated for a further 2 minutes at 170°C and poured immediately onto ice. It is extracted with ether, dried, filtered and the ether solution is evaporated in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 2/1).
Yield: 0.25 g (50% of theory),
M.p.: 153-156°C
Calculated: C 76.29 H 7.06 N 6.14
Found: 76.42 7.33 6.28

The following compound was obtained analogously to Example 13:

a) 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzaldehyde

Prepared from N^1-[2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoyl]-N^2-tosyl-hydrazine.
Yield: 51% of theory,
M.p.: 108-111°C
Calculated: C 73.90 H 8.11 N 6.63

Found: 73.79 8.29 6.75

Example 14

Benzyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

0.35 g (0.8 mmol) of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid are refluxed together with 0.15 g (0.9 mmol) of N,N'-carbonyldiimidazole in 15 ml of absolute tetrahydrofuran for 2 hours. Then 1.03 ml (10 mmol) of benzyl alcohol are added and the mixture is refluxed for 3.5 hours. It is evaporated in vacuo and purified by column chromatography on silica gel (chloroform/acetone = 9/1).
Yield: 0.10 g (23.6% of theory),
M.p.: <20°C
Calculated: Mol peak m/e = 528
Found: Mol peak m/e = 528

Example 15

Ethyl (+)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate and

Ethyl (-)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

28 mg of ethyl (±)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate are added in single doses of 0.02 mg to a chiral phase HPLC column made by Messrs. Baker, in which (R)-N-3,5-dinitrobenzoyl-phenylglycine is covalently bound to aminopropyl-silica gel (5 µm particle size, spherical, pore size 60Å; 4.6 mm internal diameter, 25 cm in length).
Flow agent: hexane/ethanol = 100/5;
Flow rate: 0.75 ml/minute;
Temperature: 22°C.
The fractions eluted at 31.2 minutes and at 32.9 minutes (UV detection at 254 nm) are separately recovered, collected and evaporated in vacuo.

The following is obtained from the 31.2 minute eluate:
7.5 mg of ethyl (+)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
M.p.: 117-119°C
Specific rotation: $[\alpha]_D^{20}$ = + 7.0° (c = 1.03 in methanol)

The following is obtained from the 32.9 minute eluate:
9.4 mg of ethyl (-)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
M.p.: 115-117°C
Specific rotation: $[\alpha]_D^{20}$ = + 6.9° (c = 1.02 in methanol)

Analogously to Example 15

a) ethyl ($\pm$)-2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

can be resolved into its (+) enantiomer and its (-) enantiomer.

Example 16

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonyl]-toluene

0.54 g (1.2 mmol) of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzyl chloride [melting point 114-115°C, prepared from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzyl alcohol using thionyl chloride in chloroform] in 10 ml of absolute dioxan are hydrogenated for 3 hours at 20°C and under 5 bar of hydrogen. The mixture is evaporated in vacuo and the residue is distributed between ethyl acetate and aqueous sodium carbonate solution. The organic extract is dried and filtered and evaporated in vacuo. The evaporation residue is purified

by column chromatography on silica gel (chloroform/acetone = 19/1).

Yield: 0.23g (47% of theory),

M.p.: 107-108°C

Calculated:	C 76.43	H 8.88	N 6.86
Found:	76.40	8.88	6.90

Example 17

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

100 mg (0.20 mmol) of tert.butyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonyl]-benzoate are refluxed in 5 ml of benzene together with a few crystals of p-toluenesulphonic acid hydrate for half a day. Then the desired product is obtained, according to a thin layer chromatograph, by the R_f value and mass spectrum.

M.p.: 87-89°C

Calculated: m/e = 438

Found: m/e = 438

Example 18

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl-aminocarbonylmethyl]-benzoic acid

0.25 g (0.47 mmol) of benzyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl-aminocarbonylmethyl]-benzoate are hydrogenated in 10 ml of ethanol with 0.12 g of 10% palladium/charcoal at 50°C under 5 bar of hydrogen. After 5 hours the catalyst is filtered off over kieselguhr and the filtrate is evaporated in vacuo. The evaporation residue is crystallised from petroleum ether/ethanol.

Yield: 0.14 g (70% of theory),

M.p.: 87-90°C

Calculated:	C 71.21	H 7.81	N 6.39
Found:	71.46	7.95	6.51

Example 19

Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-n-hexyl)-aminocarbonylmethyl-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-n-hexylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid analogousely to Example 1.

Yield: 43% of theory,

M.p.: 101-105°C

Calculated:	C	72.84	H	8.56	N 5.66
Found:		72.72		8.52	5.63

Example 20

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-n-hexyl)-aminocarbonylmethyl-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-n-hexyl)-aminocarbonylmethyl]-benzoate analogously to Example 4.

Yield: 77% of theory,

M.p.: 117-120°C

Calculated:	C	72.07	H	8.21	N 6.00
Found:		72.00		8.06	5.90

Example A

Tablets containing 5 mg of 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Composition:

1 tablet contains:

Active substance	(1)	5.0 mg
Corn starch	(2)	62.0 mg
Lactose	(3)	48.0 mg
Polyvinylpyrrolidone	(4)	4.0 mg
Magnesium stearate	(5)	1.0 mg
		120.0 mg

Method of preparation:

1, 2, 3 and 4 are mixed together and moistened with water. The moist mixture is passed through a 1.5 mm mesh screen and dried at about 45°C. The dry granulate is passed through a 1.0 mm mesh screen and mixed with 5. The finished mixture is compressed in a tablet press with 7 mm diameter punches comprising a dividing slot, to form tablets.
Weight of tablet: 120 mg

Example B

Coated tablets containing 2.5 mg of 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

1 tablet core contains:

Active substance	(1)	2.5 mg
Potato starch	(2)	44.0 mg
Lactose	(3)	30.0 mg
Polyvinylpyrrolidone	(4)	3.0 mg
Magnesium stearate	(5)	0.5 mg
		80.0 mg

Method

1, 2, 3 and 4 are thoroughly mixed and moistened with water. The moist mass is passed through a 1 mm mesh screen, dried at about 45°C and the granulate is then passed through the same screen. After 5 has been added, convex tablet cores with a diameter of 6 mm are compressed in a tablet-making machine. The tablet cores thus produced are covered in known manner with a coating consisting essentially of sugar and talc. The finished tablets are polished with wax.

Weight of coated tablet: 120 mg

Example C

Tablets containing 10 mg of 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Composition:

1 tablet contains:

Active substance	10.0 mg
Powdered lactose	70.0 mg
Corn starch	31.0 mg
Polyvinylpyrrolidone	8.0 mg
Magnesium stearate	1.0 mg
	120.0 mg

Method:

The mixture of active substance, lactose and corn starch is moistened with a 20% solution of polyvinylpyrrolidone in water. The moist mass is passed through a 1.5 mm mesh screen and dried at 45°C. The dried granulate is passed through a 1 mm mesh screen and homogeneously mixed with magnesium stearate.

Weight of tablet: 120 mg

Punch: 7 mm diameter with dividing slot.

Example D

Coated tablets containing 5 mg of 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

1 tablet core contains:

Active substance	5.0 mg
Secondary calcium phosphate	70.0 mg
Corn starch	50.0 mg
Polyvinylpyrrolidone	4.0 mg
Magnesium stearate	1.0 mg
	130.0 mg

Method:

The mixture of active substance, calcium phosphate and corn starch is moistened with a 15% solution of polyvinylpyrrolidone in water. The moist mass is passed through a 1 mm mesh screen, dried at 45°C and then rubbed through the same screen. After being mixed with the stated quantity of magnesium stearate, tablet cores are compressed from the mixture.

Weight of core: 130 mg

Punch: 7 mm in diameter

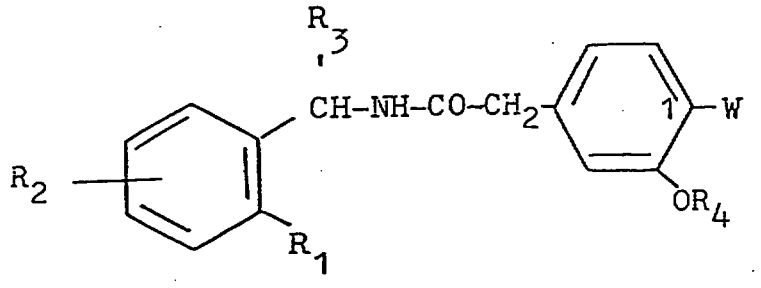
A coating of sugar and talc is applied to the cores thus produced in known manner. The finished coated tablets are polished with wax.

Weight of coated tablet: 180 mg

25K 53 662JCl

Patent Claims for the designated states: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Phenylacetic acid derivatives of general formula



(I)

wherein

R_1 represents a pyrrolidino, piperidino, hexamethyleneimino, methyl-pyrrolidino, dimethyl-pyrrolidino, 2-methyl-piperidino, 3-methyl-piperidino, 4-methyl-piperidino, 3,3-dimethyl-piperidino, cis-3,5-dimethyl-piperidino or trans-3,5-dimethyl-piperidino group,

R_2 represents a hydrogen or halogen atom or a methyl or methoxy group,

R_3 represents a hydrogen atom, an alkyl group with 1 to 4 carbon atoms, an n-pentyl or 3-methyl-n-butyl group or a phenyl group optionally substituted by a halogen atom or by a methyl or methoxy group,

R_4 represents a hydrogen atom, a methyl, ethyl or allyl group and

W represents a methyl, hydroxymethyl, formyl, carboxy or alkoxycarbonyl group with a total of 2 to 5 carbon atoms, whilst the alkyl part of the alkoxy group may be substituted by a phenyl group,

* C L M S *

the enantiomers and salts thereof.

2. Phenylacetic acid derivatives of general formula I as claimed in claim 1, wherein

R_3 and R_4 are defined as in claim 1,

R_1 represents a pyrrolidino, piperidino, 4-methyl-piperidino, 3-methyl-piperidino, 3,3-dimethyl-piperidino, 3,5-dimethyl-piperidino or hexamethyleneimino group,

R_2 represents a hydrogen, fluorine or chlorine atom or a methyl or methoxy group and

W represents a carboxy, methyl, hydroxymethyl, formyl or benzyloxycarbonyl group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms, the enantiomers and salts thereof.

3. Phenylacetic acid derivatives of general formula I as claimed in claim 1, wherein

R_1 represents a piperidino group,
R_2 represents a hydrogen, fluorine or chlorine atom,
R_3 represents a methyl, ethyl, n-propyl, n-butyl, isobutyl, n-pentyl or phenyl group,
R_4 represents a methyl or ethyl group and
W represents a carboxy, methoxycarbonyl or ethoxy-carbonyl group,
the enantiomers and salts thereof.

4. Phenylacetic acid derivatives of general formula I as claimed in claim 1, wherein

R_1 to R_4 are defined as in claim 3 and

* C L M S *

W represents the carboxy group, the enantiomers and salts thereof.

5. 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid, the enantiomers and salts thereof.

6. 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid, the enantiomers and salts thereof.

7. Physiologically acceptable salts of the compounds as claimed in claims 1 to 6 with inorganic or organic acids or bases, if the latter contain a carboxy group.

8. Pharmaceutical compositions containing a compound as claimed in claims 1 to 6, wherein R_4 represents a methyl, ethyl or allyl group or a physiologically acceptable salt thereof together with one or more inert carriers and/or diluents.

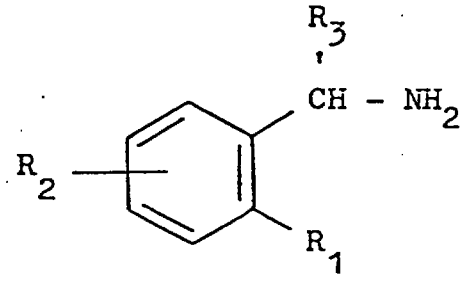
9. Use of the compounds as claimed in claims 1 to 6, wherein R_4 represents a methyl, ethyl or allyl group, or a physiologically acceptable salt thereof for the preparation of a pharmaceutical composition which is suitable for treating Diabetes mellitus.

10. Process for preparing a pharmaceutical composition as claimed in claim 8, characterised in that, by a non-chemical method, a compound as claimed in claims 1 to 6, wherein R_4 represents a methyl, ethyl or allyl group, or a physiologically acceptable salt thereof is incorporated in one or more inert carriers and/or diluents.

* C L M S *

11. Process for preparing new phenylacetic acid derivatives as claimed in claims 1 to 7, characterised in that

a) an amine of general formula

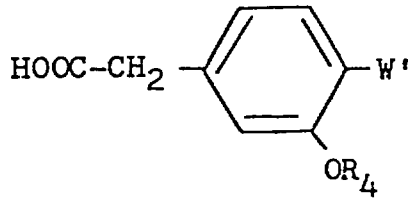


(II)

wherein

R_1 to R_3 are defined as in claims 1 to 6

is acylated with a carboxylic acid of general formula



(III)

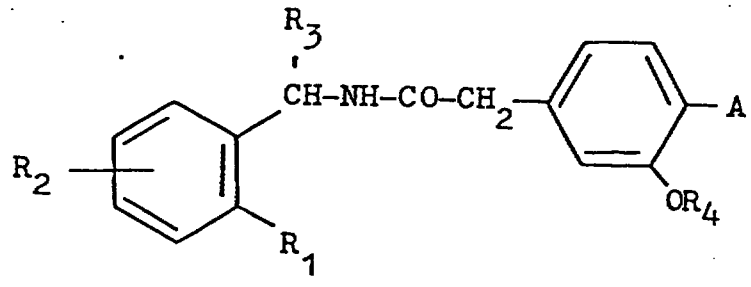
wherein

R_4 is defined as in claims 1 to 6 and

W' has the meanings given for W in claims 1 to 6 or represents a carboxy group protected by a protecting group,

or with the reactive derivatives thereof, which may optionally be prepared in the reaction mixture, and if necessary any protecting group used is split off, or

b) in order to prepare a compound of general formula I wherein W represents a carboxy group, a group A in a compound of general formula



(IV)

wherein

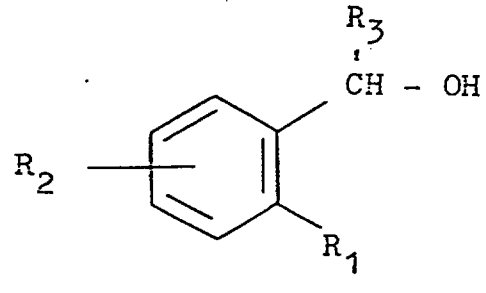
R_1 to R_4 are defined as in claims 1 to 6

and

A represents a group which may be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis,

is converted into a carboxy group,

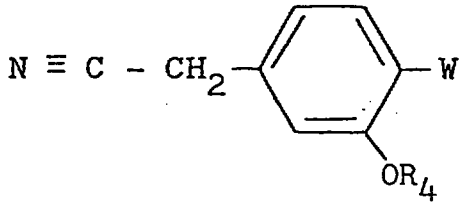
c) in order to prepare a compound of general formula I wherein R_4 represents a hydrogen atom or a methyl or ethyl group, a compound of general formula



(V)

wherein

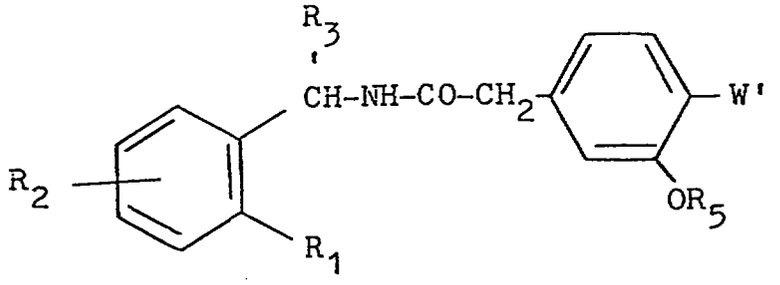
R_1 to R_3 are defined as in claims 1 to 6 is reacted with a compound of general formula



(VI)

wherein
R_4 and W are defined as in claims 1 to 6, or

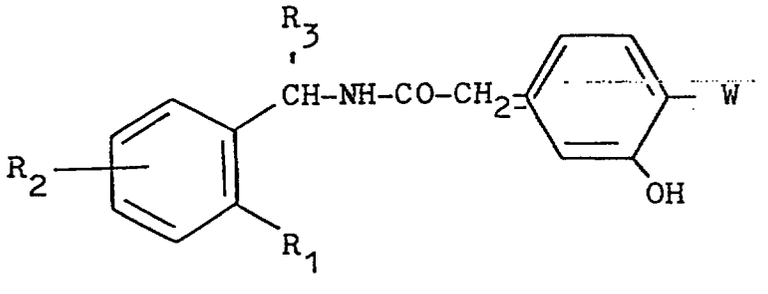
d) in order to prepare compounds of general formula I wherein R_4 represents a hydrogen atom, a protecting group is cleaved from a compound of general formula



(VII)

wherein
R_1 to R_3 are defined as in claims 1 to 6,
W' has the meanings given for W in claims 1 to 6 or represents a group which can be converted into a carboxy group and
R_5 represents a protecting group for a hydroxy group or

e) in order to prepare compounds of general formula I wherein R_4 represents a methyl, ethyl or allyl group, a compound of general formula



(VIII)

wherein
R_1 to R_3 and W are defined as in claims 1 to 6,
is reacted with a compound of general formula

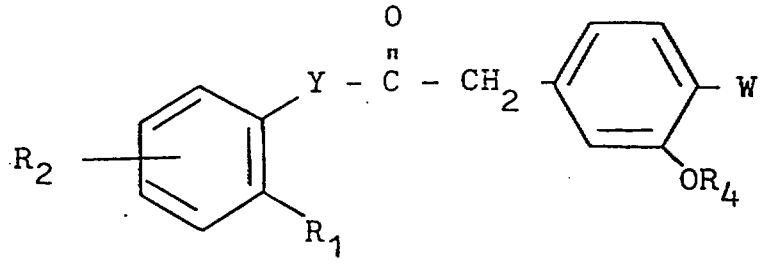
$$R_4' - X \qquad \text{(IX)}$$

* C L M S *

wherein
R_4' has the meanings given for R_4 in claims 1 to 6, with the exception of the hydrogen atom, and

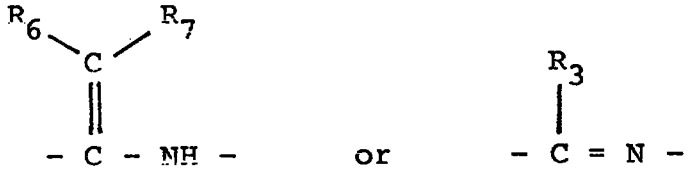
X represents a nucleophilically exchangeable group or, together with the adjacent hydrogen atom, represents a diazo group if R_4' represents a methyl or ethyl group, and subsequently, if necessary, a compound thus obtained is hydrolysed, or

f) a compound of general formula



(X)

wherein
R_1, R_2, R_4 and W are defined as in claims 1 to 6 and
Y represents a group of formula



wherein R_3 is defined as in claims 1 to 6 and R_6 and R_7 together with the carbon atom between them represent an alkylidene group with 1 to 4 carbon atoms,
is reduced and

subsequently, if desired, a compound of general formula I thus obtained wherein R_2 represents a halogen atom and/or R_3 represents a halophenyl

* C L M S *

group and/or W represents a hydroxymethyl group which has been converted into a halomethyl group, is converted by dehalogenation into a corresponding compound of general formula I wherein R_2 represents a hydrogen atom and/or R_3 represents a phenyl group and/or W represents a methyl group, and/or

a compound of general formula I thus obtained wherein W represents the carboxy group is converted by esterification into a corresponding compound of general formula I wherein W represents an alkoxycarbonyl or phenylalkoxycarbonyl group, and/or

a compound of general formula I thus obtained wherein W represents a carboxy, alkoxycarbonyl or phenylalkoxycarbonyl group is converted by reduction into a corresponding compound of general formula I wherein W represents a formyl or hydroxymethyl group, and/or

a compound of general formula I thus obtained wherein W represents a hydroxymethyl group is converted by oxidation into a corresponding compound of general formula I wherein W represents a formyl or carboxy group, and/or

a compound of general formula I thus obtained wherein W represents a carboxy group is converted by conversion into a sulphonic acid hydrazide and subsequent disproportionation into a corresponding compound of general formula I wherein W represents a formyl group, and/or

a racemic compound of general formula I thus obtained wherein R_3 has the meanings given in claims 1 to 6, with the exception of the hydrogen atom, is resolved by chromatography on chiral phases into the enantiomers thereof,

* C L M S *

and/or

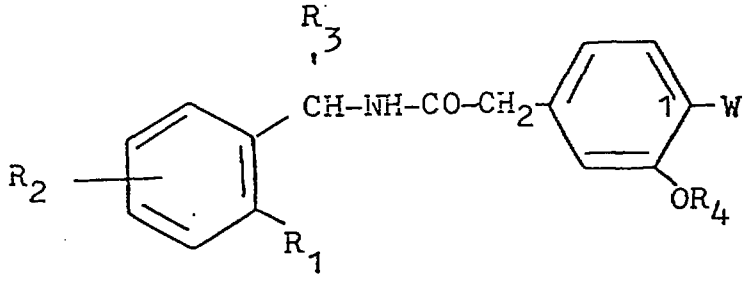
a compound of general formula I thus obtained is converted into the salts thereof, more particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

* C L M S *

25K 53 662JC2

Patent Claims for the designated state: AT

1. Process for preparing new phenylacetic acid derivatives of general formula



(I)

wherein

R_1 represents a pyrrolidino, piperidino, hexamethyleneimino, methyl-pyrrolidino, dimethyl-pyrrolidino, 2-methyl-piperidino, 3-methyl-piperidino, 4-methyl-piperidino, 3,3-dimethyl-piperidino, cis-3,5-dimethyl-piperidino or trans-3,5-dimethyl-piperidino group,

R_2 represents a hydrogen or halogen atom or a methyl or methoxy group,

R_3 represents a hydrogen atom, an alkyl group with 1 to 4 carbon atoms, an n-pentyl or 3-methyl-n-butyl group or a phenyl group optionally substituted by a halogen atom or by a methyl or methoxy group,

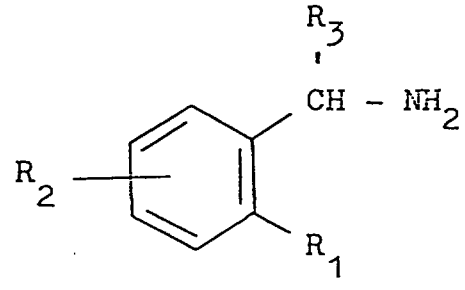
R_4 represents a hydrogen atom, a methyl, ethyl or allyl group and

W represents a methyl, hydroxymethyl, formyl, carboxy or alkoxycarbonyl group with a total of 2 to 5 carbon atoms, whilst the alkyl part of the alkoxy group may be substituted by a phenyl group,
the enantiomers and salts thereof, characterised

* C L M S *

in that

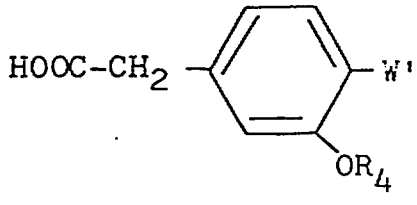
a) an amine of general formula



(II)

wherein

R_1 to R_3 are defined as hereinbefore is acylated with a carboxylic acid of general formula



(III)

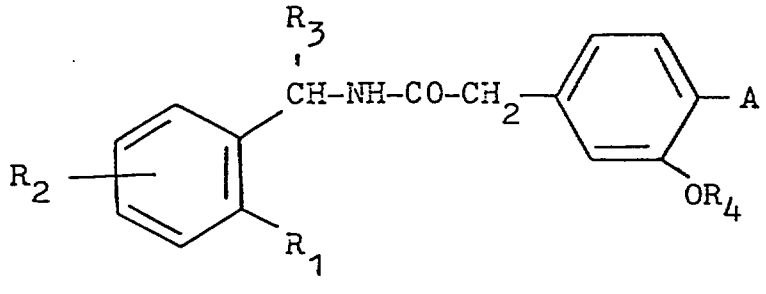
wherein

R_4 is defined as hereinbefore and

W' has the meanings given for W hereinbefore or represents a carboxy group protected by a protecting group,

or with the reactive derivatives thereof, which may optionally be prepared in the reaction mixture, and if necessary any protecting group used is split off, or

b) in order to prepare a compound of general formula I wherein W represents a carboxy group, a group A in a compound of general formula



(IV)

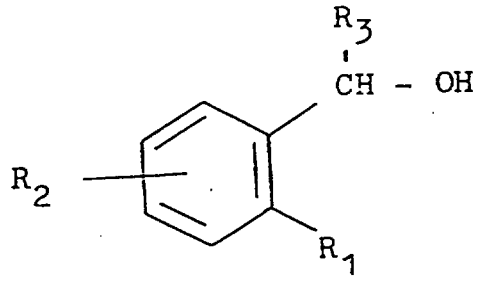
wherein

R_1 to R_4 are defined as hereinbefore and

A represents a group which may be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis,

is converted into a carboxy group,

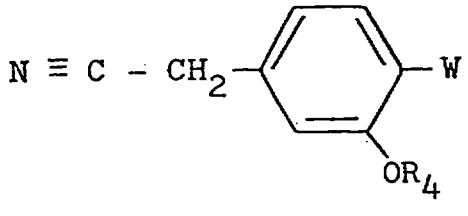
c) in order to prepare a compound of general formula I wherein R_4 represents a hydrogen atom or a methyl or ethyl group, a compound of general formula



(V)

wherein

R_1 to R_3 are defined as hereinbefore is reacted with a compound of general formula



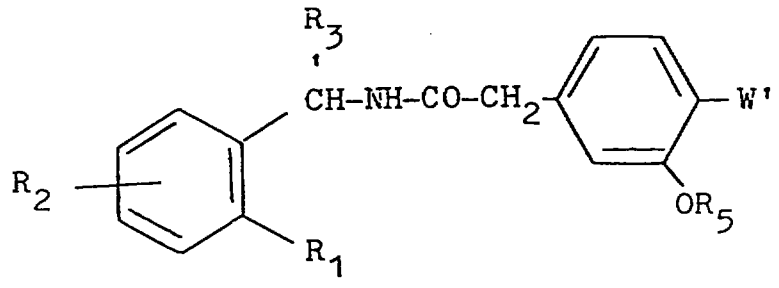
(VI)

wherein

R_4 and W are defined as hereinbefore, or

d) in order to prepare compounds of general formula I wherein R_4 represents a hydrogen atom, a protecting group is cleaved from a compound of general formula

* C L M S *



(VII)

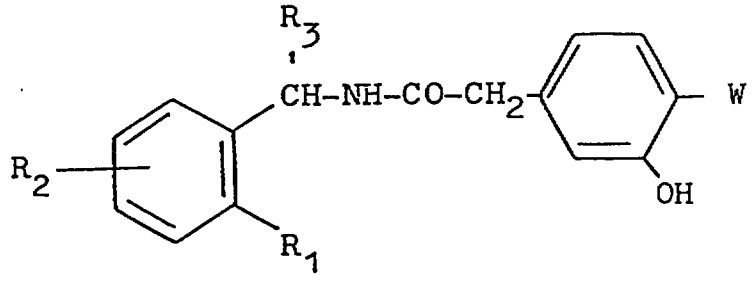
wherein

R_1 to R_3 are defined as hereinbefore,

W' has the meanings given for W hereinbefore or represents a group which can be converted into a carboxy group and

R_5 represents a protecting group for a hydroxy group or

e) in order to prepare compounds of general formula I wherein R_4 represents a methyl, ethyl or allyl group, a compound of general formula



(VIII)

wherein

R_1 to R_3 and W are defined as hereinbefore, is reacted with a compound of general formula

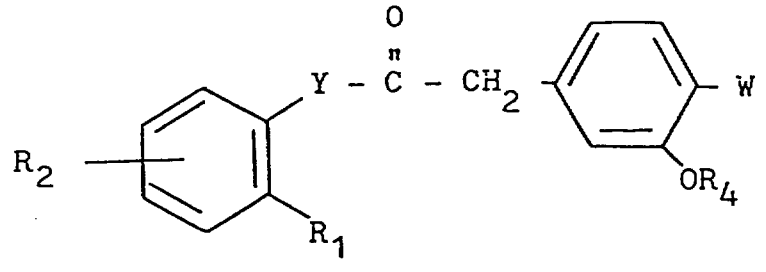
$$R_4' - X \qquad \text{(IX)}$$

wherein

R_4' has the meanings given for R_4 hereinbefore, with the exception of the hydrogen atom, and

X represents a nucleophilically exchangeable group or, together with the adjacent hydrogen atom, represents a diazo group if R_4' represents a methyl or ethyl group, and subsequently, if necessary, a compound thus obtained is hydrolysed, or

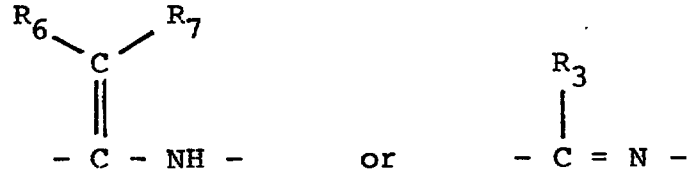
f) a compound of general formula



(X)

wherein

R_1, R_2, R_4 and W are defined as hereinbefore and Y represents a group of formula



wherein R_3 is defined as hereinbefore and R_6 and R_7 together with the carbon atom between them represent an alkylidene group with 1 to 4 carbon atoms,

is reduced and

subsequently, if desired, a compound of general formula I thus obtained wherein R_2 represents a halogen atom and/or R_3 represents a halophenyl group and/or W represents a hydroxymethyl group which has been converted into a halomethyl group, is converted by dehalogenation into a corresponding compound of general formula I wherein R_2 represents a hydrogen atom and/or R_3 represents a phenyl group

* C L M S *

and/or W represents a methyl group, and/or

a compound of general formula I thus obtained wherein W represents the carboxy group is converted by esterification into a corresponding compound of general formula I wherein W represents an alkoxycarbonyl or phenylalkoxycarbonyl group, and/or

a compound of general formula I thus obtained wherein W represents a carboxy, alkoxycarbonyl or phenylalkoxy-carbonyl group is converted by reduction into a corresponding compound of general formula I wherein W represents a formyl or hydroxymethyl group, and/or

a compound of general formula I thus obtained wherein W represents a hydroxymethyl group is converted by oxidation into a corresponding compound of general formula I wherein W represents a formyl or carboxy group, and/or

a compound of general formula I thus obtained wherein W represents a carboxy group is converted by conversion into a sulphonic acid hydrazide and subsequent disproportionation into a corresponding compound of general formula I wherein W represents a formyl group, and/or

a racemic compound of general formula I thus obtained wherein R_3 has the meanings given hereinbefore, with the exception of the hydrogen atom, is resolved by chromatography on chiral phases into the enantiomers thereof,
and/or

a compound of general formula I thus obtained is converted into the salts thereof, more particularly the physiologically acceptable salts thereof with

* C L M S *

inorganic or organic acids or bases.

2. Process as claimed in claim 1, characterised in that the reaction is carried out in a solvent.

3. Process as claimed in claims 1a and 3, characterised in that the reaction is carried out in the presence of an acid-activating or a dehydrating agent, or in the presence of an agent which activates the amine.

4. Process as claimed in claims 1a and 3, characterised in that the reaction is carried out at temperatures of between -25 and 250°C, preferably at temperatures of between -10°C and the boiling temperature of the solvent used.

5. Process as claimed in claims 1b and 3, characterised in that, if A represents the nitrile or aminocarbonyl group, the reaction is carried out in the presence of a nitrite, e.g. sodium nitrite, and in the presence of an acid such as sulphuric acid at temperatures of between 0 and 50°C or using 100% phosphoric acid at temperatures of between 100 and 180°C, preferably at temperatures of between 120 and 160°C.

6. Process as claimed in claims 1c and 3, characterised in that the reaction is carried out at temperatures of between 0 and 150°C, preferably at temperatures of between 20 and 100°C.

7. Process as claimed in claims 1d and 3, characterised in that the reaction is carried out in the presence of an acid at temperatures of between 0 and 150°C or with boron tribromide at temperatures of between -78 and 20°C.

* C L M S *

8. Process as claimed in claims 1e and 3, characterised in that the reaction is carried out at temperatures of between 0 and 100°C, preferably at temperatures of between 20 and 50°C.

9. Process as claimed in claims 1f, 3 and 17, characterised in that the reduction is carried out with hydrogen in the presence of a hydrogenation catalyst at temperatures of between 0 and 100°C, but preferably at temperatures of between 20 and 50°C.

10. Process for preparing a pharmaceutical composition for the treatment of Diabetes mellitus, characterised in that a compound of general formula I as claimed in claim 1, wherein R_4 represents a methyl, ethyl or allyl group, or a physiologically acceptable salt thereof is incorporated in one or more inert carriers and/or diluents.

* C L M S *