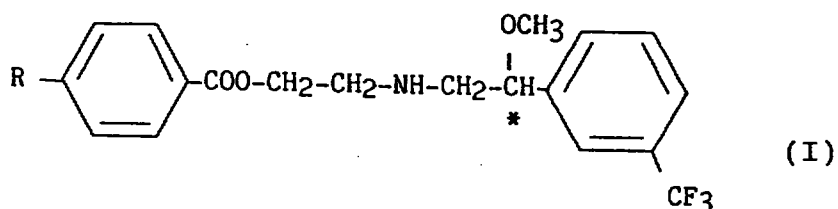


The present invention relates to new ethanolamine benzoate compounds, a process for their preparation and pharmaceutical compositions containing them.

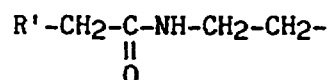
It relates especially to ethanolamine benzoate compounds of the general formula I :



wherein :

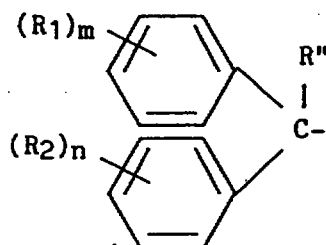
R represents :

- a hydrogen atom or
- a group of the formula :



wherein R' represents :

- a) either a radical of the formula :

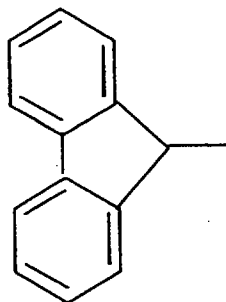


wherein :

R'' represents a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms in a straight or branched chain,
each of R₁ and R₂, which may be identical or

different, represents a hydrogen atom or an alkyl or alkoxy radical each having from 1 to 5 carbon atoms in a straight or branched chain, and each of m and n , which may be identical or different, represents 1, 2 or 3;

b) or a fluorenyl radical of the formula :

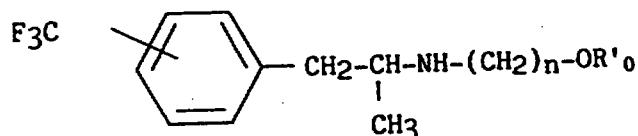


in the form of racemic compounds or enantiomers.

The prior art is illustrated especially :

- by French patents 1 517 587 and 6564 M which respectively relate to :

- compounds of the formula:



wherein :

- n represents, inter alia, the value 2, and

- R'_0 represents a hydrogen atom or a group COR''_0 , R''_0 being, inter alia, an optionally substituted phenyl radical, and

- the use of compounds A as medicaments in the treatment especially of obesity, pain and epilepsy ; and

- by US-A-4 237 165 which relates to pharmaceutical

compositions comprising 1-(3-trifluoromethylphenyl)-2-(β -hydroxyethyl)aminopropane, 1-(3-trifluoromethylphenyl)-2-(β -benzoyloxyethyl)aminopropane or benfluorex (INN), which can be used in the treatment of disorders of the metabolism,

- by FR-A-1 570 822 which relates to sulfamylbenzoic acid compounds as new chemical products, and finally

- by GB-A-1 112 526 which relates to alkoxytrifluoromethylphenalkylamines having an anti-emetic, sedative and nicotine-antagonistic activity.

Substantial structural modifications have resulted in the compounds of formula I of the present invention, which compounds regulate the metabolism of glucides and lipids and counter the oxidation of LDLs but have no effect on the level of cerebral serotonin, which is not true of the compounds of the prior art mentioned above which are inactive with respect to the oxidation of LDLs and do modify the level of cerebral serotonin, as demonstrated by the pharmacological study described in Example 10.

The present invention also relates to a process for the preparation of compounds of the general formula I which is characterised in that :

- the acid of the general formula II :

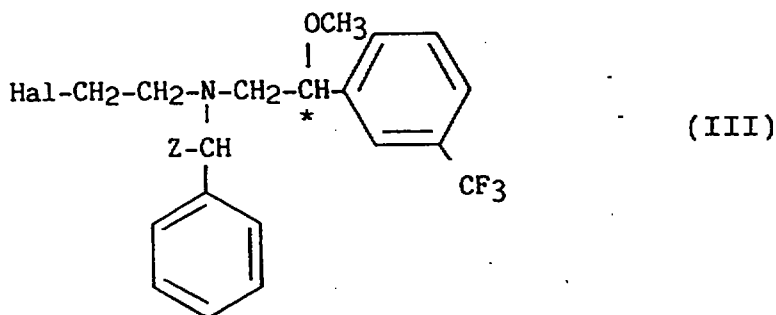


wherein R is as defined above, is converted into a salt of the general formula II' :



wherein R is as defined above and M is an alkali metal or an alkaline earth metal ;

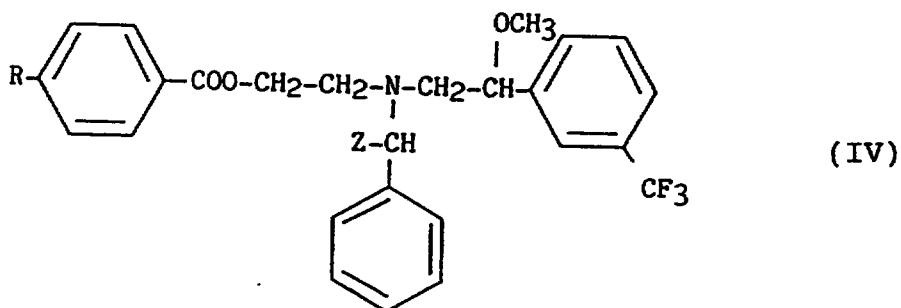
- the latter is reacted with a halogenated compound of the general formula III :



wherein :

- Z represents a hydrogen atom or a methyl radical, and
- Hal represents a halogen atom, such as a chlorine, bromine or iodine atom ;

and the compound so obtained of the general formula IV :



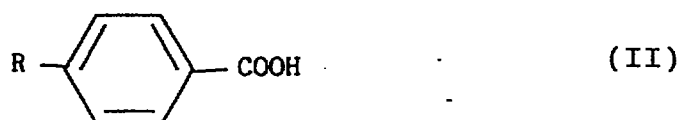
wherein R and Z are as defined above, is debenzylated catalytically.

The compounds of the general formula III wherein Z represents a hydrogen atom result in racemic compounds IV.

The compounds of the general formula III wherein Z

represents a methyl radical result either in racemic compounds IV or in laevorotatory or dextrorotatory enantiomers depending on whether the α -methylbenzyl group bonded to the nitrogen atom is RS, S or R, respectively.

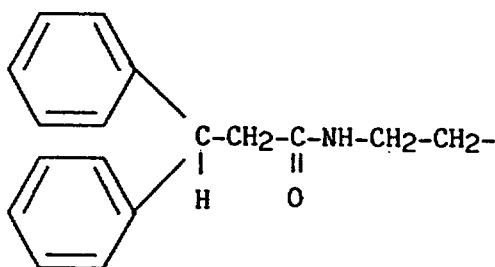
Certain starting materials of the general formula II



are known.

This is true of acids of the general formula II wherein R represents :

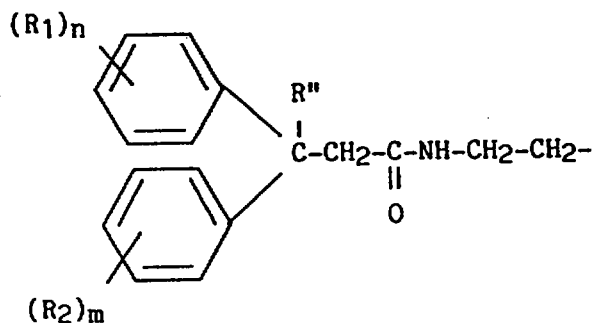
- either a hydrogen atom (in which case the compound II is benzoic acid which is a commercial product)
- or a group :



cf : European Journal of Pharmacology (1987, 141-2, 243-251 ;

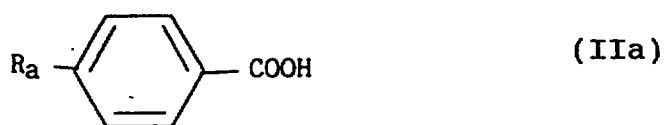
- or the fluoren-9-ylacetyl aminoethyl radical, cf : US Patent 4 136 197.

In the other cases, that is to say when R represents a group :

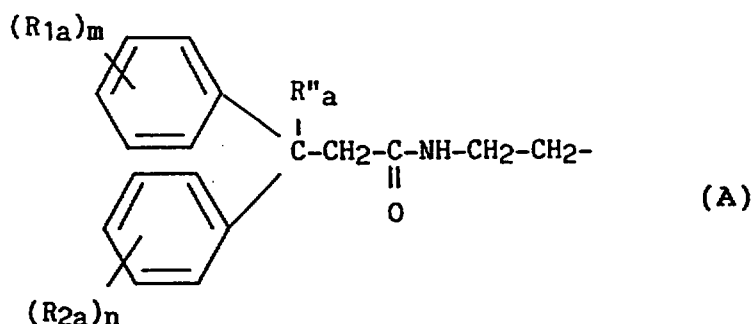


wherein R_1 , R_2 , R'' , n and m are as defined above but, in addition, R_1 , R_2 and R'' do not simultaneously represent a hydrogen atom, the corresponding compounds II are new products which, as such, form part of the present invention.

There are thus included in the present invention, as new starting materials that can be used for the synthesis of compounds of the general formula I - which can themselves be used as medicaments - compounds II corresponding more specifically to the general formula IIa :



wherein R_a represents a group of the general formula A :

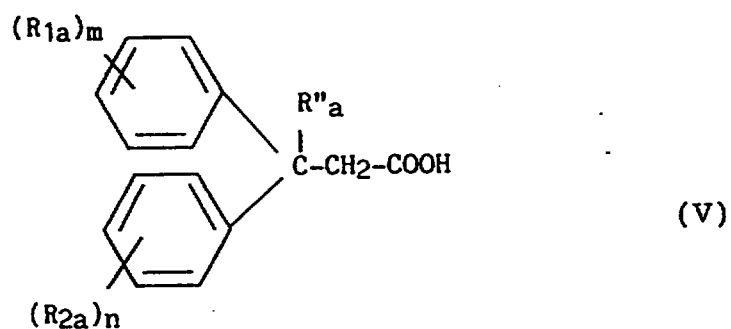


wherein :

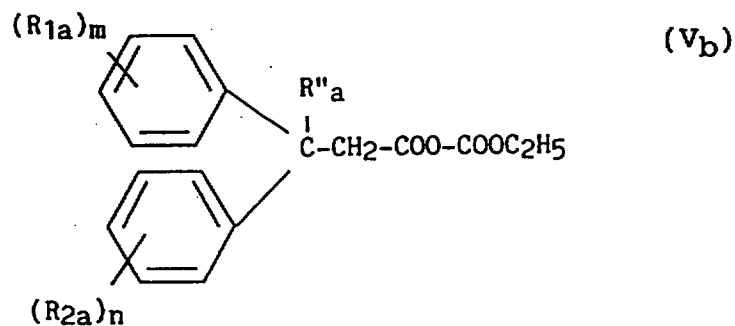
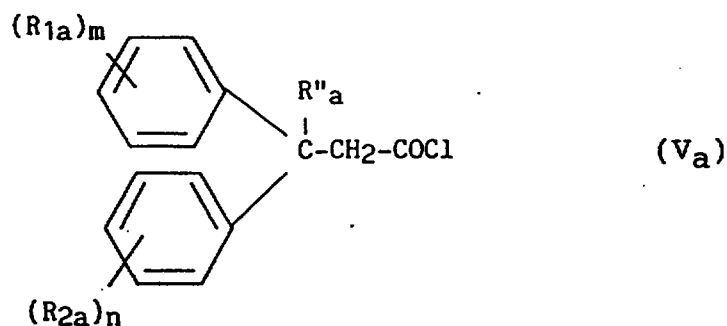
- m and n are as defined above,
- R''_a represents a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms in a straight or branched chain,
- R_{1a} and R_{2a} , which are the same or different, each represents a hydrogen atom or an alkyl or alkoxy radical each having from 1 to 5 carbon atoms in a straight or branched chain, with the proviso, however, that R_{1a} , R_{2a} and R''_a do not

simultaneously represent a hydrogen atom.

The compounds II that are new were prepared by converting acids of the general formula V :

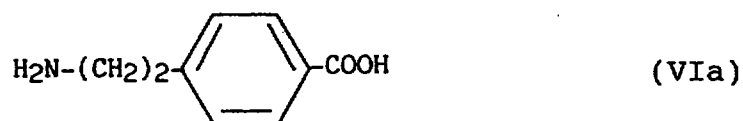


wherein R''_a , R_{1a} , R_{2a} , m and n are as defined above, into an acid chloride or mixed anhydride of the general formula V_a or V_b respectively :

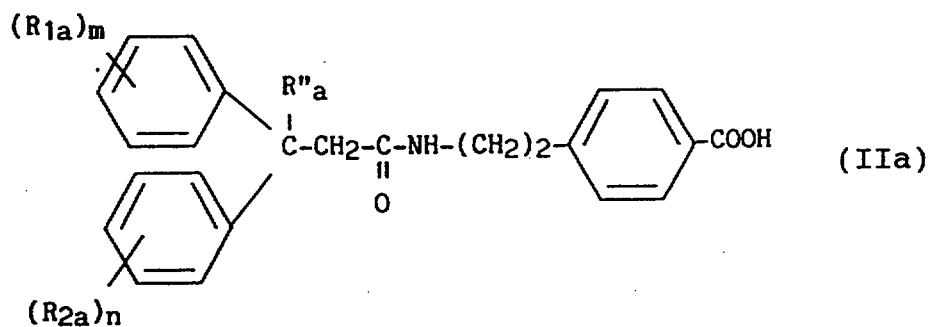


which are condensed

a) either with an amino acid of formula VIa :



to obtain a compound of formula IIa directly, a formula which can be drawn more precisely as follows :

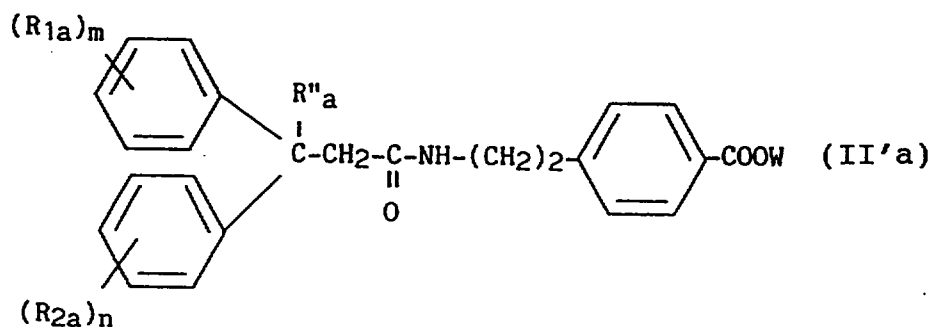


wherein R''_a , R_{1a} , R_{2a} , m and n are as defined above,

b) or with an amino ester of formula VIb :

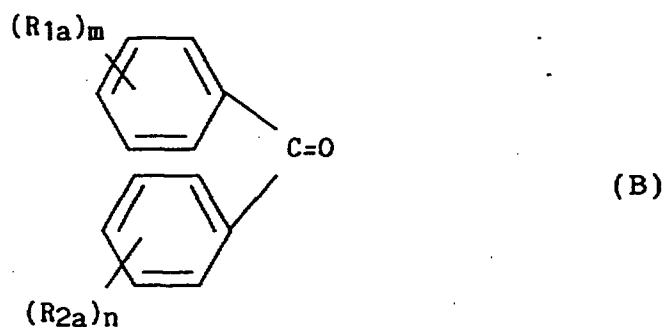


wherein W is an alkyl radical having from 1 to 5 carbon atoms in a straight or branched chain, to yield a compound of the general formula II'a :

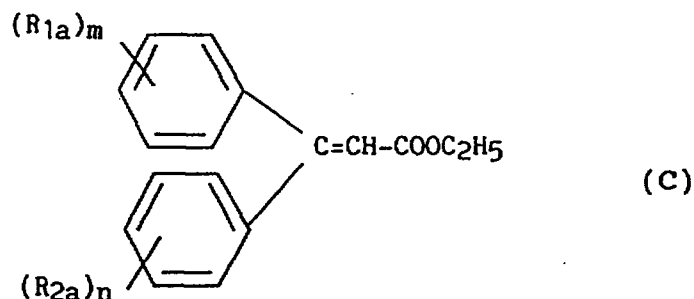


wherein R''_a , R_{1a} , R_{2a} , m , n and W are as defined above, which is hydrolysed to form an acid of formula IIa.

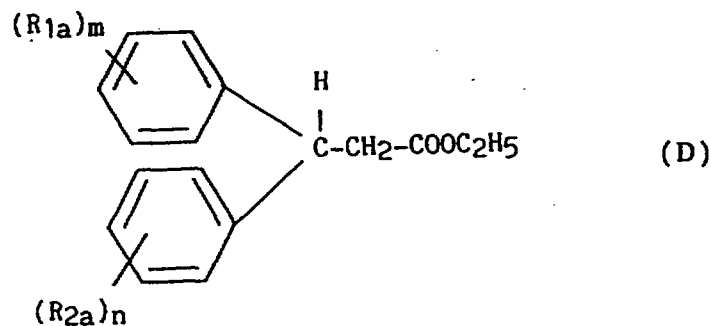
Where R''_a represents a hydrogen atom, the corresponding acids V were themselves obtained by HORNER reaction between the ketone of formula B :



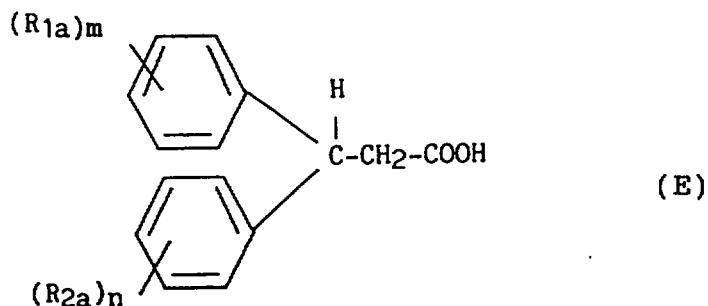
and the ethyl phosphonoacetate $[(C_2H_5O)_2OP-CH_2-COOC_2H_5]$, followed by catalytic hydrogenation of the resulting compound of formula C :



to yield the ester of formula D :

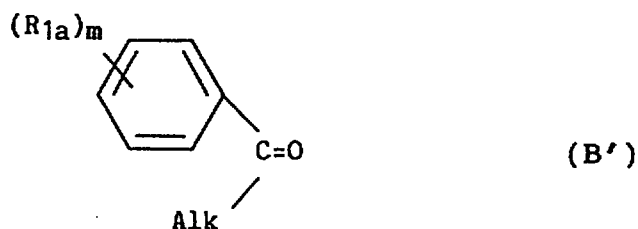


which is then hydrolysed to form the corresponding acid of formula E :

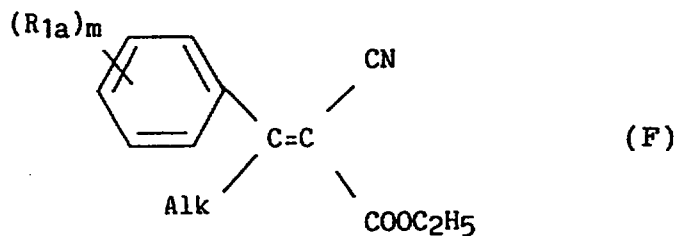


(R_{1a} , R_{2a} , m and n in each of the formulae being as defined above), that is to say to form acid V wherein R'' represents a hydrogen atom.

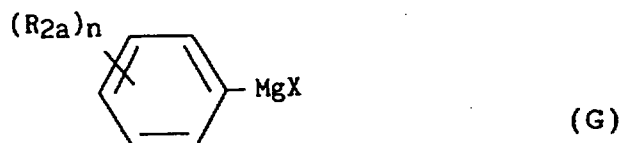
Where R''_a represents an alkyl radical having from 1 to 5 carbon atoms in a straight or branched chain, the corresponding acids V were themselves obtained by COPE condensation between the ketone of formula B' :



(wherein R_{1a} and m are as defined above and Alk represents an alkyl radical containing from 1 to 5 carbon atoms in a straight or branched chain) and ethyl cyanoacetate ($NC-CH_2-COOC_2H_5$) in toluene, in the presence of acetic acid and ammonium acetate to yield the ethylene compound of formula F :

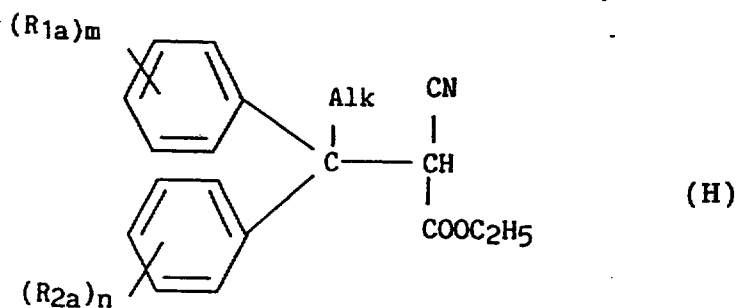


which is then subjected to the action of an organo-magnesium compound of formula G :

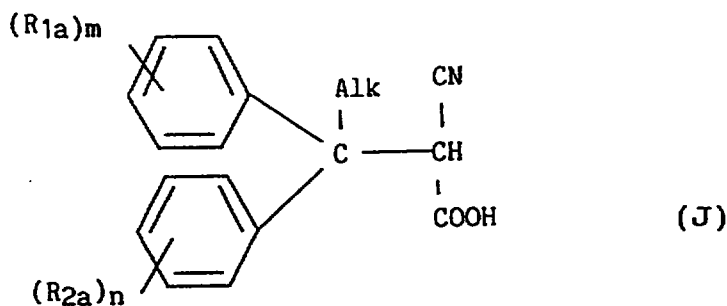


(R_{2a} and n being as defined above and X being a halogen atom)

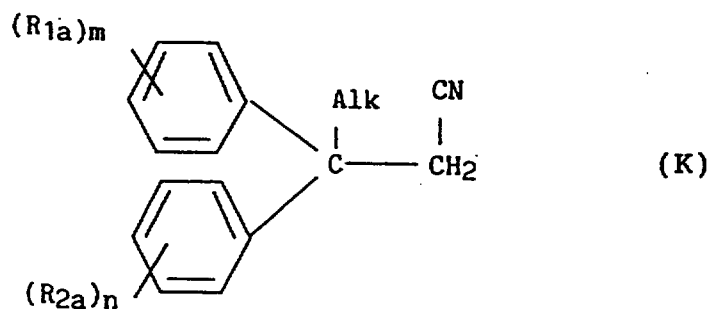
to yield the compound of formula H :



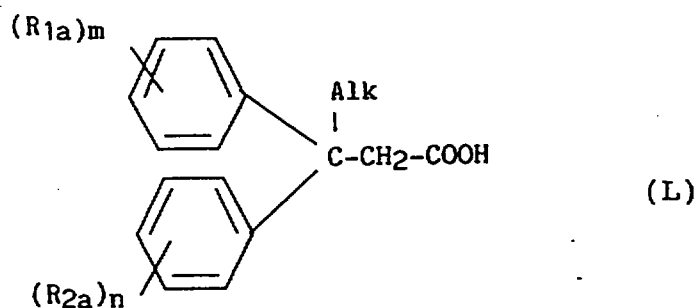
(wherein R_{1a}, R_{2a}, m, n, and Alk are as defined above),
which compound H is hydrolysed to form the acid of
formula J :



which is decarboxylated to yield the nitrile of
formula K :

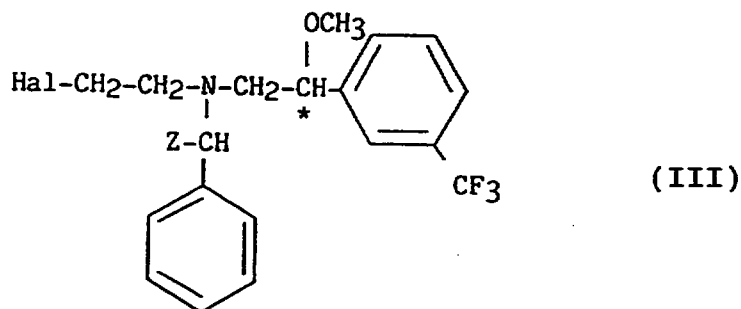


which is in turn hydrolysed to form the desired acid of formula L :

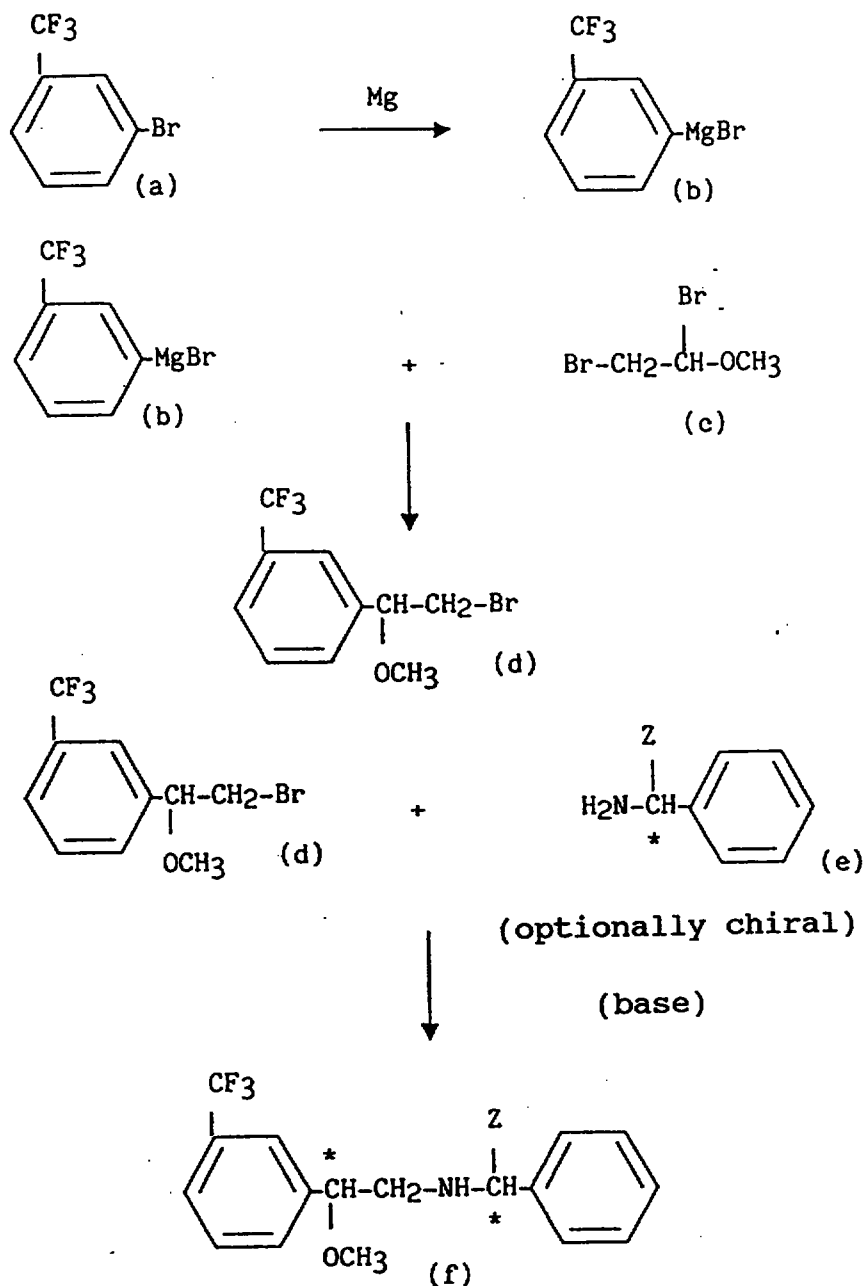


(wherein R_{1a} , R_{2a} , m , n and Alk are as defined above); that is to say to form an acid of formula V wherein R''_a represents an alkyl radical containing from 1 to 5 carbon atoms in a straight or branched chain.

The starting materials of the general formula III :



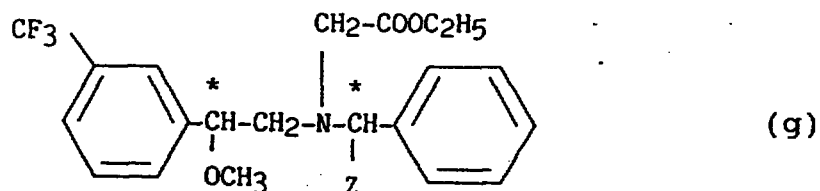
wherein Hal and Z are as defined above, were obtained in accordance with the following reaction procedure :



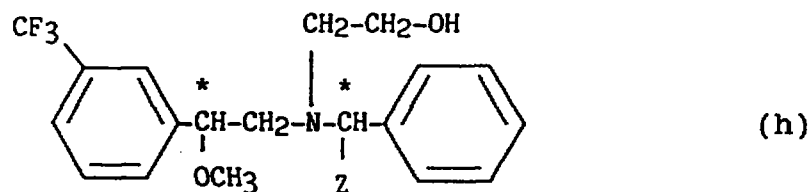
and the latter is recrystallised in the form of the hydrochloride. Where Z represents a methyl radical, depending on whether the starting α -methylbenzylamine is R or S, the hydrochloride of compound (f) is obtained by

recrystallisation in the form of one or the other diastereoisomer.

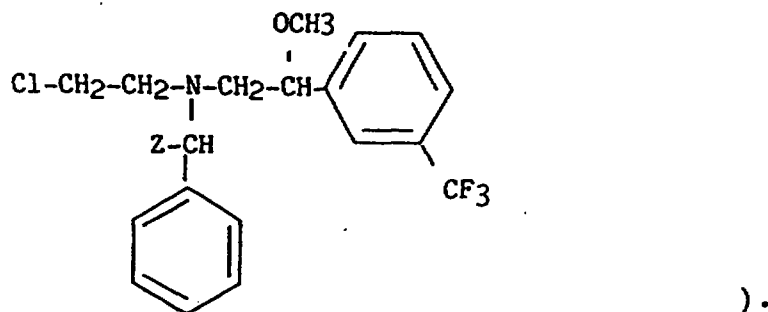
The benzylated amine of formula f (optionally in pure diastereoisomer form) is then alkylated by means of ethyl bromoacetate in the presence of a base, such as potassium carbonate, to obtain the compound of formula g :



which is then reduced with LiAlH_4 to form the alcohol of formula h :

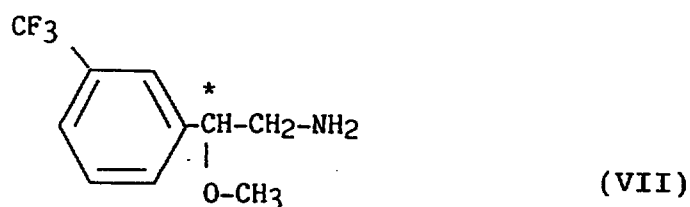


The latter is then converted into the halide III by means of a halogenated compound (such as, for example, SOCl_2 , PCl_5 or POCl_3 to obtain, more precisely, a compound of formula III wherein Hal represents a chlorine atom, that is :

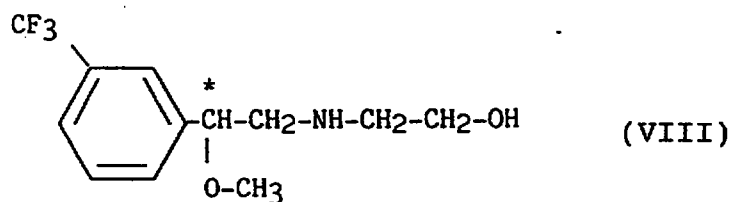


The present invention also relates to a process for the preparation of compounds of the general formula I characterised in that :

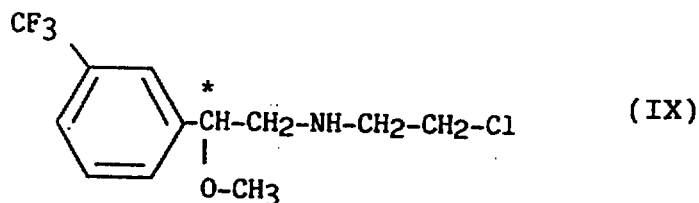
- a primary amine (optionally chiral) of formula VII :



is reacted with ethylene oxide to obtain the compound of formula VIII :



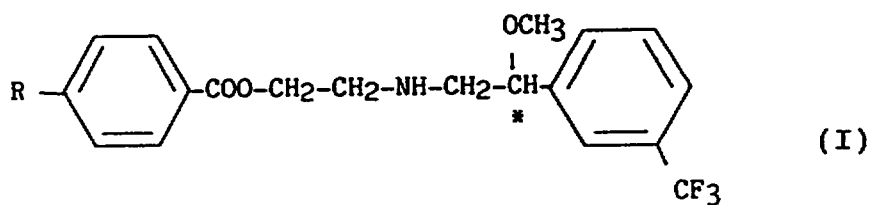
which is converted into the chloride of formula IX :



and the latter is coupled with a salt of the general formula II' :



wherein R and M are as defined above, to yield a compound of the general formula I :



The compounds of the general formula I can be converted into addition salts with acids, which salts, as

such, form part of the present invention.

There may be mentioned as acids that can be used for the formation of those salts, for example, in the mineral series, hydrochloric, hydrobromic, nitric, sulphuric and phosphoric acid and, in the organic series, acetic, propionic, maleic, fumaric, tartaric, oxalic, benzoic, methanesulphonic and isethionic acid.

The compounds of the general formula I and their physiologically tolerable addition salts have valuable pharmacological and therapeutic properties, especially properties regulating the metabolism of glucides and lipids. Moreover, they cause a moderate reduction in arterial pressure.

More precisely, the compounds of the present invention improve the efficacy of insulin at a peripheral and/or hepatic level, resulting in an improvement in glucose tolerance and in moderate hyperglycaemia, where it exists, without the risk of hypoglycaemia, as well as a reduction in hyperinsulinaemia. Further, the compounds reverse insulin resistance induced by amylin.

They also reduce hypertriglyceridaemia and combat LDL (low density lipoprotein) oxidation, thus having an implication in the prevention of macroangiopathies.

They cause a moderate reduction in weight associated with a reduction in food intake, not associated with a serotoninerbic mechanism, and as a result of the latter two properties they are differentiated from existing products in that field (benfluorex, fenfluramine).

Those properties enable them to be used therapeutically especially for the treatment of non-insulin-dependent diabetics not treated by diet, non-insulin-dependent diabetics treated with blood sugar-reducing medicaments, diabetics who are insulin-dependent or are

not treated with insulin, or non-hyperglycaemic, hypertensive or non-hypertensive, patients having hyperinsulinaemia (i.e. android obesity) and all exhibiting a resistance to insulin, whether induced or not by amylin.

The products of the invention are thus used in the treatment of diabetes, of obesity, of syndrome X (by improving the effect of insulin at the periphery and/or in the liver and by decreasing triglycerides and LDL oxidation, associated with a moderate reduction in weight), and in the treatment of hypertension in patients who are resistant to insulin or have associated or non-associated metabolic anomalies, such as, for example, hyperinsulinaemia, dyslipaemia and hyperglycaemia, whether secondary or not to the effects of amylin.

The present invention also relates to pharmaceutical compositions comprising as active ingredient a compound of the general formula I or a physiologically tolerable salt thereof, admixed or in association with one or more appropriate pharmaceutical excipients.

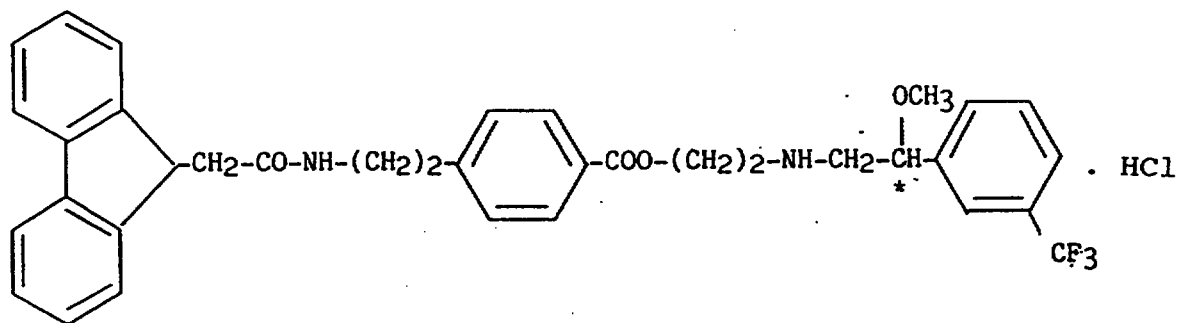
The so-obtained pharmaceutical compositions are generally in a dosage form comprising from 25 to 100 mg of active ingredient. They may be in the form of tablets, dragées, capsules, suppositories or injectable or drinkable solutions, and may be administered by the oral, rectal or parenteral route.

The dosage may vary, especially in accordance with the age and weight of the patient, the route of administration, the nature of the disorder and associated treatments, and ranges from 25 to 100 mg of active ingredient per administration from 1 to 4 times per day.

The following Examples illustrate the invention.

Example 1

Laevorotatory isomer of 2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethylamino]ethyl para-[2-(α -fluoren-9-ylacetyl-amino)ethyl]benzoate hydrochloride.

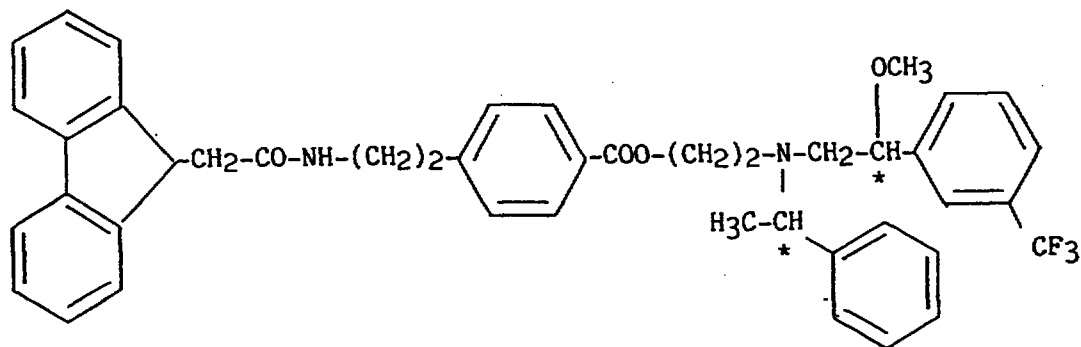


8.3 g of 1-N-(β -chloroethyl)-N-(α -phenylethyl)-N-[(β -methoxy- β -meta-trifluoromethylphenyl)ethyl]amine hydrochloride are stirred in 100 ml of water, 100 ml of ether and 2.5 ml of concentrated sodium hydroxide solution. The ethereal phase is collected by decanting, and dried over MgSO_4 ; the solvent is distilled off and the residue is dissolved in 50 ml of anhydrous dimethylformamide.

That solution is then poured slowly into a flask containing 7.3 g of para-[2-(fluoren-9-ylacetyl-amino)-ethyl]benzoic acid, 2.7 g of K_2CO_3 and 100 ml of dimethylformamide, which together have beforehand been heated to 60°C for 45 minutes.

After the addition of the chlorinated compound, the reaction mixture is heated to 90°C for 3 hours under nitrogen. The solvent is distilled off in vacuo and the residue is taken up in ether. The potassium chloride precipitate is filtered off and the ether is distilled off. The residue obtained (approximately 13 g) is filtered through 300 g of silica using a mixture of dichloromethane/ethyl acetate (95/5) as eluant.

In this manner 8 g of compound IV of formula :



are obtained. 7 g of that compound dissolved in 160 ml of anhydrous isopropanol are hydrogenated under a hydrogen pressure of approximately 90 lbs, at a temperature of 50°C, until complete absorption of the necessary amount of hydrogen.

The solution is then filtered through talc, the solvent is distilled off and the residue is filtered through 100 mg of silica using a $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{COOC}_2\text{H}_5$ mixture (50/50) as eluant.

The solvent is distilled off from the fraction containing the product. The residual oil is taken up in ether and a slight excess of ethereal hydrogen chloride solution is added. The resulting precipitate is filtered and washed with ether, yielding 4.5 g of the laevo-rotatory isomer of 2-[(β -methoxy- β -meta-trifluoromethyl-phenyl)ethylamino]ethyl para-[2-(α -fluoren-9-ylacetyl-amino)ethyl]benzoate hydrochloride.

Index of rotation : (c = 1 % in ethanol)

$[\alpha]_{589}$: -29.7

$[\alpha]_{578}$: -30.6

$[\alpha]_{546}$: -34.7

$[\alpha]_{436}$: -58.3

$[\alpha]_{365}$: -90.9

The para-[2-(fluoren-9-ylacetyl-amino)ethyl]benzoic acid starting material was prepared in accordance with US

Patent No. 4 136 197.

The 1-N-(β -chloroethyl)-N-(α -phenylethyl)-N-[(β -methoxy- β -meta-trifluoromethylphenyl)ethyl]amine hydrochloride starting material was prepared as follows :

a) 225 g of 3-trifluoromethylbromobenzene are added dropwise to a mixture of 27 g of magnesium and 500 ml of anhydrous ether to which an iodine crystal has previously been added. The reaction is effected in such a manner as to ensure a slight reflux of the ether. Once the magnesium has dissolved, 232 g of 1-methoxy-1,2-dibromoethane (prepared in accordance with the technique described in Organic Syntheses vol. IV, p 748, replacing the ethanol with methanol) are slowly added.

Refluxing is maintained for 1 hour after addition has been completed. The mixture is then cooled and subsequently hydrolysed with 250 ml of water. After decanting, the ethereal phase is washed with water and then dried.

The solvent, and then the product, are distilled off under reduced pressure. 203 g of 3-trifluoromethyl-1-(2-bromo-1-methoxyethyl)benzene are obtained (b.p./13 Pa = 68°C).

b) 202 g of that brominated compound and 173 g of (S)- α -methylbenzylamine are refluxed in 714 ml of xylene for 6 hours.

The xylene is then distilled off and the residue is taken up in ether. The α -methylbenzylammonium bromide is removed from the resulting filtrate which is then distilled to yield 144 g of product which boils at 125-128°C under 13 Pa.

94 ml of 5N ethereal hydrogen chloride are added to that compound dissolved in ether. The resulting precipitate is filtered, washed with ether and recrystallised twice from 550 ml of isopropanol each time,

yielding 80 g of pure diastereoisomer.

c) 21 g of the latter are reacted with 12 g of ethyl bromoacetate and 9.8 g of potassium carbonate in 65 ml of anhydrous ethanol. The mixture is refluxed for 8 hours, 2 ml of ethyl bromoacetate and 2.5 g of potassium carbonate are then added, and the mixture is heated again for 4 hours. The mineral compound is filtered off, the ethanol and the excess bromoacetate are distilled off and the residual oil is used as it is.

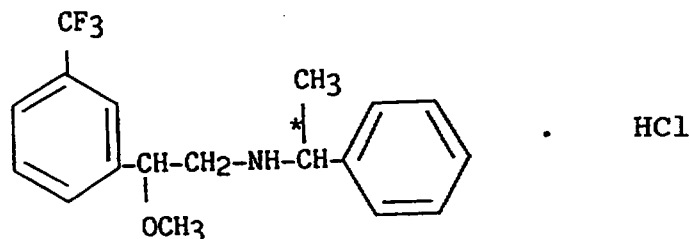
d) 27 g of the ester so obtained are reacted with 3.78 g of LiAlH_4 in 150 ml of anhydrous tetrahydrofuran under reflux for 5 hours.

The mixture is then hydrolysed with 3.8 ml of water, then with 3.8 ml of 4N NaOH and finally with 11.4 ml of water.

The organic phase is filtered and concentrated and used as it is.

e) 22.9 g of the alcohol so obtained are dissolved in 65 ml of chloroform. 10.5 ml of 6N ethereal hydrogen chloride are added dropwise to the solution. The solvent is evaporated off, the residue is taken up in 65 ml of chloroform and 8.2 g of thionyl chloride are added dropwise thereto.

The whole is refluxed for 5 hours and then the solvent is distilled off. The residue is taken up in 150 ml of ethyl acetate and dissolved with the application of heat. The solution is allowed to cool until a slight precipitate is formed corresponding to :



which is removed accordingly.

The solvent is then distilled off from the remaining solution and the residual product (which is the 1-N-(β -chloroethyl)-N-(α -phenylethyl)-N-[(β -methoxy- β -meta-trifluoromethylphenyl)ethyl]amine hydrochloride) is used as it is.

Examples 2 to 7

The following compounds were prepared by proceeding as described in Example 1 :

2. Dextrorotatory isomer of 2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethylamino]ethyl para-[2-(α -fluoren-9-ylacetyl-amino)ethyl]benzoate hydrochloride, index of rotation ($c = 1$ % in ethanol) :

$[\alpha]_{589} : +30.0$

$[\alpha]_{578} : +31.3$

$[\alpha]_{546} : +35.8$

$[\alpha]_{436} : +61.4$

$[\alpha]_{365} : +95.0$

3. dl-2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethyl-amino]ethyl para-[2-(α -fluoren-9-ylacetyl-amino)ethyl]-benzoate hydrochloride.

4. Laevorotatory isomer of 2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethylamino]ethyl para-[2-(benz-hydrylacetyl-amino)ethyl]benzoate hydrochloride.

Index of rotation ($c = 1$ % in ethanol at 21°C).

$[\alpha]_{589} : -32.3$

$[\alpha]_{578} : -33.5$

$[\alpha]_{546} : -38.1$

$[\alpha]_{436} : -64.5$

$[\alpha]_{365}$: -100.7.

5. dl-2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethyl-amino]ethyl benzoate hydrochloride, m.p. (Kofler) : 122-123°C.

6. Laevorotatory isomer of 2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethylamino]ethyl benzoate hydrochloride.

Index of rotation ($c = 1$ % in ethanol at 23°C).

$[\alpha]_{589}$: -52.9

$[\alpha]_{578}$: -55.1

$[\alpha]_{546}$: -62.7

$[\alpha]_{436}$: -106.6

$[\alpha]_{365}$: -167.3.

7. Dextrorotatory isomer of 2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethylamino]ethyl benzoate hydrochloride.

Index of rotation ($c = 1$ % in ethanol at 23°C).

$[\alpha]_{589}$: +51.5

$[\alpha]_{578}$: +53.9

$[\alpha]_{546}$: +61.1

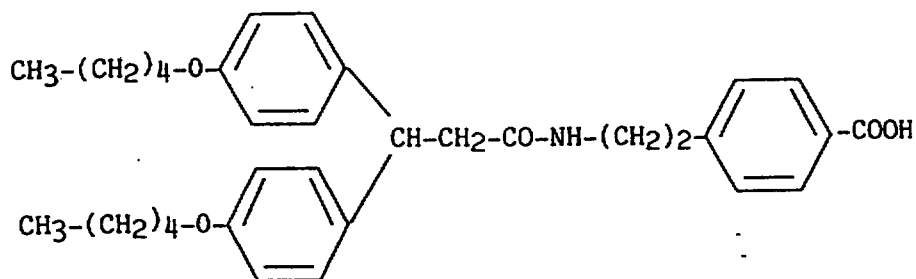
$[\alpha]_{436}$: +103.6

$[\alpha]_{365}$: +152.2.

Examples 8 and 9

The new starting materials of the general formula IIa were prepared in accordance with the method illustrated in the following Examples :

8. Para-{2-[N-(bis-4,4'-n-pentyloxybenzhydrylacetyl)-amino]ethyl}benzoic acid



a) Para-n-pentyloxybromobenzene : 276 g of anhydrous potassium carbonate are added to 173 g of p-bromophenol dissolved in 1800 ml of methanol. After stirring, the reaction mixture is treated with 164 ml of n-bromopentane and maintained at reflux for 4 hours with stirring.

After cooling, 3 litres of water are added and the methanol is removed under water-jet vacuum.

After extraction with 2 litres of ether and then twice with 1 litre of ether each time, the organic solutions are combined and washed 3 times with 1 litre of water each time. After drying over anhydrous MgSO_4 , the solution is evaporated off in vacuo and the residue is distilled.

222.8 g of para-n-pentyloxybromobenzene (b.p./ 13 Pa = $87-91^\circ\text{C}$) are obtained. Yield : 91.6 %.

b) Para-n-pentyloxybenzaldehyde : by operating as above starting with 33 g of para-hydroxybenzaldehyde, 74.5 g of potassium carbonate and 45 g of n-bromopentane, 21 g of para-n-pentyloxybenzaldehyde (b.p./ 1.3 Pa = $112-114^\circ\text{C}$) were isolated. Yield : 37 %.

c) Ethyl n-pentyloxybenzylidenemalonate : 32.6 g of dimethylamine hydrochloride and 1.7 g of

potassium fluoride are added to 38.5 g of para-n-pentyloxybenzaldehyde and 31 ml of ethyl malonate dissolved in 400 ml of anhydrous dimethylformamide. The reaction mixture is heated with stirring for 18 hours. After cooling, the solvent is evaporated off in vacuo (13×10^2 to 20×10^2 Pa). The residue is taken up twice in 250 ml of methylene chloride each time. The organic layer is washed with 200 ml of a normal hydrochloric acid solution and then twice with 200 ml of water each time.

After drying over anhydrous magnesium sulphate, the solvent is evaporated off under water-jet vacuum. Distillation of the residue yields 49.8 g of ethyl para-n-pentyloxybenzylidenemalonate (b.p./13 Pa = 170-175°C). Yield : 74.5 %.

d) Ethyl α -ethoxycarbonyl- β,β -[bis(para-n-pentyloxyphenyl)]propanoate :

To a solution of para-n-pentyloxyphenylmagnesium bromide prepared from 5.8 g of para-n-pentyloxybromobenzene and 0.64 g of magnesium turnings in 30 ml of tetrahydrofuran (THF) (poured in over a period of 1 hour under reflux, then maintained at reflux for a further 1 hour) there are added, over a period of 30 minutes, 8 g of ethyl para-n-pentyloxybenzylidenemalonate dissolved in 25 ml of THF. After refluxing for 2 hours 30 minutes with stirring, 25 ml of a normal HCl solution are poured in. The reaction mixture is extracted three times with 50 ml of water each time and then dried over MgSO_4 . After evaporation the residue is purified by chromatography. 8.7 g of the desired product are obtained.

e) β,β -[Bis(para-n-pentyloxyphenyl)]propionic acid :

8.5 g of the product obtained in d) dissolved in 22.5 ml of ethanol are added to a solution of 6.2 g of potassium hydroxide in 100 ml of water. The solution

obtained is maintained at reflux for 1 hour 30 minutes. After removal of the solvent under water-jet vacuum, the residue is taken up in 200 ml of water and then acidified with 11 ml of a 37 % concentrated HCl solution. The oil formed is extracted 3 times with 100 ml of ether each time. After washing twice in 50 ml of water each time, the ether is dried over magnesium sulphate and then evaporated off in vacuo. 5.6 g of product, m.p. : 134-136°C, are obtained, yield : 75 %.

The residue is heated for 15 minutes at 180-190°C. After washing with petroleum ether, 3.3 g of β,β -[bis-(para-n-pentyloxyphenyl)]propionic acid are obtained, m.p. : 72°C, yield : 67 %.

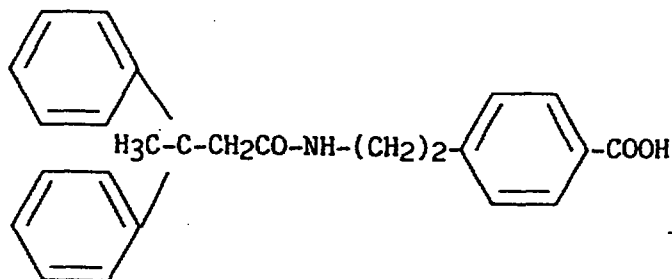
f) Ethyl para-(2-[N-(bis-4,4'-n-pentyloxybenzhydryl-acetyl)amino]ethyl)benzoate :

1.07 ml of triethylamine in 10 ml of THF are added to 3.06 g of the acid prepared in e) dissolved in 30 ml of THF. After stirring for 1 hour, the solution obtained is added to 0.76 ml of ethyl chloroformate in 30 ml of THF cooled to 0°C. 1.56 g of ethyl para-[β -(amino)ethyl]-benzoate dissolved in 10 ml of THF are then poured in over a period of 15 minutes. The temperature rises to 10°C. After stirring for 45 minutes at room temperature and 12 hours under reflux, the precipitate is suction-filtered off and the filtrate is evaporated to dryness in vacuo. Chromatography yields 3.06 g of the desired benzoate.

g) Para-(2-[N-(bis-4,4'-n-pentyloxybenzhydryl-acetyl)amino]ethyl)benzoic acid :

3 g of the ester obtained in f), 15 ml of ethanol and 5.7 ml of normal sodium hydroxide solution maintained at reflux for 2 hours result in the corresponding benzoic acid.

9. Para-{2-[N-(3-methyl-3,3-diphenylpropionyl)amino]-ethyl}benzoic acid :



a) Ethyl (α -methylbenzylidene)-cyanoacetate :

60 g of acetophenone, 56.6 g of ethyl cyanoacetate, 7.7 g of ammonium acetate, 24 g of acetic acid and 100 ml of benzene are refluxed with stirring and the water formed during the course of the reaction is removed as the reaction proceeds using a Dean Stark apparatus.

After 13 hours 40 minutes of heating, 100 ml of ether are added and the reaction mixture is washed 3 times with 100 ml of water each time. The organic layer is dried over magnesium sulphate and concentrated under water-jet vacuum and the residue is distilled, yielding 58.4 g of ethyl (α -methylbenzylidene)-cyanoacetate (b.p./13 Pa = 125-128°C).

b) α -Ethoxycarbonyl- β,β -diphenylbutyronitrile :

41 g of bromobenzene dissolved in 100 ml of anhydrous ether are added over a period of 1 hour 20 minutes, with stirring, to 6.3 g of magnesium turnings and 240 ml of anhydrous ether. The mixture is refluxed for 2 hours and then, over a period of 30 minutes, 51 g of ethyl (α -methylbenzylidene)-cyanoacetate in 150 ml of ether are added. After having been heated for 5 hours, the reaction mixture is hydrolysed with 150 ml of 2N HCl. The organic layer is decanted off. The aqueous layer is extracted twice with 100 ml of ether each time. The ethereal phases are combined, washed with 100 ml of

water, dried over MgSO_4 and, after filtration, concentrated under water-jet vacuum.

Distillation of the residue yields 30.7 g of the desired product (b.p./ 13 Pa = $150-155^\circ\text{C}$), yield : 46 %.

c) α -Carboxy- β,β -diphenylbutyronitrile :

15 g of α -ethoxycarbonyl- β,β -diphenylbutyronitrile, 65 ml of ethanol, 18.4 g of potassium hydroxide pellets and 30 ml of water are stirred at room temperature for 4 hours. After concentration in vacuo, the residue is taken up in 150 ml of water. After extracting 3 times with 50 ml of ether each time, the aqueous layer is acidified with 22 ml of concentrated HCl and extracted 3 times with 100 ml of ether each time. The organic layers are combined, dried over MgSO_4 and evaporated. 14 g of the desired product are obtained.

d) β,β -Diphenylbutyronitrile :

14 g of α -carboxy- β,β -diphenylbutyronitrile and 85 ml of triethylene glycol are heated at 80°C for 30 minutes and then, after cooling, diluted with 300 ml of water. After extracting 3 times with 150 ml of ether each time, drying the organic layer and concentrating in vacuo and purifying by chromatography, 7.3 g of β,β -diphenylbutyronitrile are obtained. Yield : 64 %.

e) β,β -Diphenylbutyric acid :

7.2 g of the product obtained in d), 9.6 ml of concentrated sulphuric acid, 12 ml of water and 12 ml of acetic acid are maintained at reflux for 22 hours. After cooling and treating with 90 ml of water, the precipitate formed is suction-filtered off and washed with water. After drying and recrystallisation from 20 ml of cyclohexane, 6.5 g of the desired acid are obtained, m.p. : 100°C , yield : 77 %.

f) β,β -Diphenylbutyryl chloride :

6.5 g of the acid above are added over a period of 15 minutes to 10 ml of thionyl chloride. After heating for 2 hours at reflux, the solution obtained is concentrated in vacuo and the residue is taken up twice in 50 ml of benzene with evaporation each time. 6.6 g of β,β -diphenylbutyryl chloride are obtained.

g) Para-(2-[N-(3-methyl-3,3-diphenylpropionyl)-amino]ethyl)benzoic acid :

31.5 g of triethylamine are added, with stirring, to a suspension of 5.2 g of para-[β -(amino)ethyl]benzoic acid hydrochloride in 200 ml of anhydrous dimethylformamide, then 6.5 g of the chloride obtained in f) dissolved in 75 ml of anhydrous THF are poured in over a period of 15 minutes. The temperature rises from 26 to 34°C. After stirring for 4 hours at room temperature, then for 5 hours at 40°C, the triethylamine hydrochloride formed is suction-filtered off and the filtrate is concentrated in vacuo. The residue is taken up in 60 ml of water. The precipitate formed is suction-filtered off, dried in air and then recrystallised from 50 ml of anhydrous isopropanol. 5 g of para-(2-[N-(3-methyl-3,3-diphenylpropionyl)amino]ethyl)benzoic acid are obtained, m.p. : 211°C.

Example 10 :

PHARMACOLOGICAL STUDY

A. STUDY OF THE EFFECT OF AN ACUTE TREATMENT ADMINISTERED BY PORTAL PERFUSION TO CONSCIOUS RATS

1. Aim of the experiment

The technique of portal perfusion in conscious rats makes it possible to study the effect of pharmacological substances on modifications of the tolerance to glucose

administered by the intravenous route.

The injection of agents directly into the portal circulation makes it possible to avoid the effects of gastric transit, absorption and release of hormone through the intestinal wall and thus to explore :

- both the direct effect on the hepatic tissue,
- and the existence of a liver-central nervous system-peripheral tissue relay (liver, muscle or endocrinal target).

2. Protocol

2.1 Animals used

In this experiment, adult male SPRAGUE DAWLEY rats were used in groups of from 5 to 12 rats.

The rats used, aged 52 weeks, exhibit

- a reduction in glucose tolerance,
- an increase in basal insulinaemia, and
- an increase in plasma lipids.

The housing (from 9 to 52 weeks) of those rats was effected in a chamber at a regulated temperature of from 21 to 22°C subjected to a fixed cycle of light (from 07.30 to 19.30 hours) and darkness (from 19.30 to 07.30 hours). Their food consisted of a maintenance diet (UAR A 03); water and food were supplied "ad libitum", with the exception of the night-fasting preceding the tests, when the food was removed.

2.2 Methods

Surgical preparation :

On d₇ before the beginning of the experiment, the rats are anaesthetized with ketamine (IMALGENE 1000 - Rhone MERIEUX), and a Silastic catheter (602-135, medical grade, DOW CORNING MIDLAND) is implanted in the hepatic portal vein [cf. Strubbe J.H., Wolsink J.G., Schutte A.M., Balkan B. and Prins A.J.A. : Hepatic-portal and

cardiac infusion of CKK-8 and glucagon induce different effects on feeding. Physiology and Behavior 46,643-646 (1989)] for the perfusion of the physiological solution (control day) and then of the product to be tested. They are then placed individually in plexiglass cages.

- After recovery, that is to say approximately 10 days later, a second Silastic catheter (602-155, medical grade, DOW CORNING MIDLAND) is introduced up into the right auricle through the right jugular vein [cf. Steffens A.B. : Method for frequent sampling of blood and continuous infusion of fluids in the rat without disturbing the animal. Physiology and Behavior 4, 833-836 (1969)]. During the experiments, the various blood samples will be taken and the intra-cardiac injection of a glucose bolus will be carried out using that catheter. During the two surgical procedures, the catheters are slid under the skin and exited at the top of the head by means of a polished needle bent back and plugged by a polyethylene (PE) cap closed with a bougie.
- 0.4 ml of a 500 U/ml heparin solution (ROUSSEL UCLAF) followed by 0.1 ml of PVP (30 % polyvinylpyrrolidone solution - MW 25000 - MERCK) are introduced into the catheters before closure with the polyethylene cap. The viscosity of the PVP makes it possible to avoid a reflux of blood into the catheter.
- The day before each experiment, the rats are subject to 18 hours of night fasting. On the day of the experiment, these rats are weighed and the catheters are checked to ensure they are working properly.
- In order to overcome the stress of connecting the catheters to the externalised needles on the top of the head, 20 minutes' rest are required before the experiment is started.
- The intraportal perfusions, carried out using a No.3 polyethylene catheter, take 60 minutes; they have a

constant flow of 2 ml/hour, that is to say approximately 0.033 ml/minute, ensured by a BRAUN perfuser. An IVGTT test (intravenous administration glucose tolerance test) is carried out 30 minutes after starting the portal perfusion.

- The control experiment (reference test) consists in the perfusion of a saline solution (0.9 % isotonic sodium chloride BIOSEDRA), which permits the basal value of tolerance (K) towards a dose of glucose to be determined for each rat.

- Resistance to insulin is induced in normal rats by means of an intraportal perfusion of amylin (IAPP, insulinoma associated pancreatic polypeptide) at 26 nmol/kg/h over a period of 90 minutes.

- 0.40 ml blood samples are taken (No.6 polyethylene catheter) immediately before the perfusion and 30 minutes after starting the perfusion. Those samples are used to determine the basal glycaemia and basal insulinaemia. Immediately after collecting basal no.2, that is to say 30 minutes after starting the perfusion, a glucose bolus is administered (1 ml/kg of a 50 % glucose solution) into the jugular vein. A series of samples is then taken every 3 minutes from t+30 to t+60 minutes after administration of the bolus. A volume of 0.40 ml is taken each time and is replaced by 0.40 ml of physiological heparinated serum.

Satisfactory functioning of the catheters is ensured by injecting PVP between each experiment.

Collection of the samples :

- To determine glycaemia, the blood is collected in URAC (deproteinating solution) using 20 μ l of blood per 200 μ l of URAC (1/10 solution).

- The samples to be used for determining insulinaemia

are collected over heparin (20 μ l of physiological heparinated serum at 500 IU/ml, that is to say 7.5 IU of heparin per tube to be centrifuged).

- All the tubes are placed in ice as soon as the samples are collected. The samples are then centrifuged for 10 minutes at 3000 revs/min (refrigerated centrifuge) to separate the substances present as quickly as possible.

- The sera (in URAC for glycaemia) and the plasma (insulinaemia) are then distributed into Eppendorf tubes which are placed in a freezer (-20°C) until the day of the determination.

Analytical procedures :

Determination of glycaemia :

The blood glucose is measured by the glucose oxidase method using a Boehringer kit.

- A quality control is effected by determining the standard values and control values.

Measurement of glucide assimilation :

(cf. Conard v. : Mesure de l'assimilation du glucose, bases théoriques et applications cliniques [Measurement of the assimilation of glucose, theoretical bases and clinical applications], "acta medica belgica" editions (1959)).

The rate of glycaemia disappearance following glucose loading is expressed by the angular coefficient K of the straight line $\log c = \log A - Kt$ obtained on semi-logarithmic paper entering the time (min) on the abscissa and the $\ln$ (glucose) on the ordinate. That coefficient is calculated for the glycaemia values corresponding to the

times between the 6th and the 30th minute after administration of the bolus. That calculation is carried out by a computer, using a linear regression program, after verification by graphical representation. That coefficient of glucide assimilation is considered as a constant, characteristic of a given subject.

Determination of insulinaemia :

- Immunoreactive plasma insulin (IRI) is determined by a PHARMACIA Phadeseph kit radio-immunological method, a solid-phase double antibody technique.

- The determination of the standards and of the samples is carried out in duplicate.

Preparation of the solutions :

- For the control experiment (reference test) :

Intraportal perfusion of 0.9 % isotonic sodium chloride (BIOSEDRA)

- For the intraportal perfusion of the pharmacological reactant :

A stock solution having 1 mg of base product per ml of distilled water is produced and is used to prepare the final solution (in 0.9 % NaCl).

Results

The results are given in the following Tables Ia and Ib.

Table I A

SDCD male rats 52 weeks	Basal insulinaemia $\mu\text{U/ml}$ % change	Peak insulinaemia $\mu\text{U/ml}$ % change	Insulinaemia 30 min after glucose $\mu\text{U/ml}$ % change	Glucose tolerance $\text{K} \times 10^{-2}$ %
Control	24.06 ± 3.03	57.4 ± 13.7	29.0 ± 3.7	2.72 ± 0.23
Benfluorex 7.5 $\mu\text{g/kg/min} \times 60 \text{ min}$	- 42% $p < 0.05$	- 5% NS	- 36% NS	+ 50% $p = 0.025$
Dimethyl biguanide 15 $\mu\text{g/kg/min} \times 60 \text{ min}$	inactive			
Product of Example 1				
0.25 $\mu\text{g/kg/min} \times 60 \text{ min}$	- 42% $p < 0.05$	0	- 21% NS	+ 3% NS
0.50 $\mu\text{g/kg/min} \times 60 \text{ min}$	- 6% $p < 0.001$	- 21% NS	- 69% $p < 0.001$	+ 40% $p = 0.025$
0.75 $\mu\text{g/kg/min} \times 60 \text{ min}$	- 25% $p = 0.05$	+ 10% NS	- 36% NS	+ 60% $p = 0.005$

An intraportal catheter and an intracardiac catheter (right auricle) are implanted in 52-week-old SDCD rats. After post-surgical recovery, the various groups of rats are subjected to an 18-hour fast. The rats are conscious during the experiment. The products are administered by intraportal perfusion for a period of 1 hour. An induced hyperglycaemia test is effected 30 minutes after starting the perfusion which is continued during the IVGTT.

TABLE IB
Insulin resistance induced by an intraportal perfusion of amylin
(In 12-week old rats)

	Basal Insulinaemia (μ U/ml)	Peak Insulinaemia (μ U/ml)	Insulinaemia 24 min after administration of glucose (μ U/ml)	Glucose tolerance $K \times 10^{-2}$
Control	5.93 $\pm$ 0.48	24.80 $\pm$ 1.86	8.86 $\pm$ 0.77	3.54 $\pm$ 0.24
Amylin perfusion	6.87 $\pm$ 0.77	23.54 $\pm$ 1.7	15.28 $\pm$ 1.90	1.71 $\pm$ 0.27
Perfusion of amylin + product of Example 1 (0.75 μ g/kg/min over a 60 min period)	8.26 $\pm$ 1.15	23.60 $\pm$ 2.17	15 $\pm$ 1.86	3.79 $\pm$ 0.38

**B. STUDY OF THE EFFECT OF A CHRONIC TREATMENT ADMINIS-
TERED PER OS TO 52-WEEK-OLD MALE SDCD RATS :**

1. Aim of the experiment

The tests are carried out on rats that have weight anomalies associated with hyperinsulism and hyperglyceridaemia.

The following are investigated :

- on the one hand the effect on those anomalies of a prolonged treatment with the product of Example 1 and with the reference substances, and
- on the other hand, the consumption of glucose by the adipose tissue is measured in the basal state and in the presence of insulin (10^{-9} M).

2. Protocol

2.1 Animals used

Rats identical to those in the acute treatment study are used (cf. paragraph A- 2.1 hereinabove), that is to say, male SDCD rats aged 52 weeks.

2.2 Methods

9 days before the beginning of the experiment (d_{-9}), the rats are divided into groups by stratified randomisation based on weight.

5 days before the beginning of the experiment (d_{-5}), the rats are conditioned by administering a gum solution.

On the first day of the experiment (d_1), the products to be tested are administered to the rats at different doses twice per day. More precisely, the products are administered suspended in gum between 09.00 and 10.00 hours and 16.00 and 17.00 hours for 14 days. The treated animals are weighed daily.

On day 15 the rats (fasted for 18 hours) are sacrificed by decapitation. The blood is collected

directly into a small cup. An aliquot (50 μ l) is transferred into 500 μ l of uranyl acetate for determining the glycaemia. An aliquot of 3 ml is transferred into a tube containing a solution of heparin (30 μ l per 1 ml of whole blood) and centrifuged to separate the plasma. Another aliquot of 300 μ l is transferred into a tube containing 15 μ l of a solution of EDTA/NaF for determining the lactates.

Epididymal adipose tissue is taken for metabolic study immediately after sacrifice.

For each animal, two fragments of right and left epididymal tissue are minced with scissors and distributed in 6 incubation flasks. Three of those flasks contain 500 μ l of medium and the others contain 500 μ l of medium to which porcine insulin (10^{-9} M) has been added; the production of CO₂ is thus measured in triplicate for each of the rats from each group.

2.3 Results

The results are given in the following Table II.

Table II

Treatment of 52-week-old male SDCCD rats	% weight change	Basal insulin- aemia $\mu\text{U/ml}$ % change	Glycaemia g/l % change	Glucose toler- ance $\text{K } 10^{-2}$ % change	Triglyceride g/l % change	Cholesterol g/l % change	Cerebral serotonin
Control	+ 0.4 %	32 ± 2.4	1.06 ± 0.05	3.01 ± 0.24	3.64 ± 0.57	1.1 ± 0.14	
Benfluorex 1 mg/kgx2	- 2% (NS)	- 10% NS	- 10% NS	+ 30% $p < 0.05$	- 43% $p = 0.025$	- 20% NS	Reduced
2.5 mg/kgx2	- 6% $p = 0.85$	- 16% NS	- 12% NS	+ 25% $p = 0.05$	- 44% $p = 0.05$	- 30% NS	Reduced
Product of Example 1							
0.5 mg/kgx2	- 1.4% $p = 0.005$	- 12% $p = 0.5$	- 5% NS	+ 26% (NS) $p = 0.088$	- 18 % (NS)	0	unchanged
1.0 mg/kgx2	- 1.9% $p = 0.005$	- 20% $p = 0.2$	+ 10% NS	+ 41% $p = 0.064$	- 38%	- 8% (NS)	unchanged
2.5 mg/kgx2	- 3.6% $p = 0.005$	- 41% $p = 0.005$	- 10% NS	+ 59% $p = 0.025$	- 50% $p = 0.01$	- 34% $p = 0.025$	unchanged

C- IN VITRO STUDY OF LDL OXIDATION

A comparative study between the product of Example 1 and the reference substances (benfluorex, dimethyl biguanide) with respect to in vitro LDL oxidation was carried out.

The results are given in the following Table III.

Table III

	<u>In vitro</u> LDL oxidation		Incorporation of oleate in the esters of cholesterol
	by copper	by monocytes	
Benfluorex	inactive at 10^{-4} M	inactive at 10^{-4} M	- 30% at 10^{-5} M
Dimethyl biguanide 10^{-4} M	inactive at 10^{-4} M	inactive at 10^{-4} M	inactive at 10^{-5} M
Product of Example 1	$IC_{50}=10^{-5}$ M	$IC_{50}=10^{-5}$ M	- 70% at 10^{-5} M

D- EXAMINATION INTO A HYPOTENSIVE EFFECT IN CONSCIOUS DOGS

The arterial pressure was measured by an external pressure band (sphygmomanometer) on the tail of a dog, before and after treatment with the product of Example 1 at a dose of 5 mg/kg p.o.

The results are given in the following Table IV.

Table IV

Product tested	Animal treated (number:n)	Decrease in arterial pressure (AP)	
		systolic AP	diastolic AP
Product of Example 1 (5 mg/kg p.o.)	dog (n=4)	-2.4x10 ³ Pa to -3.6x10 ³ Pa	-3x10 ³ Pa to -5x10 ³ Pa

E. CONCLUSION

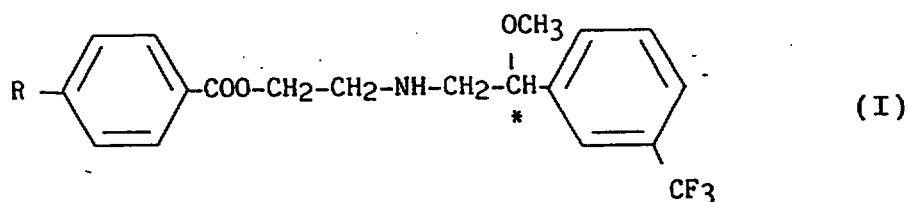
The results of the studies described above show the pharmacological and therapeutic value of the laevo-rotatory isomer of 2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethylamino]ethyl para-[2-(α -fluoren-9-ylacetyl amino)ethyl]benzoate hydrochloride (a particularly representative example of the compounds of the present invention) and the novelty and superiority thereof compared with reference substances known as being specifically adapted to the treatments in question.



CLAIMS

for the Contracting States : AT BE CH DE DK FR GB IT LI
LU NL PT SE

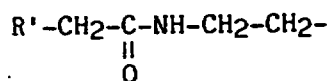
1. Ethanolamine benzoate compounds of the general
formula I :



wherein:

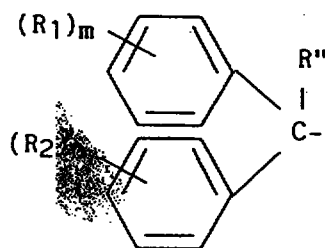
R represents :

- a hydrogen atom or
- a group of the formula:



wherein R' represents:

a) either a radical of the formula:



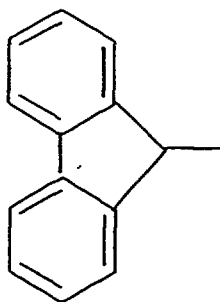
wherein:

R'' represents a hydrogen atom or an alkyl radical
containing from 1 to 5 carbon atoms in a straight or
branched chain,
each of R₁ and R₂, which may be identical or
different, represents a hydrogen atom or an alkyl or



alkoxy radical each having from 1 to 5 carbon atoms in a straight or branched chain, and each of m and n, which may be identical or different, represents 1, 2 or 3;

b) or a fluorenyl radical of the formula:



in the form of racemic compounds or enantiomers.

2. The physiologically tolerable salts of the compounds of claim 1 with appropriate acids.

3. l-2-[(β -methoxy- β -meta-trifluoromethylphenyl)-ethyl-amino]ethyl para-[2-(α -fluoren-9-ylacetyl-amino)-ethyl] benzoate hydrochloride.

4. d-2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethyl-amino]ethyl para-[2-(α -fluoren-9-ylacetyl-amino)ethyl] benzoate hydrochloride.

5. dl-2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethyl-amino]ethyl para-[2-(α -fluoren-9-ylacetyl-amino)ethyl] benzoate hydrochloride.

6. l-2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethyl-amino]ethyl para-[2-(benzhydrylacetyl-amino)ethyl] benzoate hydrochloride.

7. dl-2-[(β -methoxy- β -meta-trifluoromethylphenyl)ethyl-amino]ethyl benzoate hydrochloride.

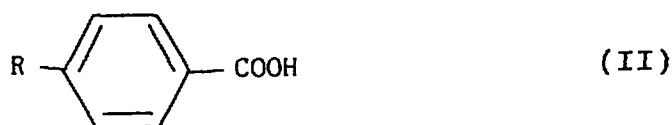


8. 1-2-[(β-methoxy-β-meta-trifluoromethylphenyl)ethyl-amino]ethyl benzoate hydrochloride.

9. d-2-[(β-methoxy-β-meta-trifluoromethylphenyl)ethyl-amino]ethyl benzoate hydrochloride.

10. Process for the preparation of the compounds of claim 1, characterised in that:

- the acid of the general formula II:

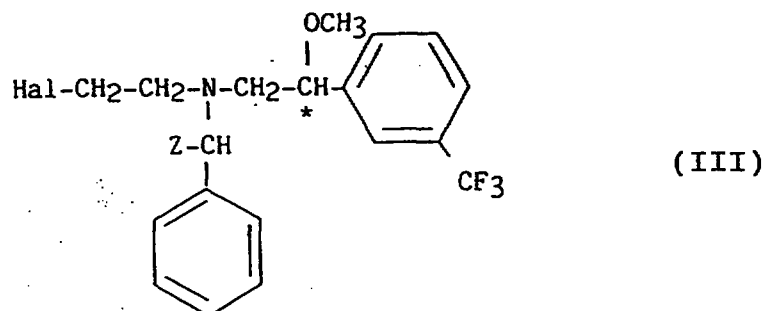


wherein R is as defined in claim 1, is converted into a salt of the general formula II':



wherein R is as defined above and M is an alkali metal or an alkaline earth metal;

- the latter is reacted with a halogenated compound of the general formula III:

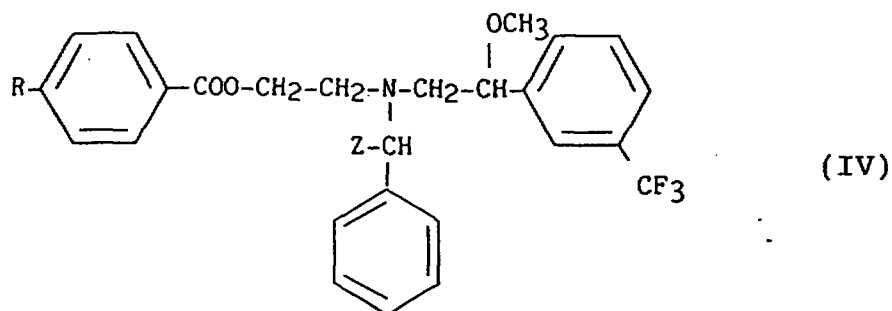


wherein

- Z represents a hydrogen atom or a methyl radical, and
- Hal represents a halogen atom;



- and the compound so obtained of the general formula IV:



wherein R and Z are as defined above, is debenzylated catalytically.

11. Pharmaceutical compositions comprising as active ingredient a compound according to claims 1 to 9 with one or more appropriate pharmaceutical excipients.

12. Pharmaceutical compositions according to claim 11 presented in a form suitable especially for the treatment of diabetes, obesity, insulin resistance syndrome, "Syndrome X", secondary or otherwise to hyperamylinemia involving a reduction in glucose tolerance, hyperinsulinaemia, dyslipaemia and hypertension, and for the treatment of hypertension in insulin-resistant subjects or subjects having one or more metabolic anomalies.