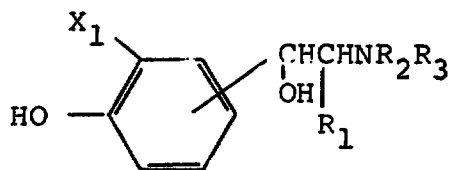


PHENETHANOLAMINE DERIVATIVES

2140800

This invention relates to phenethanolamine compounds having a stimulant action at β_2 -adrenoreceptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Certain phenethanolamine compounds are known to possess either stimulant or blocking actions at β -adrenoreceptors. For example, British Patent Specification No. 1200886 describes a group of such phenethanolamines of general structure:



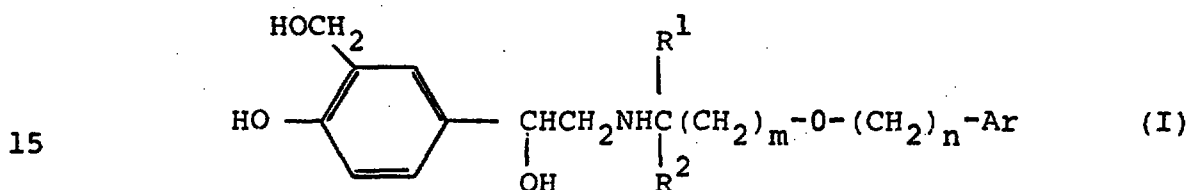
where, inter alia, X_1 is hydroxyalkyl, R_1 and R_2 is each a hydrogen atom, and R_3 is straight or branched C_{1-6} alkyl, aralkyl or aryloxyalkyl. One compound from within this particular group has been developed for clinical use. This is salbutamol [$(\alpha^1$ -tert-butylaminomethyl)-4-hydroxy-m-xylene- α^1, α^3 -diol; $X_1 = \text{CH}_2\text{OH}$, $R_1 = -\text{H}$; $R_2 = -\text{H}$; $R_3 =$ t-butyl, above] which at the present time is widely prescribed for the treatment of conditions such as bronchial asthma and chronic bronchitis. The success of salbutamol devolves from its profile of action, in particular its potency, coupled with a selective stimulant action at β_2 -adrenoreceptors.

All β_2 -stimulants currently used in clinical practice suffer from the disadvantage that they have a relatively short duration of action when administered by inhalation. A β_2 -stimulant with a relatively long duration of action would therefore offer a significant advance in the

treatment of bronchial asthma and related disorders.

In a search for new β -stimulants with advantageous properties, we have now found a novel group of phenethanolamine derivatives, which differ structurally from the group of compounds described in British Patent Specification No. 1200886, and which in our tests have shown a potent selective stimulant action at β_2 -adreno-receptors, and, in addition, have an advantageous profile of action.

Thus, the present invention provides compounds of the general formula (I)



wherein

20 m is an integer from 2 to 8 and

n is an integer from 1 to 7 with the proviso that the sum total of m + n is 4 to 12;

Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, C₁₋₃ alkyl or C₁₋₃ alkoxy groups, or by an alkylenedioxy group of formula -O(CH₂)_pO- where p is 1 or 2; and

25 R¹ and R² each represents a hydrogen atom or a C₁₋₃ alkyl group with the proviso that the sum total of carbon atoms in R¹ and R² is not more than 4;

30 and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

It will be appreciated that the compounds of general formula (I) possess one or two asymmetric carbon atoms, namely the carbon atom of the -CH- group and, when R¹ and

35 R² are different groups, the carbon atom to which these groups are attached.

12

The compounds according to the invention thus include all enantiomers, diastereoisomers and mixtures thereof, including racemates. Compounds in which the carbon atom in the -CH- group is in the R configuration are preferred.

5



In the general formula (I), the chain $\text{-(CH}_2\text{)}_m\text{-}$ may be, for example, $\text{-(CH}_2\text{)}_3\text{-}$, $\text{-(CH}_2\text{)}_4\text{-}$, $\text{-(CH}_2\text{)}_5\text{-}$, $\text{-(CH}_2\text{)}_6\text{-}$ or $\text{-(CH}_2\text{)}_7\text{-}$, and the chain $\text{-(CH}_2\text{)}_n\text{-}$ may be, for example, $\text{-(CH}_2\text{)}_2\text{-}$, $\text{-(CH}_2\text{)}_3\text{-}$, $\text{-(CH}_2\text{)}_4\text{-}$, $\text{-(CH}_2\text{)}_5\text{-}$ or $\text{-(CH}_2\text{)}_6\text{-}$.

10

Preferably the sum total of the number of carbon atoms in the chains $\text{-(CH}_2\text{)}_m\text{-}$ and $\text{-(CH}_2\text{)}_n\text{-}$ is 6 to 12 inclusive and may be, for example, 7, 8, 9 or 10. Compounds wherein the sum total of $m + n$ is 7, 8 or 9, are particularly preferred.

15

Preferred compounds of general formula (I) are those wherein m is 3 and n is 6, or m is 4 and n is 3, 4 or 5, or m is 5 and n is 2, 3, 4 or 5, or m is 6 and n is 2 or 3.

20

R^1 and R^2 , for example, may each be methyl, ethyl, propyl, or isopropyl groups except that if one of R^1 and R^2 is a propyl or isopropyl group, the other is a hydrogen atom or a methyl group. Thus, for example, R^1 may be a hydrogen atom or a methyl, ethyl or propyl group. R^2 , for example, may be a hydrogen atom or a methyl group.

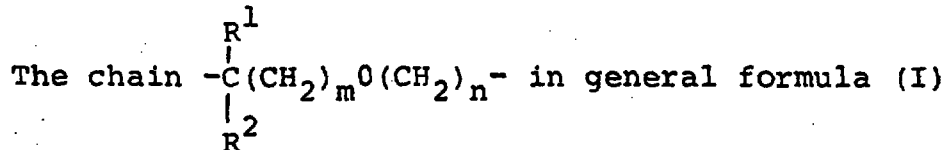
25

R^1 and R^2 are each preferably a hydrogen atom or a methyl group.

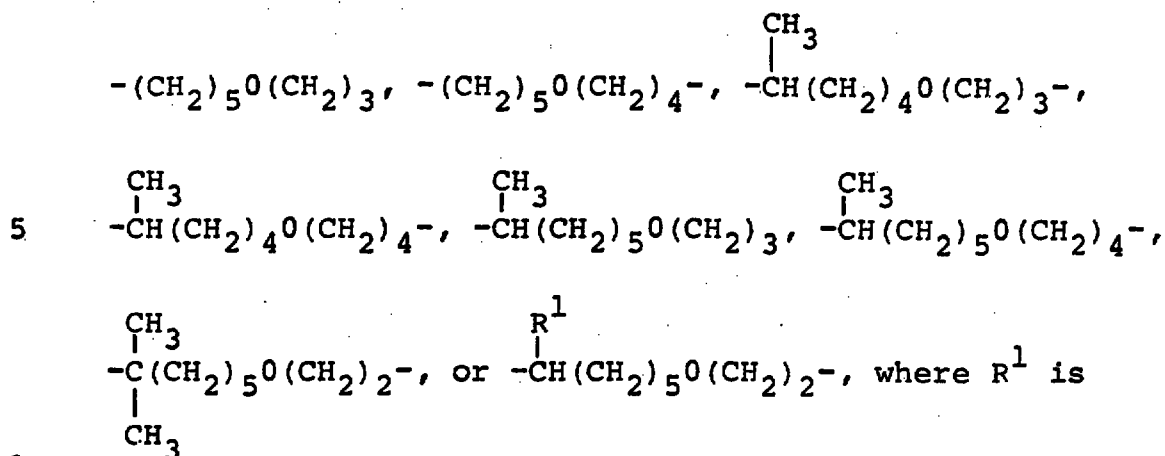
30

A preferred group of compounds is that wherein R^1 and R^2 are both hydrogen atoms. In another preferred group of compounds R^1 is a hydrogen atom and R^2 is a C_{1-3} alkyl group, particularly a methyl group. In yet another preferred group of compounds R^1 and R^2 are both methyl groups.

35



may be, for example $\text{-(CH}_2\text{)}_4^0(\text{CH}_2)_4\text{-}$, $\text{-(CH}_2\text{)}_5^0(\text{CH}_2)_2\text{-}$



methyl, ethyl or propyl.

Examples of the optional substituents which may be present on the phenyl group represented by Ar include bromine, iodine or, in particular, chlorine or fluorine atoms, or methyl, ethyl, methoxy or ethoxy groups. In general, Ar is preferably an unsubstituted phenyl group. According to another preference, Ar is a phenyl group substituted by one substituent, particularly a fluorine or chlorine atom or a methoxy or methyl group.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, maleates, tartrates, citrates, benzoates, 4-methoxybenzoates, 2- or 4-hydroxybenzoates, 4-chlorobenzoates, p-toluenesulphonates, methanesulphonates, ascorbates, salicylates, acetates, fumarates, succinates, lactates, glutarates, gluconates, tricarballates, hydroxy-naphthalenecarboxylates e.g. 1-hydroxy- or 3-hydroxy-2-naphthalenecarboxylates, or oleates. The compounds may also form salts with suitable bases. Examples of such salts are alkali metal (e.g. sodium and potassium), and alkaline earth metal (e.g. calcium and magnesium) salts.

The compounds according to the invention have a selective stimulant action at β_2 -adrenoreceptors, which

14

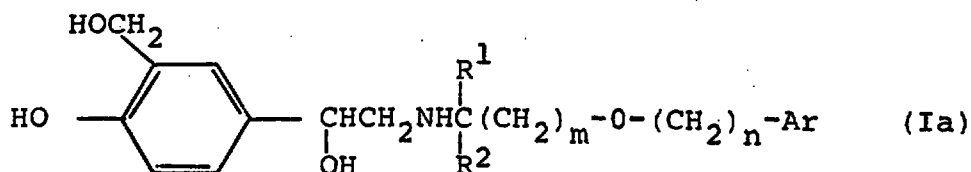
- 5 -

furthermore is of a particularly advantageous profile. The stimulant action was demonstrated in the guinea-pig, where compounds were shown to cause relaxation of PGF₂ α -contracted isolated trachea. In another test, 5 compounds of the invention were shown to afford protection against histamine-induced broncho-constriction when administered by inhalation or by an oral route in conscious guinea-pigs. In both tests, compounds according to the invention have shown a particularly long 10 duration of action. The selective action of compounds of the invention was demonstrated in the rat or guinea-pig where compounds were shown to have little or no effect on isolated rat or guinea-pig left atria (β_1 -adrenoreceptor tissues) at concentrations where 15 they cause relaxation of PGF₂ α - contracted isolated trachea. Compounds according to the invention have also been shown to inhibit the anaphylactic release of spasmagens and inflammagens from sensitised human tissues e.g. lung fragments.

20 The compounds according to the invention may be used in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

The compounds according to the invention may also 25 be used for the treatment of premature labour, depression and congestive heart failure, and are also indicated as useful for the treatment of inflammatory and allergic skin diseases, psoriasis, proliferative skin diseases, glaucoma, and in the treatment of conditions 30 in which there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

A particularly important group of compounds by virtue of the advantageously long duration of action they have shown in our tests, has the formula (Ia):



in which

R^1 and R^2 are as defined for general formula (I);

m is an integer from 3 to 6,

n is an integer from 2 to 6,

5 and Ar is phenyl or phenyl substituted by a methoxy or methyl group, or more preferably a fluorine or chlorine atom, and the physiologically acceptable salts and solvates thereof, in each instance the sum total of carbon atoms in the chains $-(CH_2)_m-$ and $-(CH_2)_n-$ being an
10 integer from 7 to 10 inclusive, in particular 7, 8 or 9.

A preferred group of compounds of formula (Ia) is that wherein R^1 and R^2 is each a hydrogen atom.

15 In another preferred group of compounds of formula (Ia) R^1 is a hydrogen atom or a methyl group and R^2 is a methyl group.

20 In a further group of compounds of formula (Ia) R^1 and R^2 each is a hydrogen atom and Ar is phenyl or phenyl substituted by a methoxy group, or more preferably a fluorine or chlorine atom.

25 A particularly preferred group of compounds has the formula (Ia) in which R^1 and R^2 each is a hydrogen atom or a methyl group, m is 4 or 5, n is 2, 3 or 4, and Ar is phenyl or phenyl substituted by a chlorine or fluorine atom or a methoxy or methyl group and the physiologically acceptable salts and solvates thereof.

Particularly important compounds are:

30 4-hydroxy- α^1 [[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

18

4-hydroxy- α^1 -[[[6-(3-phenylpropoxy)hexyl]amino]-methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

5 4-hydroxy- α^1 -[[[6-(2-phenylethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[5-(4-phenylbutoxy)pentyl]amino]-methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

10 4-hydroxy- α^1 -[[[1-methyl-6-(2-phenylethoxy)hexyl]-amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[1-methyl-5-(3-phenylpropoxy)pentyl]-amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

15 4-hydroxy- α^1 -[[[1-methyl-5-(4-phenylbutoxy)pentyl]-amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[1-ethyl-6-(2-phenylethoxy)hexyl]-amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

20 α^1 -[[[1,1-dimethyl-6-(2-phenylethoxy)hexyl]amino]-methyl-4-hydroxy-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

25 α^1 -[[[6-[2-(4-fluorophenyl)ethoxy]-1-methylhexyl]-amino]methyl]-4-hydroxy-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[6-[3-(4-methoxyphenyl)propoxy]-1-methylhexyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

30 4-hydroxy- α^1 -[[[1-methyl-6-(4-phenylbutoxy)hexyl]-amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

35 4-hydroxy- α^1 -[[[6-[2-(4-methylphenyl)ethoxy]hexyl]-amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

α^1 -[[[6-[2-(3-chlorophenyl)ethoxy]hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

5 4-hydroxy- α^1 -[[[6-[2-(4-methoxyphenyl)ethoxy]hexyl]-amino]-methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

α^1 -[[[6-[3-(4-fluorophenyl)propoxy]hexyl]amino]-methyl]-4-hydroxy-1,3-benzenedimethanol; and the physiologically acceptable salts thereof.

The compounds according to the invention may be formulated for administration in any convenient way. The invention therefore includes within its scope
5 pharmaceutical compositions comprising at least one compound of formula (I) or a physiologically acceptable salt or solvate thereof formulated for use in human or veterinary medicine. Such compositions may be presented for use with physiologically acceptable
10 carriers or excipients, optionally with supplementary medicinal agents.

The compounds may be formulated in a form suitable for administration by inhalation of insufflation, or for oral, buccal, parental, topical (including nasal)
15 or rectal administration. Administration by inhalation or insufflation is preferred.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from
20 pressurised packs, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined
25 by providing a valve to deliver a metered amount.

30

35

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For buccal administration the composition may take the form of tablets, drops or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration. Formulations for injections may be presented in unit dosage form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For topical administration the pharmaceutical composition may take the form of ointments, lotions or creams formulated in a conventional manner, with for example an aqueous or oily base, generally with the addition of suitable thickening agents and/or solvents. For nasal application, the composition may take the form of a spray, formulated for example as an aqueous solution or suspension or as an aerosol with the use of

10

a suitable propellant.

5 The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

Where pharmaceutical compositions are described above for oral, buccal, rectal or topical administration, these may be presented in a conventional manner associated with controlled release forms.

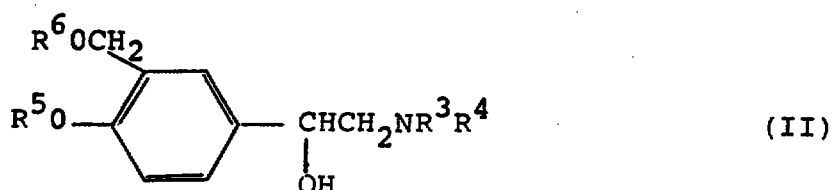
10 A proposed daily dosage of active compound for the treatment of man is 0.0005 mg to 100 mg, which may be conveniently administered in one or two doses. The precise dose employed will of course depend on the age and condition of the patient and on the route of
15 administration. Thus a suitable dose for administration by inhalation is 0.0005 mg to 10 mg, for oral administration is 0.02 mg to 100 mg, and for parenteral administration is 0.001 mg to 2 mg.

The compounds according to the invention may be prepared by a number of processes, as described in the following wherein m, n, Ar, R¹ and R² are as defined for general formula (I) unless otherwise specified.

In the general processes (1) to (3) described below the final step in the reaction may be the removal of a protecting group. Suitable protecting groups and their removal are described in general process (4) below.

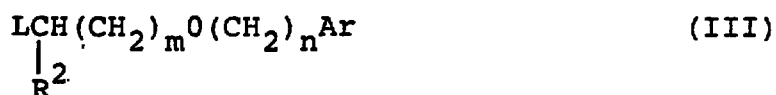
According to one general process (1), a compound of general formula (I) may be prepared by alkylation. Conventional alkylation procedures may be used.

Thus, for example, in one process (a), a compound of general formula (I) in which R¹ is a hydrogen atom may be prepared by alkylation of an amine of general formula (II):



(wherein R³, R⁵ and R⁶ each is a hydrogen atom or a protecting group and R⁴ is a hydrogen atom) followed by removal of any protecting group where present.

The alkylating reaction (a) may be effected using an alkylating agent of general formula (III):

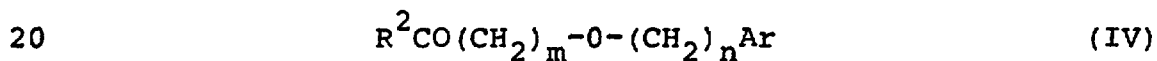


(wherein L represents a leaving group, for example a halogen atom such as chlorine, bromine or iodine, or a hydrocarbylsulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonyloxy).

The alkylation is preferably effected in the presence

of a suitable acid scavenger, for example, inorganic bases such as sodium or potassium carbonate, organic bases such as triethylamine, diisopropylethylamine or pyridine, or alkylene oxides such as ethylene oxide or propylene oxide. The reaction is conveniently effected in a solvent such as acetonitrile or an ether e.g. tetrahydrofuran or dioxan, a ketone e.g. butanone or methyl isobutyl ketone, a substituted amide e.g. dimethylformamide or a chlorinated hydrocarbon e.g. chloroform at a temperature between ambient and the reflux temperature of the solvent.

According to another example (b) of an alkylation process, a compound of general formula (I) in which R^1 represents a hydrogen atom may be prepared by alkylation of an amine of general formula (II), as previously defined except that R^4 is a hydrogen atom or a group convertible thereto under the reaction conditions, with a compound of general formula (IV):



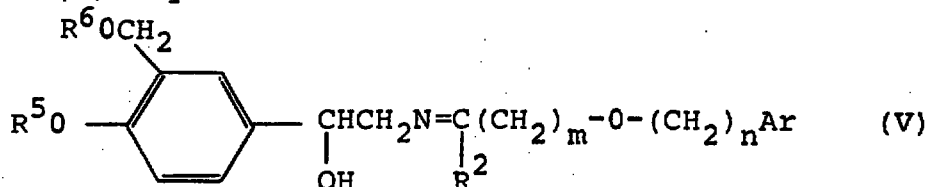
in the presence of a reducing agent, followed when necessary by removal of any protecting groups.

Examples of suitable groups represented by R^4 which are convertible into a hydrogen atom are arylmethyl groups such as benzyl, α -methyl benzyl and benzhydryl.

Suitable reducing agents include hydrogen in the presence of a metal catalyst such as platinum, platinum oxide, palladium, Raney nickel or rhodium, on a support, such as charcoal, using an alcohol, e.g. ethanol or an ester e.g. ethyl acetate or an ether e.g. tetrahydrofuran, or water, as reaction solvent, or a mixture of solvents, e.g. a mixture of two or more of those just described, at normal or elevated temperature and pressure, for example from 20 to 100°C and from 1 to 10 atmospheres.

Alternatively when one or both of R^3 and R^4 are hydrogen atoms, the reducing agent may be a hydride such as diborane or a metal hydride such as sodium borohydride, sodium cyanoborohydride or lithium aluminium hydride. Suitable solvents for the reaction with these reducing agents will depend on the particular hydride used, but will include alcohols such as methanol or ethanol, or ethers such as diethyl ether or tert-butyl methyl ether, or tetrahydrofuran.

When a compound of formula (II) wherein R^3 and R^4 are both hydrogen atoms is used, the intermediate imine of formula (V) may be formed:



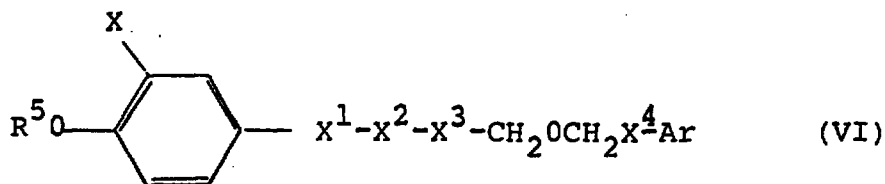
(wherein R^6 and R^5 are as defined for formula (II)).

Reduction of the imine using the conditions described above, followed, where necessary, by removal of any protecting groups, gives a compound of general formula (I).

Where it is desired to use a protected intermediate of general formula (II) it is particularly convenient to use hydrogen and a metal catalyst as described above with protecting groups R^3 , R^5 and R^6 which are capable of being converted to a hydrogen atom under these reducing conditions, thus avoiding the need for a separate deprotection step. Suitable protecting groups of this type include arylmethyl groups such as benzyl, benzhydryl and α -methylbenzyl.

In a second general process (2), a compound of general formula (I) may be prepared by reduction. Thus, for example, a compound of general formula (I) may be prepared by

reducing an intermediate of general formula (VI):



10 (wherein R^5 is as defined for general formula (II) and at least one of X , X^1 , X^2 , X^3 and X^4 represents a reducible group and the other(s) take the appropriate meaning as follows, which is X is CH_2OR^6 , X^1 is $-CH(OH)-$, X^2 is $-CH_2NR^3$, X^3 is $-CR^1R^2(CH_2)_{m-1}$ and X^4 is $-(CH_2)_{n-1}$ followed where necessary by removal of any protecting groups.

15 Suitable reducible groups include those wherein X is a group $-CO_2R^7$ (wherein R^7 represents a hydrogen atom, or an alkyl, aryl or aralkyl group) or $-CHO$, X^1 is a group $-C=O$, X^2 is a group $-CH_2NY-$ (wherein Y represents a group convertible to hydrogen by catalytic hydrogenation, for example an arylmethyl group such as benzyl, benzhydryl or α -methylbenzyl), or an imine ($-CH=N-$) group or a group $-CONH-$, and X^3 is a group $-CO(CH_2)_{m-1}$, or a group $-CR^1R^2X^5$ where X^5 is C_{2-7} alkenylene or C_{2-7} alkynylene, or X^2-X^3- is a group $-CH_2N=CR^2(CH_2)_{m-1}$, and X^4 is C_{2-6} alkenylene or C_{2-6} alkynylene. In one convenient aspect of the reduction process, the group R^5 may be a group convertible to hydrogen under the reducing conditions employed and may be for example an arylmethyl group such as benzyl, benzhydryl or α -methylbenzyl.

20
25
30 The reduction may be effected using reducing agents conveniently employed for the reduction of carboxylic acids, aldehydes, esters, ketones, imines, amides, ethylenes, acetylenes and protected amines. Thus, for example, when X in general formula (VI) represents a group $-CO_2R^7$ or $-CHO$ this may be reduced to a group $-CH_2OH$ using a hydride such as diborane or a complex metal hydride such as lithium

aluminium hydride, sodium bis(2-methoxyethoxy)aluminium hydride, sodium borohydride, diisobutylaluminium hydride or lithium triethylborohydride in a solvent such as an ether, e.g. tetrahydrofuran or diethyl ether, or a halogenated hydrocarbon e.g. dichloromethane at a temperature from 0°C to the reflux.

When X^1 in general formula (VI) represents a $-C=O$ group this may be reduced to a $-CH(OH)-$ group using hydrogen in the presence of a metal catalyst as previously described for process (1) part (b). Alternatively, the reducing agent may be, for example, a hydride such as diborane or a metal hydride such as lithium aluminium hydride, sodium bis(2-methoxyethoxy)aluminium hydride, sodium borohydride or aluminium hydride. The reaction may be effected in a solvent, where appropriate an alcohol e.g. methanol or ethanol, or an ether such as tetrahydrofuran, or a halogenated hydrocarbon such as dichloromethane.

When X^2 in general formula (VI) represents a CH_2NY group or the group $-CH=N-$, or $-X^2-X^3$ represents $-CH_2N=CR^2(CH_2)_{m-1}$ this may be reduced to a $-CH_2NH-$ or $-CH_2NHCHR^2(CH_2)_{m-1}$ group using hydrogen in the presence of a metal catalyst as previously described for process (1) part (b). Alternatively, when X^2 or $-X^2-X^3$ is the group $-CH=N-$ or $-CH_2N=CR^2(CH_2)_{m-1}$ this may be reduced to a $-CH_2NH-$ or $CH_2NHCHR^2(CH_2)_{m-1}$ group using a reducing agent and conditions as just described for the reduction of X^1 when this represents a $-C=O$ group.

When X^2 or X^3 in general formula (VI) represents a $-CONH-$ or $-CO(CH_2)_{m-1}$ group this may be reduced to a group $-CH_2NH-$ or $-CH_2(CH_2)_{m-1}$ using a hydride such as diborane or a complex metal hydride such as lithium aluminium hydride or sodium bis(2-methoxyethoxy)aluminium hydride in a solvent such as an ether, e.g. tetrahydrofuran or diethyl ether.

When X^3 in general formula (VI) represents a group $-CR^1R^2X^5-$ this may be reduced to a group $-CR^1R^2(CH_2)_{m-1}-$ using hydrogen in the presence of a catalyst such as platinum or palladium on a support such as charcoal in a solvent such as an alcohol, e.g. ethanol or methanol, or an ester, e.g. ethyl acetate, or an ether, e.g. tetrahydrofuran, at normal or elevated temperature and pressure.

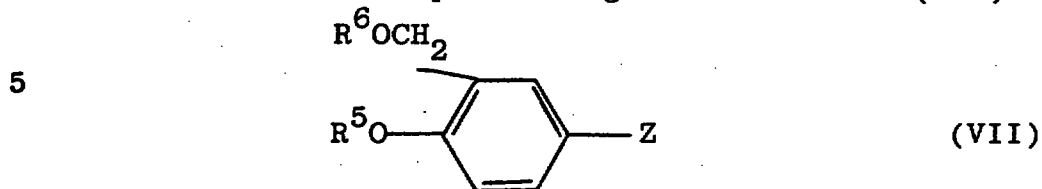
When X^4 is C_{2-6} alkenylene or C_{2-6} alkynylene this may be reduced to $-(CH_2)_{n-1}-$ using hydrogen and a catalyst as just described. In this aspect of the reduction process, suitable starting materials of formula (VI) include those in which $CR^1R^2X^5$ and/or X^4 each contains one $-C=C-$ or $-C\equiv C-$ linkage. Where both contain unsaturated linkages, these may be the same or different.

Particular examples of the reduction process are those in which a compound of general formula (I) in which $-(CH_2)_m-$ represents $-(CH_2)_5-$ is prepared from a corresponding compound in which $-(CH_2)_m-$ represents $-CH=CH(CH_2)_3-$, $-C\equiv C(CH_2)_3-$, $-(CH_2)_2CH=CHCH_2-$ or $-(CH_2)_2C\equiv CCH_2-$. In further examples, a compound of general formula (I) in which $-(CH_2)_n-$ represents $-(CH_2)_4-$ or $-(CH_2)_3-$ may be prepared by reduction of a corresponding compound of general formula (I) in which $-(CH_2)_n-$ represents $-CH_2CH=CH-CH_2-$, $-CH_2C\equiv CCH_2-$, $-CH_2CH_2CH=CH-$, $-CH_2CH_2C\equiv C-$, $-CH_2CH=CH$ or $-CH_2C\equiv C-$.

In the reduction processes just described the groups X and R^5 in a compound of formula (VI) may together conveniently represent a group $R^8 \begin{array}{c} \diagup \\ \diagdown \end{array} OCH_2-$ (where

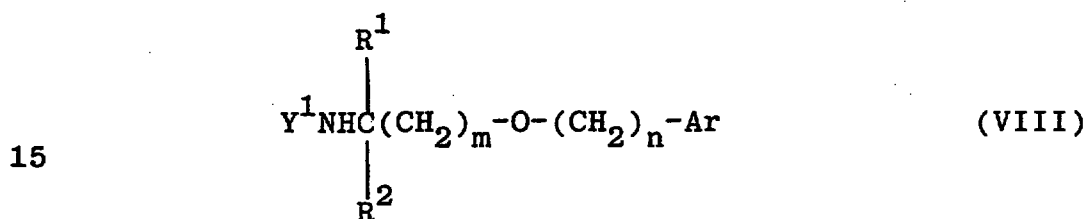
R^8 and R^9 , which may be the same or different, each represents a hydrogen atom or an alkyl or aryl group. After the reduction is complete, cleavage of this group using e.g. a dilute acid in a solvent such as water at normal temperature yields a compound of formula (I).

According to a further general process (3), a compound of general formula (I) may be obtained by reaction of a compound of general formula (VII):



(wherein Z represents a group $-\text{CH}-\text{CH}_2$ or $-\text{CHCH}_2\text{L}$, and OH

10 L, R^5 and R^6 are as previously defined, with an amine of general formula (VIII):



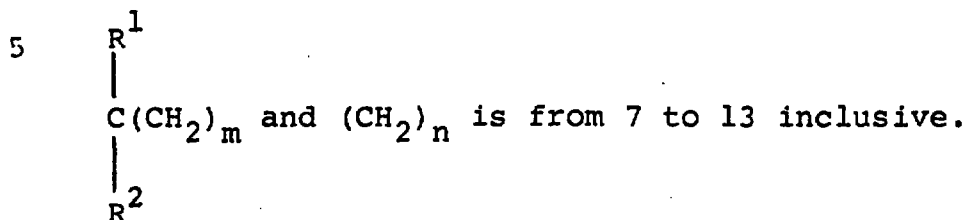
(wherein Y^1 is a hydrogen atom or a group convertible thereto by catalytic hydrogenation) followed by removal of any protecting groups where present, as described hereinafter.

Suitable Y^1 groups convertible into a hydrogen atom include arylmethyl groups such as benzyl, benzhydryl or α -methylbenzyl.

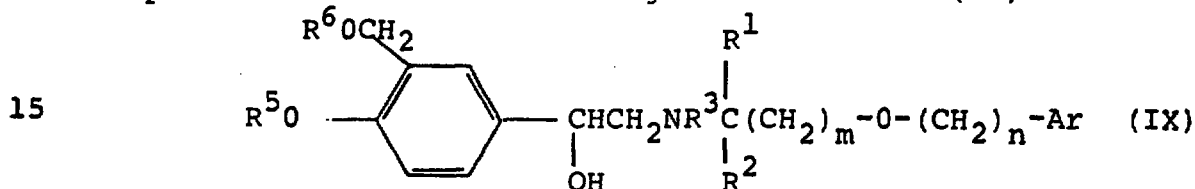
25 The reaction may be effected in the presence of a suitable solvent for example an alcohol, such as ethanol, a halogenated hydrocarbon e.g. chloroform, a substituted amide e.g. dimethylformamide or an ether such as tetrahydrofuran or dioxan at a temperature from ambient to the reflux, optionally in the presence of a base such as an organic amine e.g. diisopropyl-ethylamine or an inorganic base such as sodium carbonate.

30 The intermediate amines of general formula (VIII) and their acid addition salts are novel compounds and form the subject of our patent application. 86 12357....
35 (Publication No. 2176476A). A particularly

preferred group of amines of general formula (VIII) are those in which the total number of carbon atoms in the groups represented by



10 In another general process (4), a compound of general formula (I) may be obtained by deprotection of a protected intermediate of general formula (IX):



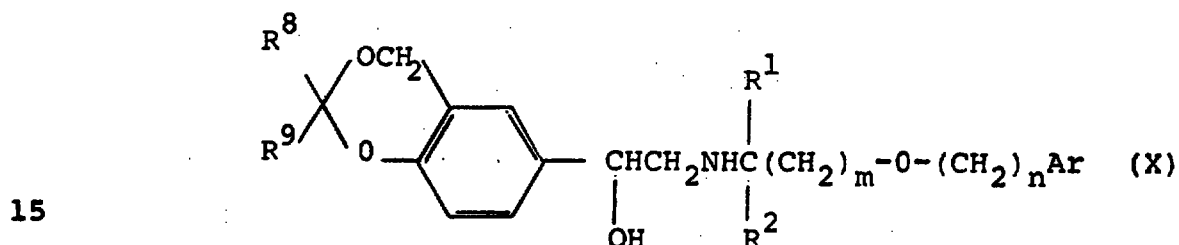
20 (wherein R^3 , R^5 and R^6 are as previously defined except that at least one of R^3 , R^5 and R^6 is a protecting group).

The protecting group may be any conventional protecting group, for example as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973). Examples of suitable hydroxyl protecting groups represented by R^5 and R^6 are aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by R^3 are aralkyl groups such as benzyl, α -methylbenzyl, diphenylmethyl or triphenylmethyl and acyl groups such as trichloroacetyl or trifluoroacetyl.

35 The deprotection to yield a compound of general formula (I) may be effected using conventional techniques. Thus, for example, when R^5 , R^6 and/or R^3 is an aralkyl group this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

When R^5 and/or R^6 is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by R^3 may be removed by hydrolysis, for example with a base such as sodium hydroxide, or
 5 a group such as trichloroacetyl, or trifluoroacetyl may be removed by reduction with, for example, zinc and acetic acid.

In a particular embodiment of the deprotection process (4), R^5 and R^6 may together represent a
 10 protecting group as in a compound of general formula (X):



(wherein R^8 and R^9 are as previously defined).

A compound of general formula (I) may be obtained by treatment of a compound of formula (X) with a dilute
 20 acid, for example hydrochloric acid in a solvent such as water or an alcohol such as ethanol at normal or elevated temperature.

In the general processes (1) to (4) described above, the compound of formula (I) obtained may be in
 25 the form of a salt, conveniently in the form of a physiologically acceptable salt. Where desired such salts may be converted to the corresponding free base using conventional methods.

Physiologically acceptable salts of the compounds
 30 of general formula (I) may be prepared by reacting a compound of general formula (I) with an appropriate acid or base in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol e.g. methanol, ethanol or iso-propanol.

35 Physiologically acceptable salts may also be

prepared from other salts, including other physiologically acceptable salts, of the compounds of general formula (I), using conventional methods.

When a specific enantiomer of a compound of general formula (I) possessing one asymmetric carbon atom is required, this may be obtained by resolution of a mixture of enantiomers of a corresponding compound of general formula (I) using conventional methods.

Thus, in one example an appropriate optically active acid may be used to form salts with a mixture of enantiomers of a compound of general formula (I). The resulting mixture of isomeric salts may be separated, for example by fractional crystallisation, into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

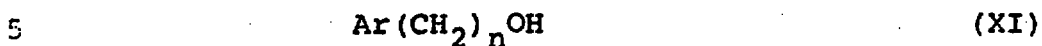
Alternatively, enantiomers of a compound of general formula (I) possessing one asymmetric carbon atom may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

When a compound of formula (I) contains two asymmetric carbon atoms, specific diastereoisomers or enantiomers thereof may be obtained from an appropriate asymmetric starting material or by separation of an appropriate mixture of isomers using techniques just described

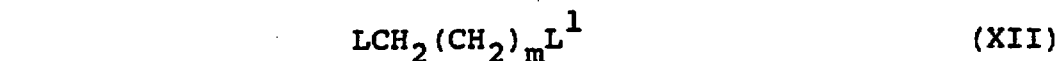
Suitable methods for preparing the intermediate compounds used in the above general processes are described below. In the following discussion, Ar, m, n, R^1 , R^2 , R^3 , R^4 , Y and Y^1 , Z, X, X^1 , X^2 , X^3 and L are as defined above except where otherwise indicated.

"Hal" represents a halogen atom. Where an intermediate with protected hydroxyl and/or amino groups is desired, this may be obtained using conventional protection methods, for example those described by McOmie (see process (4) above).

The intermediate compounds of general formula (III) may be prepared by reaction of an alcohol of general formula (XI):



with a disubstituted alkane of general formula (XII):



(wherein L^1 is as previously defined for L, and L and L^1 may be the same or different), optionally in a solvent such as tetrahydrofuran or dimethylformamide at a temperature up to the boiling point. The reaction is effected by first generating the anion of the alcohol of general formula (XI) by adding for example sodium, sodium hydride or a strong base such as sodium hydroxide and a phase transfer catalyst such as tetrabutylammonium sulphate. Optionally a solvent such as dichloromethane or tetrahydrofuran may be added. The reaction can be carried out at ambient or elevated temperatures.

20 The compounds of general formulae (XI) and (XII) are either known compounds or they may be made by methods analogous to those used for the preparation of the known compounds.

Intermediate aldehydes of general formula (IV) (in which R^2 represents a hydrogen atom) may be prepared by oxidation of an alcohol of general formula (XIII):

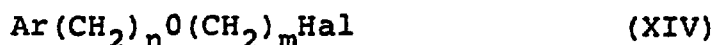


with an oxidising agent such as pyridinium chlorochromate in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane. The alcohols of formula (XIII) may be prepared from the compounds of formula (III),

24

for example by reaction with sodium acetate, followed by hydrolysis of the product with for example sodium hydroxide.

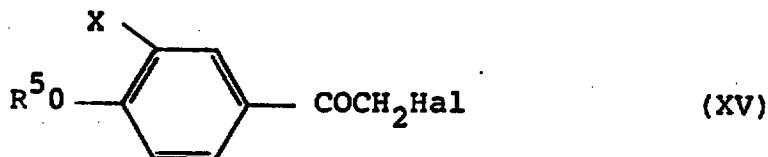
Intermediate ketones of formula (IV) (in which R^2 represents an alkyl group), may be prepared by reaction of a Grignard complex of a halide of formula (XIV):



with an acyl halide $R^2\text{COCl}$ or anhydride $(R^2\text{CO})_2\text{O}$ in a solvent such as an ether, for example diethyl ether or tetrahydrofuran. The halides of formula (XIV) may be prepared by alkylation of an alcohol of formula (XI) with a disubstituted alkane of formula $\text{L}(\text{CH}_2)_m\text{Hal}$ as described above for the preparation of compounds of formula (III). Compounds $\text{L}(\text{CH}_2)_m\text{Hal}$ are either known compounds or they may be made by methods analogous to those used for preparation of the known compounds.

Intermediate compounds of general formula (VI) for use in general process (2) may be prepared by a number of processes.

Thus for example intermediates of general formula (VI) in which X^1 is a group $-\text{C}=\text{O}$ may be prepared from a haloketone of formula (XV):



by reaction with an amine of general formula (VIII). The reaction may be effected in a cold or hot solvent, for example tetrahydrofuran, tert-butyl methyl ether, dioxan, chloroform, dimethylformamide, acetonitrile or a ketone such as butanone or methylisobutylketone,

or an ester, for example ethyl acetate preferably in the presence of a base such as diisopropylethylamine, sodium carbonate or other acid scavenger such as propylene oxide. When $-(CH_2)_m$ and/or $-(CH_2)_n$ in the amine of formula (VIII) contains an unsaturated linkage, an intermediate of formula (VI) in which X^3 is $-CR^1R^2X^5-$ and/or X^4 is C_{2-6} alkenylene or C_{2-6} alkynylene may be obtained in this process.

Intermediates of general formula (VI) in which X^1 is a group $-C=O$ may be reduced to the corresponding intermediate in which X^1 is a group $-CH(OH)-$ using for example a metal hydride such as sodium borohydride in a solvent e.g. ethanol.

Iminoketones of general formula (VI) i.e. in which X^2 is a group $-CH=N-$ may be obtained from a phenylglyoxal derivative of formula (XVI):

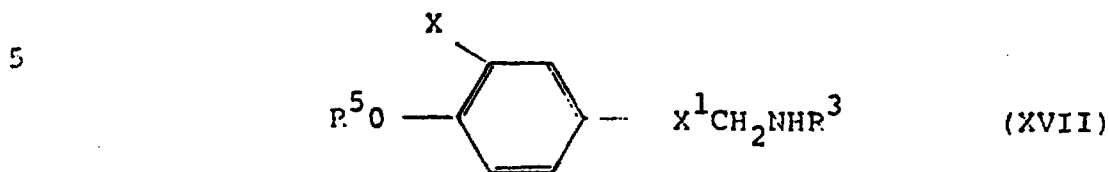


by reaction with an amine of formula (VIII) in which Y^1 represents a hydrogen atom, in a solvent such as benzene, tetrahydrofuran or an alcohol e.g. ethanol at temperatures up to the reflux. The phenylglyoxal derivatives of formula (XVI) may be obtained from a haloketone of formula (XV) by the action of a dialkylsulphoxide such as dimethylsulphoxide.

When X and R^5 in the glyoxal of formula (XVI) together represent a group $R^8 \begin{array}{c} \diagup \\ \diagdown \end{array} OCH_2-$ the iminoketone

of formula (VI) so formed using this process subsequently may be reduced using a metal hydride such as sodium borohydride in a solvent such as ethanol to yield a compound of formula (X).

Intermediates of general formula (VI) in which X^3 is a group $-CO(CH_2)_m-$ may be prepared by acylation of an amine of formula (XVII):



10 using an ester or an activated derivative of an acid of formula (XVIII):

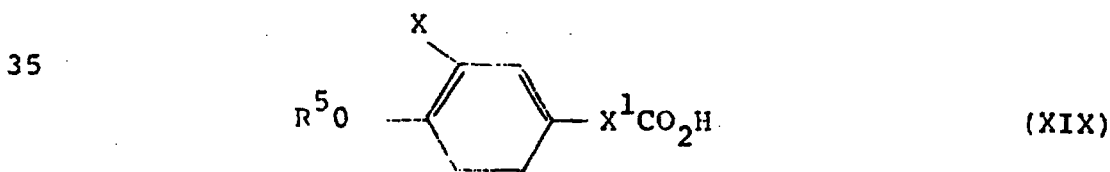


15 Suitable activated derivatives include the acid chloride, an anhydride or imidazolid. The reaction may be optionally carried out in a solvent such as tetrahydrofuran, benzene or chloroform, optionally in the presence of a base such as pyridine or triethylamine. The acids (XVIII) may be used directly if a coupling agent such as dicyclohexylcarbodiimide is added.

20 Acids of formula (XVIII) may be obtained by treatment of an alcohol of general formula (XIII) with a suitable oxidising agent, for example pyridinium dichromate in a solvent such as dimethylformamide.

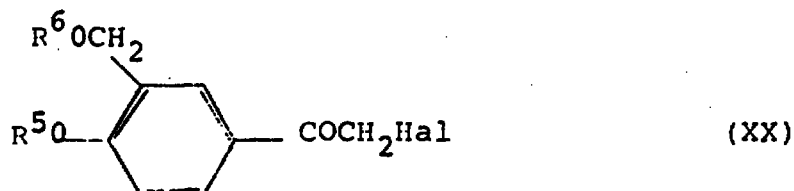
25 Intermediates of formula (VI) in which $-X^2-X^3-$ represents $-CH_2N=CR^2(CH_2)_{m-1}$ may be obtained by reaction of an amine of formula (XVII) in which R^3 is a hydrogen atom with a compound of formula (IV) in a solvent such as acetonitrile.

30 Intermediates of formula (VI) in which X^2 is $-CONH-$ may be prepared by reaction of an amine of formula (VIII) with an acid of formula (XIX)



in the presence of a coupling agent such as dicyclohexylcarbodiimide.

Compounds of formula (VII) in which Z represents a group $\begin{array}{c} \text{---CHCH}_2\text{Hal} \\ | \\ \text{OH} \end{array}$ may be prepared from a haloketone of formula (XX):



by reduction using for example a metal hydride such as sodium borohydride in a solvent such as ethanol.

The halogen atom may be displaced to yield other compounds of general formula (VII) in which Z is a group $\begin{array}{c} \text{---CHCH}_2\text{L} \\ | \\ \text{OH} \end{array}$ where L is a leaving group other than a halogen atom.

Compounds of formula (VII) wherein Z represents $\begin{array}{c} \text{---CH---CH}_2 \\ \diagdown \quad / \\ \text{O} \end{array}$ may be prepared from the corresponding compound in which Z is $\begin{array}{c} \text{CHCH}_2\text{L} \\ | \\ \text{OH} \end{array}$ by treatment with a base, for example an amine, which may be for example a compound of general formula (VIII), or an inorganic base such as sodium hydroxide in a solvent such as ethanol.

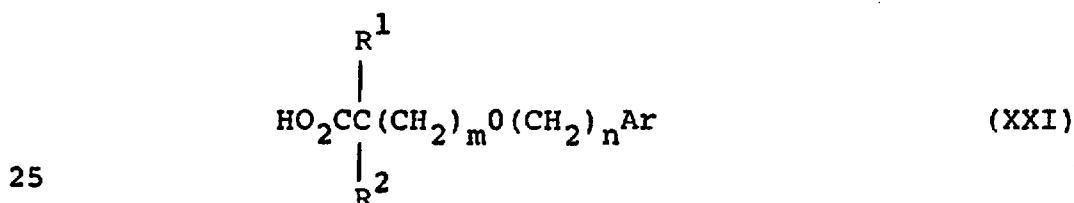
The amines of general formula (VIII) in which γ^1 is a group convertible to hydrogen and R^1 and R^2 are both hydrogen atoms may be prepared by reaction of a compound of general formula (III) in which R^2 is a hydrogen atom with an amine YNH_2 . The reaction may be effected in the absence or presence of a solvent such as a ketone e.g. butanone or methyl isobutyl ketone, an ether e.g. tetrahydrofuran or a substituted amide e.g. dimethylformamide, optionally in the presence of a base such as sodium carbonate or an organic amine e.g.

triethylamine or N,N-diisopropylethylamine at temperatures between 0°C and the reflux. Where desired, subsequent reaction with hydrogen in the presence of a metal catalyst such as platinum in a solvent such as an alcohol e.g. ethanol yields a compound of formula (VIII) where Y¹ is a hydrogen atom.

Alternatively, amines of formula (VIII) in which R¹ is a hydrogen atom may be prepared by reductive alkylation of an amine Y¹NH₂, in which Y¹ is a group convertible into hydrogen with a compound of formula (IV), if necessary followed by conversion of the Y¹ group to a hydrogen atom as just described.

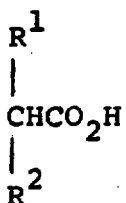
The reaction may be effected by hydrogen in the absence or presence of a solvent such as an alcohol, e.g. ethanol with a metal catalyst such as platinum or palladium, or by use of a complex metal hydride such as sodium borohydride or sodium cyanoborohydride in an alcohol, for example, ethanol.

A process to afford amines of formula (VIII) in which R¹ and R² can both be alkyl groups uses an acid of formula (XXI):



The acid is converted via its chloride and azide by a Curtius reaction into the amine of formula (VIII) in which Y¹ is a hydrogen atom. The reaction involves thermal rearrangement of the azide into an isocyanate, which is hydrolysed by treatment with an inorganic base, for example aqueous sodium hydroxide optionally in a solvent such as ethanol.

The acids of formula (XXI) can be prepared by alkylation of the acid (XXII):



(XXII)

5

via its dilithio derivative with an alkylating agent of formula (XIV) in a solvent such as an ether, for example tetrahydrofuran at low temperature such as 0°C to ambient.

10

The compounds of formulae (II), (IV), (XVII), (XIX), (XX), (XXI) and (XXII) are either known compounds or may be obtained by analogous methods to those used for the preparation of the known compounds.

The following examples illustrate the invention.

Temperatures are in °C. Thin layer chromatography (T.l.c.) was carried out over SiO₂ and 'dried' refers to drying using magnesium sulphate, except where otherwise stated.

- 5 The following abbreviations are used: DMF - dimethylformamide; THF - tetrahydrofuran; EA - ethyl acetate; ER - diethyl ether; CX - cyclohexane; HX - hexane; BR - brine; flash column chromatography [FCS] - on silica [FCTS] - on triethylamine-deactivated silica; T.l.c.EN - t.l.c. over triethylamine-deactivated SiO₂.
- 10 Eluants used for chromatography and t.l.c. are:
 [A] - CX-ER(19:1); [B] - CX-ER(9:1); [C] - ER-CX-triethylamine (60:40:1); [D] - CX-ER(1:4); [E] - CX-EA(19:1); [F] - CX-ER(4:1); [G] - ER; [H] - EA; [I] - EA-methanol-triethylamine(9:1:0.1); [J] - CX-ER(7:3); [K] - CX-EA(9:1); [L] - CX-ER (3:1); [M] -
 15 EA-CH₃OH-NH₃(9:1:0.1); [N] - EA-CH₃OH(9:1); [O] - CX-ER(1:1).

Intermediate 1 is α^1 -(aminomethyl)-4-hydroxy-1,3- benzenedimethanol.

Intermediate 2

20 [2-[(6-Bromohexyl)oxy]ethyl]benzene

- A mixture of phenethyl alcohol (20g), 1,6-dibromohexane (195g) and tetrabutylammonium bisulphate (3.0g) in 50% w/v NaOH solution (100ml) was heated at 65-70° for 4h. The cooled reaction mixture was poured into H₂O (400ml) and extracted with CX (2x300ml). The dried extracts
 25 were evaporated in vacuo to give a yellow liquid which was purified by distillation under reduced pressure to give the title compound as a colourless liquid (26g) b.p. 110°/0.1mm. T.l.c. (EA) Rf 0.62.

Intermediate 3

30 [4-[(6-Bromohexyl)oxy]butyl]benzene

- NaH (46% dispersion in oil; 6.5g) was added portionwise to a solution of 4-phenyl-1-butanol (15.0g) and 1,6-dibromohexane (48.8g) in THF (200ml) under nitrogen. The resulting suspension was refluxed for 27h and treated with H₂O (80ml). The mixture was extracted with ER (2x200ml)
 35 and the dried extract was evaporated to leave an orange oil. The oil was purified on a column of silica (800ml) [A] to give a yellow oil which on distillation gave the title compound as a colourless oil (15.0g) b.p. 90-95°/0.1mmHg.

Intermediate 4 is α^1 -[[bis(phenylmethyl)amino]methyl]-1,3-benzenedimethanol.

Intermediate 5

5 6-(4-Phenylbutoxy)hexan-1-ol

A mixture of Intermediate 3 (10g) sodium acetate trihydrate (34.8g), H₂O (25ml) and trioctylpropyl NH₄Cl (2g) was stirred vigorously on a steam bath for 2.5h. 2M NaOH (50ml) and ethanol (50ml) were added to the cooled mixture which was then stirred at RT for 30min. The mixture was
10 diluted with BR (200ml), extracted with ER and the organic phase washed with H₂O (200ml), BR (200ml), dried and evaporated under reduced pressure to give the title alcohol as a yellow oil, (7.16g).
T.l.c. [G] Rf 0.73.

15 Intermediate 6

6-(4-Phenylbutoxy)hexanal

Pyridinium chlorochromate (4.1g) was added to a solution of Intermediate
5 (3g) in CH₂Cl₂ (25ml). The mixture was stirred at RT for 0.75h,
trituated with ER (75ml), and filtered through Hyflo_(R.T.M.). The filtrate was
20 evaporated and the residue dissolved in ER (50ml), filtered through silica and evaporated under reduced pressure to give a pale yellow oil .
Purification by [FCS] (120g) [B] gave the title compound as a colourless oil (1.65g). T.l.c. [B] Rf 0.3.

25 Intermediate 7

N-[6-(4-Phenylbutoxy)hexyl]benzenemethanamine

A solution of benzylamine (16.64g) and Intermediate 3 (11.27g) in THF (45ml) was kept at RT for 4 days, diluted with ER (450ml), filtered and the filtrate evaporated to give a colourless oil which was purified by
30 [FCS] [C] to give the title compound (9.94g) as a colourless oil.
Analysis Found: C,81.60;H,10.1;N,4.2. C₂₃H₃₃NO requires C,81.35;H,9.80;N,4.15%.

Intermediate 8

35 1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]ethanone

A solution of 2-bromo-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone (1g), Intermediate 7, (1.4g) and N,N-diisopropylethylamine (0.8g) in THF

(10ml) was kept at 23⁰ for 3 days. The mixture was diluted with ER (60ml), washed with 8% NaHCO₃ (50ml) and BR (50ml), dried and evaporated in vacuo to give an oil. Purification by [FCS] (40g) [D] afforded the title compound as a viscous yellow oil (1.68g).

5 T.l.c. [D] Rf 0.42.

Intermediate 9

2-Bromo-1-(2,2-dimethyl-1,3-benzodioxan-6-yl)ethanone

10 2-Methoxypropene (10g) was added over 15min to a stirred solution of 2-bromo-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone (5g) and toluene-4-sulphonic acid (0.5g) in CH₂Cl₂ (100ml) at 23⁰. The mixture was stirred for 3h, filtered through a wad of triethylamine-deactivated silica and evaporated to give an oil. Purification by [FCTS] (300g) [E] afforded the title compound as an oil (4.8g) which solidified on cooling. A
15 small sample was crystallised from light petroleum (b.p. 60-80⁰) to give white crystals m.p. 47-48⁰.

Intermediate 10

1-(2,2-Dimethyl-1,3-benzodioxan-6-yl)-2-[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]ethanone

20 A solution of Intermediate 9 (1.6g), Intermediate 7 (2.1g) and N,N-diisopropylethylamine (1.2g) in THF (15ml) was kept at 23⁰ for 2 days. The mixture was diluted with EA (80ml) washed with 8% NaHCO₃ (50ml) and BR (50ml), dried (Na₂SO₄) and evaporated in vacuo to give a yellow oil.
25 Purification by [FCS] (150g) [F] gave the title compound as a pale-yellow oil (2.2g). T.l.c. [F] Rf 0.27.

Intermediate 11

6-(4-Phenylbutoxy)hexanoic acid

30 A mixture of Intermediate 5 (4g) and pyridinium dichromate (21.04g) in DMF (50ml) was stirred at RT for 15h, diluted with H₂O (300ml) and extracted with ER (2x100ml). The extract was washed with H₂O (2x250ml), dried, filtered through a bed of silica and evaporated in vacuo to give a colourless oil. Purification by [FCS] (80g) [F] gave
35 the title compound as a colourless oil (0.85g).
T.l.c. [F] Rf 0.27.

Intermediate 12N-[2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-1-(4-phenylbutoxy)hexanamide

DMF (0.003ml) and thionyl chloride (0.51ml) were added to a solution of
 5 Intermediate 11 (0.89g) in dry CH_2Cl_2 (17ml). The resultant solution
 was stirred at RT for 2.5h and evaporated to dryness to give the acid
 chloride. Intermediate 1 (0.934g) in THF was treated with ethyl
 (trimethylsilyl)acetate (3.57ml). Tetrabutyl ammonium fluoride (0.9ml)
 was added dropwise to the stirred suspension at 0° . The resulting
 10 solution was stirred at RT for 2h and added to a solution of the above
 acid chloride in THF (10ml) under an atmosphere of nitrogen.
 Triethylamine (3.4ml) was then added and the solution stirred at RT for
 4h, left to stand overnight, added to 2N hydrochloric acid (30ml) and
 stirred for 15min. The product was extracted into EA (3x25ml) the
 15 extracts were washed with H_2O (25ml), 8% NaHCO_3 solution (25ml) and
 BR (25ml). The dried (Na_2SO_4) organic layer was evaporated to dryness
 to give a brown oil which was chromatographed on silica (Merck art
 7754, 40g) [H] to give a pale yellow oil. The dried oil solidified to
 give the title amide as an off white solid (1.06g), m.p. $96-97.5^\circ$.

Intermediate 136-(4-Phenylbutoxy)hexanamine

Intermediate 7 (25g) in absolute ethanol (250ml) was hydrogenated over
 palladium on carbon (1g) and platinum on carbon (1g) catalysts.
 25 The mixture was filtered through Hyflo and evaporated under reduced
 pressure to give the title amine as a colourless oil (16.49g).
 T.l.c. $\text{EN}(\text{CH}_3\text{OH})$ Rf 0.3.

Intermediate 14Methyl 2-hydroxy-5-[[[6-(4-phenylbutoxy)hexyl]imino]acetyl]benzoate

A solution of Intermediate 13 (0.49g) in methanol (5ml) was added over
 15 min to a stirred suspension of methyl 5-(dihydroxyacetyl)-2-
 hydroxybenzoate in methanol (10ml) at 23° . The mixture was stirred for
 10min, evaporated in vacuo and the residue purified by [FCTS] (40g) [G]
 35 to give the title imine as a dark-orange oil (0.61g). The imine was
 unstable and should be used promptly after preparation.
 T.l.c. $\text{EN}[\text{G}]$ Rf 0.37.

Intermediate 15 α -(Bromomethyl)-2,2-dimethyl-4H-1,3-benzodioxin-6-methanol

NaBH₄ (0.1g) was added to a stirred solution of Intermediate 9 (0.6g) in ethanol (20ml) at 0°. The mixture was stirred at 0° for 1h, diluted with H₂O (50ml) and extracted with EA (2x25ml). The extract was washed with BR (25ml) dried and evaporated to give an oil which on trituration with HX afforded the title bromohydrin as a white solid (0.55g) m.p. 84-85° unchanged on recrystallisation from HX.

10 Intermediate 162,2-Dimethyl-6-oxiranyl-4H-1,3-benzodioxin

A mixture of Intermediate 15 (0.45g), methanol (10ml) and anhydrous K₂CO₃ (0.25g) was stirred at 23° for 2h. The mixture was diluted with ER (50ml) filtered through a small wad of silica and evaporated in vacuo. The residual oil was dissolved in ER (50ml), dried and evaporated to give the title epoxide as an oil (0.27g). T.l.c. (CX-EA 7:3) Rf 0.56.

Intermediate 1720 [4-(2-Propynyloxy)butyl]benzene

A mixture of propargyl alcohol (10.0g), (4-bromobutyl)benzene (38.0g), aqueous NaOH (80ml, 50% w/v), and tetrabutylammonium bisulphate (1.0g) was stirred vigorously for 3 days, treated with H₂O (100ml) and extracted with ER (2x200ml). The dried extract was evaporated and the residue was purified on a column of silica (Merck ^(R.T.M.) 9385; 500ml) [H] to give the title compound as a colourless oil (18.3g). T.l.c. [A] Rf 0.2.

Intermediate 18[[4-(6-Chloro-2-hexynyl)oxy]butyl]benzene

30 Intermediate 17 (15.0g) was added dropwise to a suspension of lithamide from lithium (0.61g) in liquid ammonia (50ml) at -33°. The mixture was stirred for 2h and bromochloropropane (13.9g) in ER (10ml) was added dropwise. The resulting suspension was stirred at -33° for 3h and ammonia was allowed to evaporate overnight. The residue was treated cautiously with H₂O (30ml) and extracted with ER (3x50ml). The dried extract was evaporated and the residue was distilled to give the title compound as a colourless oil (12.9g) b.p. 140-150°/0.3mmHg. T.l.c. [A] Rf 0.2.

Intermediate 19[[4-(6-Iodo-2-hexynyl)oxy]butyl]benzene

A mixture of Intermediate 18 (12.0g) sodium iodide (20.0g), and butanone (50ml) was refluxed for 6h and stirred at RT for 2 days, filtered and evaporated. The residue was dissolved in ER (50ml) and washed with H₂O (50ml) and aqueous sodium thiosulphate (50ml). The dried organic phase was evaporated to leave the title compound as a pale yellow oil (12.6g).

10 Intermediate 204-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)-4-hexynyl]amino]methyl]-1,3-benzenedimethanol

Intermediate 19 (8.66g) was added dropwise to a solution of Intermediate 1 (6.7g) and N,N-diisopropylethylamine (3.9g) in DMF (250ml) at 70°. The mixture was heated at 70° for 2h and DMF was removed under reduced pressure. The residue was treated with aqueous NaHCO₃ (1M; 200ml) and extracted with EA (3x250ml). The dried extract was evaporated and the residue was purified on a column of silica (Merck 9385; 250ml) [I] to give a yellow oil. Trituration of the oil with ER gave the title compound as a white solid (4.3g), m.p. 89-90°. T.l.c. [M] Rf 0.2.

Intermediate 213-[[[6-Bromohexyl)oxy]propyl]benzene

25 3-Phenylpropanol (3.00g) and 1,6-dibromohexane (16.10g, 10.2ml) were stirred rapidly at RT with tetra-n-butylammonium hydrogen sulphate (0.5g) and 12.5M aqueous NaOH (16ml) for 30h. The mixture was diluted with H₂O (80ml), extracted with ER (3x100ml), and the combined organic extracts were washed consecutively with H₂O (80ml) and BR (80ml). The dried extracts were evaporated and the residual oil purified by [FCS], eluting with CX (one columnful), followed by EA-CX (1:20) to give the title compound (5.35g) as a colourless oil.

Analysis Found: C, 60.25; H, 7.8; Br, 26.45.

C₁₅H₂₃BrO requires C, 60.2; H, 7.75; Br, 26.7%.

C19

Intermediate 22N-[6-(3-Phenylpropoxy)hexyl]benzenemethanamine hydrobromide

Intermediate 21 (317g) was added to benzylamine (1116ml) at a temperature of 115-125° with stirring under nitrogen. Excess benzylamine was removed by distillation under reduced pressure. The residue was treated with methyl isobutyl ketone (1280ml), the temperature adjusted to 50° and 47% w/v hydrobromic acid (115ml) in H₂O (800ml) was added at 50-55°. The aqueous phase was removed and the organic solution was washed with H₂O (3x800ml) at 50°. Distillation under reduced pressure and crystallisation of the residue from propan-2-ol afforded the title compound salt (318g), m.p. 135-136°.

Intermediate 23

15 Methyl 2-hydroxy-5-[[[(phenylmethyl)[6-(3-phenylpropoxy)hexyl]amino]acetyl]benzoate

A solution of N,N-diisopropylethylamine (9.93g) in CH₂Cl₂ (15ml) was added to a solution of methyl 5-bromoacetyl-2-hydroxybenzoate (10g) and Intermediate 22 (14.87g) in CH₂Cl₂ (256ml) at 16°. The solution was stirred under nitrogen for 23h at 20°, washed with H₂O (5x100ml), dried and filtered. This solution of the title compound was used without further purification. T.l.c. (ER) Rf 0.7.

Intermediate 24

25 1-[4-[(6-Bromohexyl)oxy]butyl]-2-methoxybenzene

NaH (46% dispersion in oil; 1.36g) was added portionwise to a solution of 2-methoxybenzenebutanol (5.0g) and 1,6-dibromohexane (13.8g) in THF (50ml). The suspension was refluxed for 20h and was treated cautiously with H₂O (20ml). The resulting emulsion was extracted with ER (2x50ml) and the dried extract was evaporated to leave a yellow oil. The oil was purified on a column of silica (Merck 9385, 600ml) [A] to give the title compound as a colourless oil (5.6g). T.l.c. [B] Rf 0.2.

Intermediate 25Benzenehexanol

35 (3-Bromopropyl)benzene (20g) in THF (75ml) was added dropwise to magnesium (2.43g) at a rate to maintain gentle reflux. The mixture was stirred for 2h at RT and oxetane (10g) was added dropwise. The resulting suspension was stirred at RT for 2h and at reflux for 16h and

poured into saturated aqueous NH_4Cl (100ml). The mixture was extracted with ER (3x75ml) and the dried extract was evaporated to leave a yellow oil. Distillation of the oil gave the title compound as a colourless liquid (6.05g) b.p. $100-105^\circ/0.4\text{mmHg}$. T.l.c. [O] Rf 0.3.

5

Intermediate 26

2-[(4-Chlorobutyl)oxy]tetrahydropyran

Dihydropyran (15.5g) was added dropwise to a mixture of 4-chlorobutanol (20g) and hydrochloric acid (18M, 1 drop) at RT. The mixture was stirred for 30min and washed with H_2O (100ml), aqueous NaHCO_3 (1M, 50ml) and BR (50ml). The dried liquid was heated under reduced pressure to leave the title compound as a colourless liquid (31.9g). T.l.c. [L] Rf 0.5.

15

Intermediate 27

2-[[4-[(6-Phenylhexyl)oxy]butyl]oxy]tetrahydropyran

NaH (3.85g) was added portionwise to a mixture of Intermediate 25 (5.5g), Intermediate 26 (30g), potassium iodide (1g) and THF (50ml). The mixture was refluxed for 28h and treated cautiously with H_2O (100ml). The resulting emulsion was extracted with ER (3x100ml) and the dried extract was evaporated to leave a yellow oil. Excess of Intermediate 26 was distilled from the mixture at $80^\circ/0.4\text{mmHg}$ and the residue was purified on a column of silica (300ml) [B] to give the title compound as a colourless oil (2.7g). T.l.c. [B] Rf 0.25.

25

Intermediate 28

4-[(6-Phenylhexyl)oxy]butan-1-ol

A solution of Intermediate 27 (2.65g) in methanol (20ml) and 80% acetic acid (10ml) was stirred at RT for 20h. The solution was basified with aqueous NaOH (2M). The mixture was refluxed for 2h and methanol was evaporated. The resulting emulsion was extracted with ER (2x50ml) and the dried extract was evaporated to leave the title compound as a colourless oil (2.0g). T.l.c. [O] Rf 0.3.

Intermediate 29

4-[(6-Phenylhexyl)oxy]butan-1-ol methanesulphonate

Methanesulphonyl chloride (0.4g) was added dropwise to a solution of Intermediate 28 (0.8g) and triethylamine (0.5g) in CH_2Cl_2 (5ml) at 0° . The mixture was stirred at RT for 25min and filtered. The filtrate was

washed with saturated aqueous NaHCO_3 (20ml) and BR (20ml). The dried (Na_2SO_4) organic phase was evaporated to leave the title compound as a yellow oil (1.0g).

5 Intermediate 30

2-[2-[(6-Bromohexyl)oxy]ethyl]-1,3-dimethylbenzene

NaH (46% dispersion in oil; 4.2g) was added portionwise to a solution of 2,6-dimethylbenzenethanol (6.0g) and 1,6-dibromohexane (19.52g) in THF (50ml) under nitrogen. The mixture was refluxed for 18h and treated
10 cautiously with H_2O (20ml). The resulting emulsion was extracted with ER (3x100ml) and the dried extract was evaporated to leave a yellow oil. Excess 1,6-dibromohexane was removed under reduced pressure and the residue was purified on a column of silica (300ml) [B] to give the title compound as a colourless oil (6.6g) b.p. 110-115 $^\circ$ /0.4mmHg.

15

The following intermediates were prepared in a similar manner to Intermediate 21.

Intermediate 31

20 4-[(6-Bromohexyl)oxy]butyl-1-methoxybenzene (3.3g), b.p. 180-190 $^\circ$ /0.5 torr, from 1,6-dibromohexane (8g) and 4-(4-methoxyphenyl)butanol (2g).

Intermediate 32

25 5-[(5-Bromopentyl)oxy]pentylbenzene (3.2g), b.p. 185-195 $^\circ$ /0.3 torr, from 1,5-dibromopentane (8.5g) and benzenepentanol (2g).

Intermediate 33

30 1-[2-[(6-Bromohexyl)oxy]ethyl]-4-chlorobenzene (4.0g), b.p. 169 $^\circ$ /0.8 torr, from 1,6-dibromohexane (8.65g) and 4-chlorobenzeneethanol (3.0g).

Intermediate 34

1-[3-[(6-Bromohexyl)oxy]propyl]-4-fluorobenzene (2.22g), b.p. 170 $^\circ$ /0.7 torr, from 1,6-dibromohexane (8.82g) and Intermediate 42 (2.0g).

35 Intermediate 35

[2-[(8-Bromooctyl)oxy]ethyl]benzene (4.3g), T.l.c. [B] R_f 0.3, from 1,8-dibromooctane (13.4g) and benzeneethanol (20g).

Intermediate 36

[5-[6-(Bromohexyl)oxy]pentyl]benzene (2.7g), T.l.c. [B] Rf 0.3, from 1,6-dibromohexane (9.0g) and benzenepentanol (2.0g).

5 Intermediate 37

1-[2-[(6-Bromohexyl)oxy]ethyl]-4-ethylbenzene (2.6g), T.l.c. [B] Rf 0.25, from 1,6-dibromohexane (9.8g) and 4-ethylbenzeneethanol (2.0g).

Intermediate 38

10 [3-[(7-Bromoheptyl)oxy]propyl]benzene (2.05g) from 1,7-dibromoheptane (3.83g) and 3-phenylpropanol (1.08ml).

Analysis Found: C, 62.6; H, 8.4.

$C_{16}H_{25}BrO$ requires C, 61.35; H, 8.05%.

15 Intermediate 39

5-[4-[(6-Bromohexyl)oxy]butyl]-1,3-benzodioxolane (3.2g), T.l.c. (CX-EA 4:1) Rf 0.43, from 1,6-dibromohexane (9.5g) and Intermediate 44 (2.5g).

Intermediate 40

20 1-[2-[(6-Bromohexyl)oxy]ethyl]-3-chlorobenzene (4.12g), T.l.c. (ER-HX 1:79) Rf 0.16, from 1,6-dibromohexane (11.71g) and 3-chlorobenzeneethanol (2.5g).

Intermediate 41

25 1-[3-[(6-Bromohexyl)oxy]propyl]-2-fluorobenzene (4.71g), T.l.c. (ER-CX 1:79) Rf 0.22, from 1,6-dibromohexane (14.28g) and 3-(2-fluorophenyl)-1-propanol (3.0g).

Intermediate 4230 4-Fluorobenzenepropanol

A Grignard reagent was prepared from 4-bromo-1-fluorobenzene (8.0g), magnesium turnings (1.10g), and iodine (one small crystal) in THF (40ml). Oxetane (2.3g) in THF (10ml) was added at RT and the reaction mixture was heated at reflux overnight. The cooled solution was poured
35 into aqueous saturated NH_4Cl (100ml), extracted with ER (2x150ml) and the combined, dried (Na_2SO_4) extracts were evaporated. The residual oil was purified by flash chromatography over silica gel (Merck 9285, 5.0cm wide column), eluting with ER-CX (1:5+1:3). The resultant oil was

(19)

further purified by distillation to give the title compound (3.15g) as a colourless oil, b.p. 150⁰/0.8 torr.

Intermediate 43

5 (E/Z)-4-[1,3-Benzodioxol-5-yl]-3-butenol, (E:Z=3:2)

A solution of n-butyllithium in HX (1.6M, 6.5ml) was added over 5min to a stirred suspension of [3-(1-methoxy-1-methylethoxy)propyl]-triphenylphosphonium bromide (4.8g) in dry THF (25ml) at 0⁰ under nitrogen. The mixture was stirred at 0⁰ for 45min, treated with a
10 solution of piperonal (1.2g) in dry THF (5ml) and stirred at 0⁰ to 23⁰ over 1h. ER (70ml) was added, the mixture filtered through silica and the filtrate evaporated in vacuo to give a yellow oil which was dissolved in a mixture of THF-H₂O-2M hydrochloric acid 25:5:1 (31ml) and kept at 23⁰ for 0.5h. The mixture was diluted with 8% NaHCO₃ (30ml),
15 extracted with ER (2x50ml) and the extract was washed with BR (50ml), dried and evaporated in vacuo to afford the title alcohol as a yellow oil (1.05g) (E:Z ratio of 3:2). T.l.c. [O] Rf 0.22.

Intermediate 44

20 1,3-Benzodioxole-5-butanol

A solution of Intermediate 43 (3.5g) in absolute ethanol (50ml) was hydrogenated at RT and atmospheric pressure over 10% palladium on carbon catalyst (200mg). Hydrogen absorption (392ml) ceased after 45min, the solution was filtered and the filtrate evaporated in vacuo to give the
25 title alcohol as a colourless oil (3.5g).
T.l.c. (EA-CX (3:2) Rf 0.49.

The following intermediates were prepared in a similar manner to Intermediate 21.

30

Intermediate 45

[4-(4-Bromobutoxy)butyl]benzene (2.44g), T.l.c. [K] Rf 0.68, from 1,4-dibromobutane (8.6g) and benzenebutanol (2g).

35 Intermediate 46

[5-(4-Bromobutoxy)pentyl]benzene (2.46g), T.l.c. [K] Rf 0.58 from 1,4-dibromobutane (7.89g) and benzenepentanol (2g).

Intermediate 47

[2-[(7-Bromoheptyl)oxy]ethyl]benzene (6.2g), T.l.c. (CX-ER 40:1) Rf 0.29, from 1,7-dibromoheptane (10.5g) and benzeneethanol (50.g).

5 Intermediate 48

1-[2-[(5-Bromopentyl)oxy]ethyl]-4-ethylbenzene (2.19g) T.l.c. [K] Rf 0.48, from 1,5-dibromopentane (7.8g) and 4-ethylbenzeneethanol (1.7g).

Intermediate 49

10 1-[2-[(6-Bromohexyl)oxy]ethyl]-4-methylbenzene (8.51g) T.l.c. [K] Rf 0.56 from 1,6-dibromohexane (24.2g) and 4-methylbenzeneethanol (4.5g).

Intermediate 50

15 [2-(4-Bromobutoxy)ethyl]benzene (2.85g), T.l.c. [K] Rf 0.41, from 1,4-dibromobutane (10.6g) and benzeneethanol (2g).

Intermediate 51

[2-[(5-Bromopentyl)oxy]ethyl]benzene (3.8g), T.l.c. [K] Rf 0.46 from 1,5-dibromopentane (11.3g) and benzeneethanol (2g).

20 Intermediate 52

[3-[(5-Bromopentyl)oxy]propyl]benzene (2.8g), T.l.c. [K] Rf 0.44 from 1,5-dibromopentane (10.2g) and benzenepropanol (2g).

Intermediate 5325 [4-[(5-Bromopentyl)oxy]butyl]benzene

4-Phenylbutanol (5.80g) was stirred in 1,5-dibromopentane (52ml) and 5N NaOH solution (50ml), and tetrabutyl ammonium bisulphate (0.87g) was added and the reaction mixture was stirred at RT for 72h. (After 42h the NaOH layer was replaced by a fresh solution). The two layers were separated and the aqueous phase was extracted with ER (3x50ml). The combined organic layers were dried (Na₂SO₄), and evaporated to give a clear liquid. Excess 1,5-dibromopentane was removed by distillation at 60° 1.00mmHg. The residue was chromatographed on a silica (70-230mesh, 30g) column using CX as eluant, with a slowly increasing quantity of ER until the title compound was obtained, which on evaporation gave a colourless oil (3.26g). T.l.c. (CX-ER (99:1)) Rf 0.15.

Intermediate 541-[2-[(6-Bromohexyl)oxy]ethyl]-4-methoxybenzene

4-Methoxybenzeneethanol (5.0g) and 1,6-dibromohexane (23.7g) were stirred rapidly at RT with tetra-n-butyl ammonium bisulphate (0.94g) and 12.5M aqueous NaOH (30ml) for 16h. The mixture was diluted with H₂O (125ml), extracted with ER (3x150ml) and the combined organic extracts were washed consecutively with H₂O (125ml), BR (125ml), dried and evaporated to give an oil (24.6g). The oil was purified by [FCS] eluting with ER-CX (0:100→4:96) to give the title compound as a colourless oil (8.30g). T.l.c. (CX-ER (40:1)) Rf 0.33.

Intermediate 557-[2-(Phenylethoxy)]-2-heptanone

A solution of Intermediate 51 (2.0g) in ER (15ml) was added dropwise to magnesium (0.18g). The mixture was refluxed for 1h, cooled and added during 40min to acetic anhydride (1.4g) in ER (10ml) at -78⁰. The suspension was stirred at -78⁰ for 2h, warmed to -10⁰ and treated with saturated aqueous NH₄Cl (20ml). The mixture was extracted with ER (2x25ml) and the extract was washed with 5% NaOH (20ml) and BR (20ml). The dried extract was evaporated and the residue was purified on a column of silica (100ml) [L] to give the title compound as a colourless oil (0.70g). T.l.c. [L] Rf 0.25.

The following ketones were prepared in a similar manner:

(Intermediates 57, 62 and 64 are described after Intermediate 65)

Intermediate 56

7-[4-(Phenylbutoxy)]-2-heptanone (1.15g) from Intermediate 53 (3.0g) and acetic anhydride (2g). T.l.c. [L] Rf 0.25.

Intermediate 58

6-(3-Phenylpropoxy)-2-hexanone (1.3g) from Intermediate 57 (3.5g) and acetic anhydride (2.6g). T.l.c. [L] Rf 0.25.

Intermediate 59

6-(4-Phenylbutoxy)-2-hexanone (1.3g) from Intermediate 45 (3.0g) and acetic anhydride (2.3g). T.l.c. [L] Rf 0.35.

Intermediate 60

8-(2-Phenylethoxy)-3-octanone (4.35g) from Intermediate 51 (7.0g) and propionic anhydride (6.53g). T.l.c. (CX-ER 7:1) Rf 0.22.

5 Intermediate 61

9-(2-Phenylethoxy)-4-nonanone (2.25g) from Intermediate 51 (5.0g) and butyric anhydride (6.75g). T.l.c. [B] Rf 0.2.

Intermediate 63

10 7-[2-(4-Fluorophenyl)ethoxy]-2-heptanone (1.88g) from Intermediate 62 (6.0g) and acetic anhydride (4.2g), b.p. 172⁰/0.7 Torr.

Intermediate 65

15 7-[3-(4-Methoxyphenyl)propoxy]-2-heptanone (2.17g) from Intermediate 64 (5.5g) and acetic anhydride (3.66g). T.l.c. [F] Rf 0.18.

Intermediate 57[[3-(4-Bromobutoxy)]propyl]benzene

A mixture of 3-phenylpropanol (2g), tetrabutylammonium bisulphate (0.5g) 1,4-dibromobutane (9.5g) and 50% NaOH (11ml) was stirred at RT
20 for 22h, diluted with H₂O (250ml) and extracted with ER (250ml). The organic phase was washed successively with H₂O (250ml) and BR (250ml), dried and evaporated under reduced pressure to give a colourless oil.
Purification by [FCS] [120g], eluting with CX followed by [K] afforded
25 the title compound as a colourless oil (2.72g).
T.l.c. (CX - EA 1:9) Rf 0.51.

Intermediate 621-[2-[(5-Bromopentyl)oxy]ethyl]-4-fluorobenzene

30 4-Fluorobenzeneethanol (10.0g), 1,5-dibromopentane (29ml), tetra-n-butylammonium hydrogen sulphate (3.2g, 9mmol), and aqueous 12.5M NaOH (109ml) were stirred vigorously at RT overnight. The mixture was diluted with H₂O (400ml), extracted with ER (3x200ml), and the combined organic extracts were evaporated. The residual oil was purified by
35 [FCS] eluting with CX - ER (100:0→100:6), to give the title compound as a colourless oil (14.37g). T.l.c. (ER-CX, 19:1) Rf 0.22.

Intermediate 641-[3-[(5-Bromopentyl)oxy]propyl]-4-methoxybenzene

4-Methoxybenzenepropanol (7.5g) and 1,5 dibromopentane (30.5g) were stirred rapidly at RT with tetra-n-butylammonium bisulphate (1.02g) and
 5 12.5M aqueous NaOH (36ml) for 16h. The mixture was diluted with H₂O (170ml), extracted with ER (3x200ml) and the combined organic extracts were washed consecutively with H₂O (170ml) and BR (170ml), dried and evaporated to give an oil (34.8g). The oil was purified by [FCS] eluting with ER - CX (0:100→4:96) to give the title compound as a
 10 colourless oil (8.83g). T.l.c. (CX-ER 79:1) Rf 0.1.

Intermediate 661,1-Dimethyl-5-(3-phenylpropoxy)-2-pentynamine

1,1-Dimethylpropargylamine (8.5g) was added dropwise to a suspension of
 15 lithamide [from lithium (1.7g)] in liquid ammonia (100ml) at -33°. The mixture was stirred for 90 min and a solution of [3-(2-bromoethoxy)propyl]benzene (21.5g) in ER (30ml) was added dropwise. The suspension was stirred for 4h and ammonia was allowed to evaporate overnight. The residue was treated with H₂O (100ml) and extracted with
 20 ER (3x100ml). The dried extract was evaporated and the residue was distilled to give the title compound as a colourless oil (3.0g) b.p. 160-165°/0.2mmHg. T.l.c. (ER) Rf 0.3.

Intermediate 67

25 α¹-[[[1,1-Dimethyl-5-(3-phenylpropoxy)-2,E-pentenyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol

A solution of methyl 5-(bromoacetyl)-2-hydroxybenzoate (3.3g) Intermediate 66 (2.9g) and N,N-diisopropylethylamine (1.55g) in EA (50ml) was refluxed for 3h, filtered and evaporated. The residue was
 30 dissolved in ER (50ml), filtered, and added dropwise to a suspension of LiAlH₄ (2g) in ER (100ml) at 0° under nitrogen. The mixture was stirred at 0° for 1h at RT for 1h and was treated cautiously with H₂O (10ml). The mixture was acidified to pH 1 with hydrochloric acid (2M), and basified with solid KHCO₃ to pH8. The ER layer was decanted off
 35 and the aqueous slurry was extracted with CHCl₃ (3x500ml). The dried extract was evaporated to leave an orange oil. The oil was purified on a column of silica (300ml) eluted with EA - methanol - triethylamine

(93:7:1) to give the title compound as a white solid (0.88g) m.p. 108-109°. T.l.c. [M] Rf 0.25.

Intermediate 68

- 5 1,1-Dimethyl-7-(2-phenylethoxy)heptanoic acid
 n-Butyllithium in HX (1.6M; 172ml) was added dropwise to diisopropylamine (27.5g) in THF (40ml) at -78° under nitrogen. The mixture was warmed to 0°, stirred for 45min, and isobutyric acid (12.0g) was added dropwise. The resulting suspension was stirred at
 10 RT for 4h and Intermediate 51 (25.0g) was added dropwise. The mixture was stirred for 16h at RT, treated slowly with hydrochloric acid (2M; 350ml), and extracted with ER (2x250ml). The dried extract was evaporated and the residue was purified on a column of silica (Merck 9385; 300ml) [B] to give the title compound as a colourless oil
 15 (17.0g). T.l.c. [L] Rf 0.35.

Intermediate 69

- 1-1-Dimethyl-6-(2-phenylethoxy)hexylcarbamic acid, phenylmethyl ester
 Ethyl chloroformate (3.26g) in acetone (10ml) was added to a solution
 20 of Intermediate 68 (8.0g) and triethylamine (3.03g) in acetone (100ml) and H₂O (10ml) at 0°. The mixture was stirred for 40min at 0° and sodium azide (2.25g) in H₂O (25ml) was added dropwise. The resulting suspension was stirred at RT for 30min, diluted with H₂O (200ml), and
 25 extracted with toluene (2x200ml). The dried (Na₂SO₄) extract was evaporated to half-volume, heated at 70-80° for 2h, and toluene was removed under reduced pressure. The resulting isocyanate in benzyl alcohol (20ml) was heated at 80-83° for 60h and benzyl alcohol was removed under reduced pressure (1 Torr). The residue was purified in a column of silica (Merck 9385; 300ml) eluted with CX - ER (17:3) to
 30 give the title compound as a colourless oil (7.45g). T.l.c. [L] Rf 0.25.

Intermediate 70

- 1,1-Dimethyl-6-(2-phenylethoxy)hexanamine
 35 A solution of Intermediate 69 (6.8g) in ethanol (100ml) was hydrogenated over 10% palladium on charcoal (0.5g) for 40min filtered, and evaporated to give the title compound as a colourless oil (4.3g).

52

Intermediate 71Methyl 5-[2-(dimethylamino)-1-hydroxyethyl]-2-(phenylmethoxy)benzoate

Dimethylamine (33% in ethanol, 156ml) was added to a stirred suspension of methyl 5-(bromoacetyl)-2-(phenylmethoxy)benzoate (105.8g) in absolute ethanol (1l) and THF (1l). The resulting solution was stirred at RT for 2h, treated with NaBH_4 (25g) and stirred at RT overnight. The solvent was removed in vacuo and H_2O (500ml) was added to the residue. The mixture was extracted with EA (2x500ml), the combined extracts were washed with H_2O and BR, dried (Na_2SO_4) and concentrated in vacuo. The product was purified twice by [FCS] eluted with EA-methanol-triethylamine (80:20:1) to give the title compound as a fawn solid (59.8g) m.p. 79-81°.

Intermediate 72

(R)-Methyl 5-[2-(dimethylamino)-1-hydroxyethyl]-2-(phenylmethoxy)-benzoate[S- (R*,R*)-2,3-bis[(4-methylbenzoyl)oxy]butanedioate (1:1) (salt)].

Intermediate 71 (50g) in hot methanol (250ml) was mixed with (-)-di-p-toluoyl tartaric acid, monohydrate (60g) in hot methanol (250ml). The resulting precipitate was collected by filtration and recrystallised three times from methanol (25ml/gram) to give the title compound as white needles (16.4g). m.p. 169-170° $[\alpha]_D^{18.2} - 103.3^{\circ}(\text{c } 0.51 \text{ in } \text{CH}_3\text{OH})$

Intermediate 73(R)-Methyl 5-[2-(dimethylamino)-1-hydroxyethyl]-2-(phenylmethoxy)-benzoate

Intermediate 72 (16.4g) was partitioned between EA (175ml) and 6N ammonium hydroxide (8.4ml) in H_2O (175ml). The organic layer was washed with 8% NaHCO_3 (2x100ml), BR, dried (Na_2SO_4) and concentrated in vacuo to give the title compound as a viscous oil (7.9g) T.l.c. (EA-methanol-triethylamine 80:20:1) $R_f = 0.23$.

Intermediate 74

(R)- β -Hydroxy-3-(methoxycarbonyl)-N,N,N-trimethyl-4-(phenylmethoxy)benzeneethanaminium iodide

Intermediate 73 (7.85g) and methyl iodide (17.5ml) in acetone (55ml) was stirred at reflux under nitrogen for 3h. The acetone was removed in vacuo and CHCl_3 (100ml) was added to the residue. The resulting precipitate was collected by filtration and dried in vacuo (12.2g). Recrystallisation from methanol gave the title compound as an off-white solid (4.5g) m.p. 85-120° $[\alpha]_D^{20.2} -32.2^\circ$ (c 0.7 in DMSO)

Intermediate 75

(R)-Methyl 5-oxiranyl-2-(phenylmethoxy)benzoate

A warm suspension of Intermediate 74 in dry acetonitrile (200ml) was treated with tetramethylammonium fluoride-bi-methanol solvate (5.5g) and stirred at reflux, with continuous removal of the distillate, for 2.5h. The cooled reaction mixture was filtered and the filtrate was concentrated in vacuo to a semi-solid. Dry ER (100ml) was added and the mixture was refiltered. The filtrate was concentrated to an oil which was purified by [FCS] eluting with CX-EA-triethylamine 80:20:1 give the title compound as a colourless oil (1.98g). $[\alpha]_D^{23.30} + 19.9^\circ$ (c 0.86 in benzene)

T.l.c. (CX-EA-triethylamine 80:20:1) Rf = 0.14.

Intermediate 76

(R)-Methyl 5-[1-hydroxy-2-[(phenylmethyl)[6-(3-phenylpropoxy)hexyl]-amino]ethyl]-2-(phenylmethoxy)benzoate

Intermediate 75 (1.9g) and Intermediate 22, free base (2.17g) in methanol (50ml) were stirred at reflux, under nitrogen, for 6h. The solvent was removed in vacuo and the residual oil was purified by [FCS] eluting with CX-EA-triethylamine 75:25:1 to give the title compound as a pale yellow oil (2.1g). $[\alpha]_D^{20.6} -62.4^\circ$ (c 0.74 in T.l.c.)

(CX-EA-triethylamine 80:20:1) Rf = 0.12.

Intermediate 77

(R)-(-)-4-(Phenylmethoxy)- α^1 -[[[(phenylmethyl)[6-(3-phenylpropoxy)hexyl]-amino]methyl]-1,3-benzenedimethanol

Intermediate 76 (2.0g) in dry THF (40ml) was added to a stirred

suspension of LiAlH_4 (300mg) in dry THF (40ml) at RT, under nitrogen. The reaction mixture was placed in an oil-bath, preheated to 80° , and stirred at reflux for 5 min. The cooled mixture was treated cautiously with H_2O (40ml) and ER (40ml). The phases were separated and the aqueous phase was re-extracted with ER (50ml). The combined organic phases were washed with H_2O and BR, dried (Na_2SO_4) and concentrated in vacuo. [FCS] using CX-EA-triethylamine 66:33:1 as eluant gave the title compound as a clear, colourless oil (1.70g). $[\alpha]_D^{21} - 64.6^\circ$ (c 0.6 in CHCl_3) T.l.c. (CX-EA-triethylamine 66:33:1) Rf = 0.15

In the following examples the products of examples 5,7,11,12,24 and 26 are intermediates in which either the nitrogen atom (NR^3 in formula 1X above) and/or the saligenium ring (see formula X above) is protected. Subsequent removal of the protecting groups to give compounds of formula (I) is described in examples 13,14,25.

Example 1
4-Hydroxy- α^1 -[[[6-(2-phenylethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, hydrate

A mixture of Intermediate 1 (0.93g), Intermediate 2 (1.6g), pyridine (1ml) and DMF (25ml) was left at RT for 2 weeks. The resulting solution was evaporated and the residue was purified on a column of silica (Merck 9385: 250ml) [I] to give a yellow oil. The oil was triturated with ER to give the title compound as a cream solid (0.20g) m.p. $89-91^\circ$. T.l.c. [M] Rf 0.1.

Example 2
4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 1 (8.9g), potassium iodide (4.0g), triethylamine (5ml) and DMF (250ml) at 70° was treated dropwise with Intermediate 3 (7.5g). The solution was heated at $65-70^\circ$ for 1h and DMF was removed

under reduced pressure. The residue was treated with H₂O (200ml) and the resulting emulsion was extracted with EA (3x300ml). The combined extracts were washed with H₂O (2x50ml) and BR (50ml), dried and evaporated. Trituration of the residue with ER/10% EA (200ml) for 16h gave suspension from which the title compound was collected as a white solid (2.6g), m.p. 75.5-76.5°. T.l.c. [M] Rf 0.2.

10

15

20

25

30

35

Example 34-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 4 (2.2g) and Intermediate 6 (1.0g) in absolute ethanol (25ml) was hydrogenated at RT and atmospheric pressure over 10% palladium on carbon catalyst (0.2g). The mixture was filtered through hyflo and evaporated to give an oil. Purification by [FCTS] (40g) [N] gave an oil which on trituration with ER afforded the title compound as a white solid (0.77g) m.p. 75-76⁰, mixed m.p. 74-76⁰ with the product of Example 2. T.l.c. EN [N] Rf 0.31.

Example 44-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

Intermediate 6 (0.5g) was added to a stirred suspension of Intermediate 1 (0.5g) in methanol (5ml) at 23⁰. The mixture was stirred for 0.5h, NaBH₄ (0.5g) was added and stirring continued for 7h. The mixture was diluted with H₂O (50ml), extracted with EA (2x25ml) and the organic phase was washed with BR (25ml), dried and evaporated to give an oil. Purification by [FCTS] (30g) afforded an oil which on trituration with cold ER gave the title compound as a white solid (0.25g), m.p. 76-77⁰, mixed m.p. 75-76⁰ with the product of Example 2. T.l.c. EN[N] Rf 0.31.

Example 54-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 7 (51g) and 4-bromoacetyl-2-(hydroxymethyl)phenol diacetate [prepared from 36.25g of 4-acetyl-2-(hydroxymethyl)phenol diacetate] in CHCl₃ (410ml) was stirred at the reflux for 24h, cooled and concentrated under reduced pressure. The residual oil was dissolved in toluene (75ml) and concentrated. The oil was dissolved in toluene (125ml), washed with H₂O (150ml) and BR (50ml). The aqueous solutions were extracted with toluene (30ml) and the combined extracts were washed with H₂O (50ml) and concentrated. The crude ketoamine diacetate was stirred in ethanol (155ml) and 10N hydrochloric acid (48ml) in H₂O (58ml) was added dropwise with stirring, the temperature being maintained below 20⁰. After being

allowed to stand at 0° for 2 days the solution was treated with ethanol (180ml) and NaOH (17.6g) in H₂O (18ml) whilst keeping the temperature below 15°. NaBH₄ (11.06g) and NaOH (2.11g) in H₂O were added, followed after 24h by more NaBH₄ (9.5g) over a period of 48h. The mixture was neutralised with 2N sulphuric acid and concentrated to a slurry which was partitioned between 2N Na₂CO₃ (100ml) and EA (200ml). The organic layer was treated with a further quantity of 2N Na₂CO₃ (100ml) and EA (200ml). The combined organic extracts were washed, dried and evaporated. The crude triol was chromatographed on Sorbsil^(R.T.M.) (700g), [G] to give the title compound (26.5g) identified by its n.m.r. spectrum.

Example 6

4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 8 (0.4g) in absolute ethanol (25ml) was hydrogenated at 23° and atmospheric pressure over 10% palladium on carbon (0.2g) and 10% platinum on carbon (0.2g) catalysts. The mixture was filtered through hyflo and evaporated to give an oil. Purification by [FCTS] (20g) [N] afforded an oil which on trituration with ER gave the title compound as a white solid (0.21g) m.p. 76.5 - 77.5°, mixed m.p. 75.5 - 76.5° with the product of Example 2. T.l.c. EN [N] Rf 0.31.

Example 7

2,2-Dimethyl- α -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-4H-1,3-benzodioxin-6-methanol

A solution of Intermediate 10 (1g) in absolute ethanol (20ml) was hydrogenated at 23° and atmospheric pressure over 10% palladium on carbon (0.1g) and 10% platinum on carbon (0.1g) catalysts. The mixture was filtered through hyflo and evaporated in vacuo to give an oil which slowly crystallised. The solid was slurried in HX, filtered off and dried to give the title compound as white crystals (0.72g) m.p. 68-70°. T.l.c. EN (EA - MeOH 19:1) Rf 0.45.

35

Example 8

4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 12 (0.3g) in dry THF (5ml) was added to a stirred suspension of LiAlH_4 (0.26g) in dry THF (15ml) at 0° under nitrogen. The mixture was stirred at 23° for 20h, diluted cautiously with H_2O (30ml), acidified to pH5 with 2M hydrochloric acid, basified to pH8 with NaHCO_3 and extracted with EA (3x50ml). The organic phase was washed with BR (50ml), dried (Na_2SO_4) and evaporated to give an oil which was purified by [FCTS] [N] to give an oil. Trituration with cold ER afforded the title compound as a white solid (0.064g) m.p. $75-76.5^\circ$ mixed m.p. $75-76^\circ$ with the product of Example 2. T.l.c. EN[N] Rf 0.31.

Example 9

4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 13 (0.91g) in THF (10ml) was added over 15 min to a stirred solution of methyl 5-(bromoacetyl)-2-hydroxybenzoate (1g) and *N,N*-diisopropylethylamine (0.85g) in THF (10ml) at 0° . The mixture was stirred at 0° for 2h, diluted with ether (50ml), washed with 0.5M hydrochloric acid (50ml), 8% NaHCO_3 (50ml), BR (50ml), dried and evaporated to give an oil. Purification by [FCS] (60g) [O] afforded the intermediate glycol compound as an oil (0.6g). A solution of this oil (0.6g) in dry THF (5ml) was added to a stirred slurry of LiAlH_4 (0.25g) in dry THF (25ml) under nitrogen at 23° . The mixture was stirred for 18h, diluted cautiously with H_2O (50ml), acidified to pH5 with 2M hydrochloric acid, basified to pH8 with NaHCO_3 and extracted with EA (2x100ml). The dried extract was evaporated to give an oil which was purified by [FCTS] (20g) [N] to give an oil which on trituration with ER afforded the title compound as a white powder (0.12g) m.p. $75.5-76.5^\circ$, mixed m.p. $75-76^\circ$ with the product of Example 2. T.l.c. EN [N] Rf 0.31.

Example 10

4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol.

A solution of Intermediate 14 (0.58g) in dry THF (10ml) was added over 10min to a stirred suspension of LiAlH_4 (0.5g) in dry THF (25ml) at 0° under nitrogen. The mixture was stirred at 23° for 18h, diluted cautiously with H_2O (50ml), acidified to pH5 with 2M hydrochloric acid,

basified to pH8 with NaHCO_3 and extracted with EA (3x50ml). The extract was washed with BR (50ml) dried (Na_2SO_4) and evaporated to give an oil which was purified by [FCTS] [N] to give a pale yellow oil. Trituration with cold ER gave the title compound as a white solid (0.115g) m.p. 76-77° mixed m.p. 75.5-76.5 with the product of Example 2. T.l.c. EN[N] Rf 0.31.

Example 11

2,2-Dimethyl- α -[[[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]methyl]-4H-1,3-benzodioxin-6-methanol

A solution of Intermediate 16 (0.24g) and Intermediate 7 (0.8g) in dry THF (3ml) was refluxed under nitrogen for 24h. The mixture was evaporated and the residue purified by [FCS] [J] to afford the title compound as a pale yellow oil (0.18g). T.l.c. [O] Rf 0.49.

Example 12

2,2-Dimethyl- α -[[[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]methyl]-4H-1,3-benzodioxin-6-methanol

A solution of Intermediate 15 (0.2g) and Intermediate 7 (0.7g) in dry THF (5ml) was refluxed under nitrogen for 18h. The mixture was diluted with ER (15ml), washed with 8% NaHCO_3 solution (15ml), BR (10ml), dried and evaporated to give an oil (0.8g). Purification by [FCS] (20g) [J] afforded the title compound as a pale yellow oil (0.09g). T.l.c. [O] Rf 0.49.

Example 13

4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of the product of Example 7 (0.3g) in methanol (2ml) was diluted with 2M hydrochloric acid (2ml) and the solution was kept at 23° for 5h. EA (15ml) was added and the mixture washed with 8% NaHCO_3 (15ml), BR (15ml), dried and evaporated in vacuo to give a colourless oil. Trituration with ER afforded the title compound as a white solid (0.23g) m.p. 76-77°, mixed m.p. 75.5-77° with the product of Example 2. T.l.c. EN[N] Rf 0.31.

Example 14

4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

The product described in Example 5 (230g) in ethanol (1.3l) was reduced
5 by hydrogen in the presence of 10% palladium-on-carbon catalyst (46.5%
paste in H₂O; 60g). Catalyst and solvent were removed and ER (2l) was
added to the residue. The solution was decanted from a little
insoluble gum and left to stand overnight. Filtration of the mixture
afforded the title compound (147g), m.p. 75-77°.

10

Example 15

4-Hydroxy- α^1 -[[[6-(2-phenylethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, hydrate

A solution of Intermediate 20 (30mg) in EA (20ml) was hydrogenated over
15 palladium-charcoal (10%, ~20mg) for 5h, filtered through Hyflo and
concentrated under reduced pressure to give the title compound as a pal
yellow solid (27mg). T.l.c. (EA-ethanol-NH₃ 10:1:1) Rf 0.3.

H.p.l.c. Column: 5 μ Hypersil 5mmx10mm; λ max : 276nm; Flowrate :
2ml/min; Eluant : HX-EA-Isopropanol-NH₃ 10:1:1:0.15

20 Retention time 11.5min.

Example 16

4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol benzoate salt

25 A solution of the compound of Example 2 (2.3g) in EA (5ml) at 40° was
added to a solution of benzoic acid (0.7g) in EA (5ml) at 40°. The
solution was cooled to 0° and EA was decanted from the resulting solid.
The solid was washed with ER (3x5ml) and recrystallised from EA to give
the title compound as a white solid m.p. 117-117.5°.

30

Example 17

4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 2-hydroxybenzoate (salt).

A solution of 2-hydroxybenzoic acid (0.83g) in warm isopropanol (10ml) •
35 was added to the compound of Example 2 (2.50g) in isopropanol (10ml).
The mixture was aged overnight at ambient temperature then the product
was collected, washed with isopropanol (3x5ml) and dried in vacuo at
60°, to give the title salt as a colourless solid, m.p. 134-135°

The following salts (Examples 18-21) were prepared in a similar manner from the compound of Example 2.

Example 18

- 5 4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 4-chlorobenzoate (salt)

The product melted at 117-119⁰, partially resolidified and remelted at 134⁰.

10 Example 19

- 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 4-hydroxybenzoate (salt), m.p. 136.5-138⁰.

Example 20

- 15 4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salt), m.p. 137-138⁰

Example 21

- 20 4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 3-hydroxy-2-naphthalenecarboxylate (salt), m.p. 135-137⁰

Example 22

- 25 4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol sulphate (2:1) (salt)

Sulphuric acid (98% w/w, 613mg) was added to ethanol (10ml) and a portion of the solution (5.2ml) was added to a warm solution of the base of the compound of Example 2 (2.5g) in ethanol (10ml). On being allowed
30 to stand in an open necked flask for 24h the solution deposited white needles which were filtered off, washed with ethanol (2x5ml) and dried at 50⁰ in vacuo to give the title salt (1.89g), m.p. 117.5-119.5⁰.

Example 23

- 35 4-Hydroxy- α^1 -[[[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A mixture of Intermediate 1 (0.84g), Intermediate 21 (1.0g), N,N-diisopropylethylamine (0.706g, 0.95ml) and DMF (7.3ml) was heated at 80⁰

for 1h. The clear brown solution was diluted with H₂O (75ml), acidified to pH4 with 2N hydrochloric acid and then basified to pH8 with solid KHCO₃. The cloudy aqueous phase was extracted with EA (2x75ml) and the combined extracts were washed successively with H₂O (75ml) and BR (35ml). The combined dried (Na₂SO₄) extracts were evaporated and the residual oil was purified by [FCS] [I] to give, after trituration with ER (25ml) the title compound (0.279g) as a white solid m.p. 77-78°. T.l.c. [I] Rf 0.13.

10 Example 24

4-Hydroxy- α^1 -[[[(phenylmethyl)-[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

Intermediate 23 was added during 15min to a solution of sodium bis(2-methoxyethoxy)aluminium hydride (3.4M solution in toluene; 33ml) and CH₂Cl₂ (50ml), whilst maintaining the temperature between 4° and 18°, under nitrogen. After 1.75h at 15° the mixture was cooled to 5° and treated very cautiously with H₂O (10ml). The filtrate was evaporated under reduced pressure and the residue in EA (250ml) was treated with 2N hydrochloric acid (250ml). The organic layer was washed successively with 2N Na₂CO₃ solution (200ml) and H₂O (200ml), dried and evaporated to give the title compound as an orange oil (15.8g). T.l.c. (ER) Rf 0.3.

Example 25

4-Hydroxy- α^1 -[[[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

The product of Example 24 (19g) in ethanol (150ml) was hydrogenated in the presence of 10% palladium-on-charcoal catalyst (5.2g). After 2h 40min the mixture was filtered and the filtrate evaporated under reduced pressure to a pale yellow oil, which crystallised from EA to give the title compound as a white solid, (10.1g) m.p. 82-84°.

Analysis Found: C, 71.76; H, 8.60; N, 3.43.

C₂₅H₃₅NO₄ requires C, 71.78; H, 8.79; N, 3.49%.

Example 26

35 4-Hydroxy- α^1 -[[[(phenylmethyl)-[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of 4-bromoacetyl-2-(hydroxymethyl)phenol diacetate [prepared from 4-acetyl-2-(hydroxymethyl)phenol diacetate (30g)] in CHCl₃ (221ml)

was treated with propylene oxide (16.7g) and Intermediate 22 hydrochloride (43.4g). The mixture was stirred and heated at reflux for 24h, and allowed to cool to RT. Solvent was removed under reduced pressure, the residue was dissolved in toluene (200ml) and washed with H₂O (2x50ml). The toluene solution was evaporated to dryness and the residue was dissolved in a mixture of ethanol (270ml), H₂O (117ml), and 10N hydrochloric acid (89ml). The mixture was allowed to stand at RT for 48h and evaporated to dryness to give an oil. This crude hydrochloride was dissolved in ethanol (283ml) and the stirred solution was treated with a solution of NaOH (3.53g) in H₂O (3.53ml) keeping the temperature below 20°. The solution was cooled to below 10°, and a solution of NaBH₄ (9.15g) and NaOH (1.26g) in H₂O (34.9ml) was added over 0.5h keeping the temperature below 10°. The mixture was stirred at 20° for 24h and then adjusted to pH 7.3 with 5N sulphuric acid and evaporated to dryness. The residue was dissolved in a mixture of EA (291ml) and 2N Na₂CO₃ (176ml). The aqueous phase was extracted with EA (2x117ml), the combined EA solution was washed with 1N Na₂CO₃ (162ml) and H₂O (8x162ml) and then evaporated to dryness. The resulting oil was purified by column chromatography (Sorbisil, 500g) [O] to give the title compound as an oil (17.0g). This compound was reduced, as described in Example 25, to the compound of Example 23.

Example 27

4-Hydroxy- α^1 -[[[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, sulphate (2:1) salt

A solution of concentrated sulphuric acid (0.3g) in ethanol (5ml) was added to a warm solution of the base of Example 23 (2.4g) in ethanol (10ml). The title salt precipitated as a white solid (1.9g), m.p. 111-112°.

Example 28

4-Hydroxy- α^1 -[[[6-[4-(2-methoxyphenyl)butoxy]hexyl]amino]methyl]-1,3-benzenedimethanol

Intermediate 24 (2.0g) was added dropwise to a solution of Intermediate 1 (2.13g), triethylamine (5ml), and potassium iodide (0.95g) in DMF (50ml) at 70°. The solution was heated at 70-75° for 1h and added to H₂O (800ml). The resulting emulsion was extracted with EA (3x200ml) and the dried extract was evaporated to leave an orange oil. The oil was

66

purified on a column of silica (150ml) [I] to leave a colourless oil. The oil was crystallised from EA to give the title compound as an off-white solid (0.80g) m.p. 52-54°. T.l.c. [M] Rf 0.2.

5 Example 29

4-Hydroxy- α^1 -[[[4-[(6-phenylhexyl)oxy]butyl]amino]methyl]-1,3-benzenedimethanol

Intermediate 29 (1.0g) was added dropwise to a solution of Intermediate 1 (1.2g) and triethylamine (2ml) in DMF (30ml) at 60°. The solution was stirred at 60-70° for 4h and added to H₂O (500ml). The resulting emulsion was extracted with EA (3x150ml) and the dried extract was evaporated to leave a brown oil. The oil was purified on a column of silica (Merck 9385; 150ml) [I] to leave a yellow gum. The gum was repurified on a column of silica (Merck 9385, 50ml) eluted with EA-methanol (93:7) to leave a colourless oil. Trituration of the oil with ER (10ml) gave the title compound as a white solid (0.07g) m.p. 75-77°. T.l.c. [M] Rf 0.15

Example 30

20 α^1 -[[[6-[2-(2,6-Dimethylphenyl)ethoxy]hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol, hemihydrate

Intermediate 30 (2.0g) was added dropwise to a solution of Intermediate 1 (2.34g), potassium iodide (0.9g) and triethylamine (4g) in DMF (60ml) at 60°. The solution was stirred at 60-70° for 1h and added to H₂O (800ml). The emulsion was evaporated to leave a yellow oil. Purification of the oil on a column of silica (100ml) [I] gave a colourless oil. Trituration of this oil with ER (25ml) gave a white solid which was crystallised from EA to give the title compound as a white solid (0.43g) m.p. 83-86°. T.l.c. [M] Rf 0.15

30

The following Examples were prepared in a similar manner to that described for Example 23 from Intermediate 1 and the other Intermediate shown in the Table.

35 Example 31 4-Hydroxy- α^1 -[[[6-[4-(4-methoxyphenyl)butoxy]hexyl]amino]methyl]-1,3-benzenedimethanol

Example 32 4-Hydroxy- α^1 -[[[5-[(5-phenylpentyl)oxy]pentyl]amino]methyl]-1,3-benzenedimethanol

- Example 33 α^1 -[[[6-[2-(4-Chlorophenyl)ethoxy]hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol
- Example 34 α^1 -[[[6-[3-(4-Fluorophenyl)propoxy]hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol
- 5 Example 35 4-Hydroxy- α^1 -[[8-[(2-phenylethoxy)octyl]amino]methyl]-1,3-benzenedimethanol
- Example 36 4-Hydroxy- α^1 -[[[6-[(5-phenylpentyl)oxy]hexyl]amino]methyl]-1,3-benzenedimethanol
- Example 37 α^1 -[[[6-[2-(4-Ethylphenyl)ethoxy]hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol
- 10 Example 38 4-Hydroxy- α^1 -[[[7-(3-phenylpropoxy)heptyl]amino]methyl]-1,3-benzenedimethanol
- Example 39 α^1 -[[[6-[4-(1,3-Benzodioxol-5-yl)butoxy]hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol
- 15 Example 40 α^1 -[[[6-[2-(3-Chlorophenyl)ethoxy]hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol
- Example 41 4-Hydroxy- α^1 -[[[6-(phenylmethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol
- Example 42 α^1 -[[[6-[3-(2-Fluorophenyl)propoxy]hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol
- 20 Example 43 4-Hydroxy- α^1 -[[[4-(4-phenylbutoxy)butyl]amino]methyl]-1,3-benzenedimethanol
- Example 44 4-Hydroxy- α^1 -[[[4-(5-phenylpentyl)oxy]butyl]amino]methyl]-1,3-benzenedimethanol
- 25 Example 45 4-Hydroxy- α^1 -[[7-[(2-phenylethoxy)heptyl]amino]methyl]-1,3-benzenedimethanol
- Example 46 α^1 -[[[5-[2-(4-Ethylphenyl)ethoxy]pentyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol
- Example 47 4-Hydroxy- α^1 -[[[6-[2-(4-methylphenyl)ethoxy]hexyl]-amino]methyl]-1,3-benzenedimethanol
- 30 Example 48 4-Hydroxy- α^1 -[[[4-(2-phenylethoxy)butyl]amino]methyl]-1,3-benzenedimethanol
- Example 49 4-Hydroxy- α^1 -[[[5-(2-phenylethoxy)pentyl]amino]methyl]-1,3-benzenedimethanol hydrochloride
- 35 Example 50 4-Hydroxy- α^1 -[[[5-(3-phenylpropoxy)pentyl]amino]methyl]-1,3-benzenedimethanol hydrochloride



Example	Intermediate	Chromatography eluents EA-Methanol-NEt ₃	M.p. °C
5	31	90:10:1*	81-82
	32	85:15:1*	66-67
	33	89:10:1	89-91
	34	89:10:1	63-67
	35	No chromatography	97-99
10	36	36 + KI	75-77
	37	37 + KI	96-99
	38	89:10:1	72-75
	39	4:1:0*	68-70
	40	89:10:1	76-78
15	41	+	69-70
	42	41	79-81
	43	45	63-68
	44	46	66-71
	45	47	80-81
20	46	48	75-78
	47	49	88.5-93.5
	48	50	75-78
	49	51	66-67 (hydrochloride)
	50	52	50-56 (Hydrochloride)

25

* The silica was deactivated with NEt₃

+ [1-[(6-Bromohexyl)oxy]methyl]benzene

30

35

Example 514-Hydroxy- α^1 -[[[5-(4-phenylbutoxy)pentyl]amino]methyl]-1,3-benzenedimethanol

A mixture of Intermediate 1 (1.15g), DMF (10ml), N,N-diisopropylethylamine (1.2g) and Intermediate 53 (0.9g) was heated at 75° for 2h. The mixture was diluted with H₂O (150ml) acidified to pH4 with 2M hydrochloric acid, basified to pH8 with solid KHCO₃ and extracted with EA (2x80ml). The extracts were washed with H₂O (50ml) BR (50ml), dried (Na₂SO₄) and evaporated in vacuo to give an oil which was purified by [FCTS] using EA - methanol - triethylamine (85:15:1) as the eluant to give the product as an oil. This was dissolved in warm EA (15ml) and cooled to give the title compound as an off-white solid (0.35g) m.p. 117-119°.

T.l.c. EN (EA - CH₃OH 17:3) Rf 0.32.

Example 524-Hydroxy- α^1 -[[[6-[2-(4-methoxyphenyl)ethoxy]hexyl]amino]methyl]-1,3-benzenedimethanol

A mixture of Intermediate 1 (0.95g), Intermediate 54 (1.50g) and N,N-diisopropylethylamine (1.35ml) in DMF (molecular sieve dried, 11ml) was heated at 80° for 1h under nitrogen. The clear brown solution was basified with 8% NaHCO₃ solution (36ml) and the cloudy mixture was extracted with EA (3x110ml). The combined organic extracts were washed consecutively with H₂O (110ml) and BR (50ml), dried (Na₂SO₄) and evaporated. The resultant oil (2.43g) was purified by [FCS][I] to give a solid which, on trituration with ER (25ml) gave the title compound as a white solid (0.582g), m.p. 101-102°.

Analysis Found: C, 68.65; H, 8.55; N, 3.35.

C₂₄H₃₅NO₅ requires C, 69.05; H, 8.45; N, 3.35%.

Example 534-Hydroxy- α^1 -[[[1-methyl-6-(2-phenylethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 4 (0.94g) and Intermediate 55 (0.6g) in ethanol (40ml) was hydrogenated over 10% palladium on charcoal (0.25g) and 5% platinum on charcoal (0.25g) for 20h, filtered, and evaporated. The residue was purified on a column of silica (Merck 9385, 50ml) [I]

to give a colourless oil. Trituration of the oil with ER (10ml) gave the title compound as a white solid (0.3g), m.p. 68-76°.

T.l.c. [M] Rf 0.2.

5 Example 54

4-Hydroxy- α^1 -[[[1-methyl-6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 4 (1.39g) and Intermediate 56 (1.0g) in ethanol (40ml) was hydrogenated over 10% palladium on charcoal (0.2g) and 5% platinum on charcoal (0.2g) for 26h, filtered and evaporated. The residue was purified on a column of silica (Merck 9385; 100ml) [I] to give the title compound as a white solid (0.62g) m.p. 57-60°.

T.l.c. [M] Rf 0.2.

15 Example 55

4-Hydroxy- α^1 -[[[1-methyl-5-(3-phenylpropoxy)pentyl]amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 4 (1.6g) and Intermediate 58 (1.0g) in ethanol (60ml) was hydrogenated over 10% palladium on charcoal (0.3g) and 5% platinum on charcoal (0.3g) for 20h, filtered and evaporated. The residue was purified on a column of silica (Merck 9385; 90ml) [I] to give a colourless oil. Trituration of the oil with ER (20ml) gave the title compound as a white solid (0.8g) m.p. 86-93°.

T.l.c. [M] Rf 0.25.

25

Example 56

4-Hydroxy- α^1 -[[[1-ethyl-6-(2-phenylethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol.

A solution of Intermediate 60 (1.0g) and Intermediate 4 (2.19) in absolute ethanol (60ml) was hydrogenated over a mixture of palladium on carbon catalyst (200mg) and platinum on carbon catalyst (200mg) at RT and atmospheric pressure. After 18h, the mixture was filtered and the filtrate evaporated in vacuo to give a yellow solid. Purification by [FCTS] (120g) with EA - methanol - triethylamine (95:5:1) as eluant gave the title compound as a white solid (480mg) m.p. 82-84°.

T.l.c. EN (EA-methanol)(19:1) Rf 0.37.

Example 574-Hydroxy- α^1 -[[[1-methyl-5-(4-phenylbutoxy)pentyl]amino]methyl]-1,3-benzenedimethanol

A solution of Intermediate 4 (1.45g) and Intermediate 59 (1.0g) in ethanol (60ml) was hydrogenated over 10% palladium on charcoal (0.3g) and 5% platinum on charcoal (0.3g) for 20h, filtered and evaporated. The residue was purified on a column of silica (Merck 9385; 100ml) [I] to give a colourless oil. Trituration of the oil with ER (20ml) gave the title compound as a white solid (0.9g) m.p. 64-66⁰.

T.l.c. [M] Rf 0.2.

Example 584-Hydroxy- α^1 -[[[5-(2-phenylethoxy)-1-propylpentyl]amino]methyl]-1,3-benzenedimethanol benzoate salt.

A solution of Intermediate 4 (2.77g) and Intermediate 61 (2.0g) in ethanol (120ml) was hydrogenated over 10% palladium on charcoal (0.25g) and 5% platinum on charcoal (0.45g) for 22h, filtered and evaporated. The residue was purified on a column of silica (Merck 9385; 150ml) eluted with EA - methanol - triethylamine (19:1:0.1) to give a colourless oil (0.5g). The oil in CHCl₃ (5ml) was added to benzoic acid (0.2g) in CHCl₃ (5ml) and the CHCl₃ was evaporated. The residue was triturated with ER (3x25ml) to give the title compound as a white solid (0.36g) m.p. 67-69⁰. T.l.c. [M] Rf 0.35.

Example 59 α^1 -[[[6-[2-(4-Fluorophenyl)ethoxy]-1-methylhexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol

Intermediate 63 (623mg) and Intermediate 4 (896mg) in ethanol (20ml) were hydrogenated over pre-reduced 5% platinum oxide-on-carbon (0.3g) and 10%-palladium oxide-on-carbon (50% paste with H₂O, 0.35g) until uptake of hydrogen ceased. The catalyst was removed by filtration (Hyflo) and the residue purified by [FCS] eluting with EA - methanol - triethylamine (94:5:1+89:10:1) to give, after trituration with ER the title compound as a cream solid (652mg) m.p. 60-62⁰.

Analysis Found: C, 68.75; H, 8.45; N, 3.25.

C₂₄H₃₄FNO₄ requires C, 68.7; H, 8.15; N, 3.35%.

Example 60

4-Hydroxy- α^1 -[[[6-[3-(4-methoxyphenyl)propoxy]-1-methylhexyl]amino]methyl]-1,3-benzenedimethanol

5 A solution of Intermediate 1 (1.45g) and Intermediate 65 (0.954g) in acetic acid (0.311g) and methanol (22ml) was treated with sodium cyanoborohydride (0.228g) at RT. The mixture was stirred for 16h, and poured into 8% aqueous NaHCO_3 (30ml) and extracted with EA (3x30ml). The combined dried (Na_2SO_4) extracts were evaporated to give an oil (1.06g) which was purified by [FCS][I]. The resulting oil was
10 triturated with ER (25ml) and evaporated to give the title compound as a white solid (0.713g) m.p. 75⁰-77⁰. T.l.c. [I] Rf 0.19.

Example 61

α^1 -[[[1,1-Dimethyl-5-(3-phenylpropoxy)pentyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol

15 A solution of Intermediate 67 (0.70g) in ethanol (35ml) was hydrogenated over 5% platinum on charcoal (0.2g) for 30min, filtered and evaporated. The residue was triturated with CX - ER 9:1 to give the title compound as a white solid (0.51g) m.p. 67-69⁰.
20 T.l.c. [M] Rf 0.3.

Example 62

α^1 -[[[1,1-Dimethyl-6-(2-phenylethoxy)hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol

25 A solution of methyl 5-(bromoacetyl)-2-hydroxybenzoate (2.2g) Intermediate 70 (2.0g) and N,N-diisopropyl ethylamine (1.16g) in EA (40ml) was refluxed for 3h, filtered and evaporated. The residue in ER (50ml) was filtered and the filtrate added dropwise to a suspension of LiAlH_4 (1.6g) to ER (100ml) at 0⁰. The mixture was stirred at RT
30 for 2h, treated cautiously with H_2O (10ml), acidified to pH1 with hydrochloric acid (2M), and basified to pH8 with solid K_2CO_3 . The resulting slurry was extracted with CHCl_3 (4x200ml) and the dried extract was evaporated. The residue was purified on a column of silica (Merck 9385; 150ml) to give the title compound as a beige solid (0.3g)
35 m.p. 68-71⁰. T.l.c. [M] Rf 0.2.

Example 63

(R)-(-)-4-Hydroxy- α^1 -[[[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

Intermediate 77 (750mg) was hydrogenated in absolute ethanol (60ml) over pre-reduced 10% palladium oxide on carbon (50% paste, 150mg). After 2h, uptake of hydrogen (70ml) ceased. The catalyst was removed by filtration through Hyflo and the filtrate was concentrated in vacuo.

The crude product was purified by [FCS] using EA-methanol-triethylamine 80:20:1 as eluant to give the title compound as a very viscous oil (270mg).

Specific Rotation $[\alpha]_{589}^{21} = -25.7^\circ$ ($c = 0.3$ CHCl₃)

T.l.c. (EA-methanol-triethylamine 80:20:1) $R_f = 0.22$.

Analysis Found: C, 71.44; H, 8.34; N, 3.40.

C₂₄H₃₅NO₄ requires C, 71.79; H, 8.79; N, 3.49%.

Example 64

4-Hydroxy- α -[[[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

(a) 1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-[6-(3-phenylpropoxy)hexyl](phenylmethyl)amino]ethanone

N,N-Diisopropylethylamine (2.77g) in CH₂Cl₂ (5ml) was added to a stirred suspension of 2-bromo-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-ethanone (2.5g) and Intermediate 22 (4.15g) in CH₂Cl₂ (30ml). The solution was kept at 23° for 24h, washed with H₂O (5x17.5ml) and evaporated in vacuo to give the crude product (a) as an oil.

T.l.c. (isopropyl acetate : light petroleum, b.p. 60-80°, 1:1) R_f 0.4.

(b) 4-Hydroxy- α^1 -[[[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

A solution of the crude product (a) in absolute ethanol (120ml) was hydrogenated at 40° and atmospheric pressure over 10% palladium on carbon (0.1g) and 10% platinum on carbon (0.1g) catalysts. The mixture was filtered through Hyflo and evaporated to give an oil. The oil was dissolved in EA, the solution evaporated under reduced pressure and the residual oil was triturated with EA (5ml) to give the title compound as a white solid m.p. 81-82.5°.

T.l.c. (EA:CH₃OH:NH₃ 30:10:1) R_f 0.35.

The stimulant action at β_2 -adrenoreceptors of compounds of the invention was determined using the following:

GUINEA-PIG TRACHEAL STRIP PREPARATION

- 5 Tracheal rings were mounted in a superfusion apparatus, and continuously superfused with oxygenated physiological (Kreb's) solution containing indomethacin ($2.4 \times 10^{-6}M$) and atropine ($4 \times 10^{-7}M$) at 37° at a rate of 2ml/min. Changes in tension of the preparation were measured using an isometric strain gauge.
- 10 Preparations were contracted for the duration of the test by the inclusion of prostaglandin $F_{2\alpha}$ ($2.9 \times 10^{-6}M$) in the superfusion fluid. Two bolus dose-effect curves to the standard, isoprenaline, (1×10^{-12} - 1×10^{-9} moles) were obtained at the start of each test in a cumulative fashion, allowing the relaxation obtained with each
- 15 to reach its own maximum before the next increment was made. On completion of this dose-effect curve, sufficient time was allowed for the tissue to recover (15-30min). After this time, sequential concentration-effect curves were constructed for first isoprenaline and then the test compound. These were constructed as follows: a
- 20 low concentration (isoprenaline $3 \times 10^{-10}M$; test compound $1 \times 10^{-10}M$) was infused until any response obtained had reached its maximum, then the infusion was stopped and the tissue allowed to recover for a maximum of 30min. After this period the procedure was repeated using progressively increasing concentrations of agonist,
- 25 and in this way, whole concentration-effect curves obtained.
- Potency was determined by comparison of the concentration-effect curve thus constructed with that previously obtained for isoprenaline and expressed as equipotent concentration (isoprenaline = 1) i.e. $\frac{EC_{50} \text{ test compound}}{EC_{50} \text{ isoprenaline}}$ was calculated.
- 30 Duration of action was also measured for each response, and is the time taken from stopping the infusion to 50% recovery. Graphs were drawn for duration times against response magnitude, and from these, duration times for 50% maximum responses were determined.

The ability of compounds of the invention to afford protection against histamine-induced bronchoconstriction was demonstrated using the following:

CONSCIOUS GUINEA PIG TEST

- 5 The principle of the method is that bronchoconstriction leads to a decrease in tidal volume, and hence to an increase in respiratory rate. Guinea pigs were placed in a whole body plesytmograph i.e. a chamber separated, by means of a collar, into 2 parts - a head chamber and a body chamber. Pressure changes in the body chamber
- 10 were monitored by means of a low pressure transducer, from which was derived a continuous, linear recording of respiratory rate by means of an instantaneous ratemeter connected to a chart recorder. The head chamber was connected to an expansion chamber into which a histamine aerosol was driven from a solution of set concentration
- 15 (usually 5mg/ml) for a predetermined period (usually 10-15seconds). At the end of this period, the aerosol was switched off, but the guinea pig was left in contact with the aerosolized histamine still in the expansion chamber until his respiratory rate increased by 40%, or for a total of 4 min, whichever was the sooner. The degree
- 20 of bronchoconstriction was expressed in terms of the area under the respiratory rate curve. Guinea-pigs were challenged at intervals until their rate responses were constant, then they were given a dose of the test compound by either aerosol or oral route, and the response to histamine reassessed first at 30 min post dose, and then
- 25 at intervals thereafter for up to 24h post dose. By testing a range of doses of the test compound, a dose-relationship in the maximum protection was determined, and the time taken (up to 24h) for the response to histamine challenge to return to pre-test compound protection levels determined. Each dose of each test compound was
- 30 tested in at least 4 animals.

75

The following are examples of suitable formulations of compounds of the invention. The term "active ingredient" is used herein to represent a compound of the invention and can be, for example, the compound of Example 2.

5 Tablets

These may be prepared by the normal methods such as wet granulation or direct compression.

A. Direct Compression

		<u>mg/tablet</u>
10	Active ingredient	2.0
	Microcrystalline Cellulose USP	196.5
	Magnesium Stearate BP	<u>1.5</u>
	Compression weight	200.0

15 The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using 7mm diameter punches.

20 Tablets of other strengths may be prepared by altering the ratio of active ingredient to microcrystalline cellulose or the compression weight and using punches to suit.

B. Wet Granulation

		<u>mg/tablet</u>
	Active ingredient	2.0
	Lactose BP	151.5
25	Starch BP	30.0
	Pregelatinised Maize Starch BP	15.0
	Magnesium Stearate BP	<u>1.5</u>
	Compression weight	200.0

30 The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets

35 using 7mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

C. For buccal administration

	<u>mg/tablet</u>
Active ingredient	2.0
Lactose BP	94.8
5 Sucrose BP	86.7
Hydroxypropylmethylcellulose	15.0
Magnesium Stearate BP	<u>1.5</u>
Compression weight	200.0

10 The active ingredient is sieved through a suitable sieve and blended with the lactose, sucrose and hydroxypropyl-methylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets
15 using suitable punches.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

20 Capsules

	<u>mg/capsules</u>
Active ingredient	2.0
* Starch 1500	97.0
Magnesium Stearate BP	<u>1.0</u>
25 Fill weight	100.0

* A form of directly compressible starch.

30 The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

Syrup

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup

5		<u>mg/5ml dose</u>
	Active ingredient	2.0
	Sucrose BP	2750.0
	Glycerine BP	500.0
	Buffer)	
10	Flavour)	as required
	Colour)	
	Preservative)	
	Purified Water BP	to 5.0ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup produced is clarified by filtration.

B. Sucrose-Free

		<u>mg/5ml dose</u>
	Active ingredient	2.0mg
	Hydroxypropyl methylcellulose USP (viscosity type 4000)	22.5mg
25	Buffer)	
	Flavour)	
	Colour)	as required
	Preservative)	
	Sweetener)	
	Purified Water BP	to 5.0ml

The hydroxypropyl methylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup produced is clarified by filtration.

Metered Dose Pressurised Aerosol

A. Suspension Aerosol

	<u>mg/metered dose</u>	<u>Per can</u>
Active ingredient micronised.	0.100	26.40mg
5 Oleic Acid BP	0.010	2.64mg
Trichlorofluoromethane BP	23.64	5.67g
Dichlorodifluoromethane BP	61.25	14.70g

10 The active ingredient is micronised in a fluid energy mill to a fine particle size range. The Oleic Acid is mixed with the Trichlorofluoromethane at a temperature of 10-15°C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, 15 delivering 85mg of suspension are crimped onto the cans and the Dichlorodifluoromethane is pressure filled into the cans through the valves.

B. Solution Aerosol

	<u>mg/metered dose</u>	<u>Per can</u>
20 Active ingredient	0.100	24.0mg
Ethanol BP	7.500	1.80g
Trichlorofluoromethane BP	18.875	4.53g
Dichlorodifluoromethane BP	48.525	11.65g

25 Oleic acid BP, or a suitable surfactant e.g. Span 85 (sorbitan trioleate) may also be included.

30 The active ingredient is dissolved in the ethanol together with the oleic acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoromethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the 35 valves.

Suppositories

Active ingredient		2.0mg
* Witepsol ^(R.T.M.) H15	to	1.0g

* A proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled, using suitable machinery, into 1g size suppository moulds.

10 Injection for Intravenous Administration

	<u>mg/ml</u>
Active ingredient	0.5mg
Sodium Chloride BP	as required
Water for Injection BP	to 1.0ml

15 Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively

20 suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the

25 solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

Inhalation Cartridges

	<u>mg/cartridge</u>
Active ingredient micronised	0.200
Lactose BP	to 25.0

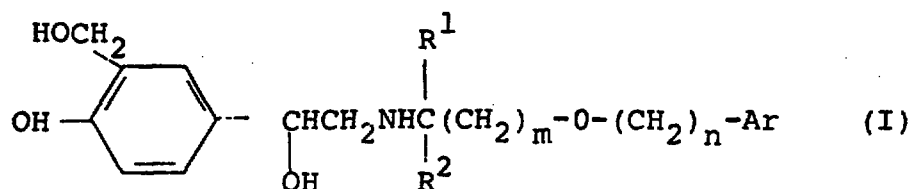
30 The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tableting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine.

35 The contents of the cartridges are administered using a powder inhaler such as the Glaxo Rotahaler^(R.T.M.).



CLAIMS:

1. Compounds of the general formula (I):



wherein

m is an integer from 2 to 8 and

n is an integer from 1 to 7 with the proviso that the sum total of m+n is 4 to 12;

Ar represents a phenyl group which may be unsubstituted or substituted by one or two substituents selected from halogen atoms, C₁₋₃ alkyl and C₁₋₃ alkoxy groups, or by an alkylenedioxy group of formula -O(CH₂)_pO- where p is 1 or 2; and

R¹ and R², which may be the same or different, each represents a hydrogen atom or a C₁₋₃ alkyl group with the proviso that the sum total of carbon atoms in R¹ and R² is not more than 4;

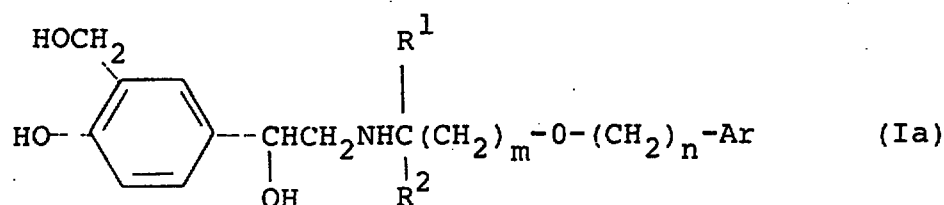
and physiologically acceptable salts and solvates thereof.

2. Compounds according to claim 1, wherein m is 3 and n is 6; or m is 4 and n is 3, 4 or 5; or m is 5 and n is 2, 3, 4 or 5; or m is 6 and n is 2 or 3.

3. Compounds according to claim 1, wherein the sum total of m+n is 7, 8, 9 or 10.



4. Compounds according to any of claims 1 to 3, wherein R^1 and R^2 , which may be the same or different, each represents a hydrogen atom or a methyl group.
5. Compounds according to any of claims 1 to 4, wherein Ar represents an unsubstituted phenyl group or a phenyl group substituted by one substituent selected from chlorine and fluorine atoms, methoxy and methyl groups.
6. Compounds of the general formula (Ia):



wherein

R^1 and R^2 are as defined for general formula I in claim 1;

m is an integer from 3 to 6 and

n is an integer from 2 to 6 with the proviso that the sum total of m+n is 7 to 10 inclusive; and

Ar is phenyl or phenyl substituted by a methyl or methoxy group or a fluorine or chlorine atom;

and the physiologically acceptable salts and solvates thereof.

7. Compounds of the general formula (Ia) according to claim 6, wherein R^1 is a hydrogen atom and R^2 is a hydrogen atom or a methyl group.

8. Compounds of the general formula Ia according to claim 6, wherein R^1 and R^2 , which may be the same or different is each a hydrogen atom or a methyl group, m is



4 or 5, n is 2, 3 or 4 and Ar is phenyl or phenyl substituted by a chlorine or fluorine atom or a methoxy or methyl group.

9. 4-Hydroxy- α^1 [[[6-(4-phenylbutoxy)hexyl]amino]methyl]-
5 1,3-benzenedimethanol
and physiologically acceptable salts thereof.
10. 4-Hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol.
1-hydroxy-2-naphthalenecarboxylate.
- 10 11. Compounds of the general formula I according to claim 1 selected from
4-hydroxy- α^1 [[[6-(3-phenylpropoxy)hexyl]amino]-
methyl]-1,3-benzenedimethanol;
4-hydroxy- α^1 [[[6-(2-phenylethoxy)hexyl]amino]methyl]-
-1,3-benzenedimethanol;
15 4-hydroxy- α^1 [[[5-(4-phenylbutoxy)pentyl]amino]methyl]-
-1,3-benzenedimethanol
4-hydroxy- α^1 [[[1-methyl-6-(2-phenylethoxy)hexyl]-
amino]methyl]-1,3-benzenedimethanol;
4-hydroxy- α^1 [[[1-methyl-5-(3-phenylpropoxy)pentyl]-
20 amino]methyl]-1,3-benzenedimethanol;
4-hydroxy- α^1 [[[1-methyl-5-(4-phenylbutoxy)pentyl]-
amino]methyl]-1,3-benzenedimethanol;
4-hydroxy- α^1 [[[1-ethyl-6-(2-phenylethoxy)hexyl]-
amino]methyl]-1,3-benzenedimethanol;
25 α^1 [[[1,1-dimethyl-6-(2-phenylethoxy)hexyl]amino]-
methyl-4-hydroxy-1,3-benzenedimethanol;
 α^1 [[[6-[2-(4-fluorophenyl)ethoxy]-1-methylhexyl]-
amino]methyl]-4-hydroxy-1,3-benzenedimethanol;
4-hydroxy- α^1 [[[6-[3-(4-methoxyphenyl)propoxyl]-1-
30 methylhexyl]amino]methyl]-1,3-benzenedimethanol;



- 74 -

4-hydroxy- α^1 -[[[1-methyl-6-(4-phenylbutoxy)hexyl]-
amino]methyl]-1,3-benzenedimethanol;

4-hydroxy- α^1 -[[[6-[2-(4-methylphenyl)ethoxy]hexyl]-
amino]methyl]-1,3-benzenedimethanol;

5 α^1 -[[[6-[2-(3-chlorophenyl)ethoxy]hexyl]amino]methyl]-
4-hydroxy-1,3-benzenedimethanol;

4-hydroxy- α^1 -[[[6-[2-(4-methoxyphenyl)ethoxy]hexyl]-
amino]methyl]-1,3-benzenedimethanol;

10 α^1 -[[[6-[3-(4-fluorophenyl)propoxy]hexyl]amino]-
methyl]-4-hydroxy-1,3-benzenedimethanol;

and the physiologically acceptable salts thereof.

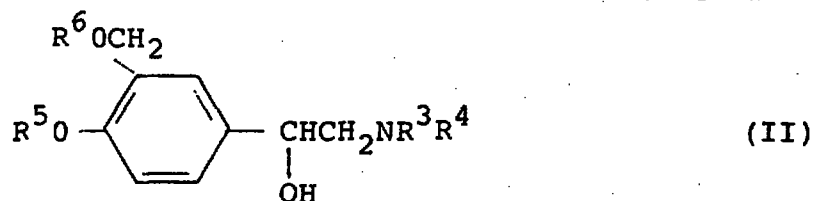
12. A pharmaceutical composition comprising at least
one compound of general formula (I) as defined in any of
claims 1 to 11 or a physiologically acceptable salt
15 or solvate thereof, together with a physiologically
acceptable carrier or excipient.

13. A composition as claimed in claim 12 in a form
suitable for administration by inhalation or insufflation.

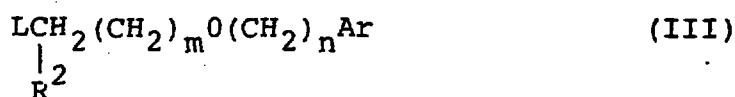
14. A composition as claimed in claim 12 in a form
20 suitable for oral, buccal, parental, topical or rectal
administration.

15. A composition as claimed in claim 13, presented
as a dry powder, an aerosol spray or in a form for
delivery from a nebuliser.

25 16. A process for the preparation of a compound of
general formula (I) as defined in claim 1 or a physio-
logically acceptable salt or solvate thereof, which
process comprises: (1) in order to obtain a compound
of general formula (I) in which R^1 is a hydrogen atom,
30 alkylating an amine of general formula (II):

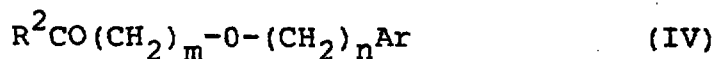


(wherein R^3 , R^5 and R^6 each represents a hydrogen atom or a protecting group and R^4 is a hydrogen atom) with an alkylating agent of general formula (III):



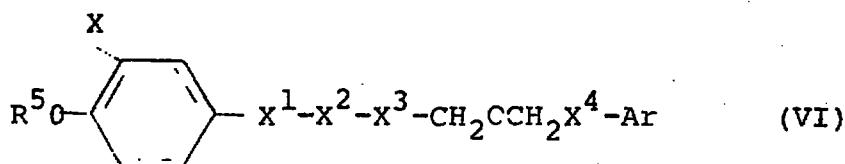
(wherein m , n , R^2 and Ar are as defined in claim 1 and L is a leaving group)

or with a compound of general formula (IV):



(wherein R^2 , m , n and Ar are as defined in claim 1) in the presence of a reducing agent, followed by removal of any protecting groups where present; or

(2) reducing an intermediate of general formula (VI):



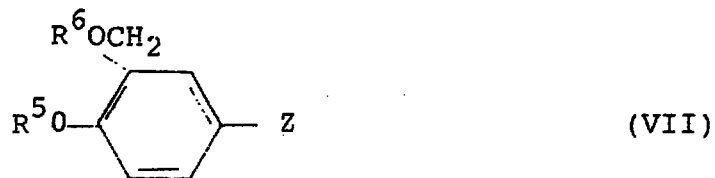
(wherein n and Ar are as defined in claim 1, R^5 is a hydrogen atom or a protecting group, and at least one of X , X^1 , X^2 , X^3 and X^4 represents a



reducible group and the other group or groups have the meanings: X is $-\text{CH}_2\text{OR}^6$, X^1 is $-\text{CH}(\text{OH})-$, X^2 is $-\text{CH}_2\text{NR}^3$, and X^3 is $-\text{CR}^1\text{R}^2(\text{CH}_2)_{m-1}$ and X^4 is $-(\text{CH}_2)_{n-1}$ where R^6 , R^3 , R^2 , R^1 and m are as defined in claim 1)

or a protected derivative thereof followed by removal of any protecting groups where present; or

(3) reacting a compound of general formula (VII):

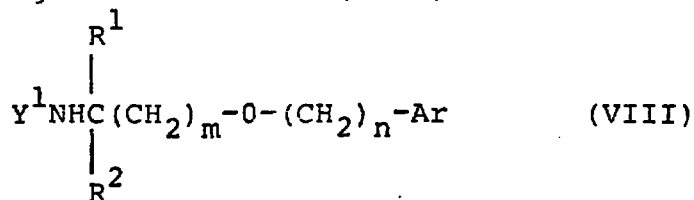


(wherein Z represents a group $-\text{CH}-\text{CH}_2$ or $\begin{array}{c} \diagup \quad \diagdown \\ \text{O} \end{array}$)

$-\text{CHCH}_2\text{L}$ where R^5 and R^6 , which may be the same or different, each represents a hydrogen atom

or a protecting group and L is a leaving group)

with an amine of general formula (VIII):

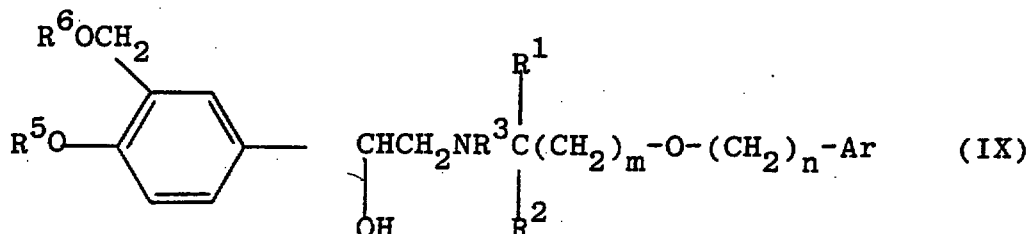


(wherein Y^1 is a hydrogen atom or a group convertible thereto by catalytic hydrogenation and R^1 , R^2 , m, n and Ar are as defined in claim 1)

followed by removal of any protecting groups where present; or



(4) deprotecting a protected derivative of general formula (IX):



(wherein R^1 , R^2 , m , n and Ar are as defined in claim 1 and R^3 , R^5 and R^6 are each a protecting group or a hydrogen atom provided that at least one is a protecting group; and, if desired, converting the resulting compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

17. Compounds of general formula (I) as defined in claim 1, substantially as herein described with particular reference to the examples.