

Description

This invention relates to new compounds, processes for their preparation, and compositions containing them.

5 The specification of United Kingdom Patent No. 1025699 discloses N₁, N₁-diphenyl-alkylene-α,ω-diamines with coronary vasodilatory properties.

The specification of United States Patent No. 3943172 discloses 2-[N-phenyl-N-(R₁,R₂-aminoalkyl or alkanoyl)]amino (1,2,3,4-tetrahydronaphthalenes) which are claimed to be active for the treatment of cardiac arrhythmia.

10 The specification of United States Patent No. 4210749 discloses amongst many other compounds, N-alkylaminoalkylbenzazepines which are claimed to be useful as analgesics and narcotic antagonists.

The specification of United States Patent No. 2653977 discloses symmetric bis-(hydroxyphenylalkylamino) bridge compounds in which alkylene is included among many other bridge groups. These compounds are claimed to have utility as blood pressure agents which are variously hyper-
15 and hypotensive.

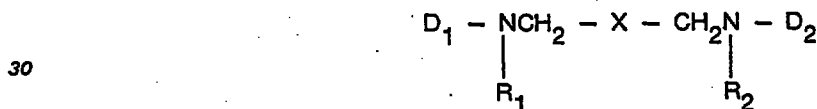
Chemical Abstracts, Vol. 63, 1965, 17940 f-h, describes bis(alkoxyphenylalkylamino) bridge compounds, in which —(CH₂)₃— is included among many other bridge groups, prepared for pharmacological screening as potential sympathomimetics.

The specification of United Kingdom patent No. 1475375 discloses amongst several other compounds,
20 N,N'-bis-(3,4-dihydroxy-6-methylphenylethyl)alkylene diamines, indicated for use as anti-hypertensive agents.

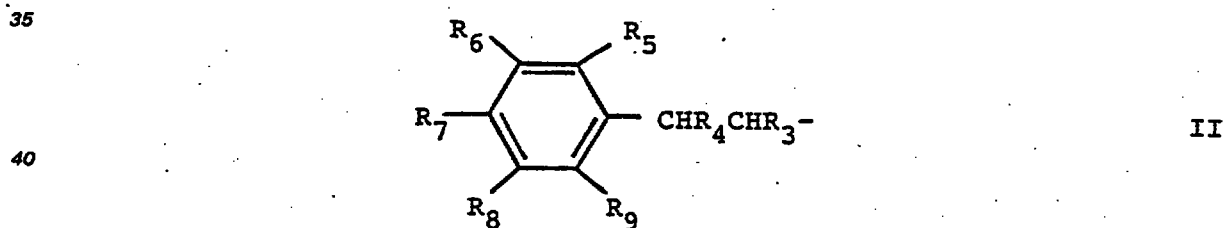
The specification of United Kingdom patent No. 1,004,071 describes N(alkylaminoalkyl)phenylethylamines which are claimed to be useful as diuretic agents.

We have now found a group of novel compounds which have pharmacological properties which are
25 advantageous to those of compounds described in the above documents.

According to the invention we provide the compounds of formula I,



in which D₁ represents a group of formula II,

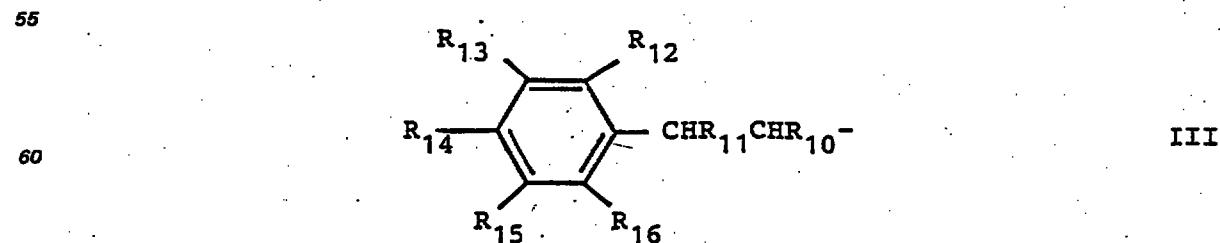


45 where R₁ and R₅, or R₃ and R₅ may form a chain —CH₂CH₂—, or R₄ and R₅ may form a chain —CH₂—, or R₃, R₄ and R₅ are each hydrogen, the remainder of R₁, R₃ and R₄, which may be the same or different, being hydrogen, alkyl or phenyl, none, one or two of R₆, R₇, R₈ and R₉ represent hydroxy and the remainder represent hydrogen,

X represents a chain —(CH₂)_n—, optionally substituted by hydroxy,
50 n is an integer from 1 to 7 inclusive,

D₂ represents hydrogen, alkyl, phenyl; alkyl substituted by one or more of hydroxy, pyridyl, phenyl; or alkyl substituted by phenyl which in turn is substituted by halogen, alkyl, amino, alkoxy or nitro, or

D₂ represents a group of formula III,



where R_2 and R_{12} , or R_{10} and R_{12} may form a chain $-\text{CH}_2-\text{CH}_2-$, or R_{11} and R_{12} may form a chain $-\text{CH}_2-$, or R_{10} , R_{11} and R_{12} are each hydrogen,

the remainder of R_2 , R_{10} and R_{11} , which may be the same or different being hydrogen, alkyl or phenyl, none, one or two of R_{13} , R_{14} , R_{15} and R_{16} represent hydroxy, and the remainder represent hydrogen,

5 or R_2 and D_2 , together with the nitrogen atom to which they are attached, form a 5 or 6 membered heterocyclic ring,

provided that when X is not substituted by hydroxy and

i) when R_3 , R_4 and R_5 are hydrogen, R_1 and R_2 are both hydrogen or lower alkyl, and two of R_6 , R_7 , R_8 and R_9 are hydroxy, D_2 is not identical to D_1 , or

10 ii) when R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are hydrogen, R_2 and D_2 do not each represent lower alkyl, or do not together with the nitrogen atom to which they are attached, form a 5 or 6 membered heterocyclic ring, or

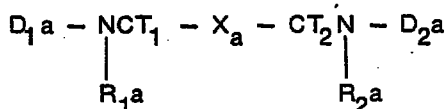
iii) when R_1 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are hydrogen, and R_3 is alkyl, D_2 is not identical to D_1 , or

15 iv) when R_1 is phenyl, R_3 and R_5 together form the chain $-\text{CH}_2\text{CH}_2-$, R_6 , R_7 , R_8 and R_9 are hydrogen, n is 1, D_2 and R_2 do not each represent hydrogen or alkyl, or do not together form a heterocyclic ring, or

v) when R_1 is hydrogen or alkyl 1 to 3 carbon atoms, R_3 is methyl, R_4 is hydrogen, n is 1, D_2 and R_2 do not each represent phenyl, and pharmaceutically acceptable derivatives thereof.

The invention also provides the compounds of formula I, and their pharmaceutically acceptable derivatives, as pharmaceuticals.

20 According to our invention we also provide a process for the production of a compound of formula I, or a pharmaceutically acceptable derivative thereof, which comprises

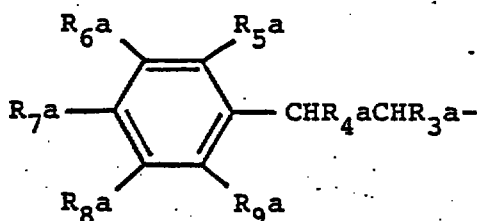


IV

in which both T_1 and T_2 represent H_2 or O , provided that at least one of T_1 and T_2 represents O ,

30 R_1a and R_2a have the same significance as R_1 and R_2 above, save that in addition they may represent a protecting group,

D_1a represents a group of formula V,



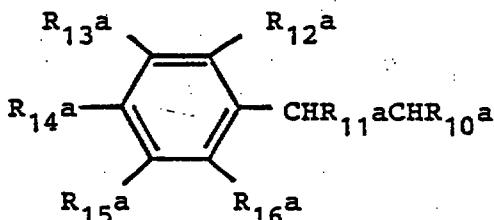
V

where R_3a , R_4a , R_5a , R_6a , R_7a , R_8a and R_9a respectively have the same significances as R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 above, save that in addition one or two of R_6a , R_7a , R_8a and R_9a may represent a protected hydroxy group,

X_a has the same significance as X above, save that in addition it may bear a protected hydroxy,

D_2a represents hydrogen, alkyl, phenyl; or alkyl substituted by one or more of hydroxy, protected hydroxy, pyridyl, phenyl; or alkyl substituted by phenyl which in turn is substituted by halogen, alkyl, 50 amino, alkoxy or nitro;

or D_2a represents a group of formula VI,

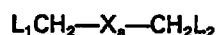


VI

where R_{10a} , R_{11a} , R_{12a} , R_{13a} , R_{14a} , R_{15a} and R_{16a} respectively have the same significance as R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} and R_{16} above, save that in addition one or more of R_{13a} , R_{14a} , R_{15a} and R_{16a} may represent a 65 protected hydroxyl group,

and, if necessary or desired thereafter, removing any protecting groups to give the corresponding compound of formula I,

(b) producing a compound of formula I in which D_2 is identical to D_1 , and R_1 is identical to R_2 , by reacting a compound of formula VII,

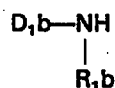


VII

in which L_1 and L_2 , which may be the same or different, represent leaving groups,

X_a is as defined above,

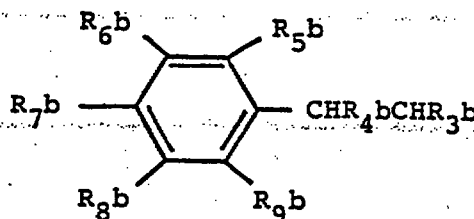
with a compound formula VIII,



VIII

or an acid addition salt thereof,

D_1b represents the group of formula IX,

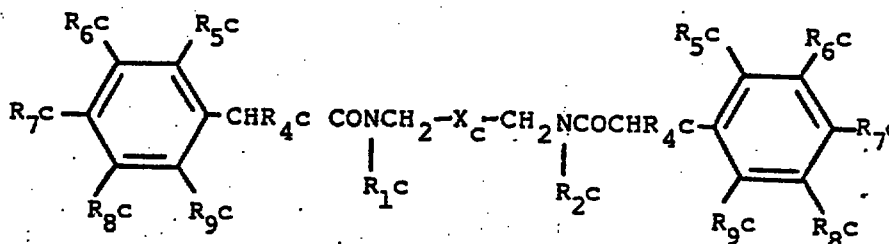


IX

in which $R_1b, R_3b, R_4b, R_5b, R_6b, R_7b, R_8b$ and R_9b respectively have the same significances as $R_1, R_3, R_4, R_5, R_6, R_7, R_8$ and R_9 above, save that in addition R_1b may represent a removable group capable of increasing the nucleophilicity of nitrogen, and one or two of R_6b, R_7b, R_8b , and R_9b may represent a protected hydroxy,

and if necessary or desired thereafter, removing any such protecting or removable groups to give the corresponding compound of formula I,

(c) producing a compound of formula I in which D_2 is identical to D_1 and both R_3 groups are hydrogen, by selectively reducing a compound of formula X,



X

in which $R_1c, R_2c, R_4c, R_5c, R_6c, R_7c, R_8c, R_9c$ and X_c respectively have the same significances as $R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9$ and X above, save that in addition,

either one or both of R_1c and R_2c may represent protecting groups,

one or two of R_6c, R_7c, R_8c and R_9c may represent a protected hydroxy group, and

X_c may bear a protected hydroxy group,

and if necessary or desired thereafter removing any such protecting groups to give the corresponding compound of formula I, or

(d) removal of a protecting group from a corresponding compound of formula I carrying one or more protected hydroxy or protected amino groups,

and where desired or necessary converting the resulting compound of formula I to a pharmaceutically acceptable derivative thereof, or vice versa.

In process (a), the reducing agent may be electrophilic, for example diborane, or nucleophilic, for example a complex metal hydride, e.g. lithium aluminium hydride or sodium (2-methoxyethoxy)-aluminium hydride. The solvent is preferably inert to the reaction conditions. Aprotic solvents are preferred, for example tetrahydrofuran, diethyl ether, or 1,2-dimethoxyethane. The reaction may be carried out at a temperature of from about 0 to 100°C.

When R_1a and/or R_2a represent a protecting group, the protecting group may be a hydrogenolisable protecting group, for example, a 1-phenylalkyl derivative, e.g. benzyl. The protecting group may be removed by reduction using, e.g. hydrogen and a suitable hydrogenation catalyst, e.g. palladium on charcoal.

When one or two of R_6a, R_7a, R_8a and R_9a represents a protected hydroxy group and/or D_2a carries a

protected hydroxy group, the protected hydroxy group may be, for example alkoxy, phenylalkoxy, e.g. phenylmethoxy, or alkanoyloxy, e.g. acetoxy. (15)

Removal of the hydroxy protecting groups depends on the nature of the protecting group, but conventional techniques may generally be employed, including acidic and basic cleavage, and hydrogenolysis. For example, protecting alkyl or phenyl alkyl groups may be removed by cleavage using a protic acid, e.g. hydrochloric acid or hydrobromic acid at 0 to 150°C, or a Lewis acid, e.g. by reacting with a boron trihalide in a chlorocarbon solvent. When the protecting group is alkanoyl, cleavage may be effected using a base, e.g. sodium hydroxide, in a suitable solvent, e.g. aqueous ethanol. Lewis bases, e.g. pyridine hydrochloride may be used to cleave alkyl or phenylalkyl groups. 1-Phenylalkyl groups, e.g. benzyl, may be removed by catalytic hydrogenation using a suitable catalyst, e.g. palladium, in a suitable solvent, e.g. ethanol, or acetic acid, preferably under pressure.

In process (b) L_1 and L_2 may be an anion forming group, for example, halogen, e.g. chlorine or bromine, or p-toluenesulphonate. The reaction is preferably carried out in a suitable solvent in the presence of a base. The solvent may also act as the base. Suitable solvents, are for example, pyridine (in which case, no added base is necessary), or ethanol or dimethylformamide (with which a base, for example pyridine, triethylamine or sodium hydroxide is preferably used). The reaction may be carried out at a temperature of from about 0 to 100°C.

When R_1b represents a removable group capable of increasing the nucleophilicity of nitrogen, R_1b may be, for example, p-toluenesulphonyl, or trihaloacetyl, e.g. trichloroacetyl or trifluoroacetyl.

The removal of protecting groups in process (b) may be carried out as described for process (a).

The reduction, and removal of protecting groups, in process (c) may be carried out as described for process (a).

The removal of protecting groups in process (d) may be carried out as described for process (a), under acidic, basic or hydrogenolytic conditions. When D_2 of formula I represents an alkyl group substituted by phenyl substituted by amino, the amino group may be obtained by reduction of a suitably placed nitro protecting group, using for example, catalytic hydrogenation, e.g. hydrogen and palladium, in a suitable solvent, e.g. ethanol, preferably at an elevated pressure, or chemical reduction, e.g. using tin and a suitable acid, e.g. hydrochloric acid, at a temperature of from about 0 to 100°C.

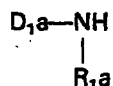
When D_1a equals D_2a , and R_1a equals R_2a , and both T_1 and T_2 equal =0, the compounds of formula IV may be prepared by reacting a compound of formula XI,



XI

where Z_1 and Z_2 , which may be the same or different, represent good leaving groups,

X_a is defined above,
with a compound of formula XII,



XII

in which D_1a and R_1a are as defined above.

Good leaving groups Z_1 and Z_2 include, for example, halogen, e.g. chlorine, bromine, 1-imidazolyl, trifluoromethane sulphonate, alkyl carbonate, e.g. ethyl or benzyl carbonate, or alkanoyloxy, e.g. trifluoroacetoxy.

The reaction may be carried out in a solvent which is inert to the reaction conditions, for example, a chlorinated hydrocarbon, e.g. chloroform, in the presence of a non-nucleophilic base, e.g. triethylamine. The reaction may be carried out at a temperature of from about 0 to 100°C.

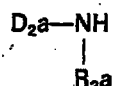
The free acid corresponding to formula XI, i.e. when Z_1 and Z_2 both equal hydroxy, may be reacted, e.g. with thionyl chloride, ethyl chloroformate or N,N'-carbonyldiimidazole to convert the COOH group to a group $-COZ_1$.

The compound of formula IV when D_2a may or may not equal D_1a and/or R_1 may or may not equal R_2a may be prepared by sequentially reacting the groups Z_1 and Z_2 , in any order in the molecule of formula XIII,



XIII

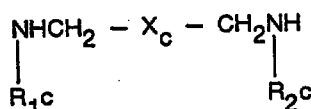
in which T_1 , T_2 , X_a , Z_1 and Z_2 are as defined above,
by reaction with a compound of formula XII and/or XIV,



XIV

where D_2a and R_2a are as defined above, as appropriate, followed by reaction of the resulting compound with a compound of formula XII or XIV.

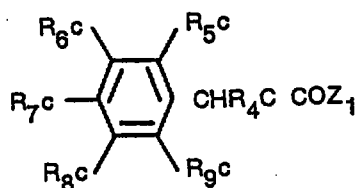
The compounds of formula X may be prepared by reacting a compound of formula XV,



XV

(16)

where R_1c , R_2c and X_c are as defined above, with a compound of formula XVI,



XVI

where Z_1 , R_4c , R_5c , R_6c , R_7c , R_8c and R_9c are as defined above.

The reaction may be carried out under the same conditions as the reaction of compounds of formula XI and XII above.

The free acid corresponding to formula XVI may be reacted with the same reagents and in the same manner as the free acid corresponding to formula XI to produce the required starting material.

The compounds of formula VII, VIII, the free acid corresponding to formula XI, XII, XIII, XIV, XV and the free acid corresponding to formula XVI are either known, or may be made from known compounds using techniques known *per se*.

When any of the starting materials or intermediates contain a chiral centre, they may be resolved using conventional techniques.

The acid addition salts of the compound of formula I may be prepared by reaction of the free-base with an appropriate acid. The acid addition salts may be converted to the corresponding free-base by the action of a stronger base.

The processes as described above may produce the compound of formula I or a derivative thereof. It is also within the scope of this invention to treat any derivative so produced to liberate the free compound of formula I, or to convert one derivative into another.

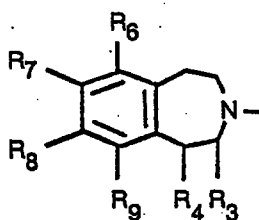
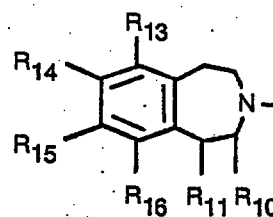
The compounds of formula I and the intermediates therefore may be isolated from their reaction mixtures using conventional techniques.

Pharmaceutically acceptable derivatives of the compounds of formula I include pharmaceutically acceptable acid addition salts. Suitable salts include salts of mineral acids, for example, hydrohalic acids, e.g. hydrochloric acid or hydrobromic acid, or organic acids, e.g. formic, acetic or lactic acids. The acid may be polybasic, for example sulphuric, fumaric or citric acid.

Other pharmaceutically acceptable derivatives are compounds which will be suitable bioprecursors (prodrugs) of the compounds of formula I and will be readily apparent to those skilled in the art and may be made from the compounds of formula I using conventional processes known *per se* or by processes analogous to those described above. Suitable bioprecursors include amides of compounds of formula I, and when a compound of formula I bears a hydroxy group, esters for example carboxylic acid esters, e.g. alkanoyl, such as acetyl or isobutyryl, or aroyl, e.g. benzoyl.

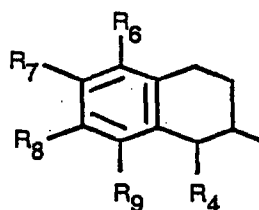
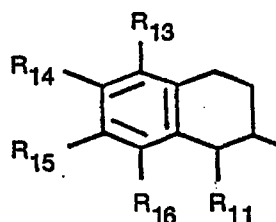
We prefer each of R_1 , R_2 , R_4 and R_{11} when they represent alkyl, to contain up to and including 8, and preferably up to and including 4 carbon atoms.

As a specific group we provide compounds of formula I in which one or both of R_1 and R_2 is, hydrogen or alkyl C1-6, for example methyl or n-propyl, or R_1 and R_5 , or R_2 and R_{12} form respectively part of the groups A_1 or A_2 .

 A_1  A_2

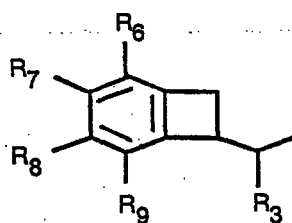
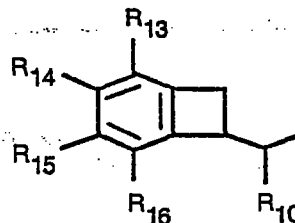
where R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{13} , R_{14} , R_{15} and R_{16} are as defined above.

As a further specific group we provide compounds of formula I in which one or both of R_3 and R_{10} is hydrogen, or R_3 and R_5 , or R_{10} and R_{12} , form respectively part of the groups B_1 or B_2 .

B₁B₂

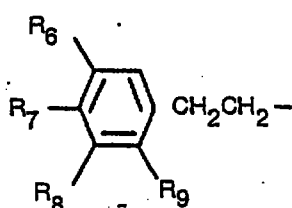
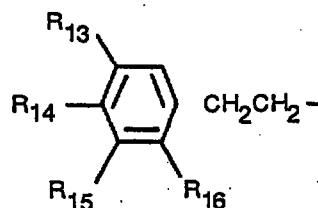
where R₄, R₆, R₇, R₈, R₉, R₁₁, R₁₃, R₁₄, R₁₅ and R₁₆ are as defined above.

As a still further specific group we provide compounds of formula I in which one or both of R₄ and R₁₁ is, hydrogen, hydroxy or phenyl or R₄ and R₅, or R₁₁ and R₁₂, form respectively part of the groups C₁ or C₂.

C₁C₂

where R₃, R₆, R₇, R₈, R₉, R₁₀, R₁₃, R₁₄, R₁₅ and R₁₆ are as defined above.

As a yet further group we provide compounds of formula I in which all of R₃, R₄ and R₅, or all of R₁₀, R₁₁, and R₁₂ are hydrogen, and form respectively part of the groups E₁ and E₂.

E₁E₂

where R₆, R₇, R₈, R₉, R₁₃, R₁₄, R₁₅ and R₁₆ are as defined above.

We prefer at least one, and preferably two, of R₆, R₇, R₈ and R₉ to be hydroxy.

We prefer at least one, and preferably two, of R₁₃, R₁₄, R₁₅ and R₁₆ to be hydroxy.

We particularly prefer an adjacent pair of R₆, R₇, R₈ and R₉, and/or an adjacent pair of R₁₃, R₁₄, R₁₅ and R₁₆ to both be hydroxy.

We specifically prefer compounds in which R₇ is hydroxy.

We prefer n to be from 2 to 6 inclusive, preferably to be from 3 to 5 inclusive and especially to be 4.

When D₂ represents alkyl, or optionally substituted alkyl, the alkyl moiety may contain up to and including 8, and preferably up to and including 4 carbon atoms.

When D₂ represents alkyl substituted by an optionally substituted phenyl, the optionally substituted phenyl moiety may contain from 6 and up to and including 10 carbon atoms.

When R₂ and D₂, together with the nitrogen to which they are attached from a 5 or 6 membered heterocyclic ring, the ring may be pyrrolidino, piperidino, morpholino or particularly piperazino. When the ring is piperazino, the 4-nitrogen may be substituted with alkyl C1-6, e.g. methyl.

We especially prefer compounds of formula 1 which contain the following pairs of groups, A₁ and E₂, B₁ and B₂, B₁ and E₂, C₁ and C₂, C₁ and E₂, and E₁ and E₂, where A₁, A₂, B₁, B₂, C₁, C₂, E₁ and E₂ are as defined above.

Specifically preferred compounds of formula I are those of Examples 1, 5, 12, 14 and 22 and the pharmaceutically acceptable acid addition salts thereof.

Certain compounds of formula I can exist in optically active and meso forms. The invention also provides the optical isomers and meso isomers of these compounds of formula I, and mixtures, including racemic mixtures thereof. These compounds may be resolved into their optical isomers using conventional techniques.

When the carbon atom bearing R₃, R₄, R₁₀ or R₁₁ is in a chiral environment, the configuration of the carbon atom may be R or S. When two carbon atoms are in chiral environments, the compounds of formula I may be RR, RS, SR or SS, with respect to these two centres, except that when X is not chiral, D₂ equals D₁, and R₂ equals R₁, in which case the compounds of formula I may have RR, SS or meso configurations.

The compounds of formula I, and pharmaceutically acceptable derivatives thereof, are useful because

they possess pharmacological activity in animals. Thus the compounds act on peripheral and/or central dopamine receptors. As such, they lower blood pressure, reduce heart rate and increase blood flow to certain vascular beds, e.g. renal beds. Some compounds also have an action on other adrenoreceptors, and these exhibit cardiac stimulant and bronchodilator effects. Activity of the compounds has been observed in

the following assay systems:

- (a) canine renal blood flow, McNay and Goldberg, *J. Pharmac, Exp. Ther.*, 151, 23—31, 1966.
- (b) rabbit isolated ear artery, McCullogh, Rand and Story, *Br. J. Pharmac*, 49, 141—142, 1973, and
- (c) cat nictitating membrane, Gyorgy and Doda, *Arch. Int. Pharmacodyn*, 226, 194—206, 1977.

The compounds of the invention are indicated for use in the treatment of congestive heart failure, renal failure, angina pectoris, ischaemic heart disease, hypertension and reversible obstructive airways disease, hyperprolactinaemia and also in Parkinson's disease and other neurological disorders.

The dosage administered will naturally depend on the compound employed, the mode of administration and the desired effect. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of from 0.05 µg to 50 mg per kilogram of body weight per day. For man, the indicated total daily dosage is in the range 2.5 µg to 3.5 g, which may be administered in divided doses of, for example 1 µg to 750 mg.

The new compounds of the present invention may be used in combination with or sequentially with a wide variety of other pharmaceutically active substances. Where appropriate the compounds may be mixed with one or more other active substances or may be chemically linked with the other active substance(s), e.g. to form a salt or ester. The particular mixture, dose regimen or chemically linked substance used, and ratio of the active ingredients will depend on a variety of factors including the condition to be treated, the mode of administration, the particular active ingredients and the patient concerned.

Examples of compounds with which the present compounds may be mixed or chemically linked include:

beta-blockers, especially cardioselective beta blockers, for example, atenolol, propranolol; diuretics, for example thiazides, e.g. furosemide; angiotensin converting enzyme inhibitors, for example captopril; inotropic agents, for example, amrinone; antiemetics, for example, sulphiride, metoclopramide, or domperidone.

The compounds of formula I, and pharmaceutically acceptable derivatives thereof, have the advantage that they are more efficacious or produce less undesirable side effects in certain pharmacological models, or are longer acting than compounds of similar structure to the compounds of formula I.

The compounds of the invention may be administered by a wide variety of routes and may act systemically or locally. Thus the compounds may be administered by oral or nasal inhalation to the lung, to the buccal cavity, oesophageally, rectally, topically to the skin or to other available surfaces of the body by injection, e.g. intravenously, intramuscularly, intraperitoneally, or by surgical implant.

According to our invention we also provide a pharmaceutical composition comprising preferably less than 80% and more preferably less than 50% by weight of a compound of formula I, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Examples of suitable adjuvants, diluents or carriers are: for tablets, capsules and dragées; microcrystalline cellulose, calcium phosphate, diatomaceous earth, a sugar such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatin;

for suppositories; natural or hardened oil or waxes; and for inhalation compositions, coarse lactose.

When the compounds are to be used in aqueous solution it may be necessary to incorporate a chelating or sequestering agent, e.g. sodium edetate, an antioxidant, e.g. sodium metabisulphite or buffering agents, e.g. sodium hydrogen phosphate and sodium phosphate. Aqueous solutions typically contain up to about 10% w/w of the new compound and may be used for intravenous injections.

According to the invention, we further provide a method of increasing the force of contraction of the heart in an animal, either human or non-human, which method comprises administering to the animal an effective amount of one or more compounds of the invention.

The invention is illustrated, but in no way limited by the following examples. All temperatures quoted are in °C.

Stereochemical nomenclature is according to Appendix IV, selection of Index Names for Chemical Substances from the Chemical Abstracts 1977 Index Guide, paragraphs 202—212.

Assignments of absolute stereochemistry are based on the observations of Helmchen et al: (a) *Tet. Letter* 3873 (1972), (b) *ibid* 1527 (1974), (c) *ibid* 1417 (1977), and McDermid: *Proceedings of the Symposium on Dopamine Agonists* (Stockholm, 1982), Swedish Pharmaceutical Press.

Examples

Example 1

(R*S*)-2,2' [1,6-Hexanediylbisamino]-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol]

(a) *N*-[1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthylidene]-(*R*)-1-phenylethylamine

A solution of 1,2,3,4-tetrahydro-5,6-dimethoxy-2-tetralone (20.6 g) and (*R*)-1-phenylethylamine (14 ml)

in dry toluene (200 ml) was heated under reflux for 4 hours with continual removal of the water formed. The mixture was evaporated to leave a brown oil (30 g) M^+309 .

(b) *(RS & RR) 1,2,3,4-Tetrahydro-5,6-dimethoxy-N-(1-phenylethyl) naphthalenamine hydrochloride*

5 A solution of the imine from step a) (28 g) in dry ethanol (250 ml) was hydrogenated over Adam's catalyst (1 g) at atmospheric pressure and room temperature until no further uptake of hydrogen was observed (~2 days).

The solution was filtered and evaporated to leave an oil which dissolved in excess ethanolic HCl. The solution was evaporated to leave a dark solid which was purified by trituration with cold isopropanol (50 ml) to give a colourless solid (23 g).

The above diastereomeric amines were separated using High Pressure Liquid Chromatography (HPLC) on a silica column eluting with a mixture containing triethylamine in petroleum ether-dichloromethane (1% in 4:1).

The free base of each diastereomer was converted to its hydrochloride salt and crystallised to >99.8% diastereomeric purity (confirmed by HPLC).

b1 1st eluted diastereomer 9.5 g mp 265—267°

b2 2nd eluted diastereomer 6.0 g mp 297° dec

(c) *S(-) 1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthalenamine hydrochloride*

20 A solution of the amine b1 (6.95 g) in dry methanol (400 ml) was hydrogenated over a 10% Pd/C catalyst (2 g) at atmospheric pressure and room temperature for 24 hours. The solution was filtered and the filtrate evaporated to leave a solid which crystallised from ethanol as colourless prisms (3.8 g) mp 270° $[\alpha]_D^{25} = -60.1$ (C = 0.15 (CH₃OH)).

(d) *R(+) 1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthalenamine hydrochloride*

A solution of the amine b2 (6.95 g) in dry methanol (500 ml) was hydrogenated over a 10% Pd/C catalyst (2 g) at atmospheric pressure and room temperature for 78 hours. The solution was filtered and the filtrate evaporated to leave a solid which crystallised from ethanol as colourless prisms (3.5 g), mp > 260° $[\alpha]_D^{25} = +58.6$ (C = 0.2, CH₃OH).

(e) *(S) Methyl-6-(1,2,3,4-tetrahydro-5,6 dimethoxy-2-naphthalenamine)-6-oxo-hexanoate*

Methyl 5-(chloroformyl)pentanoate (1.8 g) was added dropwise to a stirred solution of the amine from step (c) (2.43 g) and triethylamine (2.8 mls) in dry dichloromethane (100 ml). The solution was heated under reflux for 1 hour. The cooled solution was washed with dilute hydrochloric acid, dilute sodium bicarbonate solution and brine. The organic phase was dried over magnesium sulphate filtered and evaporated to leave a colourless solid which crystallised from toluene/petrol ether as colourless flakes (3.2 g) mp 115—116° $[\alpha]_D^{24} = -38.6$ (C = 0.17 CH₃OH).

(f) *(S) 6-(1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthalenamine)-6-oxo-hexanoic acid*

40 A solution of the ester from step (e) (3.0 g) in methanol (50 ml) and 10% sodium hydroxide solution (4 ml) was heated under reflux for 1 hour. The solution was evaporated, cooled and acidified with dilute hydrochloric acid. The precipitate was dissolved in chloroform, washed with brine, dried over magnesium sulphate, filtered and evaporated to leave a solid which crystallised from ethyl acetate/petroleum ether as colourless prisms (2.5 g) mp 147—149° $[\alpha]_D^{24} = -40.7$ (C = 0.15 CH₃OH).

(g) *(R*,S*)-N,N'-Bis[1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthyl]-hexane-1,6-diamide*

50 A solution of the acid from step (f) (1.1 g) and N,N'-carbonyldiimidazole (0.53 g) in dry dichloromethane was stirred at room temperature for 2 hours. A solution of the amine from step (d) (0.68 g) [free base] in dry dichloromethane (50 ml) was added and the mixture stirred at room temperature for 18 hours. The resulting precipitate was redissolved in chloroform and the organic phase washed with dilute hydrochloric acid, dilute sodium bicarbonate solution and brine. The organic phase was dried over magnesium sulphate filtered and evaporated to leave a colourless solid which was purified by filtering from hot methanol (1.37 g) mp 256—258° $[\alpha]_D^{25} = \pm 0.1$ (C = 0.14 CH₃OH/CHCl₃ 50/50).

(h) *(R*S*)-N,N'-Bis[1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthyl]-hexane-1,6-diamine dihydrochloride*

55 A solution of the bis amide from step (g) (1.3 g) in dry tetrahydrofuran (400 ml) was stirred during the addition of borane in tetrahydrofuran (50 ml, 1M solution). The solution was heated under reflux in a nitrogen atmosphere for 24 hours. Methanol (200 ml) was added to the cooled solution and evaporation gave a sticky solid. Methanolic HCl was added and the suspension heated under reflux for 4 hours. The solution was evaporated to leave a colourless solid which crystallised from methanol as colourless prisms (1.19 g) mp > 260° $[\alpha]_D^{25} = -0.5$ (C = 0.2 H₂O).

(i) *(R*S*)-2,2'-(2,6-Hexanediyldiamino)-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol]*

65 A solution of the bis amine from step (h) (1.05 g) in 48% aqueous hydrobromic acid (50 ml) was heated under reflux for 2 hours in a nitrogen atmosphere. The solution was evaporated to dryness and the residue

crystallised from methanol to give the title compound dihydrobromide as colourless prisms (0.70 g) mp > 250° [α]_D²⁵ = -1.2 (±0.4) (C = 0.18 H₂O).

Example 2

By analogous methods to those described in Example 1 above, the following compounds were made:

- (a) *[R-(R*R*)]-2,2'-(1,6-Hexanediylbisamino)-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol] dihydrobromide*
mp > 260° [α]_D²⁴ = +55.8 (C = 0.24, H₂O)
- (b) *[S-(R*R*)]-2,2'-(1,6-Hexanediylbisamino)-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol] dihydrobromide*
mp > 260° [α]_D²⁴ = -58.1 (C = 0.18, H₂O).

Example 3

2,2'-(1,6-Hexanediylbisamino)-bis-(1,2,3,4-tetrahydro-5,6-naphthalenediol)

- (a) *N,N'-Bis-(1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthyl)hexane-1,6-diamide*

A solution of adipoyl chloride (1.1 g, 0.006M) in chloroform (15 ml) was added dropwise to a solution of 1,2,3,4-tetrahydro-5,6-dimethoxy-2-aminonaphthalene (2.5 g, 0.012M) and triethylamine (1.4 g, 0.014M) in chloroform (15 ml). The mixture was stirred for 1 hour, quenched by addition of water and the organic phase was separated, washed with water and was dried over magnesium sulphate. The mixture was filtered and the filtrate was evaporated to dryness leaving a solid which was crystallised from methanol to give the required amide 2.0 g (63%) mp 223—5°.

- (b) *N,N'-Bis-(1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthyl) hexane-1,6-diamine dihydrochloride*

A suspension of the amide from step (a) (2.0 g) was stirred under nitrogen at room temperature in dry tetrahydrofuran (250 ml) while 10 ml of a 1M borane/tetrahydrofuran complex was added from a syringe. The resulting mixture was heated at reflux for 3 hours, cooled, and a further 10 ml of the borane complex was added. The mixture was heated at reflux overnight during which time a clear solution formed. The mixture was cooled and methanol was added cautiously and the solution was evaporated to dryness. Methanol was added to the residue and the solution was boiled for 30 minutes. The solution was evaporated to dryness and the residue was dissolved in ether containing a few drops of ethanol. Excess ethereal hydrogen chloride was added to this solution and the precipitated solid was filtered off, washed well with hot ethanol and dried to give the required amine hydrochloride 1.9 g (87%) mp 280° (decomp).

- (c) *2,2'-(1,6-Hexanediylbisamino)-bis-(1,2,3,4-tetrahydro-5,6-naphthalenediol) dihydrobromide*

A suspension of the dimethoxy amine from step (b) (1.8 g, 0.003M) in 48% aqueous hydrogen bromide (80 ml) was heated at reflux under nitrogen for 3 hours. Solution occurred briefly after 45 minutes but a white solid began to form almost immediately. After 3 hours the mixture was cooled and the solid was filtered off. It was washed with hot methanol, dissolved in methanol/water and the solution was treated with charcoal, filtered and the filtrate was evaporated to dryness. The title compound was obtained, as the dihydrobromide salt 1.1 g (57%) mp 250°.

Analysis:

Found: C, 49.7; H, 6.1; N, 4.2; 24.7% C₂₆H₃₆N₂O₄ requires with 1.5 mole H₂O (4.3%)
C, 49.6; H, 6.5; N, 4.4; Br, 25.4%

Example 4

By analogous methods to those described in Example 3 above, the following compound was made:
2,2'-(1,6-hexanediylbisamino)-bis-(1,2,3,4-tetrahydro-6,7-naphthalenediol) dihydrobromide mp > 260°

Example 5

[R(R,R*)](+)-7,7'-(1,6-Hexanediylbis(aminomethylene))-bis(bicyclo[4.2.0]octa-1,3,5-triene-2,4-diol)*

- (a) *Synthesis and separation of the S-(-)-1-phenylethylamides of (±)-2,3-bis(phenylmethoxy)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxylic acid*

(±)-2,3-Bis-(phenylmethoxy)-bicyclo-[4,2,0]octa-1,3,5-triene-7-carboxylic acid (40.0 g, 0.11 moles) in dry tetrahydrofuran (500 ml) was treated under nitrogen at 5° with N,N'-carbonyldiimidazole (20.8 g, 0.13 moles). The reaction mixture was kept at 5° for 3 hours and S-(-)-1-phenylethylamine (15.3 g, 0.125 moles) was added dropwise. The solution was maintained at 20° for 2 hours and then water and dichloromethane were added. The organic layer was separated, washed with dilute HCl, aqueous bicarbonate and brine, dried and evaporated to a solid (47.3 g). This amide mixture was separated by preparative high pressure liquid chromatography on silica using ethyl acetate/petroleum ether mixtures. Two fractions were obtained and recrystallised from ethyl acetate:

Less polar diastereomer: *[S-(R*,S*)]-N-(1-phenylethyl)-2,3-bis(phenylmethoxy)-bicyclo-[4,2,0]octa-1,3,5-triene-7-carboxamide*, m.p. 186—188°, [α]_D = +1.9° (c = 0.3, CHCl₃), δ CH₃ (CDCl₃) = 1.39 p.p.m.

More polar diastereomer: *[S-(R*,R*)]-N-(1-phenylethyl)-2,3-bis(phenylmethoxy)-bicyclo-[4,2,0]octa-1,3,5-triene-7-carboxamide*, m.p. 171—173°, [α]_D = +25.6° (c = 0.3, CHCl₃), δ CH₃ (CDCl₃) = 1.45 p.p.m.

21

(b) *[S-(R*,S*)]-N-(1-Phenylethyl)-2,3-bis(phenylmethoxy)-bicyclo-[4,2,0]-octa-1,3,5-triene-7-methanamine hydrochloride*

The *[S-(R*,S*)]*-amide from step (a) above (13.2 g, 2.85 mmoles) in dry tetrahydrofuran (330 ml) under nitrogen was treated with 1M borane in tetrahydrofuran (140 ml, 140 mmoles) and boiled under reflux for 5 hours. After cooling methanol and methanolic hydrogen chloride were added and the mixture stirred overnight. The solvents were evaporated and the residue when triturated with dry ether gave the *[S-(R*,S*)]*-amine hydrochloride as white crystals (10.5 g), m.p. 171—173°. $\delta(\text{CDCl}_3)$ 6.80 (1H, d), 6.60 (1H, d).

c) *[1S-[1R*-[1R*-[7S*(7S*)]]]]-N,N'-Bis-(1-phenylethyl)-N,N'-bis[(2,3-bis(phenylmethoxy)bicyclo[4,2,0]-octa-1,3,5-triene-7-yl)-methyl]-hexanediamide*.

A solution of adipoyl chloride (0.915 g, 5 mmoles) in dichloromethane (40 ml) was added dropwise to a stirred solution of the above *[S-(R*,S*)]*-amine hydrochloride (4.84 g, 10 mmoles) from step (b) and triethylamine (3.03 g 30 mmoles) in dichloromethane (80 ml). The mixture was stirred at 20° overnight then poured into water. The organic phase was separated, washed with aqueous hydrochloric acid, aqueous sodium bicarbonate and brine, dried and evaporated to a colourless solid (4.8 g, m.p. 48°).

d) *[1S-[1R*-[1R*-[7S*(7S*)]]]]-1,6-hexanediylbis-[N-(1-phenylethyl)-2,3-bis(phenylmethoxy)-bicyclo[4.2.0]-octa-1,3,5-triene-7-methanamine]dihydrochloride*.

The *[1S-[1R*-[1R*-[7S*(7S*)]]]]*-bis amide (4.86 g, 4.8 mmoles) in tetrahydrofuran (100 ml) was treated under nitrogen with 1M borane in tetrahydrofuran (24 ml, 24 mmoles) and then heated under reflux for 6 hours. After cooling methanol and methanolic hydrogen chloride were added and the solution stirred overnight and evaporated to dryness. The residue, on trituration with dry ether, gave the diamine dihydrochloride (4.6 g) which decomposes without melting above 90°.

e) *[R(R*,R*)](+)-7,7'-[1,6-Hexanediylbis(aminomethylene)]-bis(bicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol)-dihydrochloride*.

The above *[1S-[1R*-[1R*-[7S*(7S*)]]]]*-diamine dihydrochloride (1 g) in ethanol (20 ml) and acetic acid (2 ml) containing 10% palladium on carbon catalyst (0.1 g) was shaken under 3 atmospheres of hydrogen at ambient temperature for 72 hours. The mixture was filtered and the filter cake extracted with hot water. Evaporation of the water gave the (+)-diamine dihydrochloride (0.3 g), m.p. 235° (decomp), $[\alpha]_D^{20} = +12.4^\circ$ (C = 0.15, H₂O).

Example 6

By analogous methods to those described in Example 5 above, the following compounds were made:

(a) starting from the *[S-(R*,R*)]* amide of Example 5a,
[S-(R,R*)]-7,7'-[1,6-hexanediylbis(aminoethylene)]-bis(bicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol) dihydrochloride*

m.p. 235° (Decomp), $[\alpha]_D^{20} = -11.8$, (C = 0.15, H₂O).

(b) starting from a mixture of the *[S-(R*,S*)]* and *[S-(R*,R*)]* amides of Examples 5a,
racemic and meso *[R*S*]-7,7'-[1,6-hexanediylbis(aminomethylene)]-bis(bicyclo-[4.2.0]-octa-1,3,5-triene-2,3-diol) dihydrochloride*
m.p. 240° (decomposes).

Example 7

Racemic and meso *(R*,S*)-7,7'-[1,6-hexanediylbis(aminomethylene)]-bis(bicyclo-[4.2.0]-octa-1,3,5-triene-2,3-diol)*

(a) *Racemic and meso (R*S*)-N,N'-hexamethylene-bis-[2,3-bis(phenylmethoxy)bicyclo-[4.2.0]-octa-1,3,5-triene-7-carboxamide]*.

2,3-Bis-(phenylmethoxy)-bicyclo-[4.2.0]-octa-1,3,5-triene-7-carboxylic acid (0.72 g) was dissolved in dry dichloromethane (40 ml) and cooled to -5° and triethylamine (0.31 ml) added. To this was added a solution of ethyl chloroformate (0.19 ml) in dry dichloromethane (2 ml) dropwise over 10 minutes. The solution was stirred at -5° for 1 hour and hexane-1,6-diamine (0.11 g) added and the mixture warmed to room temperature for 4 hours. The reaction mixture was washed with water, 2N hydrochloric acid, 2N sodium hydroxide solution and brine dried (Na₂SO₄) and evaporated. The residue was recrystallised from ethanol affording the purified bis amide (0.43 g) m.p. 155—9°.

(b) *Racemic and meso (R*,S*)-7,7'-[1,6-hexanediylbis(aminomethylene)]-bis(bicyclo-[4.2.0]-octa-1,3,5-triene-2,3-diol) dihydrochloride*

The product of Example 7(a) was treated by the processes described in Examples 5(d) and 5(e) above, to give the title compound, as the dihydrochloride salt, m.p. 240° (decomposes).

Example 8

7-[6-(2-Phenylethylamino)hexylamino]methylbicyclo[4.2.0]octa-1,3,5-triene-2,3-diol

(a) *N*-(2-Phenylethyl)-*N'*-[[2,3-bis(phenylmethoxy)bicyclo[4.2.0]octa-1,3,5-triene-7-yl]methyl]hexane-1,6-diamide

5 A solution of 6-oxo-6-(2-phenylethylamino)hexanoic acid (1.25 g) and *N,N'*-carbonyldiimidazole (0.9 g) in dry dichloromethane (25 ml) was stirred at 20° for 2h, and a solution of 2,3-bis(phenylmethoxy)bicyclo[4.2.0]octa-1,3,5-triene-7-methanamine hydrochloride (1.9 g) and triethylamine (0.5 g, 0.7 ml) in dry dichloromethane (20 ml) was then added. The mixture was stirred for 2.5 h at 20° and water (50 ml) added. The organic phase was separated, washed with dilute hydrochloric acid, aqueous sodium bicarbonate and
10 brine, dried over MgSO₄ and evaporated leaving the required diamide was a colourless solid (2.3 g) m.p. 152—155°.

(b) *N*-(2-Phenylethyl)-*N'*-[[2,3-bis(phenylmethoxy)bicyclo[4.2.0]octa-1,3,5-triene-7-yl]methyl]-1,6-hexane-diamine dihydrochloride

15 The sub-title compound was prepared from the product of Example 8(a) using the method of Example 5(d) above, m.p. > 250°.

(c) 7-[6-(2-Phenylethylamino)hexylamino]methylbicyclo[4.2.0]octa-1,3,5-triene-2,3-diol dihydrochloride

The title compound was prepared from the product of Example 8(b) above, as the dihydrochloride salt,
20 using the method of Example 5(e), m.p. 208—210°.

Example 9

By analogous methods to those described above in 8, the following compound was made:
7-[6-[2-(3,4-dihydroxyphenyl)ethylamino]hexylamino]methylbicyclo[4.2.0]octa-1,3,5-triene-2,3-diol
25 dihydrochloride, m.p. 217° (decomposes).

Example 10

7-[6-(2-Phenylethylamino)hexylamino]methylbicyclo[4.2.0]octa-1,3,5-triene-3,4-diol

(a) *N*-[[3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-yl]methyl]-*N'*-(2-phenylethyl)hexane-1,6-diamide

30 6-Oxo-6-(2-phenylethylamino)hexanoic acid (8.65 g) was dissolved in dry tetrahydrofuran (220 ml) under an inert atmosphere and cooled to 0—5°. *N,N'*-Carbonyldiimidazole (6.12 g) was added over 5 minutes, and the mixture stirred at 0—5° for 3 hours.

3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-methanamine hydrochloride (7.98 g) and triethylamine (4.85 ml) were added successively, and the mixture was stirred at room temperature for 2 hours. The
35 resulting white precipitate was collected by filtration, washed with dry ether and dried *in vacuo* at 50°C. The product was crystallised from propan-2-ol to give a white solid, 8.77 g m.p. 150—152°.

(b) *N*-[[3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-yl]methyl]-*N'*-(2-phenylethyl)hexane-1,6-diamine dihydrochloride

40 A 1 molar solution of borane-tetrahydrofuran complex (75.5 ml) was added to a solution of the product of step (a) (8.0 g) in tetrahydrofuran (160 ml) under an inert atmosphere. The solution was heated at reflux overnight, cooled to room temperature, and methanol (50 ml) cautiously added. When all effervescence had ceased, methanolic hydrogen chloride (50 ml) was added, and the mixture refluxed for an hour. The suspension was reduced to dryness giving a white solid which was crystallised from aqueous ethanol to
45 give white needles, 6.88 g m.p. 258—9°.

(c) 7-[6-(2-Phenylethylamino)hexylamino]methylbicyclo[4.2.0]octa-1,3,5-triene-3,4-diol dihydrobromide

The product of step (b) (3.25 g) was dissolved in dry dichloromethane (10 ml) and cooled to -78°. Boron tribromide (3.5 ml) was added, and the solution stirred at -78° for 3 hours followed by 2 hours at
50 room temperature. Methanol (about 25 ml) was added, and the mixture reduced to dryness. The resulting white solid was crystallised from dry methanol to give the title compound as the dihydrobromide salt, m.p. 210—4° (dec).

Analysis: C₂₃H₃₂N₂O₂, 2HBr

Theoretical: C = 52.08%, H = 6.42%, N = 5.28%, Br = 30.19%;

55 Found: C = 51.69%, H = 6.29%, N = 5.11%, Br = 30.16%.

Example 11

By analogous methods to those described in Examples 5 and 10 above, the following compounds were made:

60 (a) (7,7'-[1,6-Hexanediylbis(aminomethylene)]-bis-bicyclo[4.2.0]octa-1,3,5-triene-3,4-diol) dihydrobromide m.p. 226° (decomposes).

(b) 7-[6-[2-(3,4-Dihydroxyphenyl)ethylamino]hexylamino]methylbicyclo[4.2.0]octa-1,3,5-triene-3,4-diol dihydrobromide

65 m.p. 100—105°.

23

Example 12

4-[2-(6-(2-Phenylethylamino)hexylamino)ethyl]-1,2-benzenediol

(a) *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-[2-phenylethyl]-hexane-1,6-diamide

A solution of 6-oxo-6-(2-(3,4-dimethoxyphenyl)ethylamino)hexanoic acid (9.3 g), and *N,N'*-carbonyldiimidazole (4.90 g) in dry dichloromethane (300 ml) was stirred at room temperature for 2 hours. A solution of 2-phenylethylamine (3.8 ml) in dichloromethane (50 ml) was added and the mixture stirred at room temperature for 3 hours.

The solution was washed with 2N HCl, water, 5% aqueous sodium bicarbonate solution and water. The organic phase was dried over magnesium sulphate, filtered and evaporated to leave a solid which crystallised from ethanol (11.38 g), m.p. 183—184°.

(b) *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-[2-phenylethyl]-hexane-1,6-diamine dihydrochloride

A solution of the diamide product of step 12(a) (4.94 g) in dry tetrahydrofuran (150 ml) was stirred under a nitrogen atmosphere while diborane in tetrahydrofuran (48 ml of 1M solution) was added. The solution was heated under reflux for 24 hours.

Methanol (100 ml) was added to the cooled solution and the mixture evaporated to dryness. The residue was dissolved in methanolic HCl (100 ml) and heated under reflux for 1 hour. The solution was evaporated and the solid crystallised from methanol (4.90 g), m.p. 283—285°.

20. (c) 4-[2-(6-(2-Phenylethylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide

A solution of the diamine product of step (b) (4.75 g) in 48% aqueous hydrobromic acid (70 ml) was heated under reflux in an atmosphere of nitrogen for 3.5 hours. The solid which formed on cooling was filtered off and crystallised from ethanol, to give the title compound as the dihydrobromide salt, (3.1 g), mp 227—228°.

25

Example 13

4-[2-(6-(2-(4-Aminophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol

(a) *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-[2-(4-nitrophenyl)ethyl]-hexane-1,6-diamine dihydrochloride

The sub-title compound was prepared by the method of Example 12(b), mp 153—155°.

30

(b) *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-[2-(4-aminophenyl)ethyl]-hexane-1,6-diamine trihydrochloride

A solution of the product of step (b) (1 g) was dissolved in a mixture of ethanol (50 ml) and acetic acid (25 ml) and hydrogenated at 45 p.s.i. and room temperature over a palladium catalyst. After hydrogen uptake had ceased the reaction mixture was warmed and filtered to remove the catalyst. The filtrate was evaporated to dryness and a solution of hydrogen chloride gas in methanol added. The solution obtained was evaporated to dryness and the solid triturated with ether (0.8 g) mp > 250°.

(c) 4-[2-(6-(4-Aminophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol trihydrobromide

The title compound was made as the trihydrobromide salt from the product of step (b) by the process described in Example 12(c) above, mp > 250°.

40

Example 14

4-[2-(6-(2-(4-Chlorophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol

(a) *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-[2-(4-chlorophenyl)ethyl]-hexane-1,6-diamide

The sub-title compound was prepared using the method of Example 12(a), m.p. 167—169°.

45

(b) *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-[2-(4-chlorophenyl)ethyl]-hexane-1,6-diamine dihydrochloride

The sub-title compound was prepared using the method of Example 12(b), m.p. > 260°.

50

(c) 4-[2-(6-(2-(4-Chlorophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide

The title compound was prepared, as the dihydrobromide salt, using the method of Example 12(c), m.p. 172—174°.

Example 15

By analogous methods to those described in Examples 12, 13 and 14 above, the following compounds were made:

55

(a) 4-[2-(6-phenylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 216—218°.

(b) 4-[2-(6-phenylmethylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 176—178°C.

60

(c) 4-[2-(6-(3-phenylpropylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 158—160°.

(d) 4-[2-(6-(4-phenylbutylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 196.5—199°.

(e) 4-[2-(6-amino-hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 201—202°.

(f) 4-[2-(6-(di-n-propylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 164—1654°.

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(g) 4-[2-(6-(*N*-methyl-2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 167—169°.

24

- (h) 4-[2-(6-(2-phenylpropylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 135—137°.
 (i) 4-[2-(6-(2-(4-nitrophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 164° dec.
 (j) 4-[2-(6-(2-(4-hydroxyphenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. > 260°.
 5 (k) 4-[2-(6-(2-(4-methylphenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 195° dec.
 (l) 4-[2-(6-(2-(4-pyridinyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol trihydrobromide, m.p. 197—8°.
 (m) 4-[2-(6-(4-methylpiperazinyl)hexylamino)ethyl]-1,2-benzenediol trihydrobromide, m.p. 197—8°.
 (n) 4-[2-(N-methyl-6-(4-methylpiperazinyl)hexylamino)ethyl]-1,2-benzenediol trihydrobromide, m.p.
 10 187—90°.
 (o) 4-[2-(4-(2-phenylethylamino)butylamino)ethyl]-1,2-benzenediol dihydrobromide m.p. 251—5° (dec).
 (p) 4-[2-(6-(1,2,3,4-tetrahydro-2-naphthylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 224—6°.
 (q) 4-[2-(8-(2-phenylethylamino)octylamino)ethyl]-1,2-benzenediol dihydrobromide m.p. 229—30°.
 15 (r) 4-[2-(5-(2-phenylethylamino)pentylamino)ethyl]-1,2-benzenediol dihydrobromide m.p. 187—8°.
 (s) 3-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7,8-diol dihydrobromide m.p. 115° (dec).
 (t) 4-[2-(N-methyl-6-(N'-methyl-2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide, m.p. 186—8°.

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Example 16

4-[2-(6-(2-Hydroxy-2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol

- A solution of N-(2-hydroxy-2-phenylethyl)-N'-[2-(3,4-bis(phenylmethoxy)phenyl)ethyl]hexane-1,6-diamide prepared in an analogous manner to that described in Example 12(a) above (3.48 g) in dry tetrahydrofuran (100 ml) was stirred under a nitrogen atmosphere whilst diborane in tetrahydrofuran (30 ml of 1M solution) was added and then the solution heated to reflux for 6 hours. Methanol (100 ml) was added to the cooled solution and the mixture evaporated to dryness. The residue was dissolved in methanolic HCl (100 ml) and heated to reflux for 18 hours. The solution was evaporated to dryness and the residue recrystallised from ethanol to give the title compound, as the dihydrochloride salt, colourless prisms (1.3 g) m.p. 188—9°.

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Example 17

4-[2-(N-Methyl-6-(di-n-propylamino)hexylamino)ethyl]-1,2-benzenediol

(a) N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-Methyl-N',N'-di-n-propyl-hexane-1,6-diamide

- 35 A solution of N-[2-(3,4-dimethoxyphenyl)ethyl]-N',N'-di-n-propylhexane-1,6-diamide (3.9 g) in dry dimethyl formamide (20 ml) was added to a suspension of oil free sodium hydride (0.24 g) in dry dimethyl-formamide (20 mls). The mixture was heated at 70° for 1 hour. Methyl iodide (0.75 mls) was added to the cooled suspension and the mixture stirred at room temperature for 2 hours.

The mixture was evaporated to dryness, dissolved in ethyl acetate and the organic phase washed with dilute hydrochloric acid, dilute sodium bicarbonate solution and brine. The organic phase was dried over magnesium sulphate, filtered and evaporated to leave a brown oil (3.8 g) M+ 406.

40

(b) N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-N',N'-di-n-propyl-hexane-1,6-diamine dihydrochloride

- The sub title compound was prepared from the product of step (a) by the method of Example 12(b) above, m.p. 130—132°.

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(c) 4-[2-(N-Methyl-6-(di-n-propylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide

The title compound was prepared, as the dihydrobromide salt, from the product of step (b) by the method of Example 12(c) above, mp 97—99°.

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Example 18

± 4-[2-(4-Hydroxy-6-(2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol

(a) N-[2-Phenylethyl-tetrahydro-5-oxo-2-furan-acetamide

- 55 Ethyl chloroformate (4.15 g, 3.7 ml) was added dropwise with stirring to a solution of tetrahydro-5-oxo-2-furan-acetic acid (5.5 g) and triethylamine (3.8 g, 5.3 ml) in dry dichloromethane (75 ml) at -10° and the mixture stirred for 45 minutes. 2-Phenylethylamine (4.6 g) in dry dichloromethane (25 ml) was added and the reaction kept at 20° for 18 h. The solution was washed with sodium bicarbonate solution, hydrochloric acid and water, dried (MgSO₄) and evaporated giving the required lactone-amide (3.5 g) as a pale cream solid m.p. 83—85° after trituration with ether.

(b) 3-Hydroxy-N'-[2-(3,4-dimethoxyphenyl)ethyl]-N-[2-phenylethyl]hexane-1,6-diamide

- 60 The lactone-amide from step (a) (3.45 g) and 2-(3,4-dimethoxyphenyl)ethylamine (2.54 g) were heated together at 100° under nitrogen for 1 hour. The melt was cooled and triturated with ether and the resulting solid recrystallised from ethanol to give the required diamide (5.1 g) m.p. 158—160°.

(c) 6-[2-(3,4-Dimethoxyphenyl)ethylamino]-1-[2-phenylethylamino]-3-hexanol dihydrochloride

- 65 The diamide from step (b) above (3.4 g) in dry tetrahydrofuran (150 ml) was treated with 1M borane-tetrahydrofuran (40 ml) under nitrogen and boiled under reflux for 4 hours. The solution was cooled,

methanol (25 ml) added, and the whole evaporated to dryness. The residue was taken up in methanol (50 ml) and saturated methanolic hydrogen chloride (50 ml) and stirred at 20° for 18 h. The solvent was evaporated and the residue triturated with ether giving the dihydrochloride (2.7 g) as a white solid, which decomposes without melting above 240°.

5

(d) 4-[2-[4-hydroxy-6-(2-phenylethylamino)hexylamino]ethyl]-1,2-benzenediol dihydrobromide

The dihydrochloride from step (c) (2.2 g) in dry dichloromethane (100 ml) was treated with triethylamine (1.31 ml, 0.94 g) and stirred under nitrogen for 15 minutes. The resulting suspension was cooled to -70°, boron tribromide (2.2 ml, 5.85 g) added and the mixture allowed to warm to ambient temperature with stirring over 18 hours. Methanol (10 ml) was added, the resulting solution evaporated to dryness and the solid residue recrystallised from 2-propanol giving the title compound (2.2 g), as the dihydrobromide salt, colourless needles m.p. 137—139°.

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Example 19

15 4-[2-[6-[2-(4-Chlorophenyl)ethylamino]hexylamino]-ethyl]-1,2-benzenediol dihydrochloride

4-[2-[6-[2-(4-Chlorophenyl)ethylamino]hexylamino]-ethyl]-1,2-benzenediol dihydrobromide (3.0 g) was dissolved in the minimum amount of water and saturated sodium bicarbonate was added until the pH of the solution was about 8. The precipitated free base was washed with ice cold water and then suspended in concentrated hydrochloric acid and stirred with gentle warming until all the sticky material had been replaced by a fine white solid. The suspension was cooled in ice and filtered and the precipitate recrystallised from ethanol to give the title dihydrochloride (2.0 g) as white crystals m.p. 186—188°.

20

Found Cl: 23.02%, dihydrochloride requires Cl: 22.93%.

Example 20

25 4-[2-[6-(2-Phenylethylamino)hexylamino]ethyl]-1,2-benzenediol dihydrochloride

The title compound was prepared from the corresponding dihydrobromide salt by the method of Example 19, m.p. 219—219.5°.

Example 21

30 1,2,3,4-Tetrahydro-2-[6-(2-phenylethylamino)hexylamino]-5,6-naphthalenediol

(a) 6-Oxo-6-(2-phenylethylamino)hexanoic acid

Adipic acid monomethyl ester (24 g, 0.15 mole) was dissolved in dry dichloromethane (500 ml) and cooled in ice-water, triethylamine (22.3 ml, 0.16 mole) was added followed by a solution of ethylchloroformate (14.3 ml, 0.15 mole) in dichloromethane (50 ml) which was added over a period of 30 minutes. The resulting suspension was stirred for 30 minutes and a solution of 2-phenylethylamine (18.8 ml, 0.16 mole) in dichloromethane (50 ml) added over a period of 30 minutes, and the resulting mixture stirred at room temperature for 2 hours. The reaction mixture was washed with 2N aqueous hydrochloric acid (2 x 200 ml), 10% aqueous sodium carbonate solution (200 ml) and water and evaporated *in vacuo* affording the crude amido ester. This solid was heated to reflux with a solution of potassium hydroxide (9.52 g, 0.17 mole) in water (300 ml) for 1 hour. The cooled solution was washed with ether (200 ml), acidified and the solid isolated by filtration and dried *in vacuo* affording the required amido acid (26.1 g) m.p. 113—4°. The crude acid was purified by recrystallisation from ethyl acetate (m.p. 114—6°).

35

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(b) N-[1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthyl]-N'-[2-phenylethyl]hexane-1,6-diamide

A solution of 6-oxo-6-(2-phenylethylamino)hexanoic acid (2.49 g) and carbonyldiimidazole (1.62 g) in dry dichloromethane (100 ml) was stirred under a nitrogen atmosphere for 2 hours at room temperature. A solution of 1,2,3,4-tetrahydro-5,6-dimethoxy-2-aminonaphthalene (2.07 g) in dichloromethane (20 ml) was added and the solution stirred at room temperature for 18 hours. The solution was washed with dilute hydrochloric acid, dilute sodium carbonate solution and water. The organic phase was separated, dried over magnesium sulphate, filtered and evaporated to leave the sub-title compound which crystallised from isopropanol as colourless flakes (3.8 g), m.p. 191—193°.

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50

(c) N-[1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthyl]-N'-[2-phenylethyl]hexane-1,6-diamine dihydrochloride

A solution of the product of step (b) (3.5 g) and borane-tetrahydrofuran complex (32 mls) in dry tetrahydrofuran (200 ml) was heated under reflux under a nitrogen atmosphere for 24 hours.

55

The solution was cooled, methanol (100 mls) added and the solution evaporated to dryness. A solution of the residue in methanolic/HCl was heated under reflux for 5 hours. The solution was evaporated to leave a solid which crystallised from methanol as colourless prisms (2.3 g), m.p. 265°.

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(d) 1,2,3,4-Tetrahydro-2-[6-(2-phenylethylamino)hexyl-amino]-5,6-naphthalenediol dihydrobromide

A solution of the product of step (c) (2 g) in aqueous hydrobromic acid (20 ml) was heated at reflux under a slow stream of nitrogen for 4 hours. The solution was evaporated to dryness and the residue crystallised from ethanol to give the title compound, as the dihydrobromide salt, as colourless prisms (2.0 g), m.p. 240—242°.

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Example 22

1,2,3,4-Tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexylamino]-5,6-naphthalenediol

(a) *N*-[1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthyl]-*N'*-2-(3,4-dimethoxyphenyl)ethylhexane-1,6-diamide

The sub-title compound was prepared by the method of Example 21(a), m.p. 172—174°.

(b) *N*-[1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthyl]-*N'*-[2-(3,4-dimethoxyphenyl)ethyl]hexane-1,6-diamine dihydrochloride

The sub-title compound was prepared from the product of step (a), by the method of Example 21(b), m.p. 260°.

(c) 1,2,3,4-Tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexylamino]-5,6-naphthalenediol dihydrobromide

The title compound was prepared from the product of step (b), as the dihydrobromide salt, by the method of Example 21(c), m.p. 270°.

Example 23

By analogous methods to those described in Example 21 above, the following compounds were made:

(a) 1,2,3,4-Tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)ethyl)amino]hexylamino]-6,7-naphthalenediol dihydrobromide, m.p. 258—260°.

(b) 1,2,3,4-Tetrahydro-2-[6-(2-phenylethylamino)hexylamino]-6,7-naphthalenediol dihydrobromide, m.p. 266—268°.

(c) 1,2,3,4-Tetrahydro-2-[4-(2-phenylethylamino)butylamino]-5,6-naphthalenediol dihydrobromide, m.p. > 250°.

(d) 1,2,3,4-Tetrahydro-2-[8-(2-phenylethylamino)octylamino]-5,6-naphthalenediol dihydrobromide, m.p. 248—252°.

(e) 1,2,3,4-Tetrahydro-2-[8-(2-(3,4-dihydroxyphenyl)ethylamino)octylamino]-5,6-naphthalenediol dihydrobromide, m.p. 260°.

(f) 1,2,3,4-Tetrahydro-2-[6-(2-phenylethylamino)hexylamino]-5-naphthalenol dihydrobromide, m.p. 280° (dec).

Example 24

N,N'-Bis-(1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthyl)hexane-1,6-diamine dihydrochloride

1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthalenamine hydrochloride (4.87 g) in acetonitrile (100 ml) was added slowly to a stirred suspension of potassium carbonate (3.0 g) in a refluxing solution of 1,6-dibromohexane (2.44 g) in acetonitrile (100 ml) over a period of 1 hour. When the addition was complete, reflux was continued for 24 hours, the solution filtered to remove inorganic salts, and the filtrate evaporated in vacuo to give an oil. Chromatography on silica, eluting with chloroform:methanol 95:5, gave, following trituration with ethereal hydrogen chloride, the title compound 1.15 g (20%), m.p. 275° (decomp).

Example 25

4-[2-(6-(2-Phenylethylamino)hexylamino)ethyl]-1,2-benzenediol-bis-2-methylpropionate dihydrochloride

Isobutyryl bromide (12 g) was added to a stirred solution of 4-[2-(6-(2-Phenylethylamino)hexylamino)ethyl]-1,2-benzenediol dihydrobromide (4 g) in trifluoroacetic acid (100 ml). The solution was then stirred at room temperature for 24 hours. The excess solvent was evaporated and the residue treated with sodium bicarbonate solution. The basic mixture was thoroughly extracted with chloroform. The organic phase was separated, dried over magnesium sulphate, filtered and evaporated to leave a colourless oil which gave a white precipitate when treated with ethereal HCl. The white precipitate was recrystallised to give the title compound from ethanol as colourless prisms (2.8 g), m.p. 232—234°.

Example 26

By analogous methods to those described in Example 25, the following compounds were made:

(a) 4-[2-(6-(2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol-bis-benzoate dihydrochloride, m.p. 230° (dec).

(b) 4-[2-(6-(2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol-bis-acetate dihydrobromide, m.p. 229—230°.

Example 27

Bis(Phenylmethoxy)*N*-[2-(3,4-dihydroxyphenyl)ethyl]*N'*-[2-phenylethyl]-1,6-hexanediyl bis carbamate

A suspension of 4-[2-(6-(2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol (4.2 g) in 10% aqueous borax solution (4 g in 40 ml) was adjusted to pH9 with 2N sodium hydroxide solution. The suspension was stirred for 4 hours. Benzylchloroformate (2.2 ml) was added and the mixture stirred at room temperature for 2.5 hours.

The suspension was acidified and the aqueous phase extracted with ether. The organic phase was separated, dried over magnesium sulphate, filtered and evaporated to leave an oil. The oil was purified by chromatography on silica gel eluting with dichloromethane/5% CH₃OH to give the title compound, as a pale yellow oil (2.0 g) MS *m/e* 624.

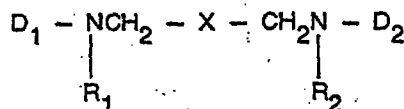
Pharmaceutical Formulations

Intravenous formulations

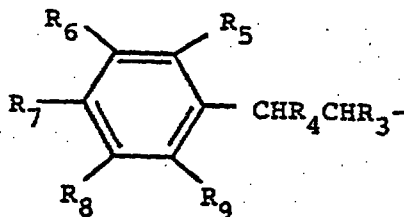
- | | | |
|----|---------------------------|---------------------|
| 1. | Compound of Example 12 | 1% w/v |
| | Sodium metabisulphite | 1% w/v |
| | Sodium chloride | 0.106% w/v |
| | Water | to 100% |
| 2. | Compound of Example 12 | 1% w/v |
| | Sodium metabisulphite | 0.1% w/v |
| | Sodium edetate | 0.01% w/v |
| | Sodium chloride | qs to make isotonic |
| | Water | to 100% |
| 3. | Compound of Example 12 | 1% w/v |
| | Sodium hydrogen phosphate | 0.94% w/v |
| | Sodium phosphate | 0.24% w/v |
| | Sodium chloride | 0.295% w/v |
| | Water | to 100% |

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of formula I,



in which D_1 represents a group of formula II,



where R_1 and R_6 , or R_2 and R_5 may form a chain $-\text{CH}_2\text{CH}_2-$, or R_4 and R_5 may form a chain $-\text{CH}_2-$, or R_3 , R_4 and R_5 are each hydrogen, the remainder of R_1 , R_3 and R_4 , which may be the same or different, being hydrogen, alkyl or phenyl,

none, one or two of R_6 , R_7 , R_8 and R_9 represent hydroxy and the remainder represent hydrogen, X represents a chain $-(\text{CH}_2)_n-$, optionally substituted by hydroxy, n is an integer from 1 to 7 inclusive,

D_2 represents hydrogen, alkyl, phenyl; alkyl substituted by one or more of hydroxy, pyridyl, phenyl; or alkyl substituted by phenyl which in turn is substituted by halogen, alkyl, amino, alkoxy or nitro, or

D_2 represents a group of formula III,



(27)

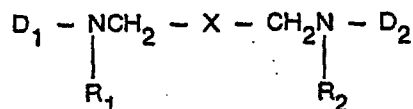
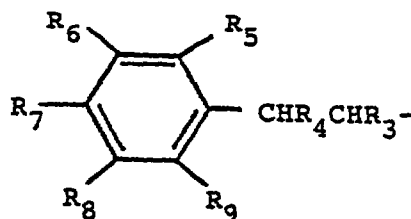
Pharmaceutical Formulations

Intravenous formulations

- | | | |
|----|---------------------------|---------------------|
| 1. | Compound of Example 12 | 1% w/v |
| | Sodium metabisulphite | 1% w/v |
| | Sodium chloride | 0.106% w/v |
| | Water | to 100% |
| 2. | Compound of Example 12 | 1% w/v |
| | Sodium metabisulphite | 0.1% w/v |
| | Sodium edetate | 0.01% w/v |
| | Sodium chloride | qs to make isotonic |
| | Water | to 100% |
| 3. | Compound of Example 12 | 1% w/v |
| | Sodium hydrogen phosphate | 0.94% w/v |
| | Sodium phosphate | 0.24% w/v |
| | Sodium chloride | 0.295% w/v |
| | Water | to 100% |

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of formula I,

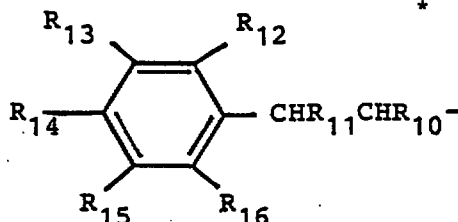
in which D_1 represents a group of formula II,

where R_1 and R_5 , or R_3 and R_5 may form a chain $-CH_2CH_2-$, or R_4 and R_5 may form a chain $-CH_2-$, or R_3 , R_4 and R_5 are each hydrogen, the remainder of R_1 , R_3 and R_4 , which may be the same or different, being hydrogen, alkyl or phenyl,

none, one or two of R_6 , R_7 , R_8 and R_9 represent hydroxy and the remainder represent hydrogen, X represents a chain $-(CH_2)_n-$, optionally substituted by hydroxy, n is an integer from 1 to 7 inclusive,

D_2 represents hydrogen, alkyl, phenyl; alkyl substituted by one or more of hydroxy, pyridyl, phenyl; or alkyl substituted by phenyl which in turn is substituted by halogen, alkyl, amino, alkoxy or nitro, or

D_2 represents a group of formula III,



III

10

where R_2 and R_{12} , or R_{10} and R_{12} may form a chain $-\text{CH}_2-\text{CH}_2-$, or R_{11} and R_{12} may form a chain $-\text{CH}_2-$, or R_{10} , R_{11} and R_{12} are each hydrogen,

the remainder of R_2 , R_{10} and R_{11} , which may be the same or different being hydrogen, alkyl or phenyl, none, one or two of R_{13} , R_{14} , R_{15} and R_{16} represent hydroxy, and the remainder represent hydrogen, or R_2 and D_2 , together with the nitrogen atom to which they are attached, form a 5 or 6 membered heterocyclic ring,

provided that when X is not substituted by hydroxy and
i) when R_3 , R_4 and R_5 are hydrogen, R_1 and R_2 are both hydrogen or lower alkyl, and two of R_6 , R_7 , R_8 and R_9 are hydroxy, D_2 is not identical to D_1 , or

ii) when R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are hydrogen, R_2 and D_2 do not each represent lower alkyl, or do not together with the nitrogen atom to which they are attached, form a 5 or 6 membered heterocyclic ring, or

iii) when R_1 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are hydrogen, and R_3 is alkyl, D_2 is not identical to D_1 , or
iv) when R_1 is phenyl, R_3 and R_5 together form the chain $-\text{CH}_2\text{CH}_2-$, R_6 , R_7 , R_8 and R_9 are hydrogen, n

is 1, D_2 and R_2 do not each represent hydrogen or alkyl, or do not together form a heterocyclic ring, or
v) when R_1 is hydrogen or alkyl 1 to 3 carbon atoms, R_3 is methyl, R_4 is hydrogen, n is 1, D_2 and R_2 do not each represent phenyl, and pharmaceutically acceptable derivatives thereof.

2. A compound according to Claim 1 for use as a pharmaceutical.

3. A compound according to Claim 1 or 2, wherein one or both of an adjacent pair of R_6 , R_7 , R_8 and R_9 , and an adjacent pair of R_{13} , R_{14} , R_{15} and R_{16} are both hydroxy.

4. A compound according to any one of the preceding Claims, wherein R_7 is hydroxy.

5. A compound according to any one of the preceding Claims, wherein n is from 3 to 5 inclusive.

6. 4-[2-(6-(2-Phenylethylamino)hexylamino)ethyl]-1,2-benzenediol, or a pharmaceutically acceptable acid addition salt thereof.

7. (R*S*)-2,2'-[1,6-Hexanediylbis(amino)]-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol],
[R(R*,R*)](+)-7,7'-(1,6-hexanediylbis(aminomethylene))-bis(bicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol),
4-[2-(6-(2-(4-chlorophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol,
1,2,3,4-tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)-ethylamino)hexylamino]-5,6-naphthalenediol,
or a pharmaceutically acceptable acid addition salt of any one thereof.

8. [S-(R*R*)]-2,2'-(1,6-hexanediylbis(amino))-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol],
[R-(R*R*)]-2,2'-(1,6-hexanediylbis(amino))-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol],
2,2'-(1,6-hexanediylbis(amino))-bis-(1,2,3,4-tetrahydro-5,6-naphthalenediol),
2,2'-(1,6-hexanediylbis(amino))-bis-(1,2,3,4-tetrahydro-6,7-naphthalenediol),
or a pharmaceutically acceptable acid addition salt of any one thereof.

9. [S-(R*,R*)]-7,7'-(1,6-hexanediylbis(aminomethylene))-bis(bicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol),
(R*S*)-7,7'-(1,6-hexanediylbis(aminomethylene))-bis(bicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol),
7-[6-(2-phenylethylamino)hexylamino]methylbicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol,
7-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexylamino]methylbicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol,
7-[6-(2-phenylethylamino)hexylamino]methylbicyclo[4.2.0]-octa-1,3,5-triene-3,4-diol,
(7,7'-(1,6-hexanediylbis(aminomethylene))-bis-bicyclo[4.2.0]-octa-1,3,5-triene-3,4-diol),
or a pharmaceutically acceptable acid addition salt of any one thereof.

10. 7-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexylamino]methylbicyclo[4.2.0]-octa-1,3,5-triene-3,4-diol,
4-[2-(6-(2-(4-aminophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol,
4-[2-(6-phenylamino)hexylamino]ethyl-1,2-benzenediol,

4-[2-(6-phenylmethylamino)hexylamino]ethyl-1,2-benzenediol,
4-[2-(6-(3-phenylpropylamino)hexylamino)ethyl]-1,2-benzenediol,
4-[2-(6-(4-phenylbutylamino)hexylamino)ethyl]-1,2-benzenediol,
4-[2-(6-amino-hexylamino)ethyl]-1,2-benzenediol,

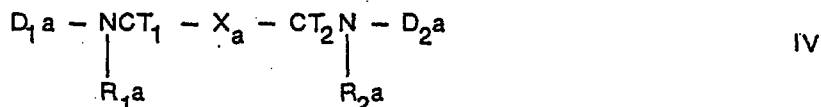
4-[2-(6-di-n-propylamino)hexylamino]ethyl-1,2-benzenediol,
4-[2-(6-N-methyl-2-phenylethylamino)hexylamino]ethyl-1,2-benzenediol,
4-[2-(6-(2-phenylpropylamino)hexylamino)ethyl]-1,2-benzenediol,

4-[2-(6-(2-(4-nitrophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol,
4-[2-(6-(2-(4-hydroxyphenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol,
4-[2-(6-(2-methylphenyl)ethylamino)hexylamino]ethyl-1,2-benzenediol,
4-[2-(6-(2-(4-pyridinyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol,



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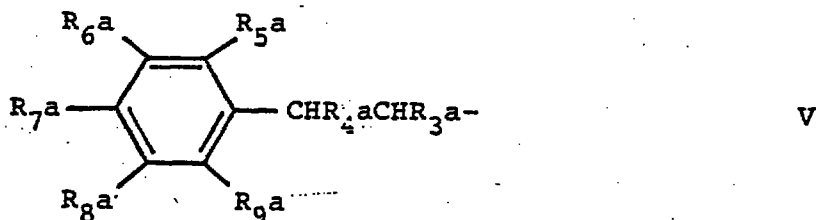
- 4-[2-(6-(4-methylpiperazinyl)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(N-methyl-6-(4-methylpiperazinyl)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(4-(2-phenylethylamino)butylamino)ethyl]-1,2-benzenediol,
 4-[2-(6-(1,2,3,4-tetrahydro-2-naphthylamino)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(8-(2-phenylethylamino)octylamino)ethyl]-1,2-benzenediol,
 4-[2-(5-(2-phenylethylamino)pentylamino)ethyl]-1,2-benzenediol,
 3-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7,8-diol,
 4-[2-(N-methyl-6-(N'-methyl-2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(6-(2-hydroxy-2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(N-methyl-6-(di-n-propylamino)hexylamino)ethyl]-1,2-benzenediol,
 (±)-4-[2-[4-hydroxy-6-(2-phenylethylamino)-hexylamino]ethyl]-1,2-benzenediol,
 or a pharmaceutically acceptable acid addition salt of any one thereof.
 11. 1,2,3,4-tetrahydro-2-[6-(2-phenylethylamino)hexylamino]-5,6-naphthalenediol,
 1,2,3,4-tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexylamino]-6,7-naphthalenediol,
 1,2,3,4-tetrahydro-2-[6-(2-phenylethylamino)hexylamino]-6,7-naphthalenediol,
 1,2,3,4-tetrahydro-2-[4-(2-phenylethylamino)butylamino]-5,6-naphthalenediol,
 1,2,3,4-tetrahydro-2-[8-(2-phenylethylamino)octylamino]-5,6-naphthalenediol,
 1,2,3,4-tetrahydro-2-[8-(2-(3,4-dihydroxyphenyl)ethylamino)octylamino]-5,6-naphthalenediol,
 1,2,3,4-tetrahydro-2-[6-(2-phenylethylamino)hexylamino]-5-naphthalenol,
 or a pharmaceutically acceptable acid addition salt of any one thereof.
 12. A pharmaceutical composition comprising a compound according to any one of the preceding
 claims in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.
 13. A process for the production of a compound of formula I, according to Claim 1, or a pharma-
 ceutically acceptable derivative thereof, which comprises:
 (a) selectively reducing a compound of the formula IV,



in which both T_1 and T_2 represent H_2 or O , provided that at least one of T_1 and T_2 represents O .

R_1a and R_2a have the same significance as R_1 and R_2 above, save that in addition they may represent a protecting group,

D_1a represents a group of formula V,

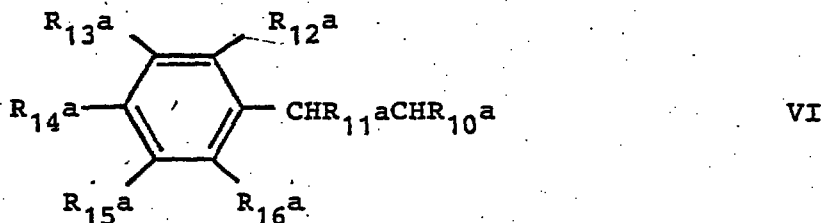


where R_3a , R_4a , R_5a , R_6a , R_7a , R_8a and R_9a respectively have the same significances as R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 above, save that in addition one or two of R_6a , R_7a , R_8a and R_9a may represent a protected hydroxy group,

X_a has the same significance as X above, save that in addition it may bear a protected hydroxy,

D_2a represents hydrogen, alkyl, phenyl; or alkyl substituted by one or more of hydroxy, protected hydroxy, pyridyl, phenyl; or alkyl substituted by phenyl which in turn is substituted by halogen, alkyl, amino, alkoxy or nitro;

or D_2a represents a group of formula VI,



where R_{10a} , R_{11a} , R_{12a} , R_{13a} , R_{14a} , R_{15a} and R_{16a} respectively have the same significance as R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} and R_{16} above, save that in addition one or more of R_{13a} , R_{14a} , R_{15a} and R_{16a} may represent a protected hydroxyl group,

and, if necessary or desired thereafter, removing any protecting groups to give the corresponding compound of formula I,

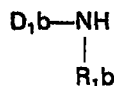
(b) producing a compound of formula I in which D_2 is identical to D_1 , and R_1 is identical to R_2 , by reacting a compound of formula VII,



VII

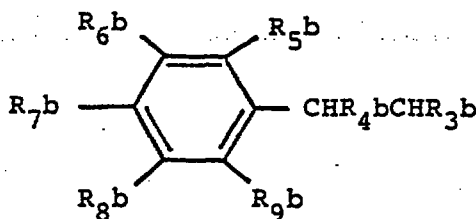
in which L_1 and L_2 , which may be the same or different, represent leaving groups,

X_a is as defined above,
with a compound formula VIII,



VIII

or an acid addition salt thereof,
 D_1b represents the group of formula IX,

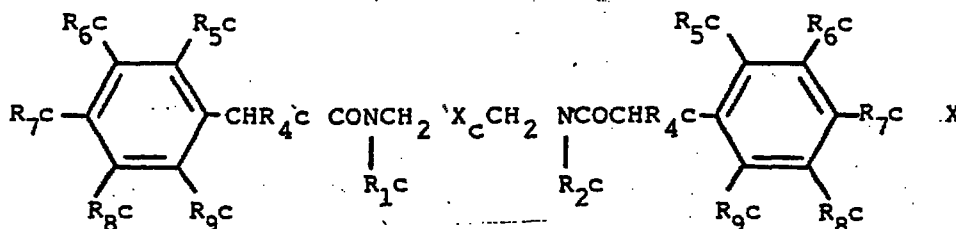


IX

in which R_1b , R_3b , R_4b , R_5b , R_6b , R_7b , R_8b and R_9b respectively have the same significances as R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 above, save that in addition R_1b may represent a removable group capable of increasing the nucleophilicity of nitrogen, and one or two of R_6b , R_7b , R_8b , and R_9b may represent a protected hydroxy,

and if necessary or desired thereafter, removing any such protecting or removable groups to give the corresponding compound of formula I,

(c) producing a compound of formula I in which D_2 is identical to D_1 and both R_3 groups are hydrogen, by selectively reducing a compound of formula X,



in which R_1c , R_2c , R_4c , R_5c , R_6c , R_7c , R_8c , R_9c and X_c respectively have the same significances as R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and X above, save that in addition,

either one or both of R_1c and R_2c may represent protecting groups,

one or two of R_6c , R_7c , R_8c and R_9c may represent a protected hydroxy group, and

X_c may bear a protected hydroxy group,

and if necessary or desired thereafter removing any such protecting groups to give the corresponding compound of formula I, or

(d) removal of a protecting group from a corresponding compound of formula I carrying one or more protected hydroxy or protected amine groups,

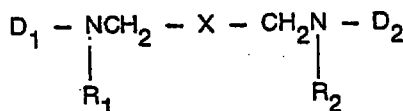
and where desired or necessary converting the resulting compound of formula I to a pharmaceutically acceptable derivative thereof, or vice versa.



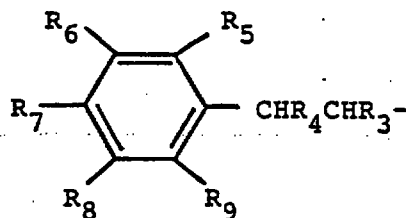


Claims for the Contracting State: AT

1. A process for the production of a compound of formula I,



in which D_1 represents a group of formula II,



II

where R_1 and R_5 , or R_3 and R_5 may form a chain $-CH_2CH_2-$, or R_4 and R_5 may form a chain $-CH_2-$, or R_3 , R_4 and R_5 are each hydrogen, the remainder of R_1 , R_3 and R_4 , which may be the same or different, being hydrogen, alkyl or phenyl,

none, one or two of R_6 , R_7 , R_8 and R_9 represent hydroxy and the remainder represent hydrogen,

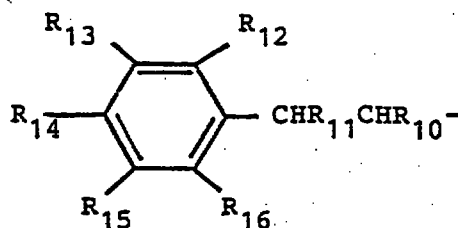
X represents a chain $-(CH_2)_n-$, optionally substituted by hydroxy,

n is an integer from 1 to 7 inclusive,

D_2 represents hydrogen, alkyl, phenyl; alkyl substituted by one or more of hydroxy, pyridyl, phenyl; or

alkyl substituted by phenyl which in turn is substituted by halogen, alkyl, amino, alkoxy or nitro, or

D_2 represents a group of formula III,



III

where R_2 and R_{12} , or R_{10} and R_{12} may form a chain $-CH_2-CH_2-$, or R_{11} and R_{12} may form a chain $-CH_2-$, or R_{10} , R_{11} and R_{12} are each hydrogen,

the remainder of R_2 , R_{10} and R_{11} , which may be the same or different being hydrogen, alkyl or phenyl,

none, one or two of R_{13} , R_{14} , R_{15} and R_{16} represent hydroxy, and the remainder represent hydrogen,

or R_2 and D_2 , together with the nitrogen atom to which they are attached, form a 5 or 6 membered heterocyclic ring,

provided that when X is not substituted by hydroxy and

i) when R_3 , R_4 and R_5 are hydrogen, R_1 and R_2 are both hydrogen or lower alkyl, and two of R_6 , R_7 , R_8 and R_9 are hydroxy, D_2 is not identical to D_1 , or

ii) when R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are hydrogen, R_2 and D_2 do not each represent lower alkyl, or do not together with the nitrogen atom to which they are attached, form a 5 or 6 membered heterocyclic ring, or

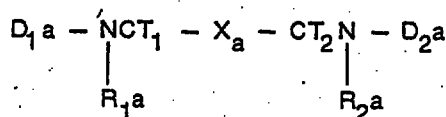
iii) when R_1 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are hydrogen, and R_3 is alkyl, D_2 is not identical to D_1 , or

iv) when R_1 is phenyl, R_3 and R_5 together form the chain $-CH_2CH_2-$, R_6 , R_7 , R_8 and R_9 are hydrogen, n

is 1, D_2 and R_2 do not each represent hydrogen or alkyl, or do not together form a heterocyclic ring, or

v) when R_1 is hydrogen or alkyl 1 to 3 carbon atoms, R_3 is methyl, R_4 is hydrogen, n is 1, D_2 and R_2 do not each represent phenyl, and pharmaceutically acceptable derivatives thereof, which comprises:

(a) selectively reducing a compound of the formula IV,



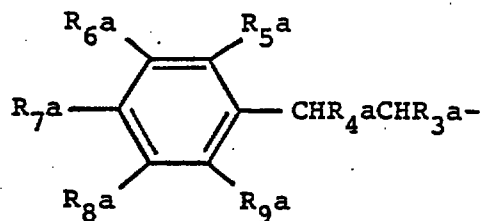
IV

in which both T_1 and T_2 represent H_2 or O , provided that at least one of T_1 and T_2 represents O ,
 R_{1a} and R_{2a} have the same significance as R_1 and R_2 above, save that in addition they may represent a protecting group,

D_{1a} represents a group of formula V,

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V

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where R_{3a} , R_{4a} , R_{5a} , R_{6a} , R_{7a} , R_{8a} and R_{9a} respectively have the same significances as R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 above, save that in addition one or two of R_{8a} , R_{7a} , R_{8a} and R_{9a} may represent a protected hydroxy group,

20

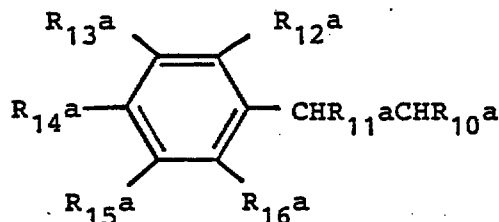
X_a has the same significance as X above, save that in addition it may bear a protected hydroxy,

D_{2a} represents hydrogen, alkyl, phenyl; or alkyl substituted by one or more of hydroxy, protected hydroxy, pyridyl, phenyl; or alkyl substituted by phenyl which in turn is substituted by halogen, alkyl, amino, alkoxy or nitro;

or D_{2a} represents a group of formula VI,

25

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VI

where R_{10a} , R_{11a} , R_{12a} , R_{13a} , R_{14a} , R_{15a} and R_{16a} respectively have the same significance as R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} and R_{16} above, save that in addition one or more of R_{13a} , R_{14a} , R_{15a} and R_{16a} may represent a protected hydroxyl group,

and, if necessary or desired thereafter, removing any protecting groups to give the corresponding compound of formula I,

(b) producing a compound of formula I in which D_2 is identical to D_1 , and R_1 is identical to R_2 , by reacting a compound of formula VII,

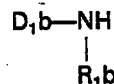


VII

in which L_1 and L_2 , which may be the same or different, represent leaving groups,

X_a is as defined above,
 with a compound formula VIII,

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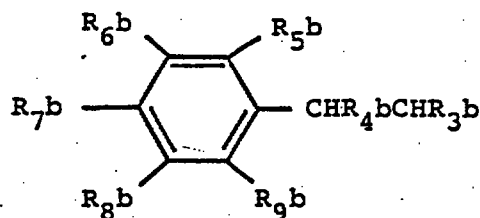
VIII

or an acid addition salt thereof,

D_{1b} represents the group of formula IX,

55

60



IX

in which R_{1b} , R_{3b} , R_{4b} , R_{5b} , R_{6b} , R_{7b} , R_{8b} and R_{9b} respectively have the same significances as R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 above, save that in addition R_{1b} may represent a removable group capable of increasing the nucleophilicity of nitrogen, and one or two of R_{8b} , R_{7b} , R_{8b} , and R_{9b} may represent a protected hydroxy,

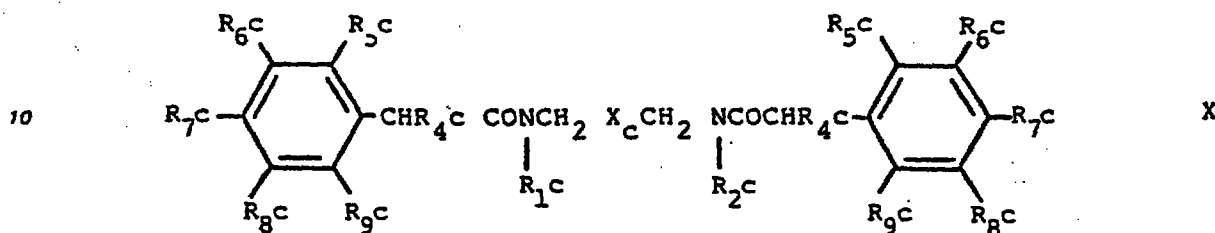




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and if necessary or desired thereafter, removing any such protecting or removable groups to give the corresponding compound of formula I,

(c) producing a compound of formula I in which D₂ is identical to D₁ and both R₃ groups are hydrogen, by selectively reducing a compound of formula X,



15 in which R_{1c}, R_{2c}, R_{4c}, R_{5c}, R_{6c}, R_{7c}, R_{8c}, R_{9c} and X_c respectively have the same significances as R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉, and X above, save that in addition, either one or both of R_{1c} and R_{2c} may represent protecting groups, one or two of R_{6c}, R_{7c}, R_{8c} and R_{9c} may represent a protected hydroxy group, and
20 X_c may bear a protected hydroxy group, and if necessary or desired thereafter removing any such protecting groups to give the corresponding compound of formula I, or

(d) removal of a protecting group from a corresponding compound of formula I carrying one or more protected hydroxy or protected amine groups,

25 and where desired or necessary converting the resulting compound of formula I to a pharmaceutically acceptable derivative thereof, or vice versa.

2. A process according to Claim 1, wherein one or both of an adjacent pair of R₆, R₇, R₈ and R₉, and an adjacent pair of R₁₃, R₁₄, R₁₅ and R₁₆ are both hydroxy.

3. A process according to Claim 1 or 2, wherein R₇ is hydroxy.

30 4. A process according to any one of the preceding Claims, wherein n is from 3 to 5 inclusive.

5. A process according to Claim 1, wherein the compound of formula I is 4-[2-(6-(2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol, or a pharmaceutically acceptable acid addition salt thereof.

6. A process according to Claim 1, wherein the compound of formula I is (R*S*)-2,2'-[1,6-hexanediylbisamino]-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol],
35 [R(R*,R*)](+)-7,7'-[1,6-hexanediylbis(aminomethylene)]-bis(bicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol), 4-[2-(6-(2-(4-chlorophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol, 1,2,3,4-tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)-ethylamino)hexylamino]-5,6-naphthalenediol, or a pharmaceutically acceptable acid addition salt of any one thereof.

40 7. A process according to Claim 1, wherein the compound of formula I is, [S-(R*R*)]-2,2'-[1,6-hexanediylbisamino]-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol], [R-(R*R*)]-2,2'-[1,6-hexanediylbisamino]-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol], 2,2'-(1,6-hexanediylbisamino)-bis-[1,2,3,4-tetrahydro-5,6-naphthalenediol], 2,2'-(1,6-hexanediylbisamino)-bis-[1,2,3,4-tetrahydro-6,7-naphthalenediol], or a pharmaceutically acceptable acid addition salt of any one thereof.

45 8. A process according to Claim 1, wherein the compound of formula I is: [S-(R*,R*)]-7,7'-[1,6-hexanediylbis(aminomethylene)]-bis(bicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol), (R*S*)-7,7'-[1,6-hexanediylbis(aminomethylene)]-bis(bicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol), 7-[6-(2-phenylethylamino)hexylamino]methylbicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol, 50 7-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexylamino]methylbicyclo[4.2.0]-octa-1,3,5-triene-2,3-diol, 7-[6-(2-phenylethylamino)hexylamino]methylbicyclo[4.2.0]-octa-1,3,5-triene-3,4-diol, (7,7'-[1,6-hexanediylbis(aminomethylene)]-bis-bicyclo[4.2.0]-octa-1,3,5-triene-3,4-diol, or a pharmaceutically acceptable acid addition salt of any one thereof.

55 9. A process according to Claim 1, wherein the compound of formula I is: 7-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexylamino]methylbicyclo[4.2.0]-octa-1,3,5-triene-3,4-diol, 4-[2-(6-(2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol, 4-[2-(6-(2-(4-aminophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol, 4-[2-(6-phenylamino)hexylamino)ethyl]-1,2-benzenediol, 4-[2-(6-phenylmethylamino)hexylamino)ethyl]-1,2-benzenediol, 60 4-[2-(6-(3-phenylpropylamino)hexylamino)ethyl]-1,2-benzenediol, 4-[2-(6-(4-phenylbutylamino)hexylamino)ethyl]-1,2-benzenediol, 4-[2-(6-amino-hexylamino)ethyl]-1,2-benzenediol, 4-[2-(6-(di-n-propylamino)hexylamino)ethyl]-1,2-benzenediol, 4-[2-(6-(N-methyl-(2-phenylethylamino)hexylamino)ethyl)-1,2-benzenediol, 65 4-[2-(6-(2-phenylpropylamino)hexylamino)ethyl]-1,2-benzenediol,



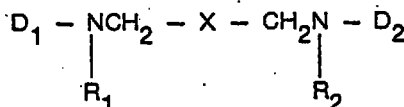
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- 4-[2-(6-(2-(4-nitrophenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(6-(2-(4-hydroxyphenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(6-(2-(4-methylphenyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(6-(2-(4-pyridinyl)ethylamino)hexylamino)ethyl]-1,2-benzenediol,
 5 4-[2-(6-(4-methylpiperazinyl)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(N-methyl-6-(4-methylpiperazinyl)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(4-(2-phenylethylamino)butylamino)ethyl]-1,2-benzenediol,
 4-[2-(6-(1,2,3,4-tetrahydro-2-naphthylamino)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(8-(2-phenylethylamino)octylamino)ethyl]-1,2-benzenediol,
 10 4-[2-(5-(2-phenylethylamino)pentylamino)ethyl]-1,2-benzenediol,
 3-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7,8-diol,
 4-[2-(N-methyl-6-(N'-methyl-2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(6-(2-hydroxy-2-phenylethylamino)hexylamino)ethyl]-1,2-benzenediol,
 4-[2-(N-methyl-6-(di-n-propylamino)hexylamino)ethyl]-1,2-benzenediol,
 15 + 4-[2-(4-hydroxy-6-(2-phenylethylamino)-hexylamino)ethyl]-1,2-benzenediol,
 1,2,3,4-tetrahydro-2-[6-(2-phenylethylamino)hexylamino]-5,6-naphthalenediol,
 or a pharmaceutically acceptable acid addition salt of any one thereof.
 10. A process according to Claim 1, wherein the compound of formula I is:
 1,2,3,4-tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)ethylamino)hexylamino]-6,7-naphthalenediol,
 20 1,2,3,4-tetrahydro-2-[6-(2-phenylethylamino)hexylamino]-6,7-naphthalenediol,
 1,2,3,4-tetrahydro-2-[4-(2-phenylethylaminobutylamino)-5,6-naphthalenediol;
 1,2,3,4-tetrahydro-2-[8-(2-phenylethylamino)octylamino]-5,6-naphthalenediol,
 1,2,3,4-tetrahydro-2-[8-(2-(3,4-dihydroxyphenyl)ethylamino)octylamino]-5,6-naphthalenediol,
 1,2,3,4-tetrahydro-2-[6-(2-phenylethylamino)hexylamino]-5-naphthalenol,
 25 or a pharmaceutically acceptable acid addition salt of any one thereof.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Eine Verbindung der Formel (I)

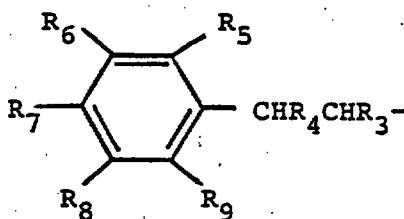
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worin D₁ eine Gruppe der Formel (II)

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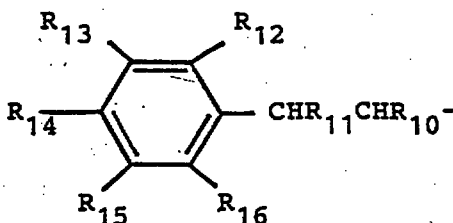


II

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bedeutet, wobei R₁ und R₅ oder R₃ und R₅ eine Kette —CH₂CH₂— bilden können oder R₄ und R₅ eine Kette —CH₂— bilden können oder R₃, R₄ und R₅ jeweils Wasserstoff sind, wobei der Rest von R₁, R₃ und R₄, die gleich oder verschieden sein können, Wasserstoff, Alkyl oder Phenyl darstellt; keines, eines oder zwei von R₆, R₇, R₈ und R₉ Hydroxy bedeuten und der Rest Wasserstoff ist; X eine Kette —(CH₂)_n—, gegebenenfalls durch Hydroxy substituiert, darstellt; n eine ganze Zahl von 1 bis 7 inklusive ist; D₂ Wasserstoff, Alkyl, Phenyl, Alkyl ein- oder mehrfach substituiert durch Hydroxy, Pyridyl, Phenyl, oder Alkyl durch Phenyl substituiert, das seinerseits durch Halogen, Alkyl, Amino, Alkoxy oder Nitro substituiert ist, oder D₂ eine Gruppe der Formel (III)

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III

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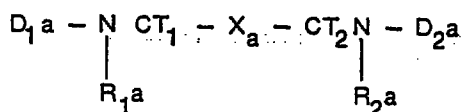
60 bedeutet, wobei R₂ und R₁₂ oder R₁₀ und R₁₂ eine Kette —CH₂—CH₂— bilden können oder R₁₁ und R₁₂ eine



- Kette $-\text{CH}_2-$ bilden können oder R_{10} , R_{11} und R_{12} jeweils Wasserstoff sind, wobei der Rest von R_2 , R_{10} und R_{11} die gleich oder verschieden sein können, Wasserstoff, Alkyl oder Phenyl ist; keines, eines oder zwei von R_{13} , R_{14} , R_{15} und R_{16} Hydroxy darstellen und der Rest Wasserstoff ist; oder R_2 und D_2 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 5- oder 6-gliedrigen heterocyclischen Ring bilden; mit der Maßgabe, daß, wenn X nicht durch Hydroxy substituiert ist und
- wenn R_3 , R_4 und R_5 Wasserstoff sind, R_1 und R_2 beide Wasserstoff oder nied. Alkyl bedeuten und zwei von R_6 , R_7 , R_8 und R_9 Hydroxy sind, D_2 nicht mit D_1 identisch ist, oder
 - wenn R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 und R_9 Wasserstoff sind, R_2 und D_2 nicht jeweils nied. Alkyl sind oder nicht zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 5- oder 6-gliedrigen heterocyclischen Ring bilden, oder
 - wenn R_1 , R_4 , R_5 , R_6 , R_7 , R_8 und R_9 Wasserstoff sind und R_3 Alkyl bedeutet, D_2 mit D_1 nicht identisch ist, oder
 - wenn R_1 Phenyl bedeutet, R_3 und R_5 miteinander die Kette $-\text{CH}_2\text{CH}_2-$ bilden, R_6 , R_7 , R_8 und R_9 Wasserstoff darstellen, n 1 ist, D_2 und R_2 nicht jeweils Wasserstoff oder Alkyl sind oder nicht miteinander einen heterocyclischen Ring bilden, oder
 - wenn R_1 Wasserstoff oder Alkyl mit 1 bis 3 C-Atomen ist, R_3 Methyl bedeutet, R_4 Wasserstoff darstellt, n 1 ist, D_2 und R_2 nicht jeweils Phenyl bedeuten, und deren pharmazeutisch annehmbare Derivate.
- Verbindung nach Anspruch 1 zur Verwendung als pharmazeutisches Mittel.
 - Verbindung nach Anspruch 1 oder 2, worin eines oder beide eines benachbarten Paares von R_6 , R_7 , R_8 und R_9 und ein benachbartes Paar von R_{13} , R_{14} , R_{15} und R_{16} beide Hydroxy sind.
 - Verbindung nach einem der vorhergehenden Ansprüche, worin R_7 Hydroxy ist.
 - Verbindung nach einem der vorhergehenden Ansprüche, worin n 3 bis 5 inklusive ist.
 - 4-[2-(6-(2-Phenyläthylamino)-hexylamino)-1,2-benzoldiol oder ein pharmazeutisch annehmbares Säureadditionssalz hiervon.
 - (R^*S^*)-2,2'-[1,6-Hexandiylbis(amino)-bis-[1,2,3,4-tetrahydro-5,6-naphthalindiol], [$\text{R}(\text{R}^*, \text{R}^*)$](+)-7,7'-[1,6-Hexandiylbis(aminomethylen)]-bis-(bicyclo[4,2,0]octa-1,3,5-trien-2,3-diol), 4-[2-(6-(2-(4-Chlorphenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 1,2,3,4-Tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)-äthylamino)-hexylamino]-5,6-naphthalindiol oder ein pharmazeutisch annehmbares Säureadditionssalz eines derselben.
 - [S-(R^*, R^*)]-2,2'-[1,6-Hexandiylbis(amino)-bis-[1,2,3,4-tetrahydro-5,6-naphthalindiol], [$\text{R}(\text{R}^*, \text{R}^*)$]-2,2'-[1,6-Hexandiylbis(amino)-bis-[1,2,3,4-tetrahydro-5,6-naphthalindiol], 2,2'-(1,6-Hexandiylbis(amino)-bis-(1,2,3,4-tetrahydro-5,6-naphthalindiol), 2,2'-(1,6-Hexandiylbis(amino)-bis-(1,2,3,4-tetrahydro-6,7-naphthalindiol), oder ein pharmazeutisch annehmbares Säureadditionssalz eines derselben.
 - (R^*S^*)-7,7'-[1,6-Hexandiylbis(aminomethylen)]-bis-(bicyclo[4,2,0]octa-1,3,5-trien-2,3-diol), 7-[6-(2-Phenyläthylamino)-hexylamino]-methylbicyclo[4,2,0]octa-1,3,5-trien-2,3-diol, 7-[6-(2-(3,4-Dihydroxyphenyl)-äthylamino)-hexylamino]-methylbicyclo[4,2,0]octa-1,3,5-trien-2,3-diol, 7-[6-(2-Phenyläthylamino)-hexylamino]-methylbicyclo[4,2,0]octa-1,3,5-trien-3,4-diol, (7,7'-[1,6-Hexandiylbis(aminomethylen)]-bis-bicyclo[4,2,0]octa-1,3,5-trien-2,3-diol, oder ein pharmazeutisch annehmbares Säureadditionssalz eines derselben.
 - 7-[6-(2-(3,4-Dihydroxyphenyl)-äthylamino)-hexylamino]-methylbicyclo[4,2,0]octa-1,3,5-trien-3,4-diol,
 - 4-[2-(6-(2-(4-Aminophenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-Phenylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-Phenylmethylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(3-Phenylpropylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(4-Phenylbutylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-Amino-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(Di-n-propylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(N-Methyl-2-phenyläthylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(2-Phenylpropylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(4-Nitrophenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(2-(4-Hydroxyphenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(2-(4-Methylphenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(2-(4-Pyridinyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(4-Methylpiperazinyl)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(N-Methyl-6-(4-methylpiperazinyl)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(4-(2-Phenyläthylamino)-butylamino)-äthyl]-1,2-benzoldiol, 4-[2-(6-(1,2,3,4-Tetrahydro-2-naphthylamino)-hexylamino)-äthyl]-1,2-benzoldiol, 4-[2-(8-(2-Phenyläthylamino)-octylamino)-äthyl]-1,2-benzoldiol, 4-[2-(5-(2-Phenyläthylamino)-pentylamino)-äthyl]-1,2-benzoldiol, 3-[6-(2-(3,4-Dihydroxyphenyl)-äthylamino)-hexyl]-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7,8-diol,

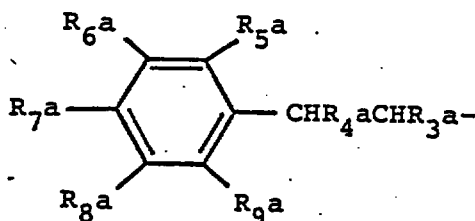
(26)

- 4-[2-(N-Methyl-6-(N'-methyl-2-phenyläthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,
 4-[2-(6-(2-Hydroxy-2-phenyläthylamino)-hexylamino)-äthyl]-1,2-benzol,
 4-[2-(N-Methyl-6-(di-n-propylamino)-hexylamino)-äthyl]-1,2-benzoldiol,
 (±)-4-[2-[4-Hydroxy-6-(2-phenyläthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,
 5 oder ein pharmazeutisch annehmbares Säureadditionssalz eines derselben.
 11. 1,2,3,4-Tetrahydro-2-[6-(2-phenyläthylamino)-hexylamino]-5,6-naphthalindiol,
 1,2,3,4-Tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)-äthylamino)-hexylamino]-6,7-naphthalindiol,
 1,2,3,4-Tetrahydro-2-[6-(2-phenyläthylamino)-hexylamino]-6,7-naphthalindiol,
 1,2,3,4-Tetrahydro-2-[4-(2-phenyläthylamino)-butylamino]-5,6-naphthalindiol,
 10 1,2,3,4-Tetrahydro-2-[8-(2-phenyläthylamino)-octylamino]-5,6-naphthalindiol,
 1,2,3,4-Tetrahydro-2-[8-(2-(3,4-dihydroxyphenyl)-äthylamino)-octylamino]-5,6-naphthalindiol,
 1,2,3,4-Tetrahydro-2-[6-(2-phenyläthylamino)-hexylamino]-5-naphthalenol
 oder ein pharmazeutisch annehmbares Säureadditionssalz eines derselben.
 12. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der vorhergehenden
 15 Ansprüche in Mischung mit einem pharmazeutisch annehmbaren Adjuvans, Verdünnungsmittel oder
 Träger umfaßt.
 13. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1 oder eines
 pharmazeutisch annehmbaren Derivates hiervon, welches umfaßt
 (a) das selektive Reduzieren einer Verbindung der Formel (IV)



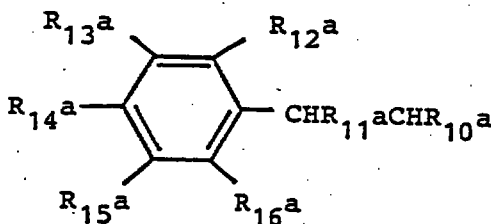
IV

25 worin sowohl T_1 als auch T_2 H_2 oder O bedeuten, mit der Maßgabe, daß zumindest eines von T_1 und T_2 O darstellt; R_1a und R_2a die gleiche Bedeutung wie R_1 und R_2 oben haben, außer daß sie zusätzlich eine Schutzgruppe darstellen können; D_1a eine Gruppe der Formel (V)



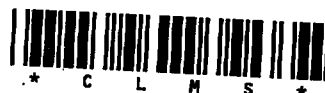
V

30 ist, worin R_3a , R_4a , R_5a , R_6a , R_7a , R_8a bzw. R_9a die gleichen Bedeutungen wie R_3 , R_4 , R_5 , R_6 , R_7 , R_8 und R_9 oben besitzen, außer daß zusätzlich eines oder zwei von R_6a , R_7a , R_8a und R_9a eine geschützte Hydroxygruppe darstellen können; X_a die gleiche Bedeutung wie X oben hat, ausgenommen daß es zusätzlich eine geschützte Hydroxygruppe tragen kann; D_2a Wasserstoff, Alkyl, Phenyl oder Alkyl ein- oder mehrfach
 35 substituiert durch Hydroxy, geschütztes Hydroxy, Pyridyl, Phenyl oder Alkyl substituiert durch Phenyl,
 40 welches seinerseits substituiert ist durch Halogen, Alkyl, Amino, Alkoxy oder Nitro, bedeutet; oder D_2a eine Gruppe der Formel (VI)



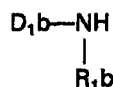
VI

50 darstellt, worin $R_{10}a$, $R_{11}a$, $R_{12}a$, $R_{13}a$, $R_{14}a$, $R_{15}a$ bzw. $R_{16}a$ die gleiche Bedeutung wie R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} und R_{16} oben haben, außer daß zusätzlich eines oder mehrere von $R_{13}a$, $R_{14}a$, $R_{15}a$ und $R_{16}a$ eine
 55 geschützte Hydroxylgruppe darstellen können, und, wenn notwendig oder gewünscht, das anschließende Entfernen beliebiger Schutzgruppen zum Erhalten der entsprechenden Verbindung der Formel (I),
 (b) das Herstellen einer Verbindung der Formel (I), worin D_2 identisch mit D_1 ist und R_1 identisch mit R_2 ist, durch Umsetzen einer Verbindung der Formel (VII)



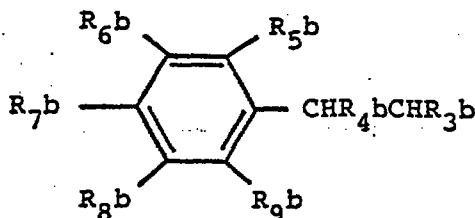


worin L₁ und L₂, die gleich oder verschieden sein können, abspaltbare Gruppen darstellen und X_a wie oben definiert ist, mit einer Verbindung der Formel (VIII)



VIII

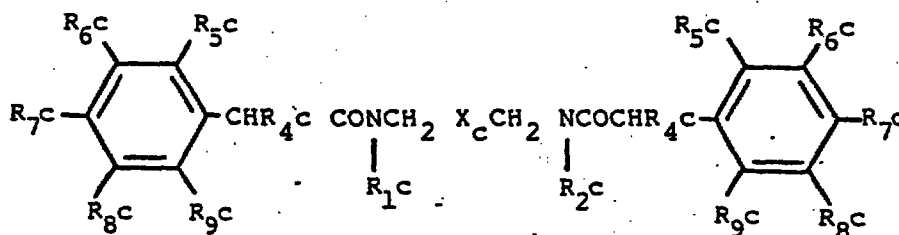
oder einem Säureadditionssalz hiervon, wobei D₁b die Gruppe der Formel (IX)



IX

darstellt, worin R₁b, R₃b, R₄b, R₅b, R₆b, R₇b, R₈b bzw. R₉b die gleichen Bedeutungen wie R₁, R₃, R₄, R₅, R₆, R₇, R₈ und R₉ oben haben, außer daß R₁b zusätzlich eine entfernbare Gruppe darstellt, die imstande ist, die Nukleophilität von Stickstoff zu erhöhen, und eines oder zwei von R₆b, R₇b, R₈b und R₉b eine geschützte Hydroxygruppe bedeuten können, und, wenn notwendig oder gewünscht, das anschließende Entfernen beliebiger derartiger Schutz- oder entfernter Gruppen zum Erhalten der entsprechenden Verbindung der Formel (I),

(c) das Herstellen einer Verbindung der Formel (I), worin D₂ identisch mit D₁ ist und beide R₃-Gruppen Wasserstoff sind, durch selektives Reduzieren einer Verbindung der Formel (X)



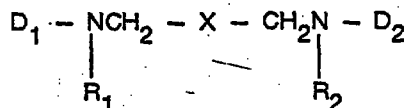
X

worin R₁c, R₂c, R₄c, R₅c, R₆c, R₇c, R₈c, R₉c bzw. X_c die gleichen Bedeutungen wie R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉ und X oben haben, ausgenommen daß zusätzlich entweder eines oder beide von R₁c und R₂c Schutzgruppen darstellen können, eines oder zwei von R₆c, R₇c, R₈c und R₉c eine geschützte Hydroxygruppe darstellen können und X_c eine geschützte Hydroxygruppe tragen kann, und, wenn notwendig oder gewünscht, das anschließende Entfernen beliebiger derartiger Schutzgruppen zum Erhalten der entsprechenden Verbindung der Formel (I) oder

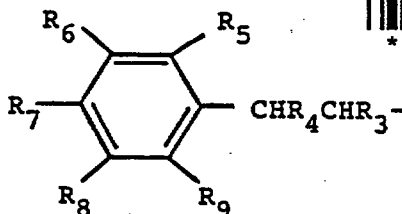
(d) das Entfernen einer Schutzgruppe von einer entsprechenden Verbindung der Formel (I), die eine oder mehrere geschützte Hydroxy- oder geschützte Aminogruppen trägt, und, wenn gewünscht oder notwendig, das Überführen der erhaltenen Verbindung der Formel (I) in ein pharmazeutisch annehmbares Derivat hiervon oder umgekehrt.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel (I)

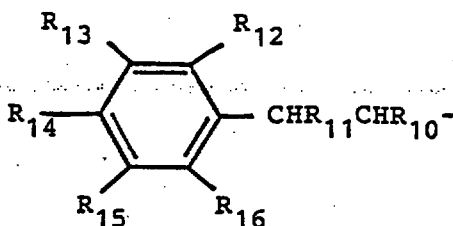


worin D₁ eine Gruppe der Formel (II)



. II

bedeutet, wobei R_1 und R_5 oder R_3 und R_5 eine Kette $-\text{CH}_2\text{CH}_2-$ bilden können oder R_4 und R_5 eine Kette $-\text{CH}_2-$ bilden können oder R_3 , R_4 und R_5 jeweils Wasserstoff sind, wobei der Rest von R_1 , R_3 und R_4 , die gleich oder verschieden sein können, Wasserstoff, Alkyl oder Phenyl darstellt; keines, eines oder zwei von R_6 , R_7 , R_8 und R_9 Hydroxy bedeuten und der Rest Wasserstoff ist; X eine Kette $-(\text{CH}_2)_n-$, gegebenenfalls durch Hydroxy substituiert, darstellt; n eine ganze Zahl von 1 bis 7 inklusive ist; D_2 Wasserstoff, Alkyl, Phenyl, Alkyl ein- oder mehrfach substituiert durch Hydroxy, Pyridyl, Phenyl, oder Alkyl durch Phenyl substituiert, das seinerseits durch Halogen, Alkyl, Amino, Alkoxy oder Nitro substituiert ist, oder D_2 eine Gruppe der Formel (III).



III

bedeutet, wobei R_2 und R_{12} oder R_{10} und R_{12} eine Kette $-\text{CH}_2\text{CH}_2-$ bilden können oder R_{11} und R_{12} eine Kette $-\text{CH}_2-$ bilden können oder R_{10} , R_{11} und R_{12} jeweils Wasserstoff sind, wobei der Rest von R_2 , R_{10} und R_{11} , die gleich oder verschieden sein können, Wasserstoff, Alkyl oder Phenyl ist; keines, eines oder zwei von R_{13} , R_{14} , R_{15} und R_{16} Hydroxy darstellen und der Rest Wasserstoff ist; oder R_2 und D_2 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 5- oder 6-gliedrigen heterocyclischen Ring bilden; mit der Maßgabe, daß, wenn X nicht durch Hydroxy substituiert ist und

i) wenn R_3 , R_4 und R_5 Wasserstoff sind, R_1 und R_2 beide Wasserstoff oder nied. Alkyl bedeuten und zwei von R_6 , R_7 , R_8 und R_9 Hydroxy sind, D_2 nicht mit D_1 identisch ist, oder

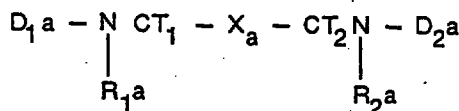
ii) wenn R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 und R_9 Wasserstoff sind, R_2 und D_2 nicht jeweils nied. Alkyl sind oder nicht zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 5- oder 6-gliedrigen heterocyclischen Ring bilden, oder

iii) wenn R_1 , R_4 , R_5 , R_6 , R_7 , R_8 und R_9 Wasserstoff sind und R_3 Alkyl bedeutet, D_2 mit D_1 nicht identisch ist, oder

iv) wenn R_1 Phenyl bedeutet, R_3 und R_5 miteinander die Kette $-\text{CH}_2\text{CH}_2-$ bilden, R_6 , R_7 , R_8 und R_9 Wasserstoff darstellen, n 1 ist, D_2 und R_2 nicht jeweils Wasserstoff oder Alkyl sind oder nicht miteinander einen heterocyclischen Ring bilden, oder

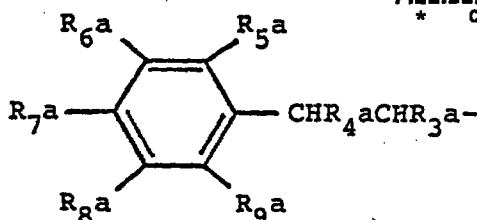
v) wenn R_1 Wasserstoff oder Alkyl mit 1 bis 3 C-Atomen ist, R_3 Methyl bedeutet, R_4 Wasserstoff darstellt, n 1 ist, D_2 und R_2 nicht jeweils Phenyl bedeuten, und deren pharmazeutisch annehmbare Derivaten, welches umfaßt:

(a) das selektive Reduzieren einer Verbindung der Formel (IV)



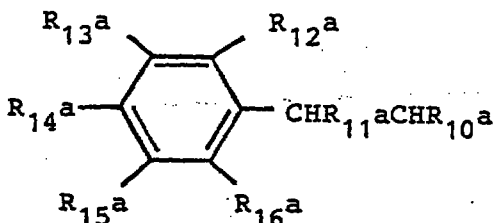
IV

worin sowohl T_1 als auch T_2 H_2 oder O bedeuten, mit der Maßgabe, daß zumindest eines von T_1 und T_2 O darstellt; R_1a und R_2a die gleiche Bedeutung wie R_1 und R_2 oben haben, außer daß sie zusätzlich eine Schutzgruppe darstellen können; D_1a eine Gruppe der Formel (V)



V

- 10 ist, worin R_3^a , R_4^a , R_5^a , R_6^a , R_7^a , R_8^a bzw. R_9^a die gleichen Bedeutungen wie R_3 , R_4 , R_5 , R_6 , R_7 , R_8 und R_9 oben besitzen, außer daß zusätzlich eines oder zwei von R_6^a , R_7^a , R_8^a und R_9^a eine geschützte Hydroxygruppe darstellen können; X_a die gleiche Bedeutung wie X oben hat, ausgenommen daß es zusätzlich eine geschützte Hydroxygruppe tragen kann; D_2^a Wasserstoff, Alkyl, Phenyl oder Alkyl ein- oder mehrfach substituiert durch Hydroxy, geschütztes Hydroxy, Pyridyl, Phenyl oder Alkyl substituiert durch Phenyl,
- 15 welches seinerseits substituiert ist durch Halogen, Alkyl, Amino, Alkoxy oder Nitro, bedeutet; oder D_2^a eine Gruppe der Formel (VI)



VI

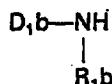
- darstellt, worin R_{10}^a , R_{11}^a , R_{12}^a , R_{13}^a , R_{14}^a , R_{15}^a bzw. R_{16}^a die gleiche Bedeutung wie R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} und R_{16} oben haben, außer daß zusätzlich eines oder mehrere von R_{13}^a , R_{14}^a , R_{15}^a und R_{16}^a eine geschützte Hydroxygruppe darstellen können, und, wenn notwendig oder gewünscht, das anschließende
- 30 Entfernen beliebiger Schutzgruppen zum Erhalten der entsprechenden Verbindung der Formel (I),

(b) das Herstellen einer Verbindung der Formel (II), worin D_2 identisch mit D_1 ist und R_1 identisch mit R_2 ist, durch Umsetzen einer Verbindung der Formel (VII)



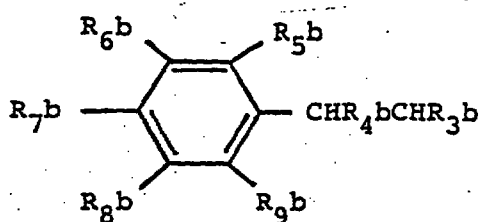
VII

- 35 worin L_1 und L_2 , die gleich oder verschieden sein können, abspaltbare Gruppen darstellen und X_a wie oben definiert ist, mit einer Verbindung der Formel (VIII)



VIII

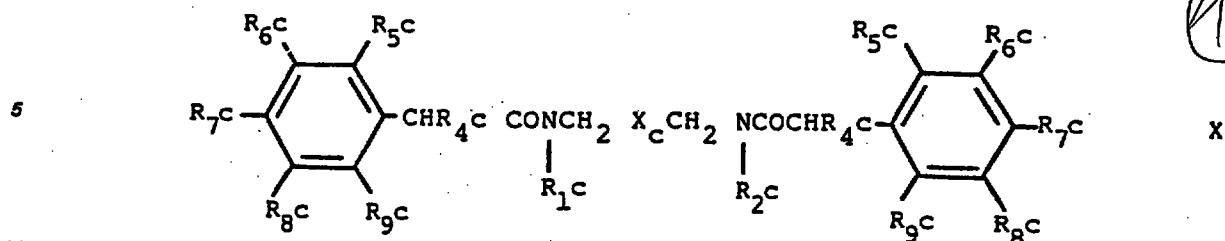
oder einem Säureadditionssalz hiervon, wobei D_1b die Gruppe der Formel (IX)



IX

- darstellt, worin R_1^b , R_3^b , R_4^b , R_5^b , R_6^b , R_7^b , R_8^b bzw. R_9^b die gleichen Bedeutungen wie R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 und R_9 oben haben, außer daß zusätzlich eine entfernbare Gruppe darstellt, die imstande ist, die Nukleophilität von Stickstoff zu erhöhen, und eines oder zwei von R_6^b , R_7^b , R_8^b , und R_9^b eine geschützte Hydroxygruppe bedeuten können, und, wenn notwendig oder gewünscht, das anschließende Entfernen beliebiger derartiger Schutz- oder entferntbarer Gruppen zum Erhalten der entsprechenden Verbindung der Formel (I),
- 55

- 60 (c) das Herstellen einer Verbindung der Formel (I), worin D_2 identisch mit D_1 ist und beide R_3 -Gruppen Wasserstoff sind, durch selektives Reduzieren einer Verbindung der Formel (X)

worin R_1^C , R_2^C , R_4^C , R_5^C , R_6^C , R_7^C , R_8^C , R_9^C bzw. X_C die gleichen Bedeutungen wie R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 und X oben haben, ausgenommen daß zusätzlich entweder eines oder beide von R_1^C und R_2^C Schutzgruppen darstellen können, eines oder zwei von R_6^C , R_7^C , R_8^C und R_9^C eine geschützte Hydroxygruppe darstellen können und X_C eine geschützte Hydroxygruppe tragen kann, und, wenn notwendig oder gewünscht, das anschließende Entfernen beliebiger derartiger Schutzgruppen zum Erhalten der entsprechenden Verbindung der Formel (I) oder

(d) das Entfernen einer Schutzgruppe von einer entsprechenden Verbindung der Formel (I), die eine oder mehrere geschützte Hydroxy- oder geschützte Aminogruppen trägt, und, wenn gewünscht oder notwendig, das Überführen der erhaltenen Verbindung der Formel (I) in ein pharmazeutisch annehmbares Derivat hiervon oder umgekehrt.

2. Verfahren nach Anspruch 1, worin eines oder beide eines benachbarten Paares von R_6 , R_7 , R_8 und R_9 und ein benachbartes Paar von R_{13} , R_{14} , R_{15} und R_{16} beide Hydroxy sind.

3. Verfahren nach Anspruch 1 oder 2, worin R_7 Hydroxy ist.

4. Verfahren nach einem der vorhergehenden Ansprüche, worin n 3 bis 5 inklusive ist.

5. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I) 4-[2-(6-(2-Phenyläthylamino)-hexylamino)-äthyl]-1,2-benzoldiol oder ein pharmazeutisch annehmbares Säureadditionssalz hiervon ist.

6. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I) (R^*S^*) -2,2'-[1,6-Hexandiylbisamino]-bis-[1,2,3,4-tetrahydro-5,6-naphthalindiol],

$[R(R^*,R^*)](+)$ -7,7'-[1,6-Hexandiylbis(aminomethylen)]-bis-(bicyclo[4,2,0]octa-1,3,5-trien-2,3-diol),

4-[2-(6-(2-(4-Chlorphenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

1,2,3,4-Tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)-äthylamino)-hexylamino]-5,6-naphthalindiol

oder ein pharmazeutisch annehmbares Säureadditionssalz hiervon ist.

7. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I) $[S-(R^*,R^*)]$ -2,2'-[1,6-Hexandiylbisamino]-bis-[1,2,3,4-tetrahydro-5,6-naphthalindiol],

$[R-(R^*,R^*)]$ -2,2'-[1,6-Hexandiylbisamino]-bis-[1,2,3,4-tetrahydro-5,6-naphthalindiol],

2,2'-(1,6-Hexandiylbisamino)-bis-(1,2,3,4-tetrahydro-5,6-naphthalindiol),

2,2'-(1,6-Hexandiylbisamino)-bis-(1,2,3,4-tetrahydro-6,7-naphthalindiol),

oder ein pharmazeutisch annehmbares Säureadditionssalz eines derselben ist.

8. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I)

$[S-(R^*,R^*)]$ -7,7'-[1,6-Hexandiylbis(aminomethylen)]-bis-(bicyclo[4,2,0]octa-1,3,5-trien-2,3-diol),

(R^*S^*) -7,7'-[1,6-Hexandiylbis(aminomethylen)]-bis-(bicyclo[4,2,0]octa-1,3,5-trien-2,3-diol),

7-[6-(2-Phenyläthylamino)-hexylamino]-methylbicyclo[4,2,0]octa-1,3,5-trien-2,3-diol,

7-[6-(2-(3,4-Dihydroxyphenyl)-äthylamino)-hexylamino]-methylbicyclo[4,2,0]octa-1,3,5-trien-2,3-diol,

7-[6-(2-Phenyläthylamino)-hexylamino]-methylbicyclo[4,2,0]octa-1,3,5-trien-2,3-diol,

(7,7'-[1,6-Hexandiylbis(aminomethylen)]-bis-bicyclo[4,2,0]octa-1,3,5-trien-2,3-diol,

oder ein pharmazeutisch annehmbares Säureadditionssalz eines derselben ist.

9. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I)

7-[6-(2-(3,4-Dihydroxyphenyl)-äthylamino)-hexylamino]-methylbicyclo[4,2,0]octa-1,3,5-trien-2,3-diol,

4-[2-(6-(2-(4-Phenyläthylamino)-hexylamino)-äthyl)-1,2-benzoldiol,

4-[2-(6-(2-(4-Aminophenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-Phenylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-Phenylmethylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(3-Phenylpropylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(4-Phenylbutylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-Aminohexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(Di-n-propylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(N-Methyl-2-phenyläthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(2-Phenylpropylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(2-(4-Nitrophenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(2-(4-Hydroxyphenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(2-(4-Methylphenyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(2-(4-Pyridinyl)-äthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(6-(4-Methylpiperazinyl)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(N-Methyl-6-(4-methylpiperazinyl)-hexylamino)-äthyl]-1,2-benzoldiol,

4-[2-(4-(2-Phenyläthylamino)-butylamino)-äthyl]-1,2-benzoldiol,

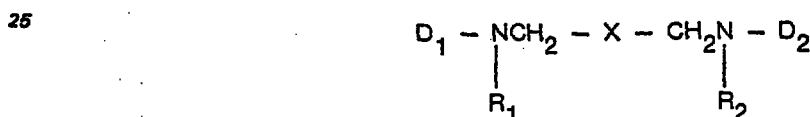


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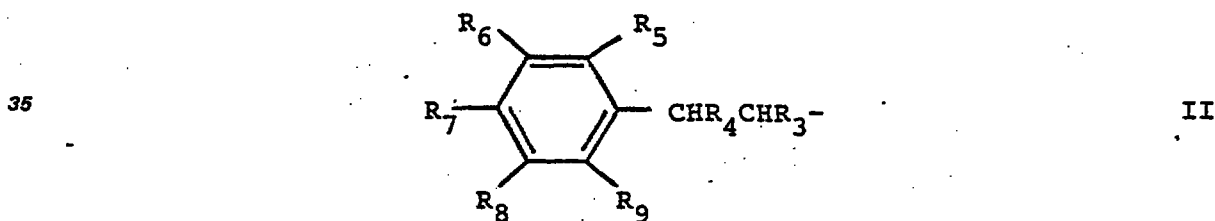
- 4-[2-(6-(1,2,3,4-Tetrahydro-2-naphthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,
 4-[2-(8-(2-Phenyläthylamino)-octylamino)-äthyl]-1,2-benzoldiol,
 4-[2-(5-(2-Phenyläthylamino)-pentylamino)-äthyl]-1,2-benzoldiol,
 3-[6-(2-(3,4-Dihydroxyphenyl)-äthylamino)-hexyl]-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7,8-
 5 diol,
 4-[2-(N-Methyl-6-(N'-methyl-2-phenyläthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,
 4-[2-(8-(2-Hydroxy-2-phenyläthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,
 4-[2-(N-Methyl-6-(di-n-propylamino)-hexylamino)-äthyl]-1,2-benzoldiol,
 10 (±)-4-[2-(4-Hydroxy-6-(2-phenyläthylamino)-hexylamino)-äthyl]-1,2-benzoldiol,
 1,2,3,4-Tetrahydro-2-[6-(2-phenyläthylamino)-hexylamino]-5,6-naphthalindiol
 oder ein pharmazeutisch annehmbares Säureadditionssalz eines derselben ist.
 10. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I)
 1,2,3,4-Tetrahydro-2-[6-(2-(3,4-dihydroxyphenyl)-äthylamino)-hexylamino]-6,7-naphthalindiol,
 1,2,3,4-Tetrahydro-2-[6-(2-phenyläthylamino)-hexylamino]-6,7-naphthalindiol,
 15 1,2,3,4-Tetrahydro-2-[4-(2-phenyläthylamino)-butylamino]-5,6-naphthalindiol,
 1,2,3,4-Tetrahydro-2-[8-(2-phenyläthylamino)-octylamino]-5,6-naphthalindiol,
 1,2,3,4-Tetrahydro-2-[8-(2-(3,4-dihydroxyphenyl)-äthylamino)-octylamino]-5,6-naphthalindiol,
 1,2,3,4-Tetrahydro-2-[6-(2-phenyläthylamino)-hexylamino]-5-naphthalenol
 oder ein pharmazeutisch annehmbares Säureadditionssalz eines derselben ist.

20 **Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE**

1. Composé de formule I



30 où D₁ représente un radical de formule II,



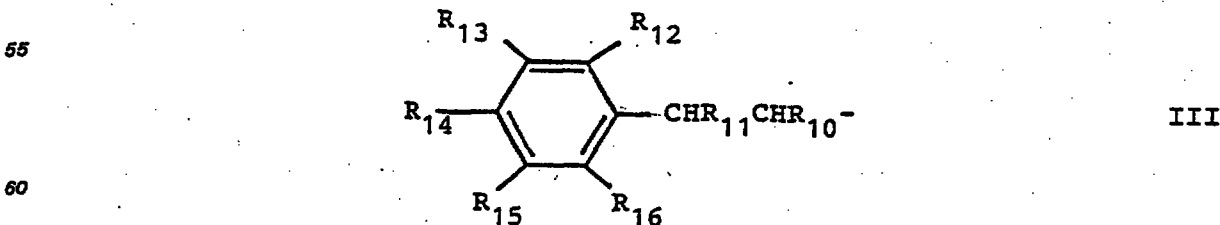
40 où R₁ et R₅, ou R₃ et R₅ peuvent former une chaîne —CH₂CH₂—, ou R₄ et R₅ peuvent former une chaîne —CH₂—, ou R₃, R₄ et R₅ représentent chacun un atome d'hydrogène, les autres d'entre R₁, R₃ et R₄, qui peuvent être identiques ou différents représentant des atomes d'hydrogène ou radicaux alcoyle ou phényle,

45 aucun, un ou deux d'entre R₆, R₇, R₈ et R₉ représentent un ou des radicaux hydroxyle et les autres représentent des atomes d'hydrogène,

X représente une chaîne —(CH₂)_n— éventuellement substituée par hydroxyle,
 n représente un nombre entier de 1 à 7 inclusivement,

50 D₂ représente un atome d'hydrogène ou radical alcoyle ou phényle, un radical alcoyle substitué par un ou plusieurs d'entre hydroxyle, pyridyle et phényle; ou bien un radical alcoyle substitué par phényle qui est à son tour substitué par halogéno, alcoyle, amino, alcoxy ou nitro, ou

D₂ représente un radical de formule III,



où R₂ et R₁₂ ou R₁₀ et R₁₂ peuvent former une chaîne —CH₂—CH₂—, ou R₁₁ et R₁₂ peuvent former une chaîne —CH₂—, ou R₁₀, R₁₁ et R₁₂ représentent chacun un atome d'hydrogène,



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- les autres d'entre R_2 , R_{10} et R_{11} , qui peuvent être identiques ou différents, représentant des atomes d'hydrogène ou radicaux alcoyle ou phényle,
- aucun, un ou deux d'entre R_{13} , R_{14} , R_{15} et R_{16} représentent un ou des radicaux hydroxyle et les autres représentent des atomes d'hydrogène ou
- 5 R_2 et D_2 , conjointement avec l'atome d'azote auquel ils sont unis, forment un radical hétérocyclique à 5 ou 6 chaînons,
- avec la restriction que lorsque X n'est pas substitué par hydroxyle et
- i) lorsque R_3 , R_4 et R_5 représentent des atomes d'hydrogène, R_1 et R_2 représentent tous deux des atomes d'hydrogène ou radicaux alcoyle inférieurs et deux d'entre R_6 , R_7 , R_8 et R_9 représentent des
- 10 radicaux hydroxyle, D_2 n'est pas identique à D_1 , ou
- ii) lorsque R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 et R_9 représentent des atomes d'hydrogène, R_2 et D_2 ne représentent pas chacun un radical alcoyle inférieur, ni ne forment conjointement avec l'atome d'azote auquel ils sont unis un radical hétérocyclique à 5 ou 6 chaînons, ou
- iii) lorsque R_1 , R_4 , R_5 , R_6 , R_7 , R_8 et R_9 représentent des atomes d'hydrogène et R_3 représente un radical
- 15 alcoyle, D_2 n'est pas identique à D_1 , ou
- iv) lorsque R_1 représente un radical phényle, R_3 et R_5 forment ensemble la chaîne $-\text{CH}_2\text{CH}_2-$, R_6 , R_7 , R_8 et R_9 représentent des atomes d'hydrogène, n représente 1, D_2 et R_2 ne représentent pas chacun un atome d'hydrogène ou radical alcoyle ou ne forment pas ensemble un radical hétérocyclique ou
- v) lorsque R_1 représente un atome d'hydrogène ou radical alcoyle de 1 à 3 atomes de carbone, R_3 représente un radical méthyle, R_4 représente un atome d'hydrogène, n représente 1, D_2 et R_2 ne
- 20 représentent pas chacun un radical phényle,
- et leurs dérivés pharmaceutiquement acceptables.
2. Composé suivant la revendication 1 pour l'utilisation comme agent pharmaceutique.
3. Composé suivant la revendication 1 ou 2, dans lequel l'un ou les deux dans une paire adjacente
- 25 parmi R_6 , R_7 , R_8 et R_9 et une paire adjacente parmi R_{13} , R_{14} , R_{15} , et R_{16} représentent chacun un radical hydroxyle.
4. Composé suivant l'une quelconque des revendications précédentes, dans lequel R_7 représente un radical hydroxyle.
5. Composé suivant l'une quelconque des revendications précédentes, dans lequel n représente 3 à 5
- 30 inclusivement.
6. Le 4-[2-(6-(2-phényléthylamino)hexylamino)éthyl]-1,2-benzènediol ou un sel d'addition pharmaceutiquement acceptable de celui-ci.
7. Le (R^*S^*) -2,2'-[1,6-hexanediylbis(amino)]-bis-[1,2,3,4-tétrahydro-5,6-naphtalènediol],
- le $[R(R^*,R^*)](+)$ -7,7'-[1,6-hexanediylbis(aminométhylène)]-bis(bicyclo[4,2,0]-octa-1,3,5-triène-2,3-diol),
- 35 le 4-[2-(6-(2-(4-chlorophényl)éthylamino)hexylamino)éthyl]-1,2-benzènediol,
- le 1,2,3,4-tétrahydro-2-[6-(2-(3,4-dihydroxyphényl)éthylamino)hexylamino]-5,6-naphtalènediol,
- ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.
8. Le $[S-(R^*R^*)]$ -2,2'-[1,6-hexanediylbis(amino)]-bis-[1,2,3,4-tétrahydro-5,6-naphtalènediol],
- le $[R-(R^*R^*)]$ -2,2'-[1,6-hexanediylbis(amino)]-bis-[1,2,3,4-tétrahydro-5,6-naphtalènediol],
- 40 le 2,2'-[1,6-hexanediylbis(amino)]-bis-(1,2,3,4-tétrahydro-5,6-naphtalènediol),
- le 2,2'-[1,6-hexanediylbis(amino)]-bis-(1,2,3,4-tétrahydro-6,7-naphtalènediol),
- ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.
9. Le $[S-(R^*R^*)]$ -7,7'-[1,6-hexanediylbis(aminométhylène)]-bis(bicyclo[4,2,0]-octa-1,3,5-triène-2,3-diol),
- 45 le (R^*S^*) -7,7'-[1,6-hexanediylbis(aminométhylène)]-bis(bicyclo[4,2,0]-octa-1,3,5-triène-2,3-diol),
- le 7-[6-(2-phényléthylamino)hexylamino]méthylbicyclo[4,2,0]-octa-1,3,5-triène-2,3-diol,
- le 7-[6-(2-(3,4-dihydroxyphényl)éthylamino)hexylamino]méthylbicyclo[4,2,0]-octa-1,3,5-triène-2,3-diol,
- 50 le 7-[6-(2-phényléthylamino)hexylamino]méthylbicyclo[4,2,0]-octa-1,3,5-triène-3,4-diol,
- le (7,7'-[1,6-hexanediylbis(aminométhylène)]-bis-bicyclo[4,2,0]-octa-1,3,5-triène-3,4-diol),
- ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.
10. Le 7-[6-(2-(3,4-dihydroxyphényl)éthylamino)hexylamino]méthylbicyclo[4,2,0]-octa-1,3,5-triène-3,4-diol,
- 55 le 4-[2-(6-(4-aminophényl)éthylamino)hexylamino]éthyl]-1,2-benzènediol,
- le 4-[(2-(6-phénylamino)hexylamino)éthyl]-1,2-benzènediol,
- le 4-[(2-(6-(4-phénylméthylamino)hexylamino)éthyl)-1,2-benzènediol,
- le 4-[2-(6-(3-phénylpropylamino)hexylamino)éthyl]-1,2-benzènediol,
- le 4-[2-(6-(4-phénylbutylamino)hexylamino)éthyl]-1,2-benzènediol,
- 60 le 4-[2-(6-amino-hexylamino)éthyl]-1,2-benzènediol,
- le 4-[2-(6-(di-n-propylamino)hexylamino)éthyl]-1,2-benzènediol,
- le 4-[2-(6-(N-méthyl-2-phényléthylamino)hexylamino)éthyl]-1,2-benzènediol,
- le 4-[2-(6-(2-phénylpropylamino)hexylamino)éthyl]-1,2-benzènediol,
- le 4-[2-(6-(2-(4-nitrophényl)éthylamino)hexylamino)éthyl]-1,2-benzènediol,
- le 4-[2-(6-(2-(4-hydroxyphényl)éthylamino)hexylamino)éthyl]-1,2-benzènediol,
- 65 le 4-[2-(6-(4-méthylphényl)éthylamino)hexylamino]éthyl]-1,2-benzènediol,

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10 le 4-[2-(N-méthyl-6-(N'-méthyl-2-phényléthylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(2-hydroxy-2-phényléthylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(N-méthyl-6-(di-n-propylamino)hexylamino)éthyl]-1,2-benzènediol,
le (±)-4-[2-[4-hydroxy-6-(2-phényléthylamino)-hexylamino)-éthyl]-1,2-benzènediol,
ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.

ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.

13. Procédé de préparation d'un composé de formule I suivant la revendication 1 ou d'un dérivé pharmaceutiquement acceptable de celui-ci, qui comprend

$$D_1a - \underset{\underset{R_1a}{|}}{N} CT_1 - X_a - CT_2 \underset{\underset{R_2a}{|}}{N} - D_2a$$

1V

R₁a et R₂a ont la même signification que R₁ et R₂ ci-dessus, sauf qu'ils peuvent représenter en outre, un radical protecteur,

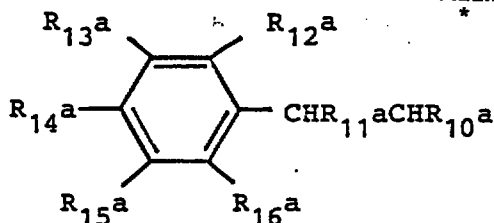
A benzene ring with substituents R_5a , R_6a , R_7a , R_8a , R_9a , and a side chain $-CHR_4aCHR_3a-$.

W

D_2a représente un radical de formule VI



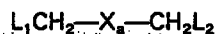
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VI

où R_{10}^a , R_{11}^a , R_{12}^a , R_{13}^a , R_{14}^a , R_{15}^a et R_{16}^a ont respectivement les mêmes significations que R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} et R_{16} ci-dessus, sauf qu'en outre, l'un ou plusieurs d'entre R_{13}^a , R_{14}^a , R_{15}^a et R_{16}^a peuvent représenter un radical hydroxyle protégé, et si nécessaire ou souhaité, l'élimination ultérieure de radicaux protecteurs quelconques pour obtenir le composé correspondant de formule I,

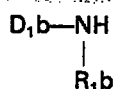
(b) la préparation d'un composé de formule I où D_2 est identique à D_1 et R_1 est identique à R_2 , par réaction d'un composé de formule VII



VII

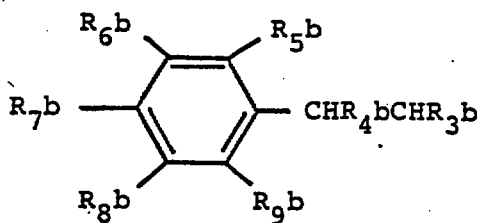
où L_1 et L_2 , qui peuvent être identiques ou différents, représentent des radicaux labiles,

X_a est tel que défini ci-dessus, avec un composé de formule VIII



VIII

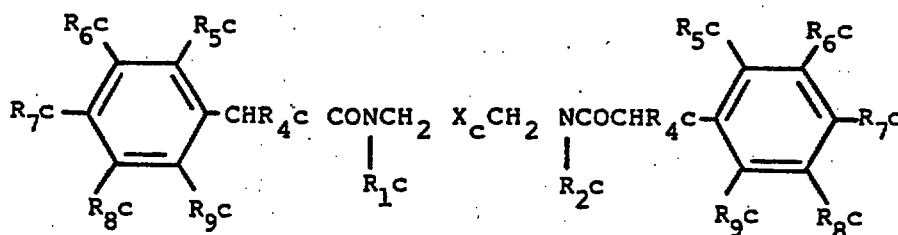
ou un sel d'addition d'acide de celui-ci, où D_1b représente un radical de formule IX



IX

où R_1^b , R_3^b , R_4^b , R_5^b , R_6^b , R_7^b , R_8^b et R_9^b ont respectivement les mêmes significations que R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 et R_9 ci-dessus, sauf qu'en outre, R_1^b peut représenter un radical éliminable capable d'augmenter le caractère nucléophile de l'azote et que l'un ou deux d'entre R_6^b , R_7^b , R_8^b et R_9^b peuvent représenter un radical hydroxyle protégé, et si nécessaire ou souhaité, l'élimination ultérieure de radicaux protecteurs ou éliminables quelconques pour former le composé correspondant de formule I,

(c) la préparation d'un composé de formule I où D_2 est identique à D_1 et les deux R_3 représentent des atomes d'hydrogène, par réduction sélective d'un composé de formule X



X

où R_1^c , R_2^c , R_4^c , R_5^c , R_6^c , R_7^c , R_8^c , R_9^c et X_c ont respectivement les mêmes significations que R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 et X ci-dessus, sauf qu'en outre,

R_1^c et/ou R_2^c peuvent représenter des radicaux protecteurs, l'un ou deux d'entre R_6^c , R_7^c , R_8^c et R_9^c peuvent représenter un radical hydroxyle protégé et

X_c peut porter un radical hydroxyle protégé, et si nécessaire ou souhaité, l'élimination ultérieure de radicaux protecteurs quelconques pour former le composé correspondant de formule I, ou

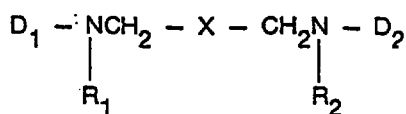
(d) l'élimination d'un radical protecteur d'un composé correspondant de formule I portant un ou plusieurs radicaux hydroxyle protégés ou amino protégés, et si souhaité ou nécessaire, la conversion du composé résultant de formule I en un dérivé pharmaceutiquement acceptable de celui-ci, ou réciproquement.



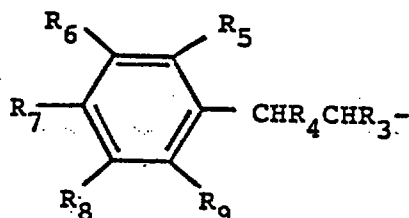
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Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule I



où D_1 représente un radical de formule II,



II

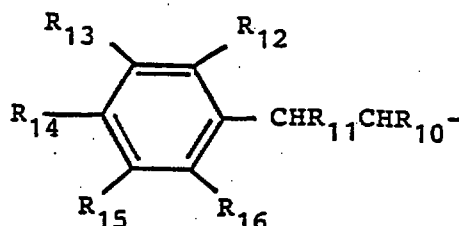
où R_1 et R_5 , ou R_3 et R_5 peuvent former une chaîne $-CH_2CH_2-$, ou R_4 et R_5 peuvent former une chaîne $-CH_2-$, ou R_3 , R_4 et R_5 représentent chacun un atome d'hydrogène, les autres d'entre R_1 , R_3 et R_4 , qui peuvent être identiques ou différentes représentant des atomes d'hydrogène ou radicaux alcoyle ou phényle,

aucun, un ou deux d'entre R_6 , R_7 , R_8 et R_9 représentent un ou des radicaux hydroxyle et les autres représentent des atomes d'hydrogène;

X représente une chaîne $-(CH_2)_n-$ éventuellement substituée par hydroxyle, n représente un nombre entier de 1 à 7 inclusivement,

D_2 représente un atome d'hydrogène ou radical alcoyle ou phényle, un radical alcoyle substitué par un ou plusieurs d'entre hydroxyle, pyridyle et phényle; ou bien un radical alcoyle substitué par phényle qui est à son tour substitué par halogéno, alcoyle, amino, alcoxy ou nitro, ou

D_2 représente un radical de formule III,



III

où R_2 et R_{12} ou R_{10} et R_{12} peuvent former une chaîne $-CH_2CH_2-$, ou R_{11} et R_{12} peuvent former une chaîne $-CH_2-$, ou R_{10} , R_{11} et R_{12} représentent chacun un atome d'hydrogène,

les autres d'entre R_2 , R_{10} et R_{11} , qui peuvent être identiques ou différents, représentant des atomes d'hydrogène ou radicaux alcoyle ou phényle,

aucun, un ou deux d'entre R_{13} , R_{14} , R_{15} et R_{16} représentent un ou des radicaux hydroxyle et les autres représentent des atomes d'hydrogène ou

R_2 et D_2 , conjointement avec l'atome d'azote auquel ils sont unis, forment un radical hétérocyclique à 5 ou 6 chaînons,

avec la restriction que lorsque X n'est pas substitué par hydroxyle et

i) lorsque R_3 , R_4 et R_5 représentent des atomes d'hydrogène, R_1 et R_2 représentent tous deux des atomes d'hydrogène ou radicaux alcoyle inférieurs et deux d'entre R_6 , R_7 , R_8 et R_9 représentent des radicaux hydroxyle, D_2 n'est pas identique à D_1 , ou

ii) lorsque R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 et R_9 représentent des atomes d'hydrogène, R_2 et D_2 ne représentent pas chacun un radical alcoyle inférieur, ni ne forment conjointement avec l'atome d'azote auquel ils sont unis un radical hétérocyclique à 5 ou 6 chaînons, ou

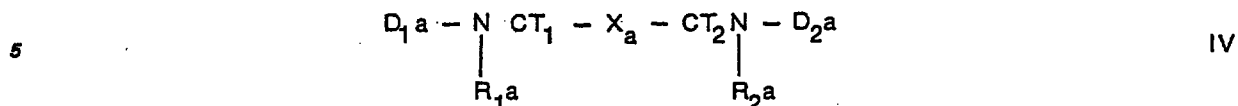
iii) lorsque R_1 , R_4 , R_5 , R_6 , R_7 , R_8 et R_9 représentent des atomes d'hydrogène et R_3 représente un radical alcoyle, D_2 n'est pas identique à D_1 , ou

iv) lorsque R_1 représente un radical phényle, R_3 et R_5 forment ensemble la chaîne $-CH_2CH_2-$, R_6 , R_7 , R_8 et R_9 représentent des atomes d'hydrogène, n représente 1, D_2 et R_2 ne représentent pas chacun un atome d'hydrogène ou radical alcoyle ou ne forment pas ensemble un radical hétérocyclique ou

v) lorsque R_1 représente un atome d'hydrogène ou radical alcoyle de 1 à 3 atomes de carbone, R_3 représente un radical méthyle, R_4 représente un atome d'hydrogène, n représente 1, D_2 et R_2 ne représentent pas chacun un radical phényle,

et des dérivés pharmaceutiquement acceptables de celui-ci que comprend:

(a) la réduction sélective d'un composé de formule IV

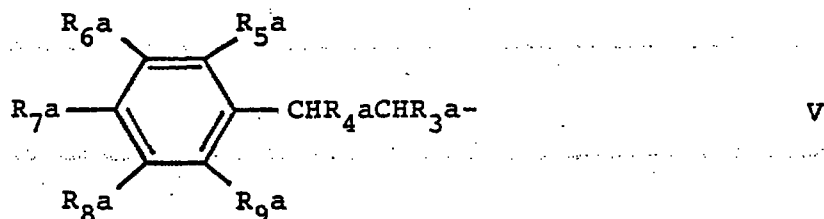


10 où T_1 et T_2 représentent tous deux H_2 ou O , avec la restriction qu'au moins l'un d'entre T_1 et T_2 représente O ,

R_1a et R_2a ont la même signification que R_1 et R_2 ci-dessus, sauf qu'ils peuvent représenter en outre, un radical protecteur,

D_1a représente un radical de formule V

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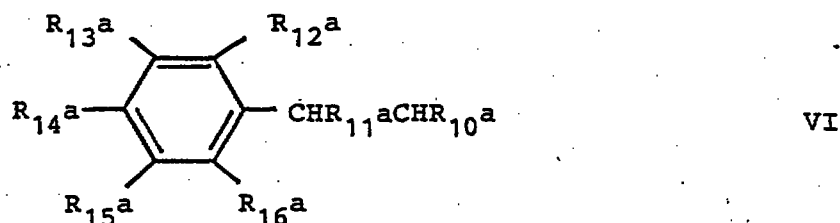
25 où R_3a , R_4a , R_5a , R_6a , R_7a , R_8a et R_9a ont respectivement les mêmes significations que R_3 , R_4 , R_5 , R_6 , R_7 , R_8 et R_9 ci-dessus, sauf qu'en outre, l'un ou deux d'entre R_6a , R_7a , R_8a et R_9a peuvent représenter un radical hydroxyle protégé,

X_a a la même signification que X ci-dessus, sauf qu'il peut porter en outre, un radical hydroxyle protégé,

30 D_2a représente un atome d'hydrogène ou radical alcoyle ou phényle ou un radical alcoyle substitué par un ou plusieurs d'entre hydroxyle, hydroxyle protégé, pyridyle et phényle; ou bien un radical alcoyle substitué par phényle qui est à son tour substitué par halogéno, alcoyle, amino, alcoxy ou nitro; ou

D_2a représente un radical de formule VI

35



40

45 où R_{10}a , R_{11}a , R_{12}a , R_{13}a , R_{14}a , R_{15}a et R_{16}a ont respectivement les mêmes significations que R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} et R_{16} ci-dessus, sauf qu'en outre, l'un ou plusieurs d'entre R_{13}a , R_{14}a , R_{15}a et R_{16}a peuvent représenter un radical hydroxyle protégé, et si nécessaire ou souhaité, l'élimination ultérieure de radicaux protecteurs quelconques pour obtenir le composé correspondant de formule I,

(b) la préparation d'un composé de formule I où D_2 est identique à D_1 et R_1 est identique à R_2 , par

50 réaction d'un composé de formule VII



où L_1 et L_2 , qui peuvent être identiques ou différents, représentent des radicaux labiles,

55 X_a est tel que défini ci-dessus, avec un composé de formule VIII

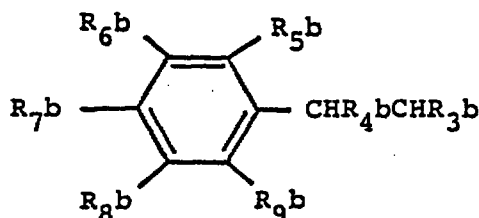
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ou un sel d'addition d'acide de celui-ci, ou D_1b représente un radical de formule IX

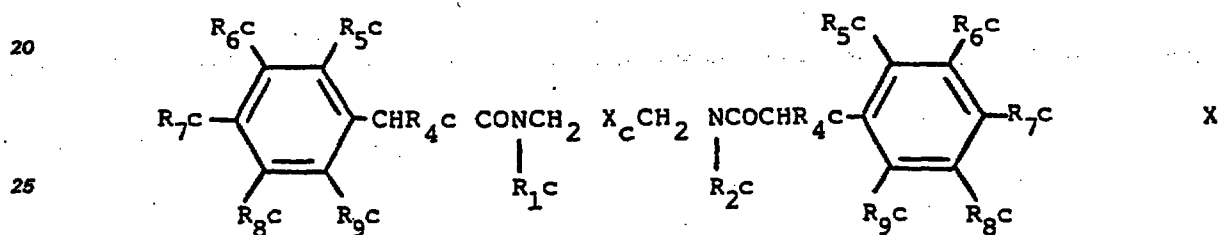
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10 où $R_1b, R_3b, R_4b, R_5b, R_6b, R_7b, R_8b$ et R_9b ont respectivement les mêmes significations que $R_1, R_3, R_4, R_5, R_6, R_7, R_8$ et R_9 ci-dessus, sauf qu'en outre, R_1b peut représenter un radical éliminable capable d'augmenter le caractère nucléophile de l'azote et que l'un ou deux d'entre R_6b, R_7b, R_8b et R_9b peuvent représenter un radical hydroxyle protégé, et si nécessaire ou souhaité, l'élimination ultérieure de radicaux protecteurs ou éliminables quelconques pour former le composé correspondant de formule I,

15 (c) la préparation d'un composé de formule I où D_2 est identique à D_1 et les deux R_3 représentent des atomes d'hydrogène, par réduction sélective d'un composé de formule X



20 où $R_1c, R_2c, R_4c, R_5c, R_6c, R_7c, R_8c, R_9c$ et X_c ont respectivement les mêmes significations que $R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9$ et X ci-dessus, sauf qu'en outre,

30 R_1c et/ou R_2c peuvent représenter des radicaux protecteurs, l'un ou deux d'entre R_6c, R_7c, R_8c et R_9c peuvent représenter un radical hydroxyle protégé et

X_c peut porter un radical hydroxyle protégé, et si nécessaire ou souhaité, l'élimination ultérieure de radicaux protecteurs quelconques pour former le composé correspondant de formule I, ou

35 (d) l'élimination d'un radical protecteur d'un composé correspondant de formule I portant un ou plusieurs radicaux hydroxyle protégés ou amino protégés, et si souhaité ou nécessaire, la conversion du composé résultant de formule I en un dérivé pharmaceutiquement acceptable de celui-ci, ou réciproquement:

2. Procédé suivant la revendication 1, dans lequel l'un ou les deux dans une paire adjacente parmi R_6, R_7, R_8 et R_9 et une paire adjacente parmi R_{13}, R_{14}, R_{15} et R_{16} représentent chacun un radical hydroxyle.

3. Procédé suivant la revendication 1 ou 2, dans lequel R_7 représente un radical hydroxyle.

4. Procédé suivant l'une quelconque des revendications précédentes, dans lequel n représente 3 à 5 inclusivement.

5. Procédé suivant la revendication 1, dans lequel le composé de formule I est le 4-[2-(6-(2-phényléthyl-amino)hexylamino)éthyl]-1,2-benzènediol ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci.

6. Procédé suivant la revendication 1, dans lequel le composé de formule 1 est le (R^*S^*) -2,2'-[1,6-hexanediyibis(amino)]-bis-[1,2,3,4-tétrahydro-5,6-naphtalènediol],
le $[R(R^*,R^*)](+)-7,7'$ -[1,6-hexanediyibis(aminométhylène)]-bis(bicyclo[4,2,0]-octa-1,3,5-triène-2,3-diol),
50 le 4-[2-(6-(2-(4-chlorophényl)éthylamino)hexylamino)éthyl]-1,2-benzènediol,
le 1,2,3,4-tétrahydro-2-[6-(2-(3,4-dihydroxyphényl)-éthylamino)hexylamino]-5,6-naphtalènediol,
ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.

7. Procédé suivant la revendication 1, dans lequel le composé de formule I est
le $[S-(R^*R^*)]$ -2,2'-[1,6-hexanediyibis(amino)]-bis-[1,2,3,4-tétrahydro-5,6-naphtalènediol],
55 le $[R-(R^*R^*)]$ -2,2'-[1,6-hexanediyibis(amino)]-bis-[1,2,3,4-tétrahydro-5,6-naphtalènediol],
le 2,2'-(1,6-hexanediyibis(amino)]-bis-(1,2,3,4-tétrahydro-5,6-naphtalènediol),
le 2,2'-(1,6-hexanediyibis(amino)]-bis-(1,2,3,4-tétrahydro-6,7-naphtalènediol),
ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.

8. Procédé suivant la revendication 1, dans lequel le composé de formule I est
le $[S-(R^*R^*)]$ -7,7'-[1,6-hexanediyibis(aminométhylène)]-bis(bicyclo[4,2,0]-octa-1,3,5-triène-2,3-diol),
60 le (R^*S^*) -7,7'-[1,6-hexanediyibis(aminométhylène)]-bis(bicyclo[4,2,0]-octa-1,3,5-triène-2,3-diol),
le 7-[6-(2-phényléthylamino)hexylamino]méthylbicyclo-[4,2,0]-octa-1,3,5-triène-2,3-diol,
le 7-[6-(2-(3,4-dihydroxyphényl)éthylamino)hexylamino]-méthylbicyclo[4,2,0]-octa-1,3,5-triène-2,3-diol,
diol,

65 le 7-[6-(2-phényléthylamino)hexylamino]méthylbicyclo-[4,2,0]-octa-1,3,5-triène-3,4-diol,



le (7,7'-[1,6-hexanediylbis(aminométhylène)]-bis-bicyclo-[4,2,0]-octa-1,3,5-triene-3,4-diol),
ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.

9. Procédé suivant la revendication 1, dans lequel le composé de formule I est

- le 7-[6-[2-(3,4-dihydroxyphényl)éthylamino]hexylamino]méthylbicyclo-[4,2,0]-octa-1,3,5-triene-3,4-
5 diol,
le 4-[2-(6-(2-phényléthylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(4-aminophényl)éthylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(2-phénylamino)hexylamino)éthyl]-1,2-benzènediol,
10 le 4-[2-(6-(3-phénylpropylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(4-phénylbutylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(4-amino-hexylamino)éthyl)-1,2-benzènediol,
le 4-[2-(6-(di-n-propylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(N-méthyl-2-phényléthylamino)hexylamino)-éthyl]-1,2-benzènediol,
15 le 4-[2-(6-(2-phénylpropylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(2-(4-nitrophényl)éthylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(2-(4-hydroxyphényl)éthylamino)hexylamino)-éthyl]-1,2-benzènediol,
le 4-[2-(6-(2-(4-méthylphényl)éthylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(2-(4-pyridinyl)éthylamino)hexylamino)éthyl]-1,2-benzènediol,
20 le 4-[2-(6-(4-méthylpipérazinyl)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(N-méthyl-6-(4-méthylpipérazinyl)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(4-(2-phényléthylamino)butylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(1,2,3,4-tétrahydro-2-naphtylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(8-(2-phényléthylamino)octylamino)éthyl]-1,2-benzènediol,
25 le 4-[2-(5-(2-phényléthylamino)pentylamino)éthyl]-1,2-benzènediol,
le 3-[6-(2-(3,4-dihydroxyphényl)éthylamino)hexyl]-1-phényl-2,3,4,5-tétrahydro-1H-3-benzazépin-7,8-
diol,

- le 4-[2-(N-méthyl-6-(N'-méthyl-2-phényléthylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(6-(2-hydroxy-2-phényléthylamino)hexylamino)éthyl]-1,2-benzènediol,
30 le 4-[2-(N-méthyl-6-(di-n-propylamino)hexylamino)éthyl]-1,2-benzènediol,
le 4-[2-(4-(4-hydroxy-6-(2-phényléthylamino)-hexylamino)éthyl)-1,2-benzènediol,
le 1,2,3,4-tétrahydro-2-[6-(2-phényléthylamino)hexylamino]-5,6-naphtalènediol,
ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.

10. Procédé suivant la revendication 1, dans lequel le composé de formule I est
35 le 1,2,3,4-tétrahydro-2-[6-(2-(3,4-dihydroxyphényl)éthylamino)hexylamino]-6,7-naphtalènediol,
le 1,2,3,4-tétrahydro-2-[6-(2-phényléthylamino)hexylamino]-6,7-naphtalènediol,
le 1,2,3,4-tétrahydro-2-[4-(2-phényléthylamino)butylamino]-5,6-naphtalènediol,
le 1,2,3,4-tétrahydro-2-[8-(2-phényléthylamino)octylamino]-5,6-naphtalènediol,
le 1,2,3,4-tétrahydro-2-[8-(2-(3,4-dihydroxyphényl)éthylamino)octylamino]-5,6-naphtalènediol,
40 le 1,2,3,4-tétrahydro-2-[6-(2-phényléthylamino)hexylamino]-5-naphtalénol,
ou un sel d'addition d'acide pharmaceutiquement acceptable de l'un quelconque de ceux-ci.

