

PATENT SPECIFICATION

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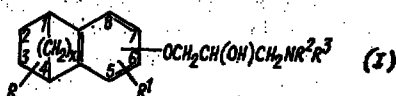
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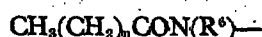
(54) 1,4-METHANO- AND ETHANO-TETRAHYDRONAPHTHYL-OXYPROPANOLS AND PROCESS FOR THEIR PREPARATION

(71) We, CARLO ERBA S.p.A., an Italian Body Corporate of, Via Carlo Imbonati 24, 20159 Milan, Italy, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following Statement:—

This invention relates to amine compounds having beta-adrenergic receptor blocking activity, to a process for preparing the compounds and to pharmaceutical compositions containing them, and is an improvement in, or modification of, the invention of British Patent Specification No. 1,263,035 which describes amine compounds of general formula (I)



wherein each of the groups R and R¹, which may be the same or different, is a hydrogen atom or halogen atom; or a C₁₋₄-alkyl, C₁₋₄-alkoxy, nitro, substituted or unsubstituted amino, C₁₋₆-alkanesulphonamido, C₁₋₆-alkylthio, C₁₋₆-alkylsulphinyl or C₁₋₆-alkylsulphonyl group; or a group of formula R⁴R⁵NSO₂—wherein each of the groups R⁴ and R⁵, which may be the same or different, is a hydrogen atom or a C₁₋₆-alkyl group; or a group of formula

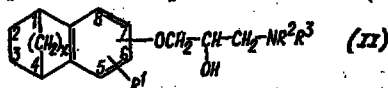


wherein n is 0 or an integer of 1 to 6, and R⁶ is a hydrogen atom or a methyl group; x is 1 or 2; and

R² is a hydrogen atom or a C₁₋₄-alkyl or benzyl group;
 R³ is a hydrogen atom or a C₁₋₁₀ alkyl group or a benzyl group;
 or a pharmaceutically acceptable salt thereof. These compounds have enhanced beta-adrenergic receptor blocking activity.

We have now found that compounds of the above general formula wherein R is a hydrogen atom and R¹ is a hydroxy or an acyloxy group also have beta-adrenergic receptor blocking activity but possess a still more favourable therapeutical index.

The invention therefore provides a compound of formula (II)



wherein x is 1 or 2; R¹ is a hydroxy or acyloxy group (which can be an aliphatic or aromatic substituted or unsubstituted acyloxy group), R² is a hydrogen atom or a benzyl or C₁₋₄ alkyl group; R³ is a hydrogen atom or a benzyl or C₁₋₁₀ alkyl group; or a pharmaceutically acceptable salt thereof. It is to be noted that the above definition of the compounds of the invention includes all the possible stereoisomers, as well as their mixture.

The alkyl group may be a branched or straight chain alkyl group. When R¹ is an acyloxy group, it is preferably an acetoxy, propionyloxy or benzyloxy group.

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Price 75p

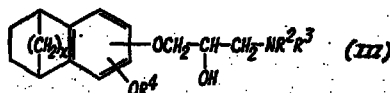
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The preferred compounds are those which R^1 is a hydroxy group, R^2 is an alkyl group having 3 or 4 carbon atoms (in particular an isopropyl or t-butyl group), and R^3 is a hydrogen atom. R^1 is preferably in the 8-position, while the ether side chain is preferably in the 5-position.

Examples of suitable salts are those of inorganic acids (for instance hydrochloric acid) and organic acids (for instance fumaric and citric acid).

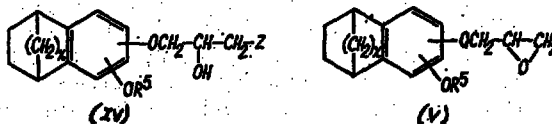
The invention also provides a process for preparing a compound of general formula (II) by

a) deetherifying a compound of general formula (III)



wherein x , R^2 and R^3 are as defined above and R^4 is an alkyl group (which may be branched or straight chain or an alkyl group, and if desired, when a compound of general formula (II) wherein R^1 is other than hydroxy is required, esterifying in known manner the deetherification product; or

b) reacting a compound of general formula (IV) or (V)



wherein x is as defined above, Z is a halogen atom and R^5 is an acyl group with an amine of general formula HNR^2R^3 , wherein R^2 and R^3 are as defined above, and then, if desired, when a compound of general formula (II) wherein R^1 is hydroxy group is required, saponifying in known manner the reaction product;

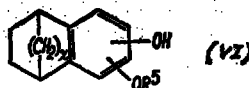
and then, if desired, reacting the compound of general formula (II), obtained in (a) or (b) with an acid to give a pharmaceutically acceptable salt and/or, if desired, resolving an obtained mixture of optical isomers into the different isomers.

Either the optional acid reaction step or the optional resolution step into the isomers can be carried out by conventional methods, as is known to those skilled in the art.

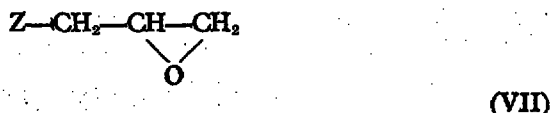
The compounds of general formula (III) can be obtained as described in British Patent Specification No. 1,263,034. Suitable deetherification agents include Lewis acids (for example boron tribromide and aluminium trichloride) or pyridine hydrochloride; when R^4 is a benzyl group catalytic hydrogenation can be used.

Reaction (b) can be performed in the presence or absence of a solvent; suitable solvents are toluene or dioxan.

The compounds of general formula (IV) can be prepared by reaction of a compound of general formula (VI)



wherein R^5 is as defined above, with a compound of general formula (VII)



wherein Z is as defined above.

The compounds of general formula (V) can be obtained from the compounds of general formula (IV) by treatment with a base, for example sodium hydroxide, bicarbonate or methoxide.

The following activities of the compounds of general formula (II) were investigated:

(a) activity as antagonist of tachycardia induced by injection of isoproterenol (beta-adrenergic receptor stimulant agent) in the reserpinized and vagotomized cat under general anaesthesia;

- (b) activity as antagonist of the increase of the heart rate induced by isoproterenol in the conscious dog;
 (c) activity on the contraction of isolated myocardium;
 (d) local anaesthetic activity;
 (e) activity on isolated bronchial smooth muscle.

The activity of the compounds in antagonizing the changes induced by stimulation of the adrenergic beta-receptors as well as the activity on the myocardial contraction were compared with that of propranolol and with that of the compounds described in our British Patent Specification No. 1,263,035. The results are shown in the Table below.

TABLE

	Propranolol	1-isopropylamino-3-(1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol	1- <i>t</i> -butylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol
Antagonism of Tachycardia induced by Isoproterenol	1	4	8
Myocardial Depressant Activity	1	0.65	0.40
Anaesthetic Activity	1	0.5	0.1
Activity on Bronchial Smooth Muscle	1	0.5	0.25

1-*t*-Butylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaph-5'-yloxy)-2-propanol has a marked specificity of action or heart beta-adrenergic receptors while unwanted effects, common to all beta-blocking agents (such as the depression of the myocardial contraction and tonic activity on the bronchial muscle) are markedly lower, and furthermore this compound has a therapeutic index which is still better than that of 1-isopropylamino-3-(1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol.

The pharmacological data hereabove reported have been confirmed by clinical trials performed on man. The compounds of the invention, by exerting a competitive antagonism against the activation of sympathetic beta-adrenergic receptors, are useful for the treatment of tachycardia (for example, hyperkinetic syndrome, thyrotoxicosis, paroxysmal tachycardia), angina pectoris and myocardial ischaemia in general, arterial hypertension and anxiety conditions.

The compounds of the present invention are preferably administered by the oral or parenteral route.

The results of the clinical trials have shown that when the compounds are administered orally, doses for adult humans may vary from 10 to 40 mg., preferably about 20 mg., while dosages of 2.5 mg. to 5 mg. are preferably for the parenteral administration.

The pharmaceutical compositions of the invention comprise the compounds of the invention and a pharmaceutically acceptable carrier or diluent, and may be prepared according to conventional practice; and they can be, for example, in the form of capsules, tablets, pills, drops or vials and suppositories.

Examples of the substances which can serve as carriers or diluents for the pharmaceutical compositions of the invention are talc, gelatin, lactose, starch, magne-

sium stearate, polyvinylpyrrolidone, as well as other non-toxic compatible substances used in pharmaceutical formulations.

The invention is illustrated by the following Examples.

EXAMPLE 1.

1 - Isopropylamino - 3 - (8' - methoxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride (4.5 g.) and pyridine hydrochloride (9 g.) were heated under nitrogen at 180°C for two hours. The solid mass was diluted in water (60 ml.), and sodium bicarbonate (6 g.) was added portionwise. The solid product which separated was then filtered and washed with water. Crystallisation from ethyl acetate gave 1-isopropylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol (3.8 g.; m.p. 134—135°C). The hydrochloride (m.p. 200—201°C) could be obtained by dissolving the base in methanol, saturating the solution with hydrogen chloride gas, diluting with diethyl ether, filtering the solid precipitate and crystallizing from 90% isopropanol.

By following the same method, 1-*t*-butylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol (m.p. 151—152°C) and its hydrochloride (m.p. 235—237°C), and 1-*s*-butylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol and its hydrochloride (m.p. of the hydrochloride 188—190°C), were prepared.

EXAMPLE 2.

1 - Isopropylamino - 3 - (8' - benzyloxy) - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol (10 g.) dissolved in 300 ml. of 99% ethanol/methylenechloride (1:1; 300 ml.) was hydrogenated at 4—5 atmospheres in the presence of 3 g. of 5% palladium on carbon. After an hour the adsorption of hydrogen (2 moles) was complete; the mixture was filtered, concentrated to dryness, and the solid product thus obtained crystallised from isopropanol to give 1-isopropylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride (7.2 g.; m.p. 198—200°C).

EXAMPLE 3.

1 - Isopropylamino - 3 - (8' - methoxybenzonorbornan - 5' - yloxy) - 2 - propanol hydrochloride (5 g.) dissolved in chloroform (300 ml.) was treated at —30°C with boron tribromide (10 g.). The solution was allowed to stand at 0°C for two hours, then concentrated to dryness, and the residue dissolved in 5% hydrochloric acid. It was then refluxed for 24 hours, neutralised with sodium bicarbonate and extracted with ethyl acetate (2 × 200 ml.). After concentration to dryness, the residue was treated with hydrogen chloride in isopropanol. Dilution with diethyl ether precipitated 1-isopropylamino-3-(8'-hydroxybenzonorbornan-5'-yloxy)-2-propanol hydrochloride (m.p. 178—180°C).

By following the same method, these compounds were obtained:

1-*t*-butylamino-3-(8'-hydroxybenzonorbornan-5'-yloxy)-2-propanol hydrochloride,
1-*s*-butylamino-3-(8'-hydroxybenzonorbornan-5'-yloxy)-2-propanol hydrochloride.

EXAMPLE 4.

5,8-Diacetoxy-1,2,3,4-tetrahydroethanenaphthalene (55 g.) in dry methanol (400 ml.) was treated with diethyl amine (10.5 ml.). The solution was allowed to stand for 48 hours and concentrated at room temperature. The residue was diluted with water and the solid product thus obtained filtered and washed with water. Two crystallisations from cyclohexane gave 5-hydroxy-8-acetoxy-1,4-ethano-1,2,3,4-tetrahydronaphthalene (23.5 g.; m.p. 90—91°C). The latter (290 g.) was heated for 15 hours at 90°C with epichlorohydrin (80 ml.) and a drop of piperidine. The excess epichlorohydrin was evaporated and the crude 3-chloro-(8'-acetoxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol was dissolved in toluene (200 ml.) containing isopropylamine (50 ml.). The solution was heated in a sealed tube for 15 hours at 100—110°C, then concentrated to dryness and the residue treated with 10% hydrochloric acid, filtering off the insoluble materials. The filtrate was neutralised with sodium bicarbonate and extracted with ethyl acetate (3 × 300 ml.). After evaporation to small volume and saturation with hydrogen chloride gas, the solid precipitate was filtered, washed with ether and crystallised from isopropanol to give 1-isopropylamino-3-(8'-acetoxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride (12.2 g.; m.p. 186—187°C).

The following compounds were prepared in a similar manner:

1 - *t* - butylamino - 3 - (8' - acetoxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride,

1 - *s* - butylamino - 3 - (8' - acetoxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride.

EXAMPLE 5.

5,8-Diacetoxybenzo-norbornane (52 g.) was converted to 5-hydroxy-8-acetoxybenzo-norbornane (m.p. 69—70°C) which was reacted with epichlorohydrin and isopropylamine as in Example 4 to give 1-isopropylamino-3-(8'-acetoxybenzo-norbornan-5'-yloxy)-2-propanol hydrochloride (7.5 g.; m.p. 165—167°C).

The following compounds were prepared in a similar manner:

1-*t*-butylamino-3-(8'-acetoxybenzonorbornan-5'-yloxy)-2-propanol hydrochloride,
1-*s*-butylamino-3-(8'-acetoxybenzonorbornan-5'-yloxy)-2-propanol hydrochloride.

EXAMPLE 6.

1 - Isopropylamino - 3 - (8' - acetoxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride (2 g.) was dissolved in methanol (50 ml.) saturated with hydrogen chloride, and refluxed for an hour. After concentration, the residue was crystallised from isopropanol to give 1-isopropylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride (1.5 g.; m.p. 200—201°C).

The following compounds were prepared in a similar manner:

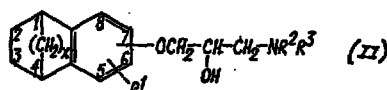
1 - *t* - butylamino - 3 - (8' - hydroxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride, m.p. 235—237°C.;
1 - *s* - butylamino - 3 - (8' - hydroxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride, m.p. 188—190°C.;
1 - isopropylamino - 3 - (8' - hydroxybenzonorbornan - 5' - yloxy) - 2 - propanol hydrochloride, m.p. 178—180°C.;
1-*t*-butylamino-3-(8'-hydroxybenzonorbornan-5'-yloxy)-2-propanol, and
1-*s*-butylamino-3-(8'-hydroxybenzonorbornan-5'-yloxy)-2-propanol.

EXAMPLE 7.

Acetyl chloride (0.98 ml.) was added to 1-isopropylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol (3.1 g.) in dry chloroform (80 ml.). The mixture was refluxed for 4 hours, then concentrated to dryness, treated with water, filtered and neutralised with solid sodium bicarbonate. The oil thus separated was extracted with ethyl acetate (3 × 100 ml.) which was then concentrated to small volume, saturated with gaseous hydrogen chloride and finally diluted with diethyl ether. 1-Isopropylamino-3-(8'-acetoxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride was filtered and crystallised from isopropanol, m.p. 185—187°C. The compounds described in Examples 4 and 5 were prepared in a similar manner.

WHAT WE CLAIM IS:—

1. A compound of general formula (II)



wherein *x* is 1 or 2;

*R*¹ is a hydroxy or acyloxy group,

*R*² is a hydrogen atom or a benzyl or C₁₋₄ alkyl, and

*R*³ is a hydrogen atom or a benzyl or C₁₋₁₀ alkyl group; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein *R*¹ is a hydroxy group, *R*² is an alkyl group having 3 or 4 carbon atoms and *R*³ is a hydrogen atom.

3. A compound according to claim 1 or 2 wherein *R*² is an isopropyl or *t*-butyl group.

4. 1 - Isopropylamino - 3 - (8' - hydroxy - 1', 4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol.

5. 1 - *t* - Butylamino - 3 - (8' - hydroxy - 1',4' - ethano-1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol.

6. 1 - *s* - Butylamino - 3 - (8' - hydroxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol.

7. 1-Isopropylamino-3-(8'-hydroxybenzonorbornan-5'yloxy)-2-propanol.



1 - *s* - butylamino - 3 - (8' - acetoxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride.

EXAMPLE 5.

5,8-Diacetoxybenzo-norbornane (52 g.) was converted to 5-hydroxy-8-acetoxybenzo-norbornane (m.p. 69—70°C) which was reacted with epichlorohydrin and isopropylamine as in Example 4 to give 1-isopropylamino-3-(8'-acetoxybenzo-norbornan-5'-yloxy)-2-propanol hydrochloride (7.5 g.; m.p. 165—167°C).

The following compounds were prepared in a similar manner:

1-*t*-butylamino-3-(8'-acetoxybenzonorbornan-5'-yloxy)-2-propanol hydrochloride,
1-*s*-butylamino-3-(8'-acetoxybenzonorbornan-5'-yloxy)-2-propanol hydrochloride.

EXAMPLE 6.

1 - Isopropylamino - 3 - (8' - acetoxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride (2 g.) was dissolved in methanol (50 ml.) saturated with hydrogen chloride, and refluxed for an hour. After concentration, the residue was crystallised from isopropanol to give 1-isopropylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride (1.5 g.; m.p. 200—201°C).

The following compounds were prepared in a similar manner:

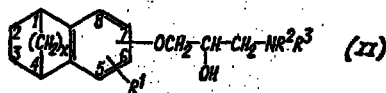
1 - *t* - butylamino - 3 - (8' - hydroxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride, m.p. 235—237°C.;
1 - *s* - butylamino - 3 - (8' - hydroxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride, m.p. 188—190°C.;
1 - isopropylamino - 3 - (8' - hydroxybenzonorbornan - 5' - yloxy) - 2 - propanol hydrochloride, m.p. 178—180°C.;
1-*t*-butylamino-3-(8'-hydroxybenzonorbornan-5'-yloxy)-2-propanol, and
1-*s*-butylamino-3-(8'-hydroxybenzonorbornan-5'-yloxy)-2-propanol.

EXAMPLE 7.

Acetyl chloride (0.98 ml.) was added to 1-isopropylamino-3-(8'-hydroxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol (3.1 g.) in dry chloroform (80 ml.). The mixture was refluxed for 4 hours, then concentrated to dryness, treated with water, filtered and neutralised with solid sodium bicarbonate. The oil thus separated was extracted with ethyl acetate (3 × 100 ml.) which was then concentrated to small volume, saturated with gaseous hydrogen chloride and finally diluted with diethyl ether. 1-Isopropylamino-3-(8'-acetoxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol hydrochloride was filtered and crystallised from isopropanol, m.p. 185—187°C. The compounds described in Examples 4 and 5 were prepared in a similar manner.

WHAT WE CLAIM IS:—

1. A compound of general formula (II)



wherein *x* is 1 or 2;

*R*¹ is a hydroxy or acyloxy group,

*R*² is a hydrogen atom or a benzyl or C₁₋₄ alkyl, and

*R*³ is a hydrogen atom or a benzyl or C₁₋₁₀ alkyl group; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein *R*¹ is a hydroxy group, *R*² is an alkyl group having 3 or 4 carbon atoms and *R*³ is a hydrogen atom.

3. A compound according to claim 1 or 2 wherein *R*² is an isopropyl or *t*-butyl group.

4. 1 - Isopropylamino - 3 - (8' - hydroxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol.

5. 1 - *t* - Butylamino - 3 - (8' - hydroxy - 1',4' - ethano-1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol.

6. 1 - *s* - Butylamino - 3 - (8' - hydroxy - 1',4' - ethano - 1',2',3',4' - tetrahydronaphth-5'-yloxy)-2-propanol.

7. 1-Isopropylamino-3-(8'-hydroxybenzonorbornan-5'yloxy)-2-propanol.

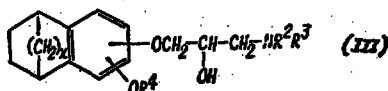


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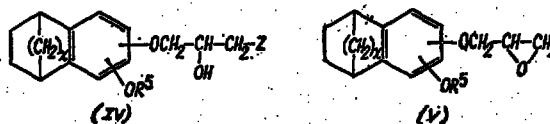
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8. 1-*t*-Butylamino-3-(8'-hydroxybenzonorbornan-5'-yloxy)-2-propanol.
 9. 1-*s*-Butylamino-3-(8'-hydroxybenzonorbornan-5'-yloxy)-2-propanol.
 10. 1-Isopropylamino-3-(8'-acetoxy-1',4'-ethano-1',2',3',4'-tetrahydrohydronaphth-5'-yloxy)-2-propanol.
 5 11. 1-*t*-Butylamino-3-(8'-acetoxy-1',4'-ethano-1',2',3',4'-tetrahydronaphth-5'-yloxy)-2-propanol.
 12. 1-Isopropylamino-3-(8'-acetoxybenzonorbornan-5'yloxy)-2-propanol.
 13. 1-*t*-Butylamino-3-(8'-acetoxybenzonorbornan-5'yloxy)-2-propanol.
 10 14. A process for the preparation of a compound according to any one of the preceding claims, the process comprising
 (a) deetherifying a compound of general formula (III)



- 15 wherein x , R^2 and R^3 are as defined in claim 1 and R^4 is an alkyl or an alkyl group, and, if desired, when a compound of general formula (II) wherein R^1 is other than a hydroxy group, is required esterifying in known manner the deetherification product; or
 (b) reacting a compound of general formula (IV) or (V)



- 20 wherein x is as defined in claim 1, Z is a halogen atom and R^5 is an acyl group, with an amine of general formula HNR^2R^3 , wherein R^2 and R^3 are as defined in claim 1, and then, if desired, when a compound of general formula (II) wherein R^1 is hydroxy group, is required, saponifying in known manner the reaction product;
 and then, if desired, reacting the compound of general formula (II) obtained in (a) or (b) with an acid to give a pharmaceutically acceptable salt and/or, if desired, resolving the mixture of optical isomers so obtained into the different isomers.

- 25 15. A process according to claim 14 substantially as described in any one of the Examples.
 16. A compound of general formula (II) prepared by a process according to claim 14 or 15.
 30 17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 and 16 and a pharmaceutically acceptable carrier or diluent.

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