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(54) Titre : UTILISATION DE COMPOSES C-(2-PHENYL-CYCLOHEXYL)-METHYLAMINE POUR TRAITER DES TROUBLES D'ANXIETE

(54) Title: USE OF C-(2-PHENYL-CYCLOHEXYL)-METHYLAMINE COMPOUNDS FOR THE TREATMENT OF ANXIETY DISORDERS

(57) **Abrégé/Abstract:**

The invention relates to the use of [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine and the metabolites thereof for producing a medicament that is used for treating anxiety attacks or for producing an adjuvant to standard antidepressants. Also disclosed are methods for the treatment of anxiety attacks or depressions.



ABSTRACT

The invention relates to the use of [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine and the metabolites thereof for producing a medicament that is used for treating anxiety attacks or for producing an adjuvant to standard antidepressants. Also disclosed are methods for the treatment of anxiety attacks or depressions.

Use of C-(2-phenyl-cyclohexyl)-methylanine compounds
for the treatment of anxiety disorders

5

The invention relates to the use of [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine and its metabolites for the preparation of a medicament for treatment of anxiety
10 disorders or for the preparation of an adjuvant to standard antidepressants and methods for treatment of anxiety disorders or depressions.

Anxiety disorders are illnesses of which the main symptoms
15 are manifestations of unrealistic or excessively pronounced anxiety. In the case of phobias, to the sub-types of which so-called simple phobias, social anxiety disorders and agoraphobias belong, the anxiety attacks are associated with particular objects or situations. However, pronounced
20 anxiety attacks can also occur without being triggered by specific situations or circumstances. Thus panic disorders are distinguished by recurring, pronounced anxiety attacks which are not foreseeable and therefore lead to anticipatory anxiety. Generalized anxiety disorders are
25 floating, lasting anxieties with diverse, in particular vegetative symptoms. Patients who suffer from posttraumatic stress disorders (PTSD) were exposed to a brief or long-lasting event or occurrence of exceptional threat or with catastrophic proportions. This event would
30 induce a deep-seated despair in virtually anyone. Those affected live through the stresses again and again in quick-fire images, accompanied by psychovegetative symptoms, such as, *inter alia*, severe outbreaks of perspiration and a racing heart. Obsessive compulsive

disorders (OCD) are characterized by recurring unpleasant thoughts, impulses or actions which last several weeks, are experienced as being part of the self and against which at least partial resistance is given since the person affected finds them senseless. Mixed anxiety disorders or anxiety disorders accompanied with depressions very often exist.

Depressions are affectivity disorders in which a depressive syndrome is of prime significance, depressive meaning associated with depression or of sad mood. The depressive illnesses include unipolar severe depressions with or without delusion, moderate depressions, mild depressions, dysthymia, melancholy, bipolar depressions (bipolar illness I, mania and severe depression; bipolar illness II, hypomania and severe depressions; cyclothymic personality disorders, hypomania and mild depressions).

Those medicaments with an anxiolytic and antidepressant action based on an inhibition of the reuptake of the monoamines noradrenaline and/or serotonin are widely used for therapy of anxiety disorders and depressions (Pacher, P., Kohegyi, E., Kecskemeti, V., Furst, S., Current Medicinal Chemistry 2001, 8, 89-100; Goddard, A.W., Coplan, J.D. Gorman, J.M., Charney, D.S., in: Neurobiology of mental illness, Charney, D.S., Nestler, E.J., Bunney, B.S. (eds.), Oxford University Press, New York, 1999, p. 548-563). A great disadvantage in this context is that the monoamine reuptake inhibitors display their anxiolytic and antidepressant action only after several weeks of treatment and achieve their full activity only after approx. 3-4 weeks. At the start of treatment of patients suffering from anxiety, and also those suffering from depression, standard medications frequently intensify or induce anxiety

states, unrest, increased irritability and thoughts of suicide. These psychomotor states of excitation and thoughts of suicide occur particularly frequently in the first days after the start of therapy both with tricyclic antidepressants, selective serotonin reuptake inhibitors (so-called SSRIs) and with mixed serotonin-noradrenalin reuptake inhibitors, and are associated with an increased risk of suicide (Jick, H., Kaye, J.A., Jick, S.S.: Antidepressants and the risk of suicidal behaviours, JAMA 10 (2004) 292, 338-343). This results in the need for strict monitoring of patients being treated with standard antidepressants, and possibly for a reduction in the dose. For anxiety disorders and depressions there is therefore a great need for a therapy which is distinguished by an early onset of action and causes no anxiogenic side effects and therefore no increased risk of suicide at the start of therapy, or inhibits those induced by antidepressants.

Since approx. 20-30 % of patients suffering from anxiety disorders and depressions show no improvement after treatment with approved antidepressants and anxiolytics, new therapeutic systems for treatment of hitherto pharmacotherapy-resistant patients are of high benefit.

25 The monoamine reuptake inhibitors used for therapy of anxiety disorders and depressions are also used for treatment of chronic pain patients. In addition to the actual antidepressant and anxiolytic actions, reuptake inhibitors of noradrenaline and serotonin lead to an independent analgesic action in that descending pain inhibition pathways at the level of the spinal marrow are activated. Monoamine reuptake inhibitors are employed clinically for monotherapy of neuropathic pain, and also as

an adjuvant to opiates for treatment of chronic pain (*inter alia* inflammatory pain, tumour pain, fibromyalgia)

(Sindrup, in: Yaksh, T.L., et al., Anesthesia. Biological foundations. Philadelphia: Lippincott-Raven, 1997, 987-

5 997). Since chronic pain is accompanied by anxiety disorders or depressions in a large number of patients, a substance with μ -opiate agonistic properties combined with a clinically relevant serotonin and/or noradrenaline reuptake inhibition is particularly favourable.

10

The object of the present invention was therefore to discover substances, in particular opioid substance, which are suitable for therapy of anxiety disorders, depressions or mixed forms of anxiety and depression with or without
15 chronic pain. In particular, compounds with an earlier onset of action compared with the monoamine reuptake inhibitors widely used for anxiety disorders and depressions were to be found.

20 It has now been found, surprisingly, that 2-(3-methoxyphenyl)-cyclohexylmethyl)-dimethylamine and also its metabolites, and in this context in particular 3-(2-dimethylaminomethyl-cyclohexyl)-phenol, have a therapeutically relevant anxiolytic and antidepressant
25 action component which is distinguished by an early onset of action and the absence of anxiogenic effects.

Mechanistic investigations show the content of the μ -opiate agonistic component in the anxiolytic as well as in the antidepressant action and in particular in the early onset
30 of action. The substances have pronounced anxiolytic, antidepressant and analgesic actions and are therefore suitable for treatment of depressions, anxiety disorders and pain. On the basis of the potentiation, induced by the

μ -opiate agonistic action component, of the anxiolytic and antidepressant actions mediated by serotonin and noradrenaline reuptake inhibition, the use according to the invention of the compounds mentioned is a particularly effective treatment possibility precisely also for pharmacoresistant anxiety and depression patients.

The invention accordingly provides the use of

- 10 ▪ 3-(2-dimethylaminomethyl-cyclohexyl)-phenol,
- (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol,
- [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine,
- 15 ▪ (1R,2R)-[2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine,
- sulfuric acid mono-[3-(2-dimethylaminomethyl-cyclohexyl)-phenyl] ester,
- sulfuric acid mono-(1R,2R)-[3-(2-
- 20 dimethylaminomethyl-cyclohexyl)-phenyl] ester,
- 3-(2-methylaminomethyl-cyclohexyl)-phenol,
- (1R,2R)-3-(2-methylaminomethyl-cyclohexyl)-phenol,
- 3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide,
- 25 ▪ (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide,
- 6-[3-(2-dimethylaminomethyl-cyclohexyl)-phenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid,
- 30 ▪ 6-[(1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid,
- 4-(2-dimethylaminomethyl-cyclohexyl)-catechol,

- (1R,2R) -4- (2-dimethylaminomethyl-cyclohexyl) - catechol,
- 3- (2-aminomethyl-cyclohexyl) -phenol,
- (1R,2R) -3- (2-aminomethyl-cyclohexyl) -phenol,
- 5 ▪ C- [2- (3-methoxy-phenyl) -cyclohexyl] -methylamine,
- (1R,2R) -C- [2- (3-methoxy-phenyl) -cyclohexyl] -methylamine,
- [2- (3-methoxy-phenyl) -cyclohexylmethyl] -methylamine,
- 10 ▪ (1R,2R) - [2- (3-methoxy-phenyl) -cyclohexylmethyl] -methylamine,
- [2- (3-methoxy-phenyl) -cyclohexylmethyl] -dimethylamine, N-oxide
or
- 15 ▪ (1R,2R) - [2- (3-methoxy-phenyl) -cyclohexylmethyl] -dimethylamine, N-oxide,

optionally in the form of their racemates, their pure stereoisomers, in particular enantiomers or
20 diastereomers, or in the form of mixtures of the stereoisomers, in particular the enantiomers or diastereomers, in any desired mixture ratio; in the form shown or in the form of their acids or their bases or in the form of their salts, in particular the
25 physiologically acceptable salts, or in the form of their solvates, in particular the hydrates;

for the preparation of a medicament for treatment of anxiety states or for the preparation of an adjuvant
30 to standard antidepressants.

It is particularly preferable in this context if the compounds used are in the form of 1R,2R enantiomers.

The term salt is to be understood as meaning any form of the active compound according to the invention in which this assumes an ionic form or is charged and is coupled
5 with a counter-ion (a cation or anion) or is in solution. This is also to be understood as meaning complexes of the active compound with other molecules and ions, in particular complexes which are complexed via ionic interactions. In particular, this is understood as meaning
10 (and this is also a preferred embodiment of this invention) physiologically acceptable salts, in particular physiologically acceptable salts with cations or bases and physiologically acceptable salts with anions or acids or also a salt formed with a physiologically acceptable acid
15 or a physiologically acceptable cation.

The preferred salt of the compounds used is the hydrochloride.

20 Physiologically acceptable is to be understood as meaning that the substance, in particular the salt as such, is acceptable when used on humans or mammals, that is to say, for example, does not have a non-physiological (e.g. toxic) action.

25

In the context of this invention, the term physiologically acceptable salt with anions or acids is understood as meaning salts of at least one of the compounds according to the invention - usually protonated, for example on the
30 nitrogen - as the cation with at least one anion which is physiologically acceptable - in particular when used on humans and/or mammals. In particular, in the context of this invention this is understood as meaning the salt

formed with a physiologically acceptable acid, namely salts of the particular active compound with inorganic or organic acids which are physiologically acceptable - in particular when used on humans and/or mammals. Examples of

5 physiologically acceptable salts of particular acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid,

10 glutamic acid, 1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[d]isothiazol-3-one (saccharin), monomethylsebacic acid, 5-oxoproline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α -liponic acid, acetylglycine, acetylsalicylic acid, hippuric acid

15 and/or aspartic acid. The hydrochloride salt is particularly preferred.

In the context of this invention, the term salt formed with a physiologically acceptable acid is understood as meaning

20 salts of the particular active compound with inorganic or organic acids which are physiologically acceptable - in particular when used on humans and/or mammals. The hydrochloride is particularly preferred. Examples of physiologically acceptable acids are: hydrochloric acid,

25 hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[d]isothiazol-3-one (saccharin), monomethylsebacic

30 acid, 5-oxoproline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α -liponic acid, acetylglycine, acetylsalicylic acid, hippuric acid and/or aspartic acid.

In the context of this invention, the term physiologically acceptable salt with cations or bases is understood as meaning at least one of the compounds according to the invention - usually a (deprotonated) acid - as the anion with at least one, preferably inorganic cation, which are physiologically acceptable - in particular when used on humans and/or mammals. Particularly preferred salts are the salts of the alkali metals and alkaline earth metals, but also with NH_4^+ , in particular (mono)- or (di)sodium, (mono)- or (di)potassium, magnesium or calcium salts.

In the context of this invention, the term salt formed with a physiologically acceptable cation is understood as meaning salts of at least one of the particular compounds as the anion with at least one inorganic cation which is physiologically acceptable - in particular when used on humans and/or mammals. Particularly preferred salts are the salts of the alkali metals and alkaline earth metals, but also NH_4^+ , in particular (mono)- or (di)sodium, (mono)- or (di)potassium, magnesium or calcium salts.

The present invention also provides a method for treatment of anxiety disorders in a mammal and/or human, in which a therapeutically active amount of a compound used according to the invention is administered.

In this context, it is of advantage to administer this compound at the first occurrence of anxiety disorders, since they show an early onset of action.

30

The present invention also provides a method for treatment of anxiety disorders or depressions, in which a compound used according to the invention is administered as an

adjuvant to standard antidepressants, in order to inhibit the psychomotor states of excitation induced by the antidepressants at the start of therapy and the increased risk of suicide. In the context of this invention,
5 standard antidepressants are understood as meaning all the approved antidepressants.

According to the present investigations, the substances used, and in particular (1R,2R)-3-(2-diethylaminomethyl-
10 cyclohexyl)-phenol, are potent anxiolytics, antidepressants and analgesics, that is to say have an additional and clinically relevant anxiolytic action component.

The compounds used according to the invention can moreover
15 also be employed for the preparation of a medicament for treatment of obsessive compulsive disorders, migraine, fibromyalgia, eating disorders, bulimia, hyperactivity, drug dependency, addiction and withdrawal, trichotillomania, Tourette's syndrome, skin diseases, in
20 particular postherpetic neuralgia and pruritus, psychoses, impaired memory, cognitive disorders and/or Alzheimer's disease.

Suitable additives and/or auxiliary substances to the
25 compounds used according to the invention in the process for the preparation of the medicament are all the substances known to the expert from the prior art for achieving galenical formulations. The choice of these auxiliary substances and the amounts thereof to be employed
30 depend on whether the medicament is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally or locally. Formulations in the form of tablets, chewable tablets,

coated tablets, capsules, granules, drops, juices or syrups are suitable for oral administration, and solutions, suspensions, easily reconstitutable dry formulations and sprays are suitable for parenteral, topical and inhalatory administration. Suppositories for use in the rectum are a further possibility. The use in a depot in dissolved form, a carrier film or a patch, optionally with the addition of agents which promote penetration through the skin, are examples of suitable forms for percutaneous administration.

Examples of auxiliary substances and additives for the oral administration forms are disintegrating agents, lubricants, binders, fillers, mould release agents, optionally solvents, flavourings, sugars, in particular carrier agents, diluents, dyestuffs, antioxidants etc. For suppositories, *inter alia*, waxes and fatty acid esters can be used, and for parenteral administration compositions carrier substances, preservatives, suspension auxiliaries etc. can be used. The amounts of active compound to be administered to patients vary as a function of the weight of the patient, the mode of administration and the severity of the disease. The compounds used according to the invention can be released in a delayed manner from formulation forms which can be used orally, rectally or percutaneously. Corresponding sustained-release formulations, in particular in the form of a "once daily" preparation which has to be taken only once a day, are particularly preferred for the indication according to the invention.

Medicaments which comprise at least 0.05 to 90.0 % of the active compound, in particular low active dosages, in order to avoid side effects or analgesic actions, are preferred. 0.1 to 5,000 mg/kg, in particular 1 to 500 mg/kg,

preferably 2 to 250 mg/kg of body weight of a least one compound used according to the invention are conventionally administered. However, the administration of 0.01 - 5 mg/kg, preferably 0.03 to 2 mg/kg, in particular 0.05 to 1 mg/kg, is also preferred and conventional.

Auxiliary substances can be, for example: water, ethanol, 2-propanol, glycerol, ethylene glycol, propylene glycol, polyethylene glycol, polypropylene glycol, glucose, fructose, lactose, sucrose, dextrose, molasses, starch, modified starch, gelatine, sorbitol, inositol, mannitol, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, cellulose acetate, shellac, cetyl alcohol, polyvinylpyrrolidone, paraffins, waxes, naturally occurring and synthetic gums, gum acacia, alginates, dextran, saturated and unsaturated fatty acids, stearic acid, magnesium stearate, zinc stearate, glyceryl stearate, sodium lauryl sulfate, edible oils, sesame oil, coconut oil, groundnut oil, soya bean oil, lecithin, sodium lactate, polyoxyethylene and -propylene fatty acid esters, sorbitan fatty acid esters, sorbic acid, benzoic acid, citric acid, ascorbic acid, tannic acid, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, magnesium oxide, zinc oxide, silicon dioxide, titanium oxide, titanium dioxide, magnesium sulfate, zinc sulfate, calcium sulfate, potash, calcium phosphate, dicalcium phosphate, potassium bromide, potassium iodide, talc, kaolin, pectin, crospovidone, agar and bentonite.

The medicaments and pharmaceutical compositions are prepared with the aid of means, devices, methods and processes which are well-known in the prior art of pharmaceutical formulation, such as are described, for

example, in "Remington's Pharmaceutical Sciences", ed. A.R. Gennaro, 17th ed., Mack Publishing Company, Easton, Pa. (1985), in particular in part 8, chapter 76 to 93.

5 Thus e.g. for a solid formulation, such as a tablet, the active compound of the medicament, i.e. a compound of the general structure I or one of its pharmaceutically acceptable salts, can be granulated with a pharmaceutical carrier, e.g. conventional tablet constituents, such as
10 maize starch, lactose, sucrose, sorbitol, talc, magnesium stearate, dicalcium phosphate or pharmaceutically acceptable gums, and pharmaceutical diluents, such as e.g. water, in order to form a solid composition which comprises a compound according to the invention or a pharmaceutically
15 acceptable salt thereof in homogeneous distribution. Homogeneous distribution is understood here as meaning that the active compound is uniformly distributed over the entire composition, so that this can easily be divided into unit dose forms, such as tablets, pills or capsules, having
20 the same activity. The solid composition is then divided into unit dose forms. The tablets or pills of the medicament according to the invention or of the compositions according to the invention can also be coated or compounded in another manner in order to provide a dose
25 form with delayed release. Suitable coating compositions are, *inter alia*, polymeric acids and mixtures of polymeric acids with materials such as e.g. shellac, cetyl alcohol and/or cellulose acetate.

30 Although the medicaments show only few side effects, it may be of advantage - should this be necessary at all - for example to avoid certain forms of dependency, also to use

morphine antagonists, in particular naloxone, naltrexone and/or levallorphan, in addition to the compounds used.

[2-(3-Methoxyphenyl)-cyclohexylmethyl]-dimethylamine and
5 (1R,2R)-[2-(3-methoxyphenyl)-cyclohexylmethyl]-
dimethylamine and their preparation are known from DE 195
25 137 A1 example 8 and US 5,733,936 example 8, where the
absolute stereochemistry of the compound (-6) prepared
according to example 8 is certainly correctly (1R,2R) and
10 not (1R,2S). 3-(2-Dimethylaminomethyl-cyclohexyl)-phenol
and (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol and
their preparation are also known from DE 195 25 137 A1
example 10 and US 5,733,936 example 10, where the absolute
stereochemistry of the compound (-7) prepared according to
15 example 10 is certainly correctly (1R,2R) and not (1R,2S).

The compounds and their preparation which are not yet known
from DE 195 25 137 A1 or US 5,733,936 were prepared in
accordance with the examples.

20

The following examples are intended to explain the
invention, without the subject matter of the invention
being linked thereto.

25 **Examples**

Generally, the purification and enantiomer separation in
all the processes mentioned as an example are carried out
at the various stages by column chromatography or,
30 predominantly, HPLC, where appropriate on chiral stationary
phases.

Example 1: Preparation of (1R,2R) - [2 - (3-methoxyphenyl) - cyclohexylmethyl] -methylamine hydrochloride

[2 - (3-Methoxyphenyl) -cyclohexylmethyl] -methylamine and
5 (1R,2R) - [2 - (3-methoxyphenyl) -cyclohexylmethyl] -methylamine,
in particular the hydrochloride salt thereof, are prepared
as follows:

3.16 ml (25.2 mmol) phenyl chloroformate were added
10 dropwise to a solution of 5.67 g (22.9 mmol) (1R,2R) - [2 - (3-
methoxyphenyl) -cyclohexylmethyl] -dimethylamine in 390 ml
dry toluene at the boiling point. After the mixture had
been heated under reflux for three hours, it was cooled to
20 °C, and washed successively with 100 ml each of sodium
15 hydroxide solution (2.5N), distilled water, hydrochloric
acid (1N) and a saturated sodium chloride solution. It was
dried over sodium sulfate and evaporated in vacuo. The
residue was taken up in 192.5 ml ethylene glycol and 46 ml
sodium hydroxide solution (5N) and the mixture was stirred
20 at 110 °C for a total of 8 hours, it being topped up twice
with 10 ml sodium hydroxide solution (5N) each time. After
cooling, it was diluted with 100 ml distilled water and
extracted three times with 50 ml methylene chloride each
time. The extracts were washed with distilled water and a
25 saturated sodium chloride solution, dried over sodium
sulfate and evaporated in vacuo and the residue was dried.
The residue (5.03 g) was dissolved in 32.3 ml 2-butanone,
2.7 ml trimethylchlorosilane were added to the solution and
the mixture was stirred for 15 minutes. 100 ml dry diethyl
30 ether were then added, the mixture was stirred at 20 °C for
a further 2 hours and the solid was filtered off with
suction. It was washed thoroughly with diethyl ether and
dried in vacuo. By this procedure, 3.56 g (57.6 % of

theory) of the title compound were obtained in the form of colourless crystals which melted at 165-167 °C.

Example 2: Preparation of (1R,2R)-3-(2-methylaminomethyl-cyclohexyl)-phenol hydrochloride

3.55 g (15.2 mmol) of the product from example 1 were stirred under reflux in 4.59 ml hydrobromic acid (47-48 % HBr) for 7.5 h. After cooling, ice/water was added and the mixture was then rendered alkaline with sodium hydroxide solution (6N). It was extracted three times with 50 ml ethyl acetate each time. The extracts were washed with a saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuo. The residue (2.91 g) was dissolved in 16.4 ml 2-butanone and converted into the hydrochloride with 1.63 ml trimethylchlorosilane as described under example 1. By this procedure, 2.98 g (76.5 % of theory) of the title compound were obtained as a slightly yellow-coloured solid which melted at 173 - 175 °C.

Example 3: Preparation of sulfuric acid mono-(1R,2R)-[3-(2-dimethylaminomethyl-cyclohexyl)-phenyl] ester

Sulfuric acid mono-[3-(2-dimethylaminomethyl-cyclohexyl)-phenyl] ester or sulfuric acid mono-(1R,2R)-[3-(2-dimethylaminomethyl-cyclohexyl)-phenyl] ester was prepared as follows:

15.9 g (4.70 mmol) of a 2.9 % strength solution of sulfuric acid in dimethylformamide were added dropwise to a solution of 1.00 g (3.92 mmol) (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol; hydrochloride and 0.94 g (4.70 mmol)

dicyclohexylcarbodiimide in 20 ml dimethylformamide at 0 °C, while stirring. When the addition had ended, the mixture was stirred further for another 10 minutes and a pH of 9 was then established with dilute ammonium hydroxide solution. The precipitate formed was separated off, washed with ethyl acetate and dried in vacuo. 0.26 g (21 % of theory) of the title compound was obtained in this way as a white solid.

Example 4: Preparation of 6-[(1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid

6-[3-(2-Dimethylaminomethyl-cyclohexyl)-phenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid and 6-[(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid were prepared as follows:

A mixture of 2.33 g (10 mmol) (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol, 3.58 g (9 mmol) acetobromo- α -D-glucuronic acid methyl ester and 0.23 g (9.5 mmol) lithium hydroxide in 23 ml dry methanol was first stirred at 20 °C for 30 minutes, a solution of 0.65 g lithium hydroxide in 25 ml water was then added and the mixture was stirred again for 30 minutes. It was extracted with ethyl acetate and the aqueous phase was adjusted to a pH of 3.5 by addition of acetic acid and extracted again with ethyl acetate. The aqueous phase was evaporated in vacuo and the residue was purified by HPLC. 0.85 g (23 % of theory) of the title compound was obtained in this manner in the form of a white powder.

Example 5: Preparation of (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide

3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, N-oxide and
5 (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide were prepared as follows:

10.5 ml hydrogen peroxide were added to a solution of
5.60 g (24 mmol) (1R,2R)-3-(2-dimethylaminomethyl-
10 cyclohexyl)-phenol in 28 ml methanol and the mixture was stirred first at 50 °C for 3 hours and then at 20 °C for 15 hours. After addition of 3.30 g potassium carbonate, the mixture was stirred again for 3 hours, the solid was then filtered off and the filtrate was evaporated in vacuo.
15 The residue was taken up in 30 ml ethanol. Solid constituents were separated off by filtration, the filtrate was evaporated in vacuo and the residue was dried. 5.50 g (80 % of theory) of the title compound were obtained in this way in the form of an oil which gradually solidified.

20

Example 6: Preparation of [2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylamine, N-oxide

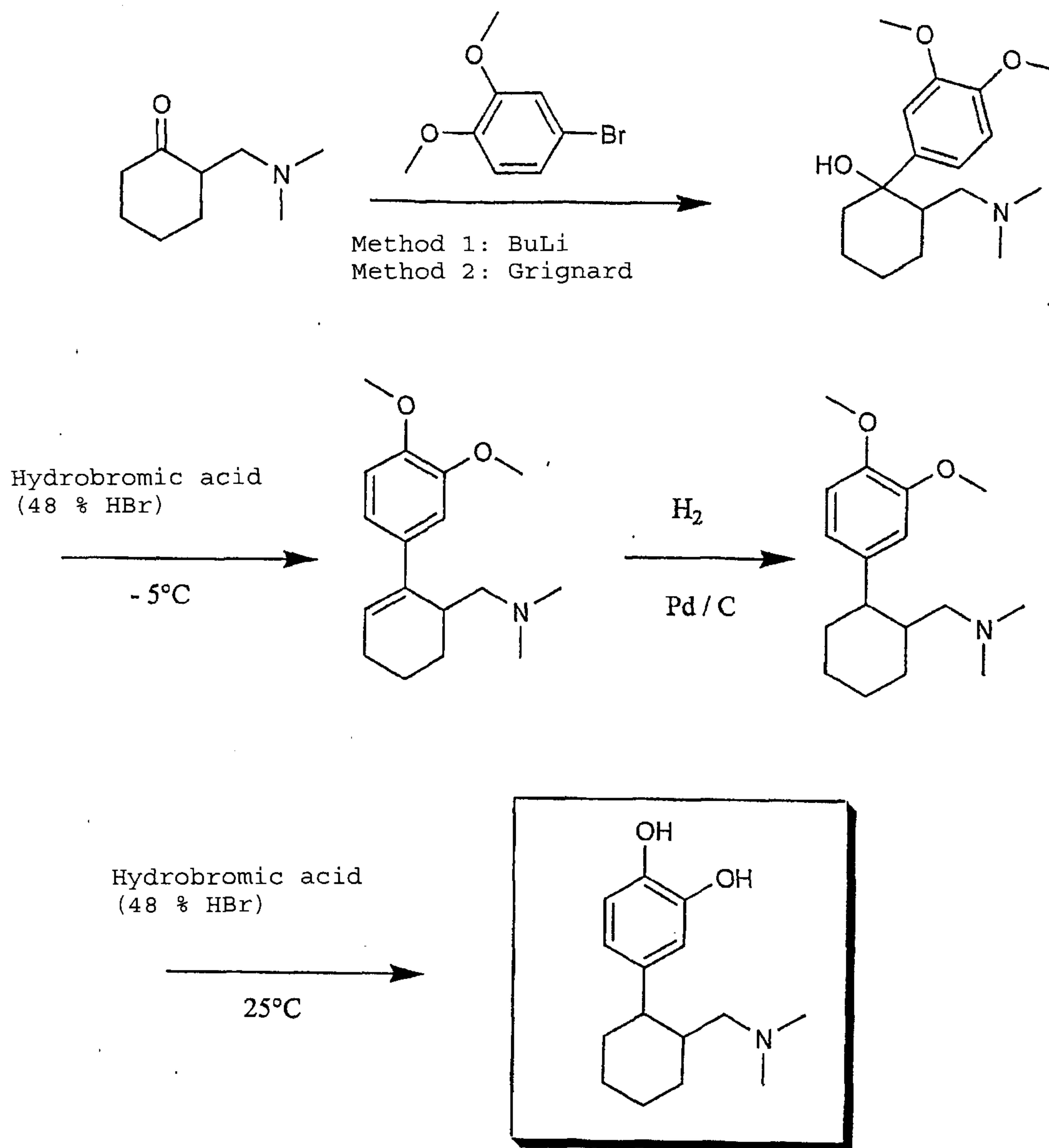
[2-(3-Methoxy-phenyl)-cyclohexylmethyl]-dimethylamine, N-
25 oxide and (1R,2R)-[2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylamine, N-oxide were prepared by the procedure in example 5 using corresponding starting substances.

Example 7: Preparation of 4-(2-dimethylaminomethyl-cyclohexyl)-catechol

30

The preparation of 4-(2-dimethylaminomethyl-cyclohexyl)-catechol was carried out in accordance with the following

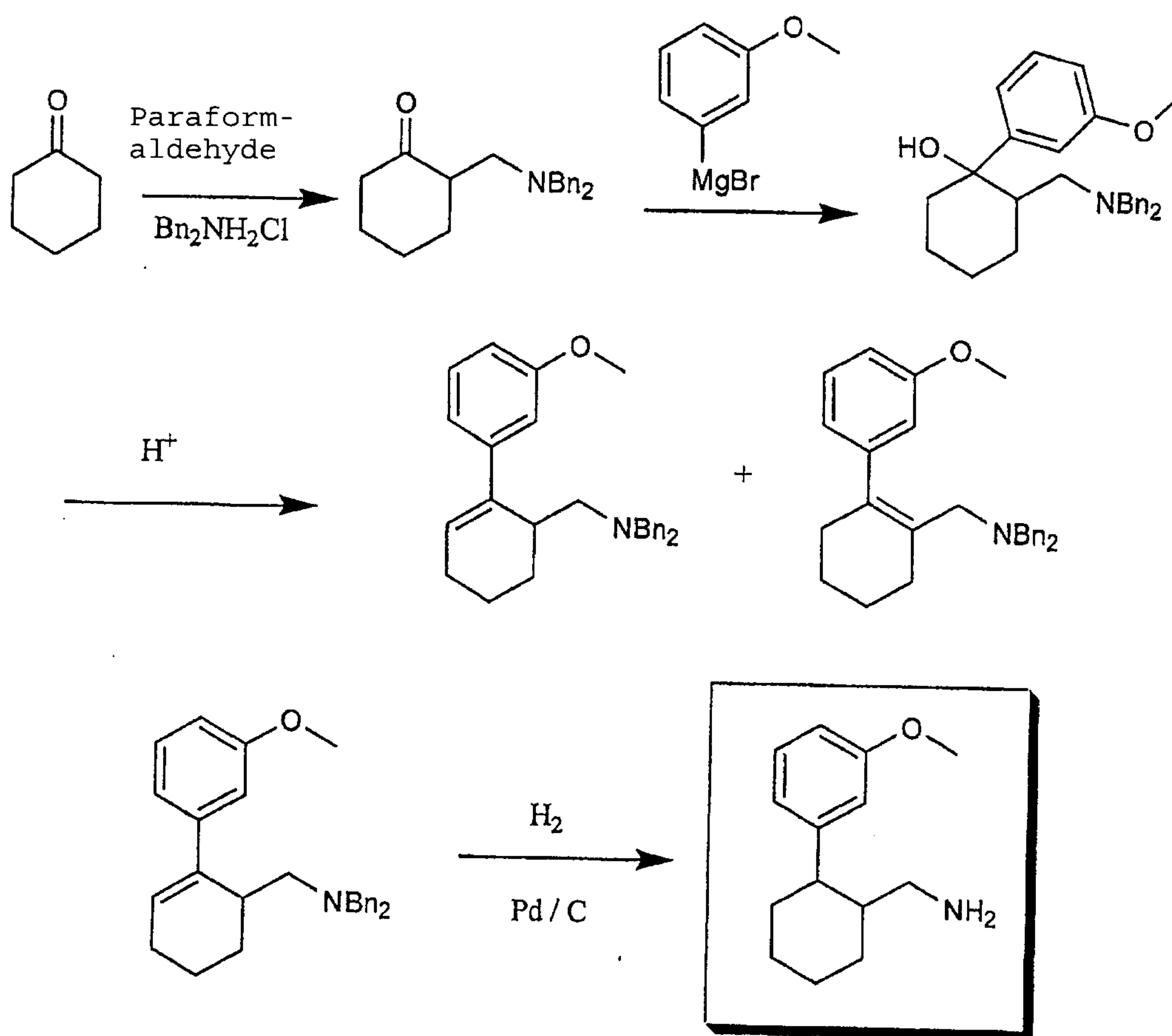
reaction equation (stereochemistry not taken into consideration):



In this equation, Method 1 BuLi moreover means the
5 synthesis, well-known to the expert, via bromine-lithium
exchange with BuLi reagents and Method 2 Grignard means the
synthesis, well-known to the expert, via Mg reagents.

Example 8: Preparation of C-[2-(3-methoxy-phenyl)-cyclohexyl]-methylaniline.

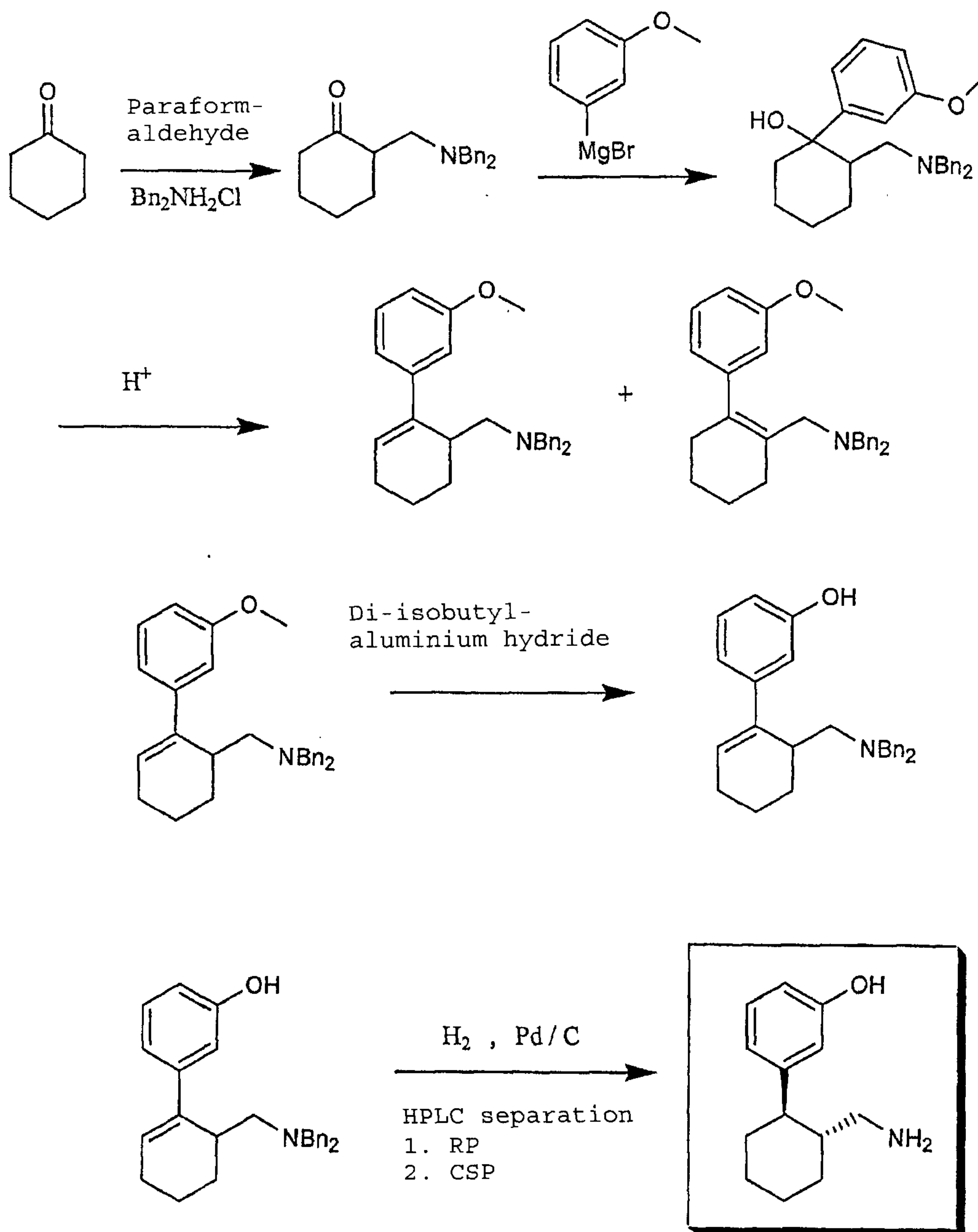
The preparation of C-[2-(3-methoxy-phenyl)-cyclohexyl]-methylaniline was carried out in accordance with the following reaction equation (stereochemistry not taken into consideration; Bn represents the benzyl radical):



Example 9: Preparation of (1R,2R)-3-(2-aminomethyl-cyclohexyl)-phenol.

The preparation of 3-(2-aminomethyl-cyclohexyl)-phenol or (1R,2R)-3-(2-aminomethyl-cyclohexyl)-phenol was carried out in accordance with the following reaction equation:

21



RP = Reversed Phase

CSP = Chiral Stationary Phase

Example 10: In vitro isolation of the metabolites:

5

[2-(3-Methoxyphenyl)-cyclohexylmethyl]-dimethylamine hydrochloride and in another example (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol hydrochloride was

dissolved in TRIS/HCl buffer pH 7.4. MgCl and, where appropriate, the other necessary cofactors for cytochrome P450 (CytP450) known from the literature were then added and the mixture was incubated with CytP450 3A4 (N-
5 demethylation) and/or CytP450 2D6 (O-demethylation) at 37 °C. The batch was subsequently separated via HPLC and the metabolites in the fractions were identified via NMR and then isolated from the fractions.

10 **Example 11: In vivo isolation of the metabolites:**

A mammal was injected with [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine hydrochloride and in a further example (1R,2R)-3-(2-dimethylaminomethyl-
15 cyclohexyl)-phenol hydrochloride. Blood was taken from the mammal and, after separating off corpuscular constituents, was separated via HPLC and the metabolites in the fractions were identified via NMR and then isolated from the fractions.

20

Example 12: Parenteral administration form

1 g (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol hydrochloride is dissolved in 1 l water for injection
25 purposes at room temperature and the solution is then adjusted to isotonic conditions by addition of NaCl.

Pharmacological studies

- a) **Methods for determination of the affinity for the human μ -opiate receptor and the 5-HT and NA reuptake inhibition**

Investigation of the affinity for the human μ -opiate receptor

10 The receptor affinity for the human μ -opiate receptor is determined in a homogeneous set-up in microtitre plates. For this, dilution series of the substances to be tested are incubated with a receptor membrane preparation (15 - 40 μ g protein/250 μ l incubation batch) of CHO-K1 cells
15 which express the human μ -opiate receptor (RB-HOM receptor membrane preparation from Perkin Elmer, Zaventem, Belgium) in the presence of 1 nmol/l of the radioactive ligand [3 H]-naloxone (NET719, Perkin Elmer, Zaventem, Belgium) and 1 mg WGA-SPA-Beads (wheat germ agglutinin SPA beads from
20 Amersham/Pharmacia, Freiburg, Germany) in a total volume of 250 μ l for 90 minutes at room temperature. 50 mmol/l Tris-HCl supplemented with 0.05 % sodium azide and with 0.06 % bovine serum albumin is used as the incubation buffer. 25 μ mol/l naloxone are additionally added for determination
25 of the non-specific binding. After the end of the ninety-minute incubation time, the microtitre plates are centrifuged for 20 minutes at 1,000g and the radioactivity is measured in a β -counter (Microbeta-Trilux, PerkinElmer Wallac, Freiburg, Germany). The percentage displacement of
30 the radioactive ligand from its binding to the human μ -opiate receptor is determined at a concentration of the test substances of 1 μ mol/l and stated as the percentage inhibition of the specific binding. Starting from the

percentage displacement by various concentrations of the test substances, IC_{50} inhibitory concentrations which cause a 50 per cent displacement of the radioactive ligand are calculated. By conversion by means of the Cheng-Prusoff relationship, K_i values for the test substances are obtained (Cheng and Prusoff 1973).

Investigations of the 5-HT and NA reuptake inhibition

10 In order to be able to carry out these in vitro studies, synaptosomes are freshly isolated from areas of the rat brain. In each case a so-called "P₂" fraction, which is prepared exactly in accordance with the instructions of Gray and Whittaker (1962), is used. For the NA reuptake 15 these vesicular particles are isolated from the hypothalamus, and for the 5-HT reuptake from the medulla + pons region of male rat brains.

The following characteristic data were determined for the 20 NA and 5-HT reuptake:

NA uptake: $K_m = 0.32 \pm 0.11 \mu M$

5-HT uptake: $K_m = 0.084 \pm 0.011 \mu M$

25

(In each case $N = 4$, i.e. means $\pm$ SEM from 4 independent series of experiments, which were carried out in triplicate parallel studies).

30 A detailed description of the method is contained in the publication of Frink, Hennies, Englberger et al. (1996) (the study can also be conducted on microtitre plates (250 μl /well) at room temperature).

Evaluations:

In addition to % inhibitions at fixed test substance
5 concentrations (e.g. 1×10^{-6} M or 1×10^{-5} M in the batch),
dose dependencies were investigated. IC_{50} values are
obtained by this means, and can be converted into inhibitor
constants (K_i) in accordance with the "Cheng-Prusoff
equation" (Cheng and Prusoff 1973). The IC_{50} values were
10 obtained with the aid of the computer program "Figure P"
(version 6.0, Biosoft, Cambridge, England). K_m values were
calculated in accordance with the method of Lineweaver and
Burk (1934). The computer program "Ligand" (version 4,
Biosoft, England) was used to display K_D values.

15

Literature:

- Frink; M. Ch., Hennies, H.-H., Englberger, W., Haurand,
M. and Wilffert B. (1996) *Arzneim.-Forsch./Drug Res.* 46
(III), 11, 1029-1036
- 20 - Gray, E.G. and Whittaker V.P. (1962) *J. Anat.* 76, 79-88
- Cheng, Y.C. and Prusoff, W.H. (1973) *Biochem. Pharmacol.*
22, 3099-3108
- Lineweaver, H. and Burk, D. (1934) *J. Am. Chem. Soc.* 56,
658-666

25

A clear affinity for the μ -opiate receptor and an
inhibition of serotonin or noradrenaline reuptake were
measured for the compounds according to the invention. For
the compound 3-(2-dimethylaminomethyl-cyclohexyl)-phenol in
30 particular a balanced ratio between the μ -opioid component
and the monoamine reuptake inhibition was found, the latter
being in the order of magnitude of substances used
clinically. The compound 3-(2-dimethylaminomethyl-

cyclohexyl)-phenol therefore has a very promising potential for use as an anxiolytic, antidepressant and analgesic.

The results of examples and for the reference substance
5 venlafaxine are shown in the following table.

Table 1

Compound	μ -Opioid receptor affinity (K _i values (μ mol/l)	5-HT reuptake inhibition (K _i values, μ mol/l)	NA reuptake inhibition (K _i values, μ mol/l)
3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, hydrochloride	0.14	0.05	0.16
3-(2-Methylaminomethyl-cyclohexyl)-phenol hydrochloride	0.87	5.67	0.48
Venlafaxine	inactive	0.062	0.45

10 **b) Investigation of the onset of anxiolytic actions in
the elevated plus maze test on rats**

In the elevated plus maze test the actions of substances on
the endogenous anxiety of rodents towards open and elevated
15 places are determined.

The apparatus was placed approx. 1 m above the floor and
comprised four arms arranged in a cross, two opposite arms
being open and two closed. The rats were placed
individually in the central square compartment, from where
20 access to all four arms was possible, and the behaviour of
the animals was observed for 5 minutes. The duration of
stay and the number of entries into the open arms were

evaluated. The group size was 10-15 animals. The single administration of the test substances or of the control vehicle took place 30 min before testing.

5 It is reported in the literature that benzodiazepines induce an increased duration of stay and entries into the open compartment. In contrast, antidepressants of which the main mechanism is inhibition of reuptake of the monoamines serotonin and/or noradrenaline cause no
10 anxiolytic action, but in some cases anxiogenic effects, after a single administration in the elevated plus maze test, and anxiolytic effects can be observed only after chronic administration over 2-4 weeks (Borsini, F., Podhorna, J., Marazziti, D., Psychopharmacology, 2002, 163,
15 p. 121-141). The typical disadvantages of monoamine reuptake inhibitors in the therapy of anxiety patients, namely the delayed onset of action and the initially anxiogenic-like effects, can thus be followed in the elevated plus maze test on rats. The elevated plus maze
20 test is therefore a suitable animal model for the investigation of new therapies which have the aim of accelerating the onset of action of monoamine reuptake inhibitors.

25 After a single administration of the compound 3-(2-dimethylaminomethyl-cyclohexyl)-phenol, a significant increase in the duration of stay and a clear increase in the number of entries into the open arms and therefore significant anxiolytic actions were measured. In no case
30 was an anxiogenic-like action induced after acute administration of the example of 3-(2-dimethylaminomethyl-cyclohexyl)-phenol. When 3-(2-dimethylaminomethyl-cyclohexyl)-phenol was combined with the μ -opiate receptor

- antagonist naloxone, the anxiolytic effects of 3-(2-dimethylaminomethyl-cyclohexyl)-phenol could thereby be eliminated completely. The naloxone sensitivity of the anxiolytic effects of 3-(2-dimethylaminomethyl-cyclohexyl)-phenol demonstrate that the opiate component of 3-(2-dimethylaminomethyl-cyclohexyl)-phenol is decisive for the early onset of action after a single administration of the substance.
- 10 Diazepam caused an increase in the duration of stay and the entries into the open arms. The mixed serotonin and noradrenaline reuptake inhibitor venlafaxine showed no anxiolytic action after a single administration.
- 15 The results for 3-(2-dimethylaminomethyl-cyclohexyl)-phenol and for the reference substances diazepam and venlafaxine are shown in the following table.

Table 2

Substance	Dose (mg/kg i.p.)	Open arms	
		Duration of stay (sec)	Number of entries
Vehicle	-	16.8	2.2
3-(2-Dimethylamino- methyl-cyclohexyl)- phenol	8	29.0	3.2
	16	118.2*	8.5
3-(2-Dimethylamino- methyl-cyclohexyl)- phenol + naloxone	16 + 1	37.1#	1.6
Naloxone	1	28.6	4.5
Diazepam	2	77.7*	8.1*
Vehicle	-	41.6	4.3
Venlafaxine	16	66.9	4.6

Statistical evaluation: Anova plus post-hoc Dunnett's test
 5 (Significance level: $p < 0.05$; *: significant versus
 vehicle; #: significant versus intrinsic effect of 16 mg/kg
 i.p. 3-(2-dimethylaminomethyl-cyclohexyl)-phenol)

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CLAIMS:

1. A use of a C-(2-phenyl-cyclohexyl)-methamphetamine compound selected from the group consisting of:

- 5

- 3-(2-dimethylaminomethyl-cyclohexyl)-phenol,
 - (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol,
 - [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine,
 - (1R,2R)-[2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine,
 - sulfuric acid mono-[3-(2-dimethylaminomethyl-cyclohexyl)-phenyl] ester,
- 10

- sulfuric acid mono-(1R,2R)-[3-(2-dimethylaminomethyl-cyclohexyl)-phenyl] ester,
 - 3-(2-methylaminomethyl-cyclohexyl)-phenol,
 - (1R,2R)-3-(2-methylaminomethyl-cyclohexyl)-phenol,
 - 3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide,
- 15

- (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide,
 - 6-[3-(2-dimethylaminomethyl-cyclohexyl)-phenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid,
 - 6-[(1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid,
- 20

- 4-(2-dimethylaminomethyl-cyclohexyl)-catechol,

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- (1R,2R)-4-(2-dimethylaminomethyl-cyclohexyl)-catechol,
- 3-(2-aminomethyl-cyclohexyl)-phenol,
- (1R,2R)-3-(2-aminomethyl-cyclohexyl)-phenol,
- C-[2-(3-methoxy-phenyl)-cyclohexyl]-methylamine,
- 5 ▪ (1R,2R)-C-[2-(3-methoxy-phenyl)-cyclohexyl]-methylamine,
- [2-(3-methoxy-phenyl)-cyclohexylmethyl]-methylamine,
- (1R,2R)-[2-(3-methoxy-phenyl)-cyclohexylmethyl]-methylamine,
- [2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylamine, N-oxide

and

- 10 ▪ (1R,2R)-[2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylamine,
N-oxide;

or an enantiomer thereof, a diastereomer thereof, a mixture of enantiomers thereof,
a mixture of diastereomers thereof, a physiologically acceptable salt thereof,
a physiologically acceptable solute thereof or a physiologically acceptable
15 hydrate thereof

in preparation of a pharmaceutical composition for treatment of an anxiety disorder.

2. A use according to claim 1, wherein the compound is in the form of an
1R,2R enantiomer.

3. A use according to claim 1 or 2 for administration at first occurrence of
20 the anxiety disorder.

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4. A use of a C-(2-phenyl-cyclohexyl)-methylamine compound selected from the group consisting of:

- 3-(2-dimethylaminomethyl-cyclohexyl)-phenol,
- (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol,
- 5 ▪ [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine,
- (1R,2R)-[2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine,
- sulfuric acid mono-[3-(2-dimethylaminomethyl-cyclohexyl)-phenyl]
ester,
- sulfuric acid mono-(1R,2R)-[3-(2-dimethylaminomethyl-cyclohexyl)-
10 phenyl] ester,
- 3-(2-methylaminomethyl-cyclohexyl)-phenol,
- (1R,2R)-3-(2-methylaminomethyl-cyclohexyl)-phenol,
- 3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide,
- (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide,
- 15 ▪ 6-[3-(2-dimethylaminomethyl-cyclohexyl)-phenoxy]-3,4,5-trihydroxy-
tetrahydropyran-2-carboxylic acid,
- 6-[(1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenoxy]-
3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid,
- 4-(2-dimethylaminomethyl-cyclohexyl)-catechol,
- 20 ▪ (1R,2R)-4-(2-dimethylaminomethyl-cyclohexyl)-catechol,

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- 3-(2-aminomethyl-cyclohexyl)-phenol,
 - (1R,2R)-3-(2-aminomethyl-cyclohexyl)-phenol,
 - C-[2-(3-methoxy-phenyl)-cyclohexyl]-methylamine,
 - (1R,2R)-C-[2-(3-methoxy-phenyl)-cyclohexyl]-methylamine,
 - 5 ▪ [2-(3-methoxy-phenyl)-cyclohexylmethyl]-methylamine,
 - (1R,2R)-[2-(3-methoxy-phenyl)-cyclohexylmethyl]-methylamine,
 - [2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylamine, N-oxide
and
 - (1R,2R)-[2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylamine,
 - 10 N-oxide;
- or an enantiomer thereof, a diastereomer thereof, a mixture of enantiomers thereof,
a mixture of diastereomers thereof, a physiologically acceptable salt thereof,
a physiologically acceptable solute thereof or a physiologically acceptable
hydrate thereof
- 15 for treatment of an anxiety disorder.
5. A use according to claim 4, wherein the compound is in the form of an
1R,2R enantiomer.
6. A use according to claim 4 or 5 for administration at first occurrence of
the anxiety disorder.
- 20 7. A pharmaceutical composition comprising a pharmaceutically
acceptable carrier and a C-(2-phenyl-cyclohexyl)-methylamine compound selected
from the group consisting of:

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- 3-(2-dimethylaminomethyl-cyclohexyl)-phenol,
- (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol,
- [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine,
- (1R,2R)-[2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine,
- 5 ▪ sulfuric acid mono-[3-(2-dimethylaminomethyl-cyclohexyl)-phenyl]
ester,
- sulfuric acid mono-(1R,2R)-[3-(2-dimethylaminomethyl-cyclohexyl)-
phenyl] ester,
- 3-(2-methylaminomethyl-cyclohexyl)-phenol,
- 10 ▪ (1R,2R)-3-(2-methylaminomethyl-cyclohexyl)-phenol,
- 3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide,
- (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol, N-oxide,
- 6-[3-(2-dimethylaminomethyl-cyclohexyl)-phenoxy]-3,4,5-trihydroxy-
tetrahydropyran-2-carboxylic acid,
- 15 ▪ 6-[(1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenoxy]-
3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid,
- 4-(2-dimethylaminomethyl-cyclohexyl)-catechol,
- (1R,2R)-4-(2-dimethylaminomethyl-cyclohexyl)-catechol,
- 3-(2-aminomethyl-cyclohexyl)-phenol,
- 20 ▪ (1R,2R)-3-(2-aminomethyl-cyclohexyl)-phenol,

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- C-[2-(3-methoxy-phenyl)-cyclohexyl]-methylanine,
- (1R,2R)-C-[2-(3-methoxy-phenyl)-cyclohexyl]-methylanine,
- [2-(3-methoxy-phenyl)-cyclohexylmethyl]-methylanine,
- (1R,2R)-[2-(3-methoxy-phenyl)-cyclohexylmethyl]-methylanine,
- 5 ▪ [2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylanine, N-oxide
and
- (1R,2R)-[2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylanine,
N-oxide;

or an enantiomer thereof, a diastereomer thereof, a mixture of enantiomers thereof,
10 a mixture of diastereomers thereof, a physiologically acceptable salt thereof,
a physiologically acceptable solute thereof or a physiologically acceptable
hydrate thereof

for treatment of an anxiety disorder.

8. A pharmaceutical composition according to claim 7, wherein the
15 compound is in the form of an 1R,2R enantiomer.

9. A pharmaceutical composition according to claim 7 or 8 for
administration at first occurrence of the anxiety disorder.