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CA 2440758 A1 2002/09/19

(21) 2 440 758

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2002/03/13
(87) Date publication PCT/PCT Publication Date: 2002/09/19
(85) Entrée phase nationale/National Entry: 2003/09/12
(86) N° demande PCT/PCT Application No.: EP 2002/002723
(87) N° publication PCT/PCT Publication No.: 2002/072550
(30) Priorité/Priority: 2001/03/14 (101 12 198.9) DE

(51) Cl.Int.^{7}/Int.Cl.^{7} C07D 211/48, A61K 31/451, C07D 211/52

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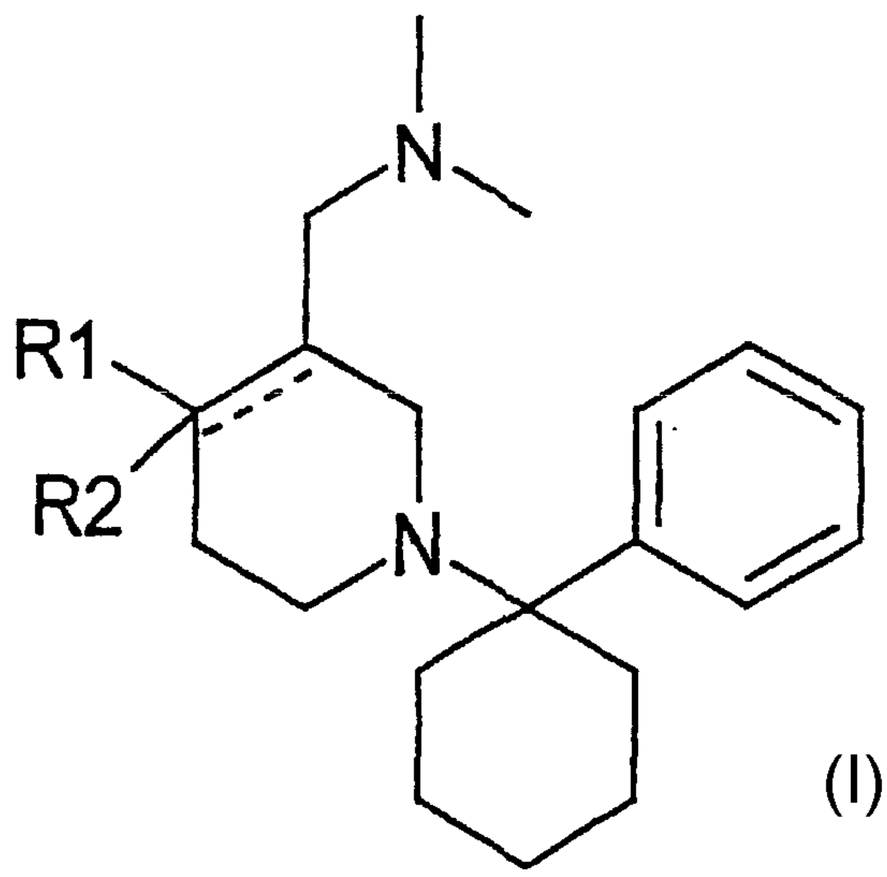
(54) Titre : DIMETHYL-[1-(1-PHENYL-CYCLOHEXYL)-PIPERIDINE-3-YL METHYL]-AMINES SUBSTITUEES
(54) Title: SUBSTITUTED DIMETHYL-[1-(1-PHENYL-CYCLOHEXYL)-PIPERIDIN-3-YLMETHYL]-AMINES



(I)

(57) Abrégé/Abstract:
The invention relates to substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-yl methyl]-amines, a method for the production thereof, pharmaceuticals containing said compounds and the use of said substances for producing pharmaceuticals.

ABSTRACT

The invention relates to substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-yl methyl]-amines, a method for the production thereof, pharmaceuticals containing said compounds and the use of said substances for producing pharmaceuticals.

Substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amines

The invention relates to substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amines, to processes for their preparation, to medicaments containing those compounds and to the use of those substances in the preparation of medicaments.

Pain is one of the basic clinical symptoms. There is a worldwide need for effective therapies for pain. The urgent need for action for the treatment of chronic and non-chronic pain in a targeted manner which is fair to the patient, which is to be understood as meaning the successful and satisfactory treatment of pain for the patient, is documented in the large number of scientific works which have recently appeared in the field of applied analgesics or the fundamental research into nociception. For example, phencyclidine derivatives having analgesic activity are known from J. Med. Chem. 1981, 24, 496-499 and Arzneim.-Forsch./Drug Res. 44 (II), No. 10 (1994), 1141-1144.

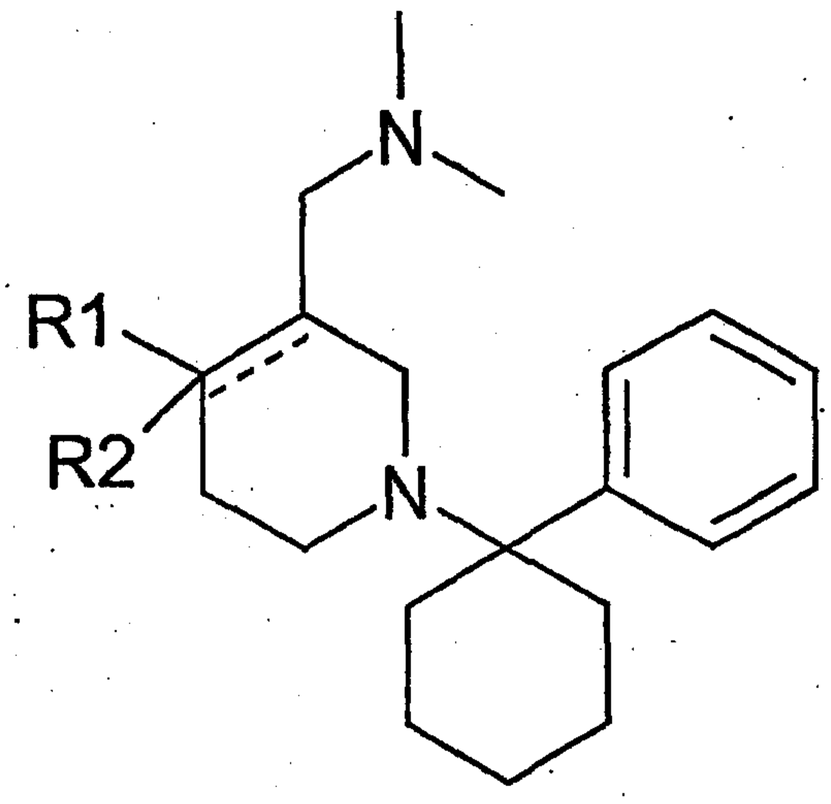
Conventional opioids, such as, for example, morphine, are effective in the therapy of severe to very severe pain. However, they have, *inter alia*, respiratory depression, vomiting, sedation, constipation and the development of tolerance as undesirable side-effects. In addition, they are less effective in the case of neuropathic or incidental pain, as frequently occurs in tumour patients in particular.

Tramadol hydrochloride - (1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol - occupies a special position among the centrally acting analgesics, because that active ingredient brings about pronounced inhibition of pain without the side-effects known for opioids (J. Pharmacol. Exptl. Ther. 267, 33 (1993)).

The object underlying the invention was to provide substances having analgesic activity which are suitable for the treatment of severe pain, especially for the treatment of chronic and neuropathic pain. In addition, those active ingredients should have as few as possible of the side-effects of the opioid analgesics, such as, for example, nausea, vomiting, dependence, respiratory depression, constipation.

That is achieved according to the invention by substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amines of the general formula I, those compounds having pronounced analgesic activity.

Accordingly, the invention provides substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amines of the general formula I



I

wherein

R1 = H, C_{1-12}-alkyl (branched, unbranched), vinyl, phenyl (mono- or poly-substituted by C_{1-5}-alkyl (branched, unbranched), H, F, Cl, Br, OMe, OEt, OPr, OBu, SMe, OH and/or by CF_3),

benzyl (mono- or poly-substituted by C_{1-5}-alkyl (branched, unbranched), H, F, Cl, Br, OMe, OEt, OPr, OBu, SMe, OH and/or by CF_3),

phenethyl (mono- or poly-substituted by C_{1-5}-alkyl (branched, unbranched), H, F, Cl, Br, OMe, OEt, OPr, OBu, SMe, OH and/or by CF_3) or

naphthyl (mono- or poly-substituted by C_{1-5}-alkyl (branched, unbranched), H, F, Cl, Br, OMe, OEt, OPr, OBu, OBz, SMe, OH and/or by CF_3), and

R2 = H, F, Cl, Br, OMe, OEt, OPr, OBu, OBz, SMe, OH, CF_3 or bond to the double bond,

and/or their enantiomers, diastereoisomers, bases or salts of physiologically tolerable acids.

The following substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amines are particularly preferred:

3-dimethylaminomethyl-4-methyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-ethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-4-vinyl-piperidin-4-ol or the corresponding dihydrochloride

4-butyl-3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-octyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-(3-methoxy-phenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-(2-fluoro-phenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

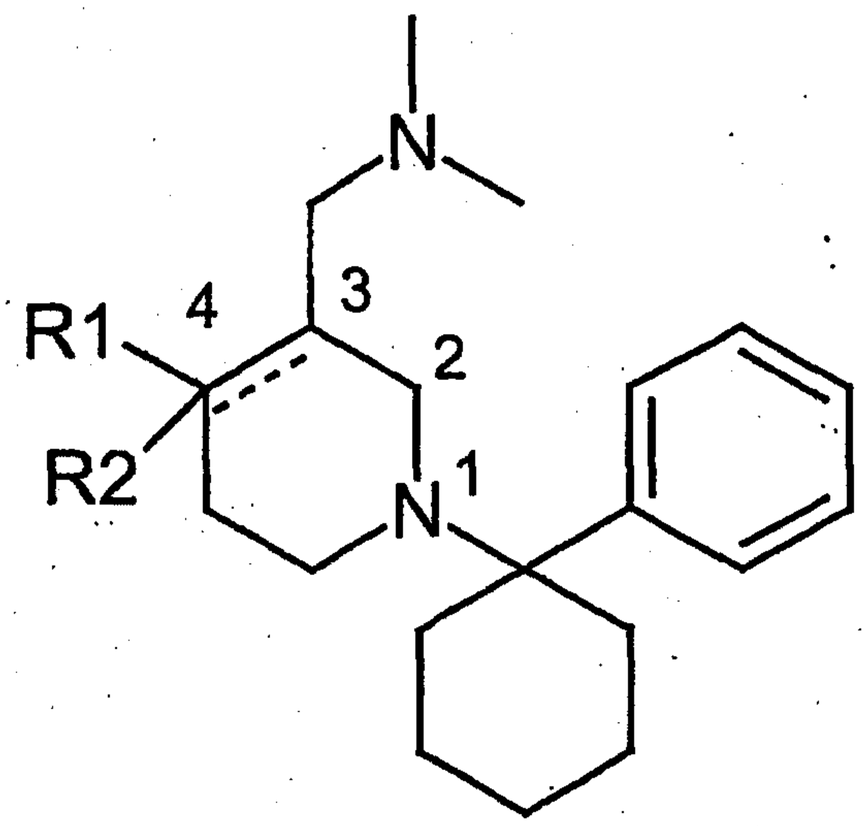
4-(3-chloro-phenyl)-3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

4-benzyl-3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-phenethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-(3-hydroxy-phenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride.

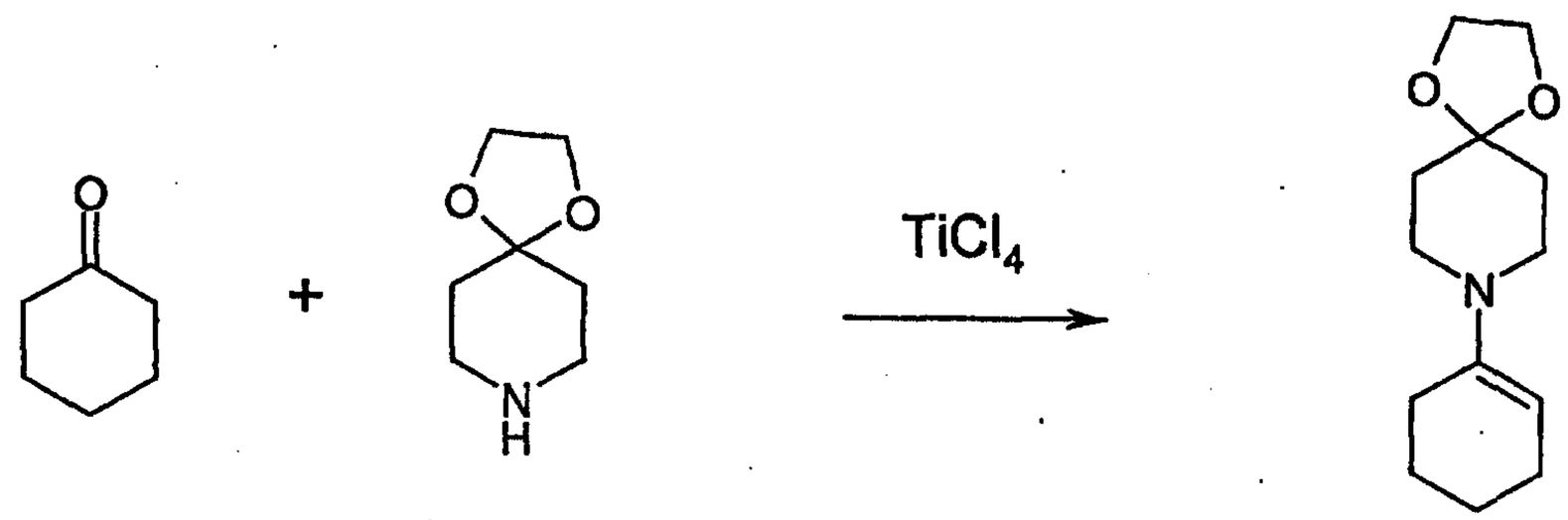
The invention further provides a process for the preparation of dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amines of the general formula **I**, which may have different substituents at R1 and R2. If only either R1 or R2 is present, there is a double bond in the piperidine ring between positions 3 and 4.



I

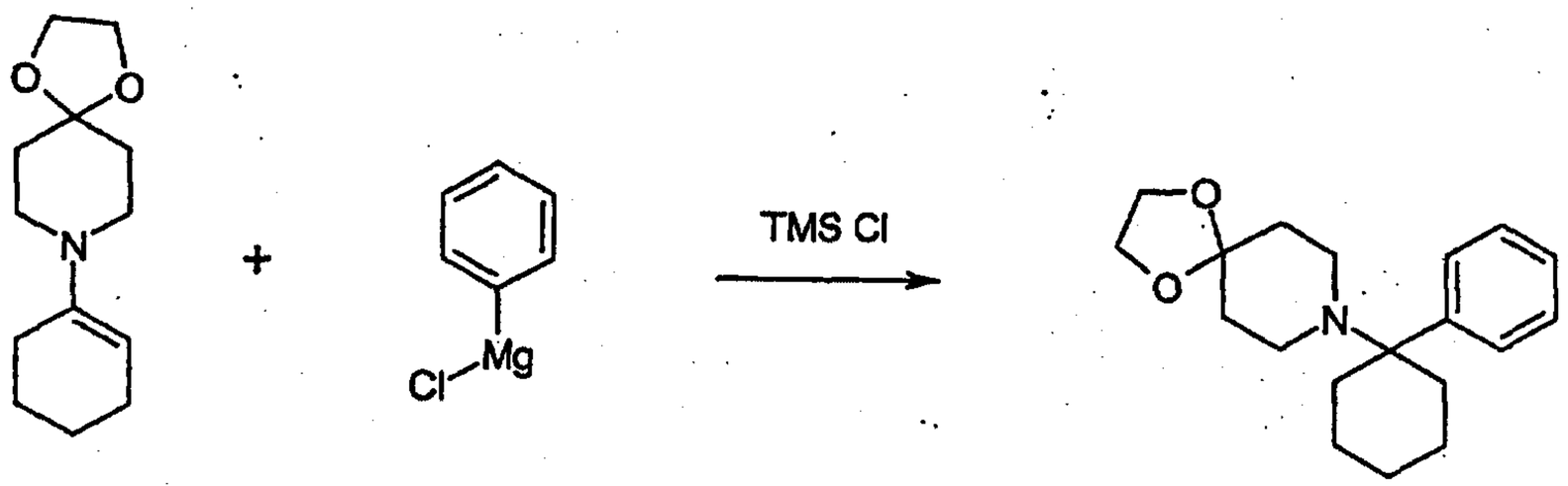
The preparation of the compounds according to the invention is carried out in the following steps:

The enamine **IV** is formed from cyclohexanone **II** and 1,4-dioxa-8-aza-spiro[4.5]decane **III**.



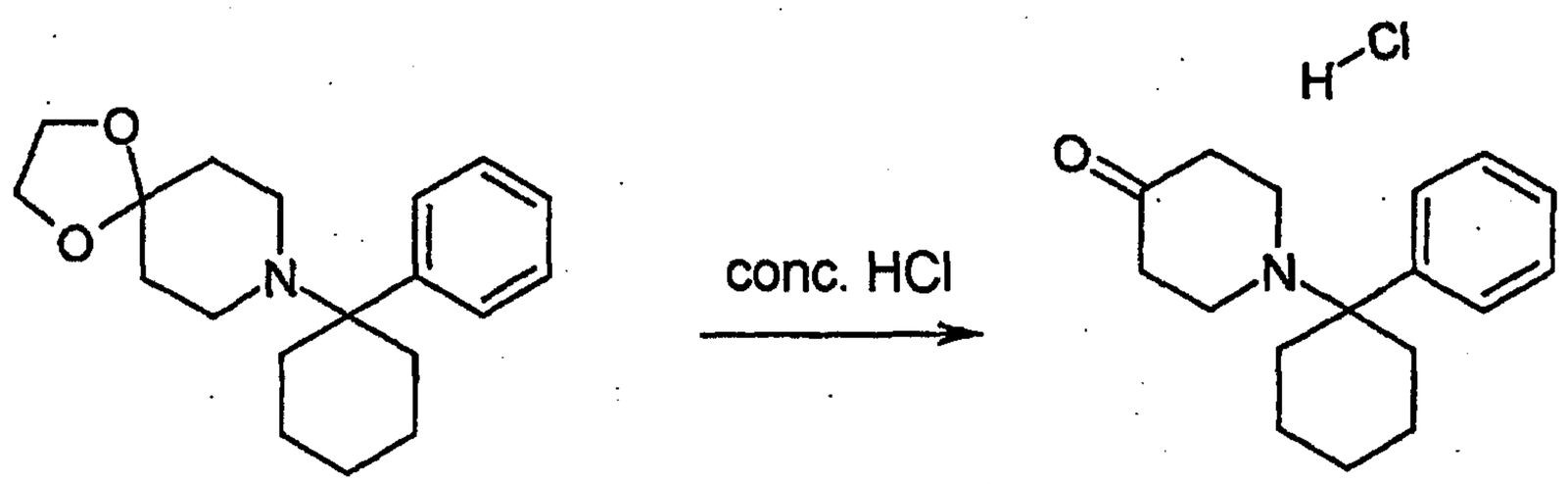
II III IV

The enamine **IV** is directly reacted further with phenylmagnesium chloride **V** to form the amine **VI**:



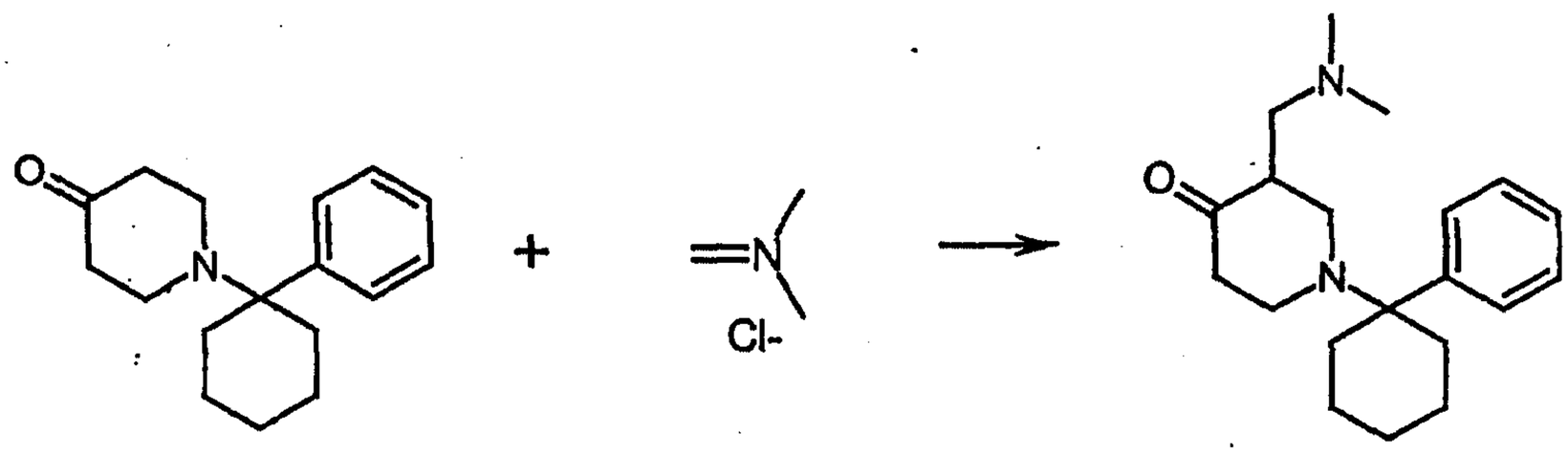
IV V VI

The amine **VI** is hydrolysed in a further step, and **VII** is precipitated in the form of the hydrochloride.



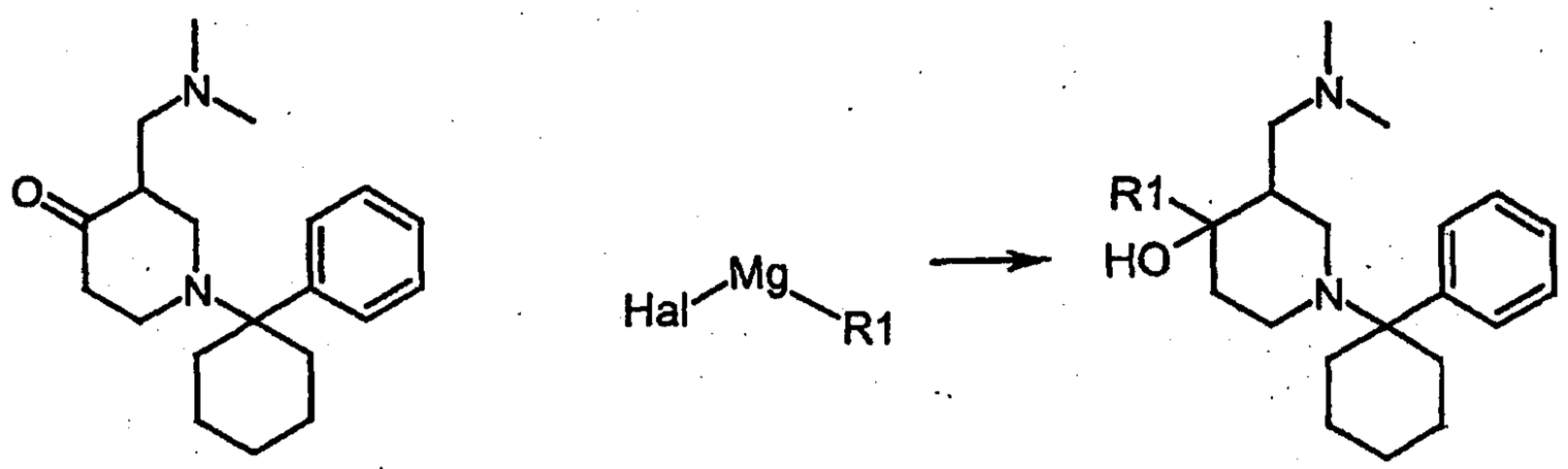
VI VII

The hydrochloride **VII** is reacted further with a variant of the Eschenmoser salt **VIII** to form the Mannich base **IX**.



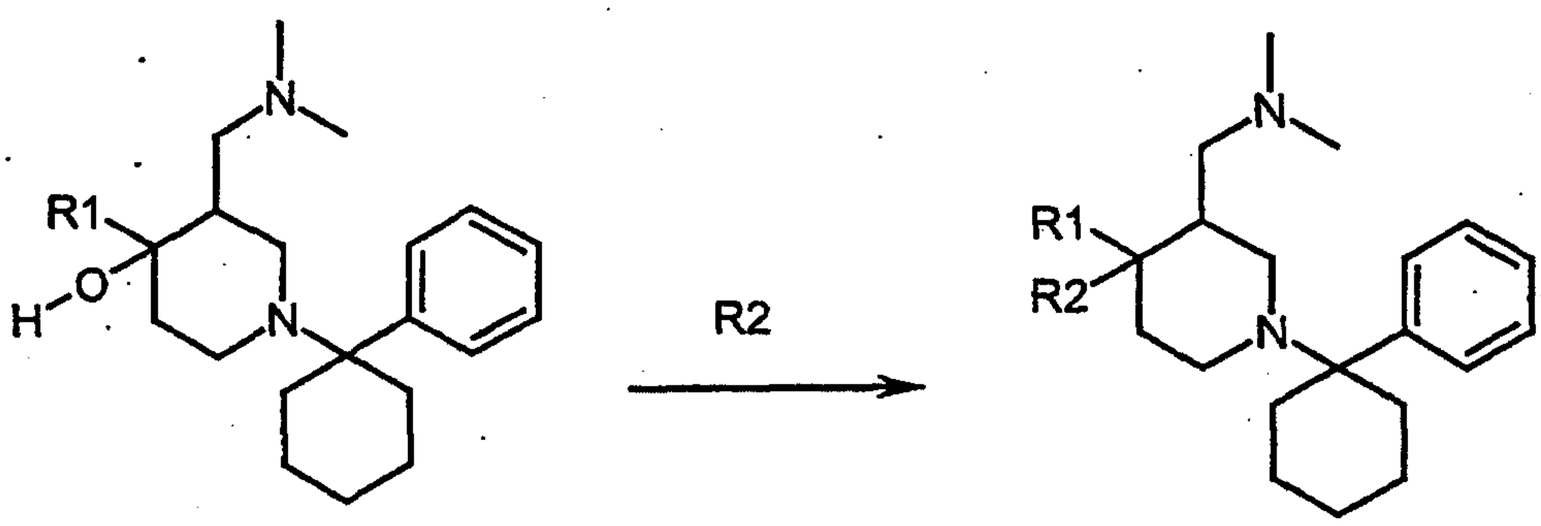
VII VIII IX

Reaction with a Grignard reagent **X** is then carried out to form the products **XI**.



IX X XI

The compounds of the general formula **XI** can be reacted further with a number of reagents that introduce the above-defined radical R2, especially halogenated hydrocarbons, ethers, esters, ureas, amides, carbonates and related compounds, to form the compounds **XII**.



XI XII

The compounds according to the invention can be converted into their salts in a manner known *per se* with succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid and/or aspartic acid. The salt formation is preferably carried out in a solvent, for example diethyl ether, diisopropyl ether, an alkyl acetate, acetone and/or 2-butanone. Trimethylchlorosilane in methyl ethyl ketone is also suitable for preparing the hydrochlorides.

The substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amines of the general formula I according to the invention are toxicologically harmless and are therefore suitable pharmaceutical active ingredients.

Accordingly, the invention further provides medicaments which contain as active ingredient at least one substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amine of the general formula I and/or their enantiomers, diastereoisomers, bases or salts of physiologically tolerable acids.

The medicaments preferably contain enantiomeric mixtures of the active ingredient in non-equimolar amounts, one of the enantiomers having a relative content in the mixture of from 5 to 45 wt.%.

The medicaments according to the invention are suitable for controlling pain.

Accordingly, the invention relates also to the use of at least one substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amine of the general formula I and/or its enantiomers, diastereoisomers, bases or salts of physiologically tolerable acids, in the preparation of a medicament for controlling pain.

For the preparation of corresponding pharmaceutical formulations there are used, in addition to at least one substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amine of the general formula I, carriers, fillers, solvents, diluents, colourants and/or binders. The choice of auxiliary substances, and the amounts thereof to

be used, depend on whether the medicament is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally or locally, for example to infections of the skin, of the mucosa and of the eyes. There are suitable for oral administration preparations in the form of tablets, dragées, capsules, granules, drops, juices and syrups, and for parenteral and topical administration and for administration by inhalation there are suitable solutions, suspensions, readily reconstitutable dry preparations, and also sprays. Suitable preparations for percutaneous administration are compounds of the general formula I according to the invention in a depot formulation in dissolved form or in a plaster, optionally with the addition of agents promoting penetration of the skin. Forms of preparation for oral or percutaneous administration may release the compounds of the general formula I according to the invention in a delayed manner.

The amount of active ingredient to be administered to the patient varies in dependence on the weight of the patient, the mode of administration, the indication and the severity of the disease. From 50 to 500 mg/kg of at least one dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amine of the general formula I are usually administered.

Examples

General remarks

The Examples which follow serve to illustrate the invention in greater detail, but do not limit the general idea underlying the invention.

The yields of the prepared compounds have not been optimised.

All melting points are uncorrected.

Unless indicated otherwise, petroleum ether having a boiling range of from 50 to 70°C has been used. Ether means diethyl ether.

Silica gel 60 (0.040 to 0.063 mm) from E. Merck, Darmstadt was used as the stationary phase for the column chromatography.

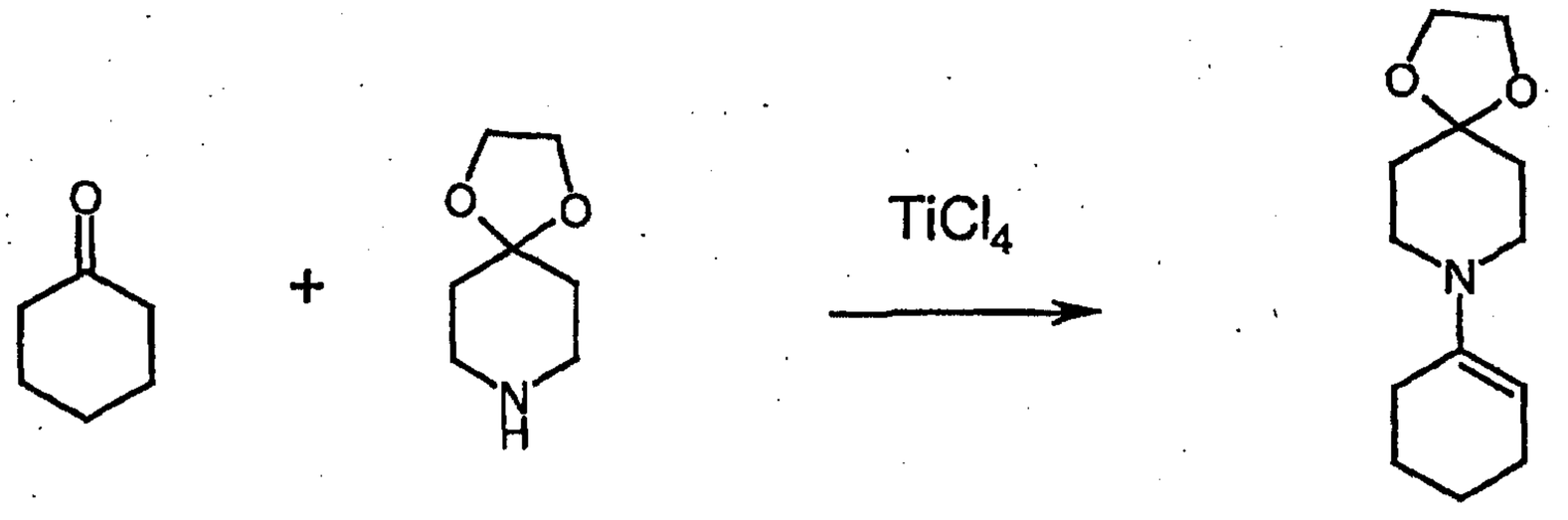
The thin-layer chromatographic investigations were carried out using commercial HPLC plates, silica gel 60 F 254, from E. Merck, Darmstadt.

The mixing ratios of the eluants for all the chromatographic investigations are always given in volume/volume.

Example 1

3-Dimethylaminomethyl-4-methyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(1)**

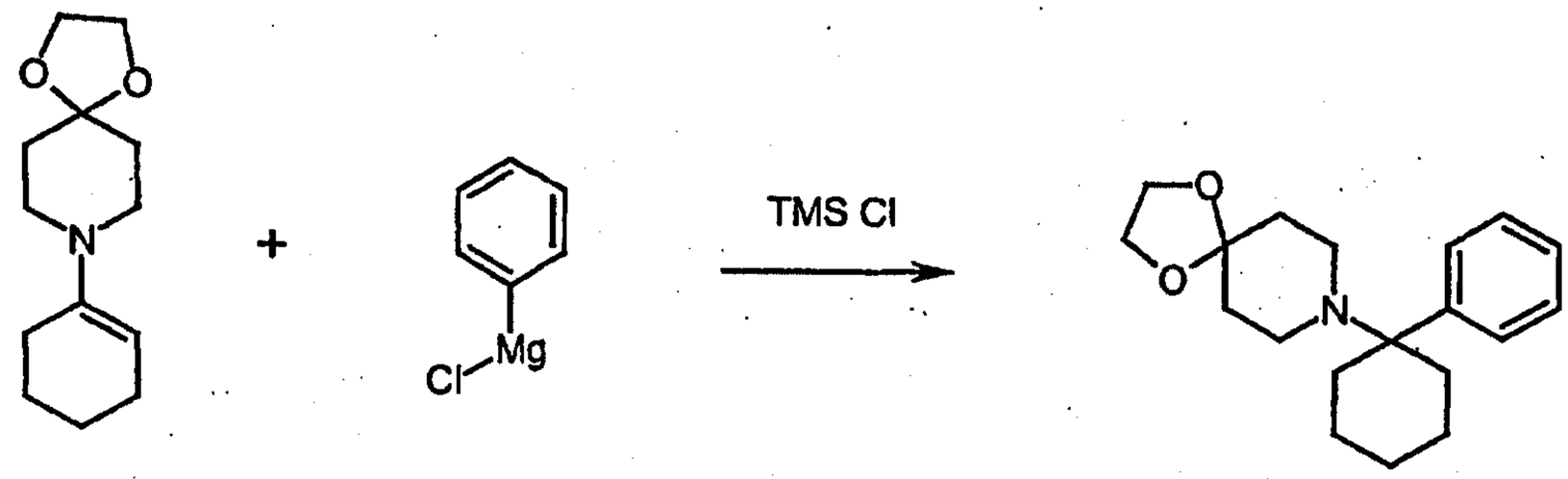
1st step



II III IV

For the preparation of 8-cyclohex-1-enyl-1,4-dioxa-8-aza-spiro[4.5]decane **IV**, 54 ml (0.5 mol.) of cyclohexanone were dissolved with 200 ml (1.5 mol.) of 1,4-dioxa-8-aza-spiro[4.5]decane **III** in 0.5 litre of diethyl ether, and the solution was stirred for half an hour. 31 ml of titanium tetrachloride in 0.5 litre of n-hexane were then added dropwise at 0°C in the course of 60 minutes. When the addition was complete, the mixture was slowly heated to 20°C and then stirred for 24 hours. The resulting precipitate was filtered off with suction and discarded. The filtrate was concentrated and reacted further directly. The yield was 83 g (0.37 mol., 71 %).

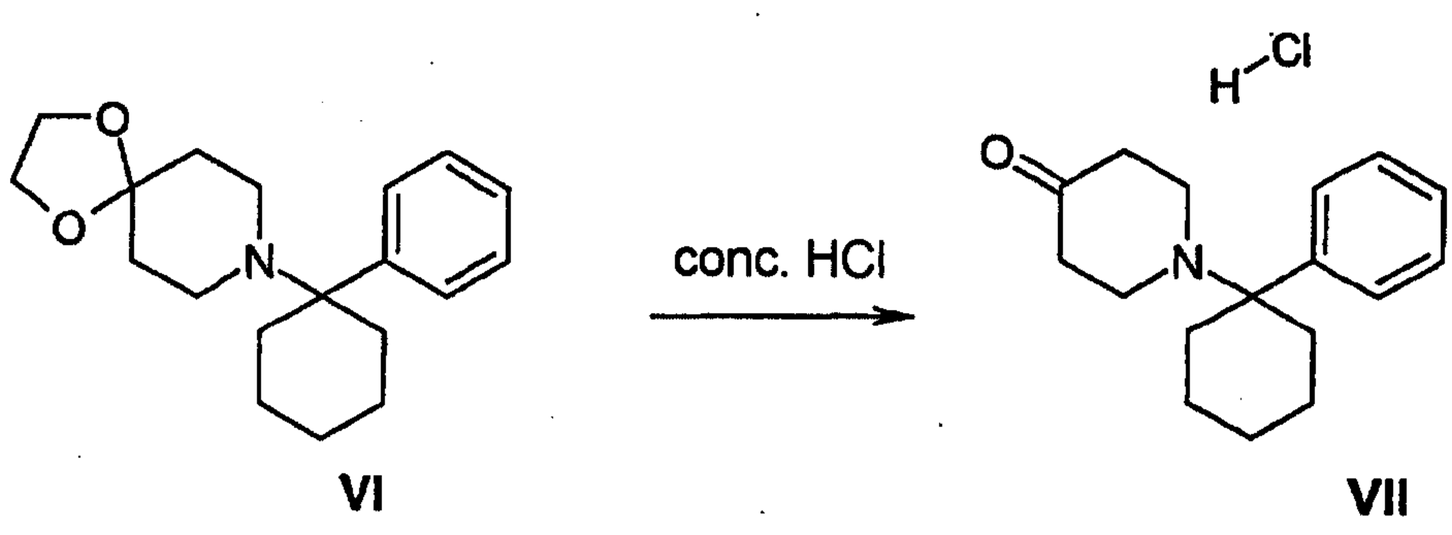
2nd step



IV **V** **VI**

83 g (0.37 mol.) of 8-cyclohex-1-enyl-1,4-dioxa-8-aza-spiro[4.5]decane **IV** were reacted with 200 ml of 2M phenylmagnesium chloride solution **V**. To that end, 52 ml of trimethylchlorosilane in 0.75 litre of methylene chloride were placed in a reaction vessel with 2 ml of water, and the enamine **IV** was added dropwise. The Grignard reagent was then added, while cooling with an ice bath, and the whole was stirred for 3 hours. Hydrolysis was then carried out with 200 ml of ammonium chloride solution, and the aqueous phase was extracted with 0.5 litre of methylene chloride. The product **VI** was purified by column chromatography on silica gel using diisopropyl ether. The yield was 36 g (0.12 mol., 32 %).

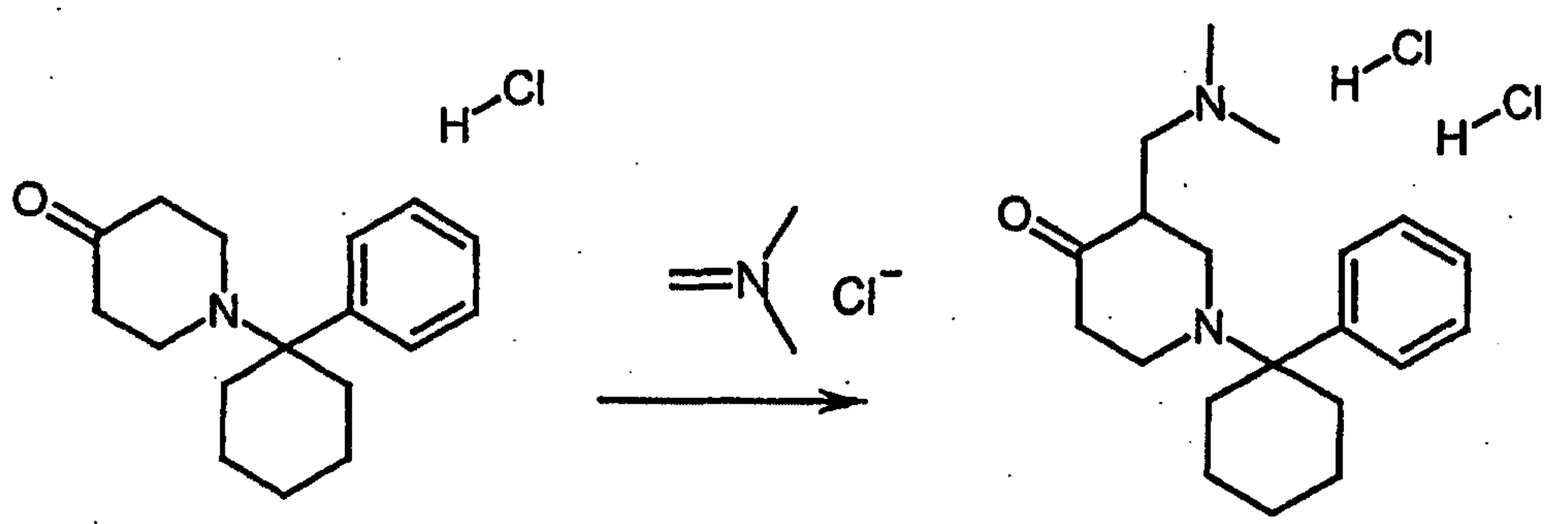
3rd step



VI **VII**

The amine **VI** was hydrolysed in a further step and precipitated in the form of the hydrochloride **VII**. To that end, 250 ml of concentrated HCl were added at 20°C to 36 g (0.12 mol.) of **VI**, followed by stirring for 12 hours. The mixture was rendered alkaline with ammoniacal solution and extracted with diethyl ether. The free base was precipitated in the form of the hydrochloride using trimethylchlorosilane. The yield was 21 g (0.072 mol., 60 %).

4th step

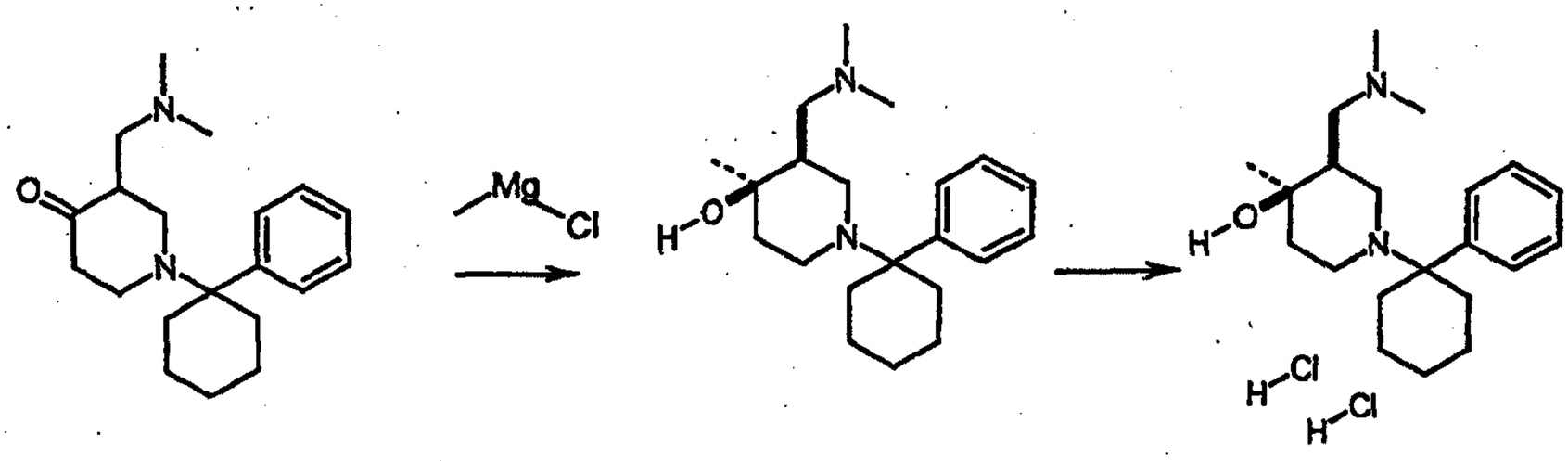


VII **VIII** **IX**

The hydrochloride **VII** was reacted with a variant of the Eschenmoser salt **VIII** to form the Mannich base **IX**. In that reaction, 6.0 g (20 mmol.) of compound **VII** were stirred for 48 hours at 20°C with 2.1 g (22 mmol.) of compound **VIII** in 50 ml of dry tetrahydrofuran. The reaction mixture was then poured into a basic, aqueous ammoniacal solution, and the free base of **IX** was extracted with 3 x 100 ml of methylene chloride. The organic phases were combined and dried, and the solvent was removed *in vacuo*. The residue was dissolved in 50 ml of methyl ethyl ketone, and 5 ml of trimethylsilyl chloride were added thereto. 3.0 g (8 mmol., 40 %) of compound **IX** were obtained.

5th step

After the freeing of the hydrochloride **IX** into the free base, **IX** was reacted with a methylmagnesium chloride **X** to form **XI** and, after precipitation in the form of the dihydrochloride, to form **(1)**.



IX **X** **XI** **1**

To that end, 0.57 g (1.8 mmol.) of **IX** was dissolved in 2.5 ml of tetrahydrofuran and cooled to -20°C. Under protecting gas, 1.0 ml (3 mmol.) of 3M methylmagnesium chloride solution in THF was added, and stirring was carried out overnight. 2 ml of ammonium chloride solution were then added for the purposes of hydrolysis, and the aqueous phase was extracted with ether. After precipitation in the form of the dihydrochloride, the yield of **(1)** was 0.2 g (0.3 mmol., 16 %). The decomposition point of compound **(1)** was 220°C.

Example 2

3-Dimethylaminomethyl-4-ethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(2)**

The synthesis instructions are described under **Example 1.** Ethylmagnesium chloride was used instead of methylmagnesium chloride. In the reaction of 0.57 g (1.8 mmol.) of **IX**, the yield of **(2)** was 21 mg (0.036 mmol., 2 %). The compound decomposed at 190°C and above.

Example 3

3-Dimethylaminomethyl-4-vinyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(3)**

The synthesis instructions are described under **Example 1.** Vinylmagnesium chloride was used instead of methylmagnesium chloride. In the reaction of 0.57 g (1.8 mmol.) of **IX**, the yield of **(3)** was 37 mg (0.09 mmol., 3 %). The compound decomposed at 190°C and above.

Example 4

4-Butyl-3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(4)**

The synthesis instructions are described under **Example 1.** Butylmagnesium chloride was used instead of methylmagnesium chloride. In the reaction of 0.57 g (1.8 mmol.) of **IX**, the yield of **(4)** was 37 mg (0.09 mmol., 3 %). The melting point of the compound was 225°C.

Example 5

4-Octyl-3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(5)**

The synthesis instructions are described under **Example 1.** Octylmagnesium chloride was used instead of methylmagnesium chloride. In the reaction of 0.57 g (1.8 mmol.) of **IX**, the yield of **(5)** was 104 mg (0.22 mmol., 12 %).

Example 6

3-Dimethylaminomethyl-4-(3-methoxyphenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(6)**

The synthesis instructions are described under **Example 1.** 3-Methoxy-phenylmagnesium bromide was used instead of methylmagnesium chloride. In the reaction of 0.57 g (1.8 mmol.) of **IX**, the yield of **(6)** was 491 mg (1.07 mmol., 60 %). The melting point of the compound was 245°C.

Example 7

3-Dimethylaminomethyl-4-(2-fluoro-phenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(7)**

The synthesis instructions are described under **Example 1.** 2-Fluoro-phenylmagnesium iodide was used instead of methylmagnesium chloride. In the reaction of 0.57 g (1.8 mmol.) of **IX**, the yield of **(7)** was 267 mg (0.55 mmol., 31 %). The compound decomposed at 96°C and above.

Example 8

3-Dimethylaminomethyl-4-(3-chloro-phenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(8)**

The synthesis instructions are described under **Example 1.** 3-Chloro-phenylmagnesium iodide was used instead of methylmagnesium chloride. In the reaction of 0.57 g (1.8 mmol.) of **IX**, the yield of **(8)** was 177 mg (0.35 mmol., 19 %). The compound decomposed at 96°C and above.

Example 9

3-Dimethylaminomethyl-4-(benzyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(9)**

The synthesis instructions are described under **Example 1.** Benzylmagnesium chloride was used instead of methylmagnesium chloride. In the reaction of 0.57 g (1.8 mmol.) of **IX**, the yield of **(9)** was 213 mg (0.48 mmol., 27 %).

Example 10

3-Dimethylaminomethyl-4-(phenethyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(10)**

The synthesis instructions are described under **Example 1.** Phenylmagnesium bromide was used instead of methylmagnesium chloride. In the reaction of 0.57 g (1.8 mmol.) of **IX**, the yield of **(10)** was 255 mg (0.56 mmol., 31 %). The compound decomposed at 234°C and above.

Example 11

3-Dimethylaminomethyl-4-(3-hydroxy-phenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol dihydrochloride **(11)**

The synthesis instructions are described analogously to **Example 6**, except for the last step. The methyl ether was then cleaved into the phenol. To that end, 0.5 g (1.2 mmol.) of the free base of compound **(6)** was dissolved in 5 ml of toluene, and 10 ml of dibutylaluminium hydride solution (1.5 M in toluene) were added at 0°C and under a nitrogen atmosphere. After 12 hours' stirring, the batch was hydrolysed with 5 ml of ethyl acetate and 5 ml of ethanol, the solvent was removed *in vacuo*, the residue was dissolved in methyl ethyl ketone, and 1.0 ml of trimethylsilyl chloride was added thereto. The yield of **(11)** was 71 mg (0.15 mmol., 12 %). The compound melted between 245 and 248°C.

Pharmacological studies

Writhing test in mice

The analgesic activity of the compounds according to the invention in the phenylquinone-induced writhing test, modified according to I.C. Hendershot, J. Forsaith in J. Pharmacol. Exp. Ther. 125, 237-240 (1959), was studied in mice. Male mice weighing from 25 to 30 g were used for that purpose. Groups of 10 animals per substance dose were each given, 10 minutes after the intravenous administration of the test substances, 0.3 ml/mouse of a 0.02 % aqueous solution of phenylquinone (phenylbenzoquinone, Sigma, Deisenhofen; preparation of the solution with addition of 5 % ethanol and storage in a water bath at 45°C), administered intraperitoneally. The animals were then placed individually in observation cages. By means of a push-button counter, the number of pain-induced stretching

movements (so-called writhing reactions = straightening of the body with stretching of the rear extremities) was counted 5 to 20 minutes following the administration of the phenylquinone. Animals that had been given only physiological saline with phenylquinone were used as control.

All the substances were tested in the standard dose of 10 mg/kg. The percentage inhibition (% inhibition) of the writhing reactions by a substance was calculated according to the following formula:

$$\% \text{ inhibition} = 100 - \left[\frac{\text{writhing reaction treated animals}}{\text{writhing reaction control}} \times 100 \right]$$

All the compounds according to the invention which were studied exhibited moderately pronounced to pronounced analgesic activity.

The results of selected writhing studies are summarised in **Table 1**.

Table 1: Analgesia test in the writhing test in mice

Example No.	% inhibition of the writhing reactions 10 mg/kg i.v.
1	33
5	31
6	54
8	40
9	35
11	73

Formalin test, mice

Studies to determine the antinociceptive activity of compounds 6 and 11 according to the invention were carried out in the formalin test on male mice (NMRI, 20 to 30 g).

In the formalin test, a distinction is made between the first (early) phase (0 to 15 minutes after the formalin injection) and the second (late) phase (15 to 60 minutes after the formalin injection) (D. Dubuisson, S.G. Dennis, Pain 4, 161-174 (1977)). The early phase, as a direct reaction to the formalin injection, represents a model for acute pain, while the late phase is regarded as a model for persistent (chronic) pain (T.J. Coderre, J. Katz, A.L. Vaccarino, R. Melzack, Pain 52, 259-285 (1993)).

The compounds according to the invention were studied in the second phase of the formalin test, in order to obtain information regarding the activity of substances in the case of chronic/inflammatory pain.

By means of a single subcutaneous formalin injection (20 µl, 1 %) into the dorsal side of the right rear paw, a nociceptive reaction was induced in free-moving test animals; the nociceptive reaction manifests itself in pronounced licking and biting of the affected paw. For the test period of three minutes in the second (late) phase of the formalin test (21st to 24th minute following formalin administration), the nociceptive behaviour was recorded continuously by observation of the animals. The pain behaviour was quantified by adding the number of seconds for which the animals exhibited licking and biting of the affected paw during the test period. After injection of substances that have antinociceptive activity in the formalin test, the described behaviours of the animals are reduced and in some cases even eliminated. A comparison was made with control animals that had received vehicle (solvent) prior to the formalin administration. On the basis of the quantification of the pain behaviour, the action of the substance in the formalin test was determined as a change relative to the control in percent. The time of administration prior to the formalin injection was chosen in dependence on the mode of administration of the compounds according to the invention (intravenous: 5 minutes).

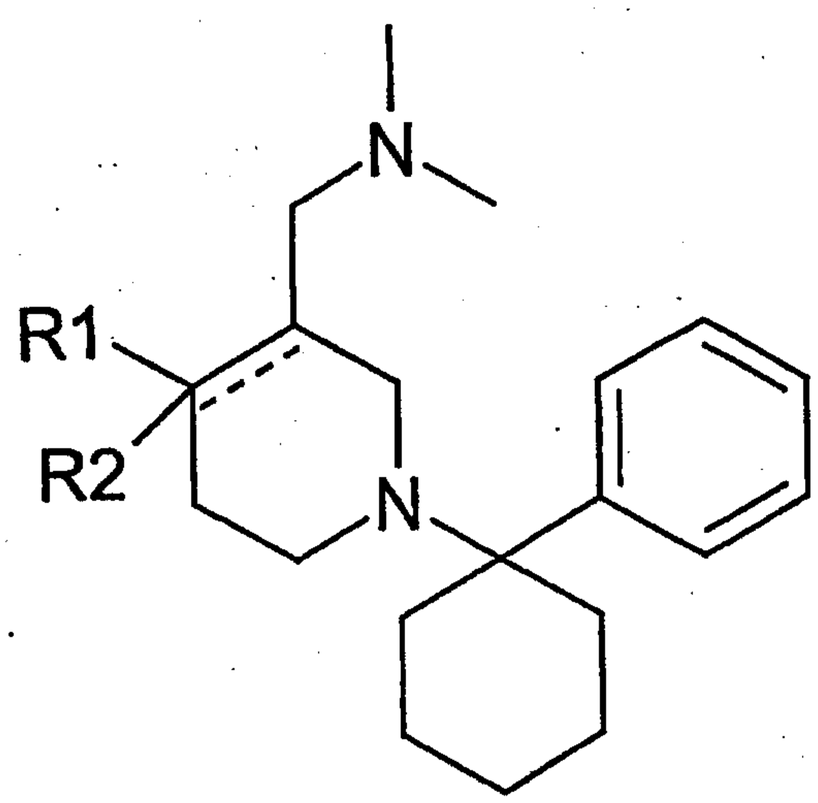
The results of selected studies in the formalin test in mice are summarised in the Table below.

Table 2: Antinociceptive activity of the compounds according to the invention in the formalin test in mice

Example No.	% inhibition relative to control 10 mg/kg i.v.
6	55
11	59

Patent Claims

1. Substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]-amines of the general formula **I**



I

wherein

R1 = H, C_{1-12}-alkyl (branched, unbranched), vinyl, phenyl (mono- or poly-substituted by C_{1-5}-alkyl (branched, unbranched), H, F, Cl, Br, OMe, OEt, OPr, OBu, SMe, OH and/or by CF_3),
benzyl (mono- or poly-substituted by C_{1-5}-alkyl (branched, unbranched), H, F, Cl, Br, OMe, OEt, OPr, OBu, SMe, OH and/or by CF_3),
phenethyl (mono- or poly-substituted by C_{1-5}-alkyl (branched, unbranched), H, F, Cl, Br, OMe, OEt, OPr, OBu, SMe, OH and/or by CF_3) or
naphthyl (mono- or poly-substituted by C_{1-5}-alkyl (branched, unbranched), H, F, Cl, Br, OMe, OEt, OPr, OBu, OBz, SMe, OH and/or by CF_3), and

R2 = H, F, Cl, Br, OMe, OEt, OPr, OBu, OBz, SMe, OH, CF_3 or bond to the double bond,

and/or their enantiomers, diastereoisomers, bases or salts of physiologically tolerable acids.

2. Compounds according to claim 1, characterised in that R1 is unbranched C_{1-8}-alkyl and R2 has the meaning according to claim 1.

3. Compounds according to claim 1, characterised in that R1 is vinyl and R2 has the meaning according to claim 1.

4. Compounds according to claim 1, characterised in that R1 is a phenyl radical substituted by F, Cl, OH or by OMe and R2 has the meaning according to claim 1.

5. Compounds according to claim 1, characterised in that R1 is benzyl and R2 has the meaning according to claim 1.

6. Compounds according to claim 1, characterised in that R1 is phenethyl and R2 has the meaning according to claim 1.

7. Compounds according to claim 1, characterised in that R2 is OH and R1 has the meaning according to claim 1.

8. Compounds according to claim 1:

3-dimethylaminomethyl-4-methyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-ethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-4-vinyl-piperidin-4-ol or the corresponding dihydrochloride

4-butyl-3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-octyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-(3-methoxy-phenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-(2-fluoro-phenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

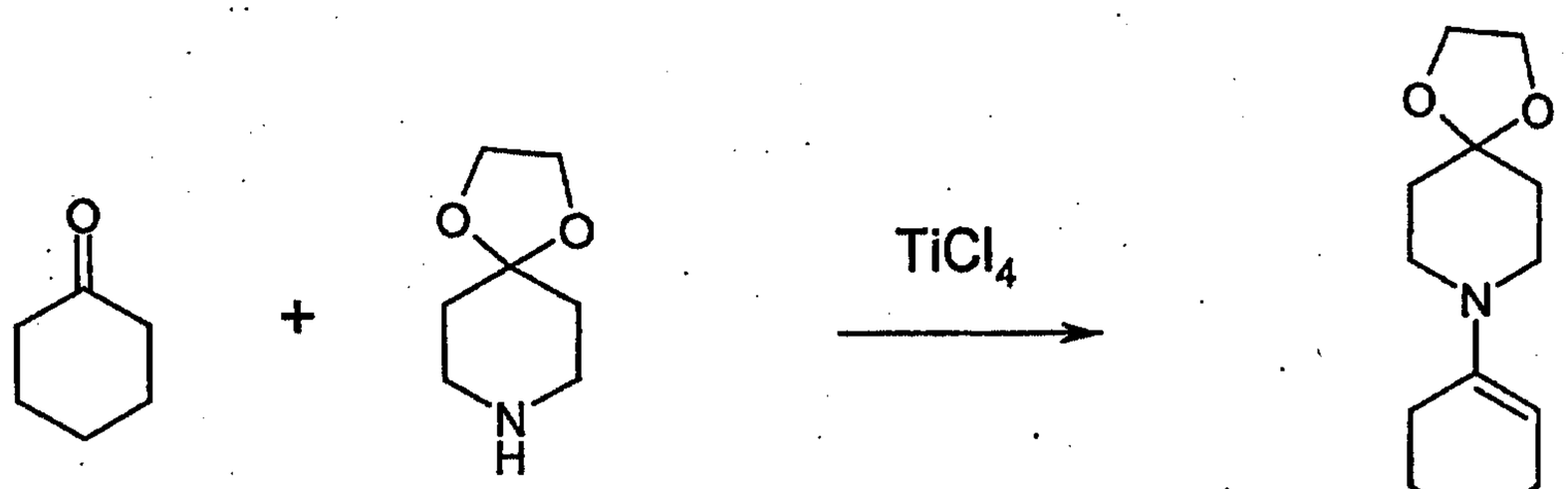
4-(3-chloro-phenyl)-3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

4-benzyl-3-dimethylaminomethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

3-dimethylaminomethyl-4-phenethyl-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride

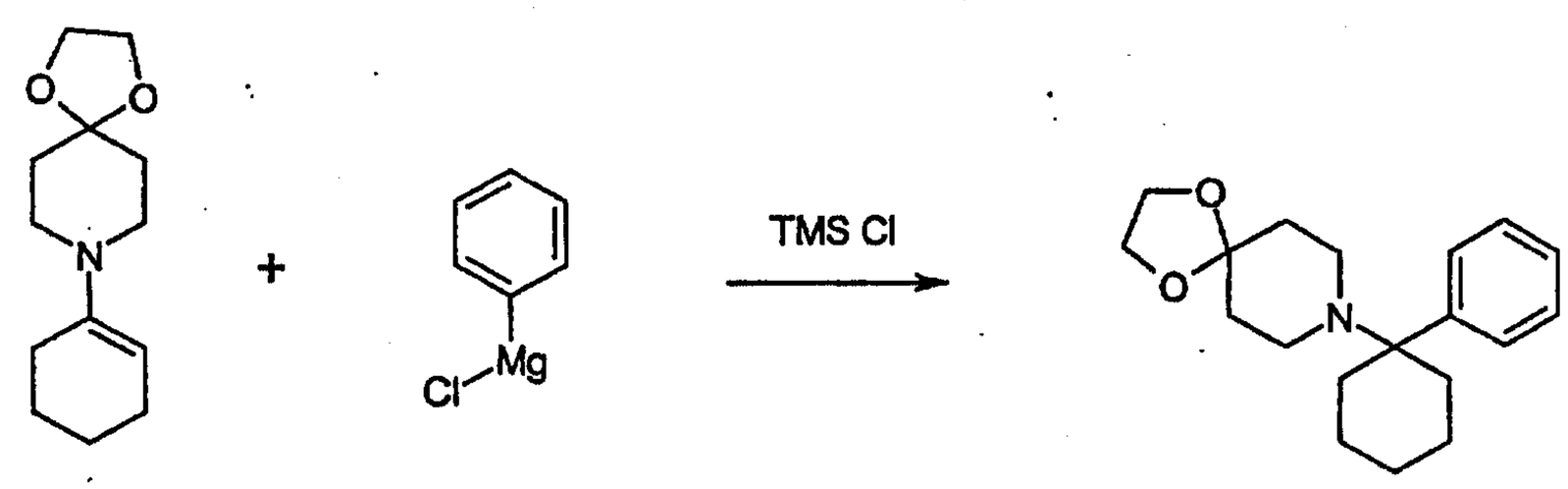
3-dimethylaminomethyl-4-(3-hydroxy-phenyl)-1-(1-phenyl-cyclohexyl)-piperidin-4-ol or the corresponding dihydrochloride.

9. Process for the preparation of substituted dimethyl-[1-(1-phenyl-cyclohexyl)-piperidin-3-ylmethyl]amines of the general formula **I** according to claim 1, wherein cyclohexanone (formula **II**) is reacted with 1,4-dioxa-8-aza-spiro[4.5]decane (formula **III**) in the presence of titanium tetrachloride to form the enamine of formula **IV**



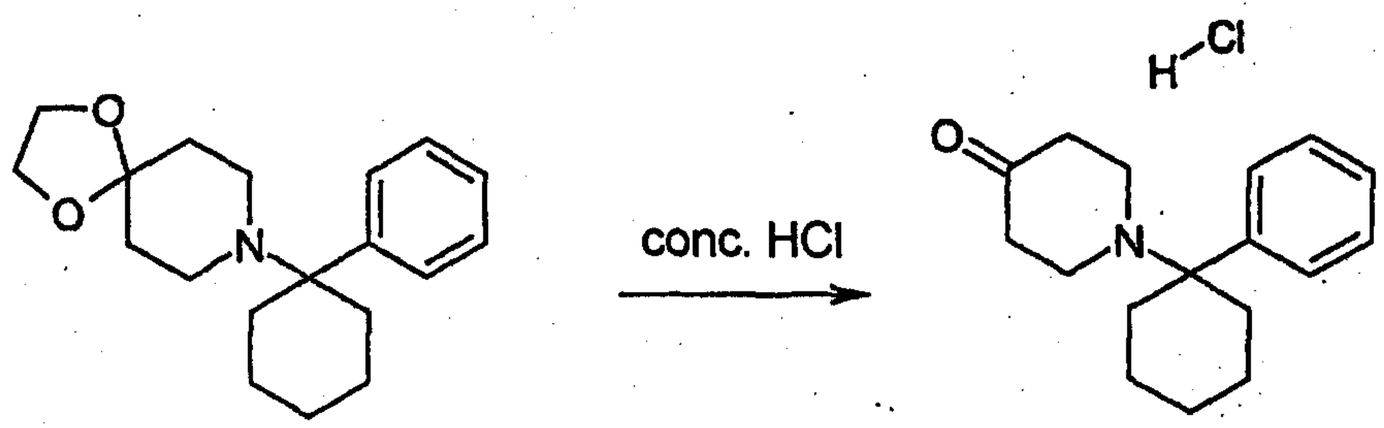
II **III** **IV**

which is reacted further with phenylmagnesium chloride (formula **V**) in the presence of trimethylchlorosilane to form the amine of formula **VI**



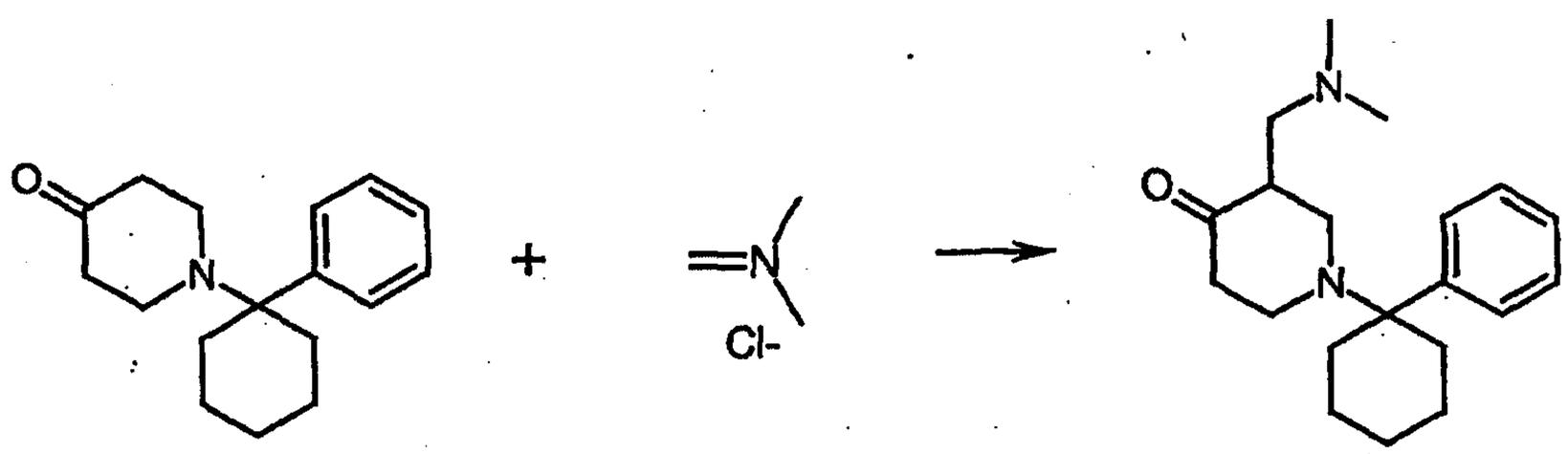
IV **V** **VI**

the resulting amine of formula **VI** is then hydrolysed and precipitated in the form of the hydrochloride of formula **VII**



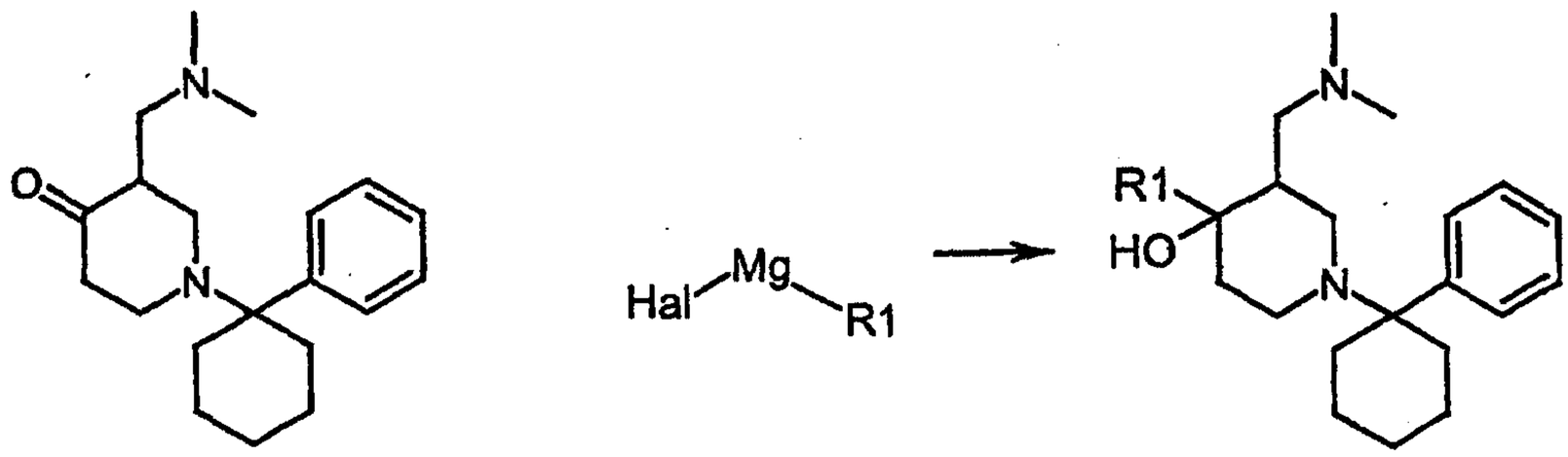
VI VII

which is reacted further with a variant of the Eschenmoser salt according to formula **VIII** to form the Mannich base of formula **IX**



VII VIII IX

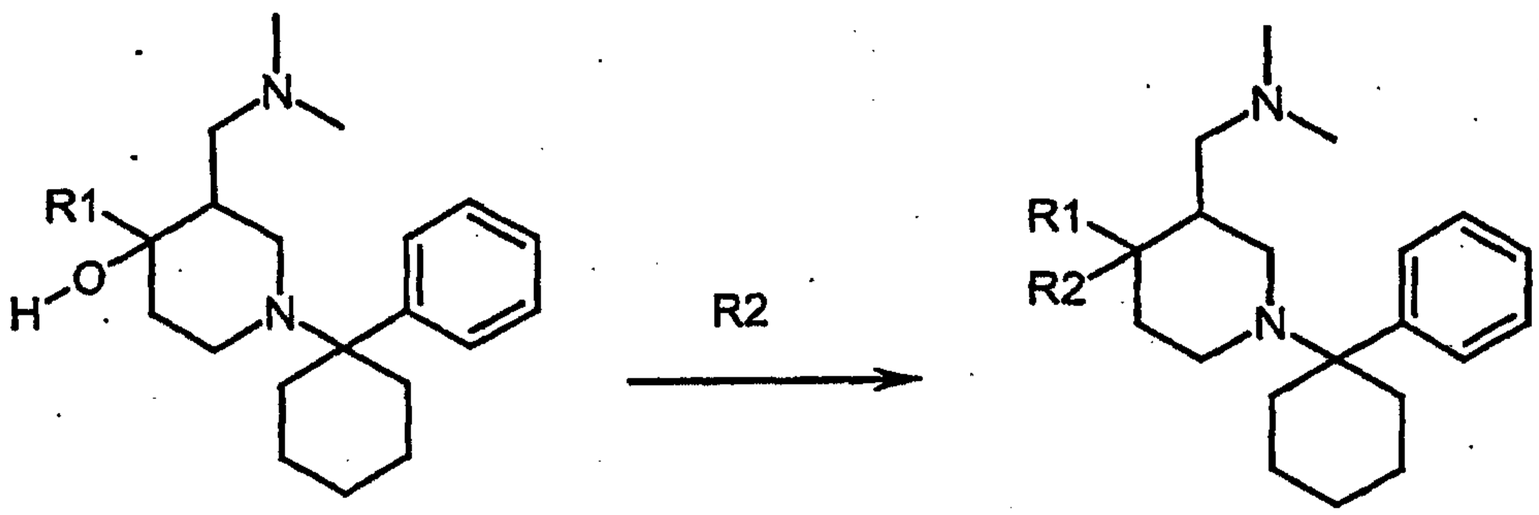
following which reaction of the free base according to formula **IX** with a Grignard reagent of formula **X**, which has the organic radical R1, is carried out to form the compounds of formula **XI**



IX X XI

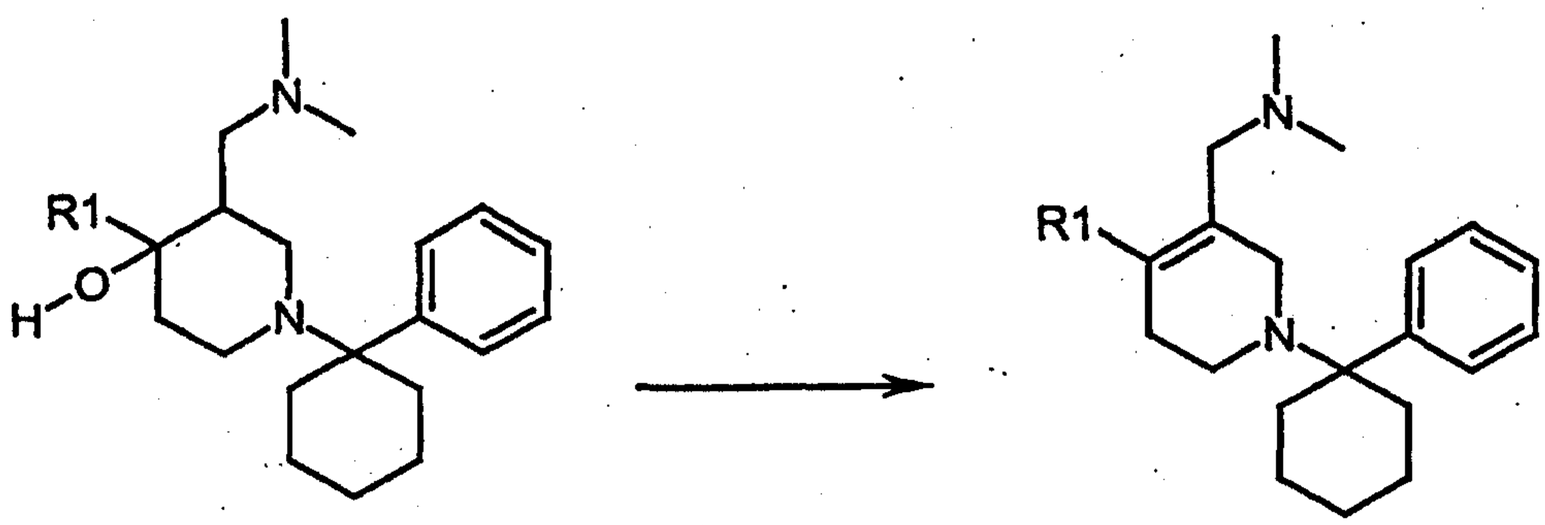
which are purified by conventional methods and isolated in the form of salts of physiologically tolerable acids, wherein

- compounds of formula **XII** are obtained by reacting compounds of formula **XI** with reagents that replace the OH group in the 4-position of the compounds of formula **XI** by the above-defined radical R2, with the exception of the OH group, especially halogenated hydrocarbons, ethers, esters, ureas, amides, carbonates and related compounds



XI **XII**

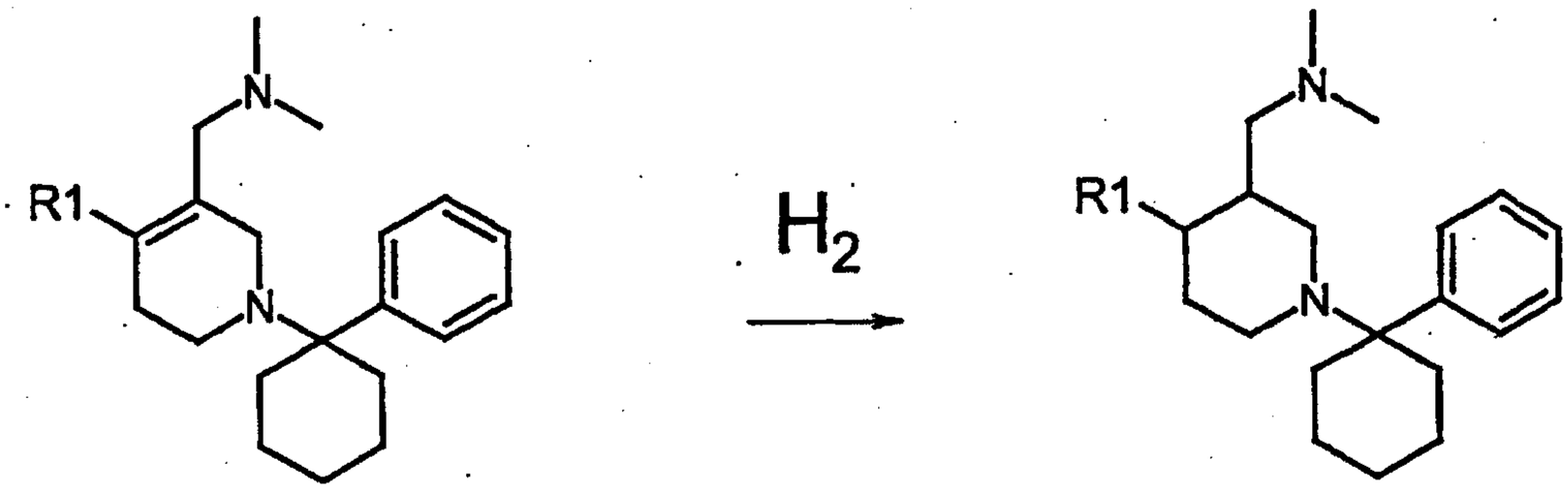
- compounds of formula **XIII** are obtained by dehydrating compounds of formula **XI**



XI XIII

and

- compounds of formula **XIV** are obtained by reducing compounds of formula **XIII** with hydrogen



XIII XIV

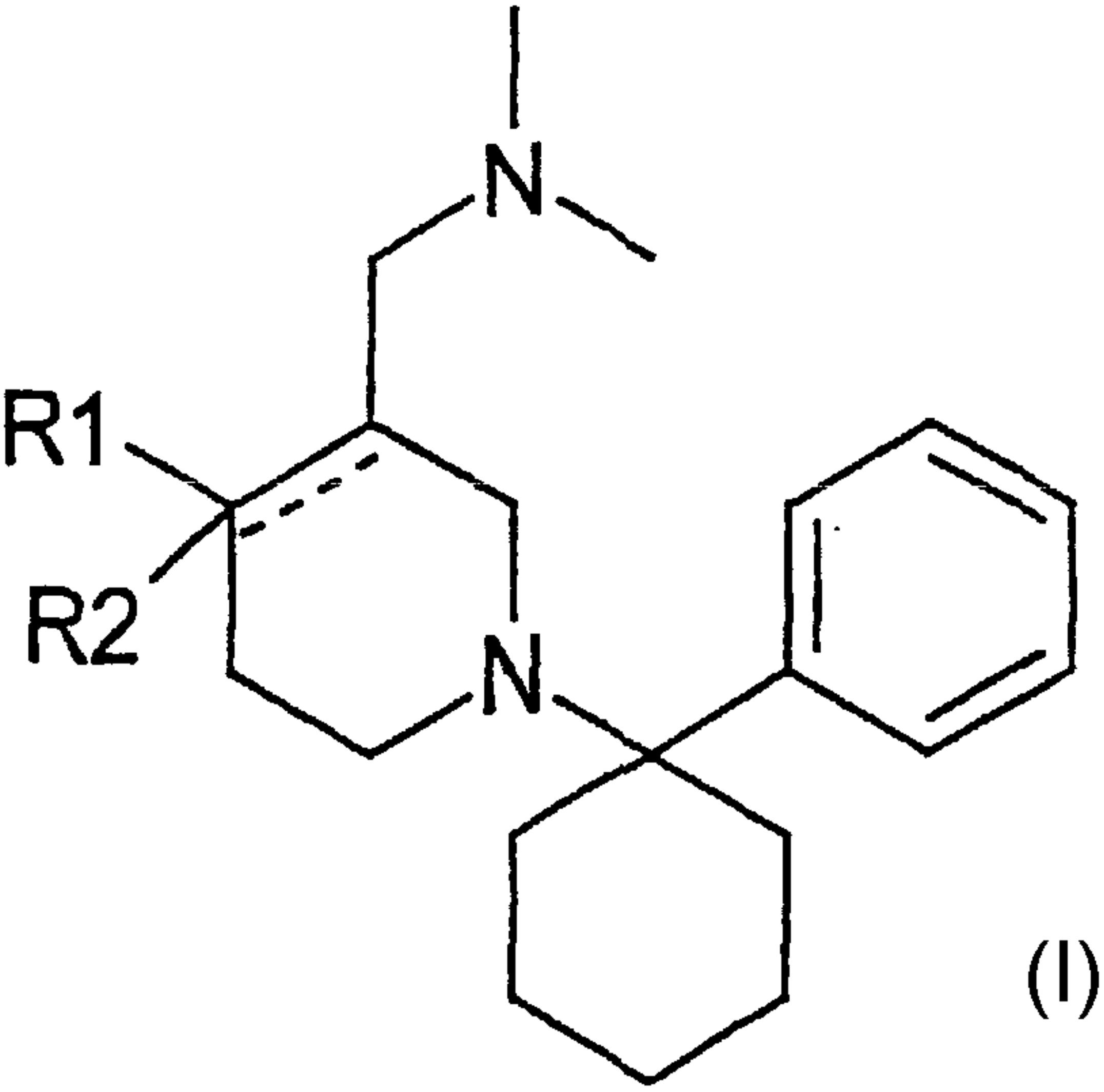
10. Medicament containing as active ingredient at least one compound of the general formula **I** according to claim 1 and/or its enantiomers, diastereoisomers, bases or salts of physiologically tolerable acids.

11. Medicament according to claim 10 containing as active ingredient a mixture of the enantiomers of a compound of the general formula **I** according to claim 1, wherein the two enantiomers are not present in equimolar amounts.

12. Medicament according to claim 11, wherein one of the enantiomers has a relative content of from 5 to 45 wt.% in the enantiomeric mixture.

13. Medicament according to any one of claims 10 to 12 for controlling pain.

14. Use of at least one compound of the general formula **I** according to claim 1 and/or its enantiomers, diastereoisomers, bases or salts of physiologically tolerable acids in the manufacture of a medicament for controlling pain.



(I)