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Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

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(54) Title: SUBSTITUTED 2-DIALKYLAMINOALKYLBIPHENYL DERIVATIVES

(54) Bezeichnung: SUBSTITUIERTE 2-DIALKYLAMINOALKYLBIPHENYL-DERIVATE

(57) Abstract: The invention relates to substituted 2-dialkylaminoalkylbiphenyl derivatives, a method for the preparation thereof, drugs containing them and the use thereof for the production of drugs.

(57) Zusammenfassung: Die Erfindung betrifft substituierte 2-Dialkylaminoalkylbiphenyl-Derivate, Verfahren zu deren Herstellung, Arzneimittel enthaltend diese Verbindungen, sowie die Verwendung dieser Verbindungen zur Herstellung von Arzneimitteln.

Substituted 2-dialkylaminoalkylbiphenyl derivatives

The invention relates to substituted 2-dialkylaminoalkylbiphenyl derivatives, processes for their preparation, medicaments comprising these compounds and the use of these compounds for the preparation of medicaments.

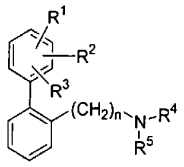
The treatment of chronic and non-chronic states of pain is of great importance in medicine. There is a worldwide demand for pain treatments which have a good efficacy. The urgent need for action in respect of patient-relevant and target-orientated treatment of chronic and non-chronic states of pain, this being understood as meaning successful and satisfactory pain treatment for the patient, is documented in the large number of scientific works which have recently appeared in the field of applied analgesia and fundamental research into nociception.

Conventional opioids, such as e.g. morphine, have a good action in the treatment of severe to very severe pain. However, their use is limited due to the known side effects, e.g. respiratory depressions, vomiting, sedation, constipation, addiction, dependency and development of tolerance. They can therefore be administered over a relatively long period of time or in relatively high dosages only with particular safety precautions, such as e.g. specific prescription instructions (Goodman, Gilman, The Pharmacological Basis of Therapeutics, Pergamon Press, New York 1990). Furthermore, they have a relatively low efficacy for some states of pain, in particular neuropathic pain.

An object on which the invention is based was to provide analgesically active substances which are suitable for treatment of pain. Furthermore, these substances should have as few as possible of the side effects of opioid analgesics, such as e.g. nausea, vomiting, dependency, respiratory depression or constipation. Further objects were to provide active compounds for treatment of inflammatory and allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses and/or epilepsy.

According to the invention, this is achieved by provision of new substituted 2-dialkylaminoalkylbiphenyl derivatives which are suitable for treatment of inflammatory and allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses and/or epilepsy and which moreover have a pronounced analgesic action.

According to a first embodiment of the invention there is provided substituted 2-aminoalkylbiphenyl derivatives of the general formula I



I,

wherein

n is 1 or 2,

the radical R^1 represents CN, NO_2, SO_2CH_3, SO_2CF_3, -O-aryl, -O-C_{1-6}-alkylene-aryl, $NR^{6a}R^{7a}$, an aryl, an acetyl, an acetamidyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radical R^2 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

or R^1 and R^2 together in each case denote the group OCH_2O, OCH_2CH_2O, CH=CHO, $CH=C(CH_3)O$ or CH=CHNH,

the radical R^3 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radicals R^4, R^5, which are identical or different, represent H, or represent a C_{1-6}-alkyl radical,

the radicals R^6, R^7 which are identical or different, represent H, a C_{1-6}-alkyl, an aryl radical or an aryl radical bonded via a C_{1-6} alkylene group,

the radical R^{6a} represents H, a C_{1-6}-alkyl radical, an aryl radical or an aryl radical bonded via a C_{1-6} alkylene group,

the radical R^{7a} represents a C_{1-6}-alkyl radical, an aryl radical or an aryl radical bonded via a C_{1-6} alkylene group,

in the form of their bases and/or salts of physiologically tolerated acids, the compound 4-chloro-2'-dimethylaminomethylbiphenyl-2-carbonitrile being excluded.

Alkyl radicals are also understood as meaning hydrocarbons which are at least monosubstituted, preferably by halogen and/or a hydroxyl group, particularly preferably by fluorine and/or a hydroxyl group. If these contain more than one substituent, these can be identical or different. The alkyl radicals methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, CHF_2, CF_3 or CH_2OH are preferred.

An aryl radical is also understood as meaning phenyls or naphthyl radicals which are at least monosubstituted by an OH, a halogen, preferably F and/or Cl, a CF_3 a C_{1-6}-alkyl, a C_{1-6}-alkoxy, a C_{1-7}-cycloalkoxy, a C_{3-7}-cycloalkyl, a C_{2-6}-alkylene or a phenyl radical. The phenyl radicals can also be condensed with further rings.

The following examples of substituted 2-dimethylaminoalkylbiphenyl derivatives are disclosed herein:

(3'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-chlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-3-ol and the corresponding hydrochloride;

(2'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-chlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

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(3'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(4'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(3'-chloro-4'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(3'-methoxybiphenyl-2-ylethyl)dimethylamine and the corresponding hydrochloride

dimethyl-[2-(2-methylbenzofuran-4-yl)benzyl]amine and the corresponding hydrochloride

2'-dimethylaminomethylbiphenyl-2-carbaldehyde and the corresponding hydrochloride

(3'-difluoromethylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

2'-dimethylaminomethylbiphenyl-3-carbaldehyde and the corresponding hydrochloride

biphenyl-2-ylmethyldimethylamine and the corresponding hydrochloride

(3',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(3',5'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

dimethyl-(4'-nitro-3'-trifluoromethylbiphenyl-2-ylmethyl)-amine and the corresponding hydrochloride

(3',4'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(4'-fluoro-3'-trifluoromethylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(4'-chloro-3'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

N-(2'-dimethylaminomethyl-3-trifluoromethoxybiphenyl-4-yl)acetamide and the corresponding hydrochloride

(3'-isopropoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding and the corresponding hydrochloride

2'-(2-dimethylaminoethyl)biphenyl-3-ol and the corresponding hydrochloride

4-chloro-2'-dimethylaminomethylbiphenyl-3-ol and the corresponding hydrochloride

[2-(1*H*-indol-5-yl)benzyl]dimethylamine and the corresponding hydrochloride

(4'-methanesulfonylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(2',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(2',3'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(2',5'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

(2-benzo[1,3]dioxol-5-ylbenzyl)dimethylamine and the corresponding hydrochloride

1-[2'-(2-dimethylaminoethyl)biphenyl-3-yl]ethanone and the corresponding hydrochloride

[2-(3',4'-dimethoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride

[2-(3'-isopropoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride

[2-(4'-chloro-3'-methoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride

4-chloro-2'-(2-dimethylaminoethyl)biphenyl-3-ol and the corresponding hydrochloride

dimethyl-(3'-nitrobiphenyl-2-ylmethyl)amine and the corresponding hydrochloride

4-amino-2'-dimethylaminomethylbiphenyl-3-ol and the corresponding dihydrochloride

(3',5'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride

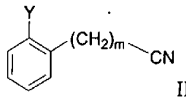
(2',5'-dimethoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-ylamine and the corresponding dihydrochloride;

N-(2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-yl)acetamide and the corresponding hydrochloride; and

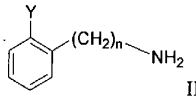
3,5-dichloro-2'-dimethylaminomethyl-biphenyl-4-ylamine and the corresponding hydrochloride.

According to a second embodiment of the invention there is provided a process for the preparation of substituted 2-aminoalkylbiphenyl derivatives of the general formula I according to any one of claims 1 to 7, wherein compounds of the general formula II



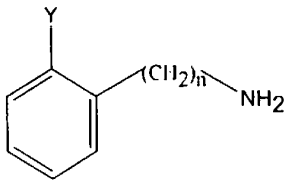
II

wherein Y denotes Cl, Br or I and m denotes 0 or 1, are reduced in solution with a reducing agent to give compounds of the general formula III,



III

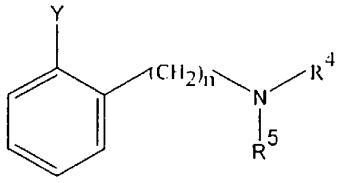
wherein n denotes 1 or 2,



III

and these are purified and isolated by conventional methods.

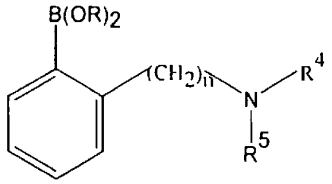
The compounds of the general formula III are reacted with aliphatic C_{1-6}-aldehydes in the presence of a reducing agent, preferably formic acid and/or sodium borohydride, to give compounds of the general formula IV



IV

wherein R^4 and R^5 have the meaning according to the general formula I, and these are purified and isolated by conventional methods.

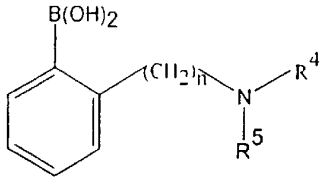
The compounds of the general formula IV are converted by halogen-metal exchange, preferably with magnesium and/or butyllithium, and subsequent reaction with a boric acid ester, preferably a trialkyl borate, particularly preferably with a trimethyl borate, at temperatures of $\leq 0°C$ to give compounds of the general formula V, wherein R denotes a C_{1-6}-alkyl radical



V

and these are isolated and purified by conventional methods.

The compounds of the general formula V can be reacted with aqueous acids, preferably hydrochloric acid, to give compounds of the general formula VI

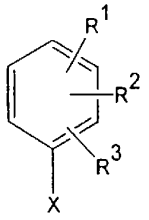


VI

and these can be purified and isolated by conventional methods.

The compounds of the general formula V or VI are reacted in a transition metal-catalysed reaction, preferably in a reaction catalysed by palladium(0) compounds or by palladium(II) salts, particularly preferably by tetrakis(triphenylphosphine)palladium, bis(dibenzylideneacetone)palladium, elemental palladium on active charcoal, palladium(II) chloride and/or palladium(II) acetate, in an aliphatic ether, preferably 1,4-dioxane and tetrahydrofuran, or a hydrocarbon, preferably toluene or hexane, an alcohol, preferably ethanol or isopropanol, a chlorinated hydrocarbon, preferably chloroform or methylene chloride, in water or

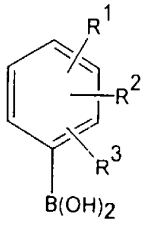
mixtures of these solvents at temperatures between 20 and 150°C with compounds of the general formula VII



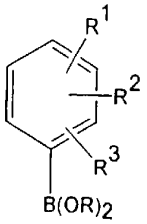
VII,

wherein X denotes Cl, Br, I or $OSO_2C_pF_{(2p+1)}$ and the radicals R^1 to R^3 have the meaning according to the general formula I, to give compounds of the general formula I and these are purified and isolated by conventional methods.

Alternatively to this, the compounds of the general formula VIII or IX



VIII



IX,

wherein R^1 to R^3 have the meaning according to the general formula I, are reacted in a transition metal-catalysed reaction, preferably in a reaction catalysed by palladium(0) compounds or by palladium(II) salts, particularly preferably by tetrakis(triphenylphosphine)palladium, bis(dibenzylideneacetone)palladium, elemental palladium on

active charcoal, palladium (II) chloride and/or palladium (II) acetate, in an aliphatic ether, preferably 1,4-dioxane and tetrahydrofuran, or a hydrocarbon, preferably toluene or hexane, an alcohol, preferably ethanol or isopropanol, a chlorinated hydrocarbon, preferably chloroform or methylene chloride, in water or mixtures of these solvents at temperatures between 20 and 150°C with compounds of the general formula III or IV to give compounds of the general formula I and these are purified and isolated by conventional methods.

The compounds of the general formula I can be converted into their salts in the manner known *per se* with physiologically tolerated acids, for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, 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, acetic acid alkyl esters, acetone and/or 2-butanone. Trimethylchlorosilane in aqueous solution is moreover suitable for preparation of the hydrochlorides.

The substituted 2-dialkylaminoalkylbiphenyl derivatives of the general formula I according to the invention are toxicologically acceptable and are therefore suitable pharmaceutical active compounds.

According to a third embodiment of the invention there is provided a medicament which comprises, as the active compound, at least one substituted 2-dialkylaminoalylbiphenyl derivative of the general formula I in the form of its base and/or a salt of a physiologically tolerated acid and optionally further active compounds and auxiliary substances.

The medicaments are preferably employed for treatment/control for/of pain, inflammatory and allergic reactions, depressions, drug and alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing mental illnesses and/or epilepsy.

Accordingly, in a fourth embodiment the invention additionally provides the use of at least one substituted 2-dialkylaminoalkylbiphenyl derivative of the general formula I in the form of its base and/or a salt of a physiologically tolerated acid for the preparation of a medicament for treatment/control for/of pain, inflammatory and allergic reactions, depressions, drug and alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing mental illnesses or epilepsy.

According to a fifth embodiment of the invention there is provided a method for treatment/control for/of pain, inflammatory reactions, allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses or epilepsy in a subject, said method comprising administering to said subject at least one substituted 2-aminoalkylbiphenyl derivative of the general formula I, or a medicament according to the third embodiment of the invention.

To prepare corresponding pharmaceutical formulations, in addition to at least one substituted 2-dimethylaminoalkylbiphenyl derivative of the general formula I, carrier materials, fillers, solvents, diluents, dyestuffs and/or binders are employed. The choice of auxiliary substances and the amounts thereof to be employed depend on whether the medicament is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, bucally or locally, for example on infections on the skin, the mucous membranes and on the eyes. Formulations in the form of tablets, coated tablets, capsules, granules, drops, juices and syrups are suitable for oral administration, and solutions,

suspensions, easily reconstitutable dry formulations and sprays are suitable for parenteral, topical and inhalatory administration. Compounds of the general formula I according to the invention in a depot, in dissolved form or in a patch, optionally with the addition of agents which promote penetration through the skin, are suitable percutaneous administration formulations. Formulation forms which can be used orally or percutaneously can release the compounds of the general formula I according to the invention in a retarded manner.

The amount of active compound to be administered to the patient varies according to the weight of the patient, the mode of administration, the indication and the severity of the illness. 0.5 to 500 mg/kg of at least one 2-dialkylaminoalkylbiphenyl derivative of the general formula I are usually administered.

Examples

The following examples serve to illustrate the invention, but do not limit the general inventive idea.

The yields of the compounds prepared are not optimized.

All temperatures are uncorrected.

The statement ether means diethyl ether.

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

The thin layer chromatography analyses were carried out with HPTLC precoated plates, silica gel 60 F 254 from E. Merck, Darmstadt.

The mixing ratios of the mobile phases for all the chromatography analyses are always stated in volume/volume.

Vol.% denotes per cent by volume and wt.% denotes per cent by weight.

Example 1:
(3'-Methoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride

1st stage
3-Methoxybenzeneboronic acid

41.3 g (220 mmol) 3-bromoanisole were dissolved in 880 ml tetrahydrofuran and the solution was cooled to -70°C in a cooling bath (ethanol/dry ice). 160 ml (250 mmol) butyllithium solution (1.6 M in hexane) were added dropwise under nitrogen such that the temperature did not rise above -60°C. After stirring at -70°C for 1.5 hours, 75 ml (660 mmol) trimethyl borate were also added dropwise such that the temperature did not rise above -60°C. After stirring in the cold for a further hour, the mixture was warmed to 25°C in the course of two hours, 720 ml hydrochloric acid (1 M) were added and the mixture was stirred at 25°C for 15 hours.
For working up, the mixture was extracted three times with 300 ml ether each time, the organic phases were combined, washed with 100 ml each of water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500-10 mbar). 30.8 g 3-methoxybenzeneboronic acid (92.1% of theory) were obtained in this manner.

2nd stage
(2-Bromobenzyl)dimethylamine

25.1 g (113 mmol) 2-bromobenzylamine hydrochloride were dissolved in 26 ml (678 mmol) formic acid and 52 ml (678 mmol) formaldehyde solution (36 wt.% in water) and the mixture was heated at 95°C for 6 hours, while stirring.

The solution was then cooled to 0°C in an ice-bath and 90 g of cold potassium hydroxide solution (50 wt.%) were added. The mixture was extracted three times with 100 ml ether each time at 25°C, the organic phases were combined, a little active charcoal was added, the mixture was dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500-10 mbar). 22.2 g (2-bromobenzyl)dimethylamine (91.9% of theory) were obtained in this manner.

3rd stage
(3'-Methoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.13 g (7.43 mmol) 3-methoxybenzeneboronic acid, 1.67 g (7.78 mmol) (2-bromobenzyl)dimethylamine and 2.62 g (24.7 mmol) sodium carbonate were dissolved in a mixture of 50 ml toluene, 20 ml water and 10 ml ethanol. 175 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated at 110°C for 16 hours, while stirring.
For working up, 75 ml ether were added and the mixture was extracted three times with 75 ml of a potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were extracted with 30 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500-10 mbar). 2.12 g of crude base (118% of theory) were added and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:1 (v:v) gave 0.61 g base, which was dissolved in 6.0 ml 2-butanone, and 25 µl (1.39 mmol) water and 350 µl (2.78 mmol) chlorotrimethylsilane were added in succession. The mixture was kept at 25°C for 15 hours and the solid

which had precipitated out was filtered off, washed with small portions of ether and dried to constant weight in an oil pump vacuum. 0.56 g (27.2% of theory) of (3'-methoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 144°C was obtained in this manner.

Example 2:
(4'-Chlorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

0.88 g (5.65 mmol) 4-chlorobenzeneboronic acid, 1.27 g (5.93 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.00 g (18.8 mmol) sodium carbonate were dissolved in a mixture of 39 ml toluene, 16 ml water and 8 ml ethanol. 133 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 65 ml ether were added and the mixture was extracted three times with 65 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500-10 mbar). 1.30 g of crude base (93.8% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v/v) gave 0.61 g of base, which was separated by HPLC for further purification. Separation conditions: mobile phase acetonitrile/water (80:20 (v/v) + 0.5 vol.% isopropylamine), flow rate 10 ml/min, wavelength 254 nm, column Eurogel PRP 100 (manufacturer Knauer, 250 x 16 mm, with pre-column). 0.31 g of crude base was obtained, from which 0.33 g (20.7% of theory) (4'-chlorobiphenyl-2-

ylmethyl)dimethylamine hydrochloride with a melting point of 232°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 3:
2'-Dimethylaminomethylbiphenyl-3-ol hydrochloride

0.70 g (2.52 mmol) of the (3'-methoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride prepared according to example 1 (3rd stage) were dissolved in 10 ml water, the base was liberated with 10 ml water and 2 ml sodium hydroxide solution (32 wt.%), the mixture was extracted three times with 20 ml ether each time, the combined organic extracts were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). 0.59 g (2.44 mmol) of this base was heated under reflux (bath temperature 145°C) with 55 ml hydrogen bromide solution (48 wt.% in water) for two hours.
For working up, the mixture was poured into 600 ml sodium bicarbonate solution (1 M) (pH 7-8), and extracted three times with 100 ml ethyl acetate each time, the combined organic extracts were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). 0.61 g crude base (109% of theory) was obtained and was introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether gave 0.51 g of base, from which 0.51 g (79.7% of theory) 2'-dimethylaminomethylbiphenyl-3-ol hydrochloride with a melting point of 180°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 4:
(2'-Methoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.00 g (6.58 mmol) 4-methoxybenzeneboronic acid, 1.48 g (6.91 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.32 g (21.9 mmol) sodium carbonate were dissolved in a mixture of 45 ml toluene, 18 ml water and 9 ml ethanol. 160 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 75 ml ether were added and the mixture was extracted three times with 75 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). 1.62 g of crude base (102% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:2 (v/v) gave 0.64 g of base, from which 0.31 g (17.1% of theory) (2'-methoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 163°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 5:
(3'-Chlorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.00 g (6.39 mmol) 3-chlorobenzeneboronic acid, 1.44 g (6.71 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.26 g (21.3 mmol) sodium carbonate were dissolved in a mixture of 44 ml

toluene, 17 ml water and 9 ml ethanol. 160 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.

For working up, 75 ml ether were added and the mixture was extracted three times with 75 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). 1.49 g of crude base (94.7% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:1 (v/v) gave 0.62 g of base, from which a hydrochloride was precipitated according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone. The base was liberated from this with 10 ml water and 2 ml sodium hydroxide solution (32 wt.%), the mixture was extracted three times with 20 ml ether each time, the combined organic extracts were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). The resulting crude base was purified by HPLC. Separation conditions: mobile phase acetonitrile/water (80:20 (v/v) + 0.5 vol.% isopropylamine), flow rate 10 ml/min, wavelength 254 nm, column Eurogel PRP 100 (manufacturer Knauer, 250 x 16 mm, with pre-column). 0.32 g of crude base was obtained, from which 0.29 g (16.3% of theory) (3'-chlorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 169°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 6:
(2'-Fluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.02 g (7.27 mmol) 2-fluorobenzeneboronic acid, 1.63 g (7.63 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.57 g (24.2 mmol) sodium carbonate were dissolved in a mixture of 50 ml toluene, 20 ml water and 10 ml ethanol. 172 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 80 ml ether were added and the mixture was extracted three times with 80 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). 1.73 g of crude base (104% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v/v) gave 0.13 g of base, from which 0.10 g (4.7% of theory) (2'-fluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 184°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 7:
(3'-Fluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.03 g (7.39 mmol) 3-fluorobenzeneboronic acid, 1.05 g (4.93 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.61 g (24.6 mmol) sodium carbonate were dissolved in a mixture of 50 ml

toluene, 20 ml water and 10 ml ethanol. 175 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.

For working up, 80 ml ether were added and the mixture was extracted three times with 80 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.38 g of crude base (122% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v/v) gave 0.57 g of base, from which 0.53 g (41.9% of theory) (3'-fluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 183°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 8:
(4'-Fluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.00 g (7.15 mmol) 4-fluorobenzeneboronic acid, 1.02 g (4.76 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.52 g (23.8 mmol) sodium carbonate were dissolved in a mixture of 50 ml toluene, 20 ml water and 10 ml ethanol. 170 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 80 ml ether were added and the mixture was extracted three times with 80 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions

were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.21 g of crude base (111% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v/v) gave 0.56 g of base, from which 0.56 g (44.0% of theory) (4'-fluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 222°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 9:
(3'-Chloro-4'-fluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.12 g (6.41 mmol) 3-chloro-4-fluorobenzeneboronic acid, 1.44 g (6.73 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.26 g (21.4 mmol) sodium carbonate were dissolved in a mixture of 44 ml toluene, 18 ml water and 9 ml ethanol. 151 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 70 ml ether were added and the mixture was extracted three times with 70 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.66 g of crude base (98.2% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane

1:1 (v/v) gave 0.66 g of base, which was purified by HPLC. Separation conditions: mobile phase acetonitrile/water (80:20 (v/v) + 0.5 vol.% isopropylamine), flow rate 10 ml/min, wavelength 254 nm, column Eurogel PRP 100 (manufacturer Knauer, 250 x 4.6 mm, with pre-column). 0.37 g of crude base was obtained, from which 0.34 g (17.6% of theory) (3'-chloro-4'-fluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 205°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 10:
(3'-Methoxybiphenyl-2-ylethyl)dimethylamine hydrochloride

1st stage
2-(2-Bromo-phenyl)-ethylamine

10.0 g (51.0 mmol) 2-bromophenylacetonitrile were dissolved in 80 ml ether and the solution was added dropwise to 5.81 g (153 mol) lithium aluminium hydride in 230 ml ether. The mixture was heated under reflux for three hours, while stirring, and, after cooling, 80 ml potassium hydroxide solution (10 wt.%) were slowly added dropwise, with vigorous stirring. After stirring overnight, the supernatant was decanted off, the residue was rinsed twice with 100 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 9.48 g 2-(2-bromo-phenyl)-ethylamine (93% of theory) were obtained in this manner.

2nd stage
[2-(2-Bromophenyl)ethyl]dimethylamine

9.42 g (47.3 mmol) 2-(2-bromophenyl)ethylamine were dissolved in 18 ml (473 mmol) formic acid and 36 ml (473 mmol) formaldehyde solution (36 wt.% in water) and the solution was heated at 95°C under reflux for 6 hours, while stirring. This solution was then cooled to 0°C in an ice-bath and 61 g cold potassium hydroxide solution (50 wt.%) were added. The mixture was extracted three times with 40 ml ether each time at 25°C, the organic phases were combined, a little active charcoal was added, the mixture was dried over magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 11.3 g slightly contaminated [2-(2-bromophenyl)ethyl]dimethylamine (105% of theory) were obtained in this manner.

3rd stage
(3'-Methoxybiphenyl-2-ylethyl)dimethylamine hydrochloride

2.0 g (13.2 mmol) of the 4-methoxybenzeneboronic acid prepared according to example 1 (1st stage), 3.15 g (13.8 mmol) [2-(2-bromophenyl)ethyl]dimethylamine from stage 1 and 4.66 g (43.8 mmol) sodium carbonate were dissolved in a mixture of 90 ml toluene, 36 ml water and 18 ml ethanol. 312 mg tetrakis(triphenylphosphine)-palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours. For working up, 150 ml ether were added and the mixture was extracted three times with 150 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 50 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary

evaporator (500 - 10 mbar). 3.52 g of crude base (104% of theory) were obtained and were introduced on to a 4.5 x 33 cm column packed with silica gel. Elution with ether/n-hexane 1:1 (v/v) gave 2.24 g of base, which was purified by HPLC. Separation conditions: mobile phase acetonitrile/water (70:30 (v/v) + 0.05 vol.% isopropylamine), flow rate 10 ml/min, wavelength 254 nm, column Eurogel PRP 100 (manufacturer Knauer, 250 x 16 mm, with pre-column). 0.96 g of crude base was obtained, from which 0.65 g (3'-methoxybiphenyl-2-ylethyl)dimethylamine hydrochloride (17.3% of theory) with a melting point of 143°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 11:
Dimethyl-[2-(2-methylbenzofuran-4-yl)benzyl]amine hydrochloride

1st stage
2-(Dimethylaminomethyl)benzeneboronic acid

23.3 g (109 mmol) of the (2-bromobenzyl)dimethylamine prepared in example 1 (2nd stage) were dissolved in 400 ml tetrahydrofuran and the solution was cooled to -70°C in a cooling bath (ethanol/dry ice). 78 ml (125 mmol) butyllithium solution (1.6 M in hexane) were added dropwise under nitrogen such that the temperature did not rise above -65°C. After the mixture had been stirred at -70°C for 1.5 hours, 37 ml trimethyl borate were added dropwise such that the temperature did not rise above -60°C. After stirring in the cold for a further hour, the mixture was warmed to 25°C in the course of two hours, 350 ml hydrochloric acid

(1 M) were added and the mixture was stirred at 25°C for 15 hours.

For working up, the mixture was neutralized with 10 ml sodium hydroxide solution (32 wt.%), rendered alkaline (pH approx. 9) with 3.5 g sodium carbonate and extracted three times with 150 ml ether each time, the organic phases were combined, dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 9.29 g 2-(dimethylaminomethyl)benzeneboronic acid (47.7% of theory) were obtained in this manner.

2nd stage

Dimethyl-[2-(2-methylbenzofuran-4-yl)benzyl]amine hydrochloride

1.00 g (5.59 mmol) 2-(dimethylaminomethyl)benzeneboronic acid from stage 1, 1.24 g (5.86 mmol) 4-bromo-2-methylbenzofuran and 1.97 g (18.6 mmol) sodium carbonate were dissolved in a mixture of 38 mol toluene, 15 ml water and 8 ml ethanol. 132 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.

For working up, 75 ml ether were added and the mixture was extracted three times with 75 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.75 g of crude base (124% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane

1.3 (v:v) gave 0.78 g of base, from which 0.64 g (39.5% of theory) dimethyl-[2-(2-methylbenzofuran-4-yl)benzyl]amine hydrochloride with a melting point of 217°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 12:
2'-Dimethylaminomethylbiphenyl-2-carbaldehyde hydrochloride

1.20 g (7.97 mmol) 4-formylbenzeneboronic acid, 1.63 g (7.59 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.68 g (25.3 mmol) sodium carbonate were dissolved in a mixture of 52 ml toluene, 21 ml water and 10 ml ethanol. 180 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 85 ml ether were added and the mixture was extracted three times with 85 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.87 g of crude base (98.2% of theory) were obtained. The base was dissolved in 50 ml ether, the solution was extracted three times with 25 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 11) with 15 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 25 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 -

10 mbar). 1.28 g of crude base (70.3% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:1 (v:v) gave 0.42 g of base, from which 0.43 g (20.5% of theory) 2'-dimethylaminomethylbiphenyl-2-carbaldehyde hydrochloride with a melting point of 230°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 13:
(3'-Difluoromethylbiphenyl-2-ylmethyl)dimethylamine hydrochloride

0.98 g (5.46 mmol) of the 2-(dimethylaminomethyl)benzeneboronic acid prepared according to example 11 (1st stage), 1.19 g (5.73 mmol) 1-bromo-3-difluoromethylbenzene and 1.93 g (18.2 mmol) sodium carbonate were dissolved in a mixture of 37 ml toluene, 15 ml water and 8 ml ethanol. 130 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 60 ml ether were added and the mixture was extracted three times with 60 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.46 g of crude base (103% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v/v) gave 0.79 g of base, from which 0.67 g (40.9% of theory) (3'-difluoromethylbiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 147°C was obtained

according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 14:

2'-Dimethylaminomethylbiphenyl-3-carbaldehyde hydrochloride

1.03 g (6.89 mmol) 3-formylbenzeneboronic acid, 1.40 g (6.56 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.32 g (21.8 mmol) sodium carbonate were dissolved in a mixture of 45 ml toluene, 18 ml water and 9 ml ethanol. 156 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.

For working up, 75 ml ether were added and the mixture was extracted three times with 75 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.66 g of crude base (100% of theory) were obtained. The base was dissolved in 50 ml ether, the solution was extracted three times with 25 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 11) with 15 ml sodium hydroxide solution (32 wt.%). the mixture was extracted three times with 25 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.08 g of crude base (68.7% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3

(v:v) gave 0.40 g base, from which 0.31 g (17.3% of theory) 2'-dimethylaminomethylbiphenyl-3-carbaldehyde hydrochloride with a melting point of 185°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 15:
Biphenyl-2-ylmethyldimethylamine hydrochloride

1.01 g (8.30 mmol) benzeneboronic acid, 1.69 g (7.90 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 2.79 g (26.3 mmol) sodium carbonate were dissolved in a mixture of 54 ml toluene, 22 ml water and 11 ml ethanol. 187 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 90 ml ether were added and the mixture was extracted three times with 90 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.64 g of crude base (93.3% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v/v) gave 0.26 g of base, from which 0.28 g (14.2% of theory) biphenyl-2-ylmethyldimethylamine hydrochloride with a melting point of 189°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 16:
(3',4'-Dichlorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.01 g (5.29 mmol) 3,4-dichlorobenzeneboronic acid, 1.19 g (5.56 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 1.87 g (17.6 mmol) sodium carbonate were dissolved in a mixture of 36 ml toluene, 15 ml water and 7 ml ethanol. 125 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 60 ml ether were added and the mixture was extracted three times with 60 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.43 g of crude base (96.5% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v/v) gave 0.52 g of base, which was separated by HPLC for further purification. Separation conditions: mobile phase acetonitrile/water (90:10 (v/v) + 0.05 vol.% isopropylamine), flow rate 10 ml/min, wavelength 254 nm, column Eurogel PRP 100 (manufacturer Knauer, 250 x 16 mm, with pre-column). 0.20 g of crude base was obtained, from which 0.19 g (11.4% of theory) (3',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 219°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 17:
(3',5'-Dichlorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

0.89 g (4.66 mmol) 3,5-dichlorobenzeneboronic acid, 0.95 g (4.44 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 1.57 g (14.8 mmol) sodium carbonate were dissolved in a mixture of 30 ml toluene, 12 ml water and 6 ml ethanol. 106 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 50 ml ether were added and the mixture was extracted three times with 50 ml potassium hydroxide solution (0.5 M) each time. The combined aqueous solutions were re-extracted with 20 ml ether, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.25 g of crude base (95.5% of theory) were obtained. The base was dissolved in 50 ml ether, the solution was extracted three times with 25 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 11) with 15 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 25 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 0.46 g of crude base (37.3% of theory) was obtained and was introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v:v) gave 0.23 g of base, from which 0.20 g (14.9% of theory)

(3',5'-dichlorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 198°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 18:
Dimethyl-(4'-nitro-3'-trifluoromethylbiphenyl-2-ylmethyl)amine hydrochloride

1st stage
Dimethyl 2-(dimethylaminomethyl)benzeneboronate

20.2 g (94.2 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) were dissolved in 350 ml tetrahydrofuran and the solution was cooled to -70°C in a cooling bath (isopropanol/dry ice). 68 ml (108 mmol) butyllithium solution (1.6 M in hexane) were added dropwise under nitrogen such that the temperature did not rise above -60°C. After the mixture had been stirred at -70°C for two hours, 32 ml (282 mmol) trimethyl borate were also added dropwise such that the temperature did not rise above -60°C. The mixture was warmed to 25°C in the course of 15 hours and the solution was concentrated on a rotary evaporator (500 - 10 mbar) without heat being supplied. The residue was taken up in 200 ml n-hexane, the mixture was stirred for one hour and filtered over an inert gas frit under nitrogen and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar) without heat being supplied. 12.0 g dimethyl 2-(dimethylaminomethyl)benzene-boronate (61.5% of theory) were obtained in this manner.

2nd stage

Dimethyl-(4'-nitro-3'-trifluoromethylbiphenyl-2-ylmethyl)amine hydrochloride

1.84 g (8.89 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to stage 1, 1.20 g (4.44 mmol) 5-bromo-2-nitrobenzotrifluoride and 1.57 g (14.8 mmol) sodium carbonate were dissolved in a mixture of 30 ml toluene, 12 ml water and 6 ml ethanol. 105 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.

For working up, 45 ml ether were added and the mixture was washed three times with 45 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 17 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 10 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 20 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.29 g of crude base (89.4% of theory) were obtained and were introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:10 (v:v) gave 1.05 g of base, from which 1.02 g (66.1% of theory) dimethyl-(4'-nitro-3'-trifluoromethylbiphenyl-2-ylmethyl)amine hydrochloride with a melting point above 240°C were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 19:
(3',4'-Difluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.01 g (4.87 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.88 g (9.75 mmol) 3,4-difluorobromobenzene and 1.72 g (16.2 mmol) sodium carbonate were dissolved in a mixture of 33 ml toluene, 13 ml water and 7 ml ethanol. 116 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 55 ml ether were added and the mixture was washed three times with 55 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 22 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 13 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 20 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 0.67 g of crude base (55.3% of theory) was obtained and was introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:10 (v:v) gave 0.47 g of base, from which 0.52 g (37.6% of theory) (3',4'-difluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 222°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 20:
(4'-Fluoro-3'-trifluoromethylbiphenyl-2-ylmethyl)dimethyl-amine hydrochloride

1.02 g (4.91 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 2.38 g (9.81 mmol) 5-bromo-2-fluorobenzotrifluoride and 1.73 g (16.3 mmol) sodium carbonate were dissolved in a mixture of 34 ml toluene, 14 ml water and 7 ml ethanol. 117 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 55 ml ether were added and the mixture was washed three times with 55 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 22 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 13 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 20 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 0.55 g of crude base (37.5% of theory) was obtained and was introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:10 (v:v) gave 0.39 g of base, from which 0.37 g (22.8% of theory) 4'-fluoro-3'-trifluoromethylbiphenyl-2-ylmethyl)dimethyl-amine hydrochloride with a melting point of 180°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 21:
(4'-Chloro-3'-methoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.52 g (4.87 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.08 g (4.88 mmol) 5-bromo-2-chloromethoxybenzene and 1.72 g (16.3 mmol) sodium carbonate were dissolved in a mixture of 33 ml toluene, 13 ml water and 7 ml ethanol. 116 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 55 ml ether were added and the mixture was washed three times with 55 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 22 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 13 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 20 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.26 g of crude base (93.3% of theory) were obtained and were introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:20 (v:v) gave 0.44 g of base, from which 0.46 g (29.9% of theory) (4'-chloro-3'-methoxybiphenyl-2-ylmethyl)-dimethylamine hydrochloride with a melting point of 218°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 22:
N-(2'-Dimethylaminomethyl-3-trifluoromethoxybiphenyl-4-yl)acetamide hydrochloride

1.55 g (7.48 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.49 g (4.99 mmol) 4-bromo-2-(trifluoromethoxy)acetanilide and 1.76 g (16.6 mmol) sodium carbonate were dissolved in a mixture of 34 ml toluene, 14 ml water and 7 ml ethanol. 118 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.

For working up, 55 ml ether were added and the mixture was washed three times with 55 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 22 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 13 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 20 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.72 g of crude base (97.6% of theory) were obtained and were introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:10 (v:v) gave 0.91 g of base. 0.39 g (45.5% of theory) *N*-(2'-dimethylaminomethyl-3-trifluoromethoxybiphenyl-4-yl)acetamide hydrochloride with a melting point of 182°C was obtained from 0.40 g of this base according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 23:
(3'-Isopropoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.51 g (7.31 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.05 g (4.87 mmol) 1-bromo-3-isopropoxybenzene and 1.72 g (16.2 mmol) sodium carbonate were dissolved in a mixture of 33 ml toluene, 13 ml water and 7 ml ethanol. 116 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 55 ml ether were added and the mixture was washed three times with 55 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 22 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 13 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 20 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.25 g of crude base (94.8% of theory) were obtained and were introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:20 (v:v) gave 0.65 g of base, from which 0.36 g (24.0% of theory) *N*-(2'-dimethylaminomethyl-3-trifluoromethoxy-biphenyl-4-yl)acetamide hydrochloride was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 24:
2'-(2-Dimethylaminoethyl)biphenyl-3-ol hydrochloride

0.89 g (3.49 mmol) of the base, prepared according to example 10 (2nd stage), of (3'-methoxybiphenyl-2-ylethyl)dimethylamine hydrochloride (10) were heated under reflux (bath temperature 145°C) with 89 ml hydrogen bromide solution (48 wt.% in water) for two hours.
For working up, the mixture was poured into 1,000 ml sodium bicarbonate solution (1 M) (pH 7-8) and extracted four times with 100 ml ether each time, the combined organic extracts were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). 0.32 g of crude base (38.5% of theory) was obtained, from which 0.26 g (27.9% of theory) 2'-(2-dimethylaminoethyl)biphenyl-3-ol hydrochloride with a melting point of 161°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 25:
4-Chloro-2'-dimethylaminomethylbiphenyl-3-ol hydrochloride

0.59 g (2.15 mmol) of the base, prepared according to example 21, of (4'-chloro-3'-methoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride (21) were heated under reflux (bath temperature 145°C) with 60 ml hydrogen bromide solution (48 wt.% in water) for two hours.
For working up, the mixture was poured in 140 ml water, brought to a pH of 7 - 8 by addition of solid sodium bicarbonate and extracted three times with 50 ml ether each time, the combined organic extracts were dried over anhydrous magnesium sulfate and filtered and the filtrate

was concentrated on a rotary evaporator (500 to 10 mbar). 0.55 g of crude base (98.1% of theory) was obtained, from which 0.56 g (88.0% of theory) 4-chloro-2'-dimethylaminomethylbiphenyl-3-ol hydrochloride with a melting point of 194°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 26:
[2-(1*H*-Indol-5-yl)benzyl]dimethylamine

4.77 g (23.0 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 3.01 g (15.4 mmol) 5-bromoindole and 5.42 g (51.1 mmol) sodium carbonate were dissolved in a mixture of 105 ml toluene, 42 ml water and 21 ml ethanol. 364 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 100 ml ether were added and the mixture was washed three times with 100 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 45 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 20 ml ether and rendered alkaline (pH approx. 12) with 25 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 45 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 2.23 g of crude base (58.1% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:1 (v:v) gave 0.33 g (37.6% of theory) [2-(1*H*-indol-5-yl)benzyl]dimethylamine (37.6% of theory).

Example 27:
(4'-Methanesulfonylbiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.59 g (7.69 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.21 g (5.13 mmol) 4-bromophenyl methyl sulfone and 1.81 g (17.1 mmol) sodium carbonate were dissolved in a mixture of 35 ml toluene, 14 ml water and 7 ml ethanol. 122 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 55 ml ether were added and the mixture was washed three times with 55 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 22 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 13 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 20 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 0.67 g of crude base (55.3% of theory) was obtained and was introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:1 (v:v) gave 0.65 g of base, from which 0.62 g (37.2% of theory) (4'-methanesulfonylbiphenyl-2-ylmethyl)-dimethylamine hydrochloride with a melting point of 173°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 28:
(2',4'-Dichlorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.69 g (8.17 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.23 g (5.44 mmol) 2,4-dichlorobenzene bromide and 1.92 g (18.1 mmol) sodium carbonate were dissolved in a mixture of 37 ml toluene, 15 ml water and 8 ml ethanol. 129 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 60 ml ether were added and the mixture was washed three times with 60 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 24 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 14 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 25 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 0.62 g of crude base (40.3% of theory) was obtained and was introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v:v) gave 0.39 g of base, from which 0.25 g (15.2% of theory) (2',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 170-171°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 29:
(2',3'-Difluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.97 g (9.53 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.23 g (6.35 mmol) 2,3-difluorobenzene bromide and 2.24 g (21.2 mmol) sodium carbonate were dissolved in a mixture of 43 ml toluene, 17 ml water and 9 ml ethanol. 151 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 70 ml ether were added and the mixture was washed three times with 70 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 27 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 16 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 30 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 0.99 g of crude base (63.2% of theory) was obtained and was introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v:v) gave 0.61 g of base, from which 0.55 g (34.3% of theory) (2',3'-difluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 214°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 30:
(2',5'-Difluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.86 g (8.98 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.16 g (5.99 mmol) 2,5-difluorobenzene bromide and 2.11 g (19.9 mmol) sodium carbonate were dissolved in a mixture of 41 ml toluene, 17 ml water and 8 ml ethanol. 142 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 65 ml ether were added and the mixture was washed three times with 65 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 26 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 15 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 25 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 0.66 g of crude base (44.4% of theory) was obtained and was introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v:v) gave 0.40 g of base, from which 0.36 g (23.4% of theory) (2',5'-difluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 165°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 31:
(2-Benzo[1,3]dioxol-5-ylbenzyl)dimethylamine hydrochloride

1.71 g (8.24 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.10 g (5.49 mmol) 4-bromo-1,2-(methylenedioxy)-benzene and 1.94 g (18.3 mmol) sodium carbonate were dissolved in a mixture of 38 ml toluene, 15 ml water and 8 ml ethanol. 130 mg tetrakis(triphenylphosphine)-palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours. For working up, 55 ml ether were added and the mixture was washed three times with 55 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 22 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 13 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 20 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.46 g of crude base (104% of theory) were obtained and were introduced on to a 3 x 15 cm column packed with silica gel. Elution with ether/n-hexane 1:1 (v:v) gave 1.17 g of base, from which 1.20 g (74.8% of theory) (2-benzo[1,3]dioxol-5-ylbenzyl)dimethyl)amine hydrochloride with a melting point of 181°C were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 32:
1-[2'-(2-Dimethylaminoethyl)biphenyl-3-yl]ethanone hydrochloride

2.13 g (13.0 mol) 3-acetylbenzeneboronic acid, 1.98 g (8.68 mmol) [2-(2-bromophenyl)ethyl]dimethylamine prepared according to example 10 and 3.06 g (28.9 mmol) sodium carbonate were dissolved in a mixture of 60 ml toluene, 23 ml water and 12 ml ethanol. 206 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 90 ml ether were added and the mixture was washed three times with 90 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 35 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 20 ml ether and rendered alkaline (pH approx. 12) with 20 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 40 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 2.08 g of crude base (89.5% of theory) were obtained, from which 1.57 g (59.6 % of theory) 1-[2'-(2-dimethylaminoethyl)biphenyl-3-yl]ethanone hydrochloride with a melting point of 141°C were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 33:
[2-(3',4'-Dimethoxybiphenyl-2-yl)ethyl]dimethylamine hydrochloride

2.22 g (12.2 mmol) 3,4-dimethoxybenzeneboronic acid, 1.86 g (8.14 mmol) of the [2-(2-bromophenyl)ethyl]dimethylamine prepared according to example 10 and 2.87 g (27.1 mmol) sodium carbonate were dissolved in a mixture of 55 ml toluene, 22 ml water and 11 ml ethanol. 193 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.

For working up, 90 ml ether were added and the mixture was washed three times with 90 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 35 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 20 ml ether and rendered alkaline (pH approx. 12) with 20 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 35 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.82 g of crude base (78.0% of theory) were obtained, from which 2.02 g (76.8% of theory) [2-(3',4'-dimethoxybiphenyl-2-yl)ethyl]dimethylamine hydrochloride with a melting point of 179°C were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 34:
[2-(3'-Isopropoxybiphenyl-2-yl)ethyl]dimethylamine hydrochloride

1st stage
Dimethyl 2-(2-dimethylaminoethyl)benzeneboronate

19.0 g (83.2 mmol) of the [2-(2-bromophenyl)ethyl]dimethylamine prepared according to example 10 (2nd stage) were dissolved in 300 ml tetrahydrofuran and the solution was cooled to -70°C in a cooling bath (isopropanol/dry ice). 60 ml (95.7 mmol) butyllithium solution (1.6 M in hexane) were added dropwise under nitrogen such that the temperature did not rise above -60°C. After the mixture had been stirred at -70°C for two hours, 28 ml (250 mmol) trimethyl borate were also added dropwise such that the temperature did not rise above -60°C. The mixture was warmed to 25°C in the course of 15 hours and the solution was concentrated on a rotary evaporator (500 - 10 mbar) without heat being supplied. The residue was taken up in 200 ml n-hexane, the mixture was stirred for one hour and filtered over an inert gas frit under nitrogen and the filtrated was concentrated on a rotary evaporator (500 - 10 mbar) without heat being supplied. 14.1 g dimethyl 2-(2-dimethylaminoethyl)-benzeneboronate (76.5% of theory) were obtained in this manner.

2nd stage
[2-(3'-Isopropoxybiphenyl-2-yl)ethyl]dimethylamine hydrochloride

1.20 g (5.43 mmol) dimethyl 2-(dimethylaminoethyl)benzeneboronate from stage 1, 1.75 g (8.14 mmol) 3-bromoisopropoxybenzene and 1.92 g (18.1 mmol) sodium carbonate were dissolved in a mixture of 37 ml toluene, 15 ml water and 8 ml ethanol. 129 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.

For working up, 60 ml ether were added and the mixture was washed three times with 60 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 23 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 14 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 25 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.32 g of crude base (86.0% of theory) were obtained, from which 1.11 g (63.9% of theory) [2-(3'-isopropoxybiphenyl-2-yl)ethyl]dimethylamine hydrochloride with a melting point of 164°C were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 35:
[2-(4'-Chloro-3'-methoxybiphenyl-2-yl)ethyl]dimethylamine hydrochloride

1.20 g (5.43 mmol) of the dimethyl 2-(dimethylaminoethyl)-benzeneboronate prepared according to example 34 (1st stage), 1.80 g (8.14 mmol) 5-bromo-2-chloroanisole and 1.92 g (18.1 mmol) sodium carbonate were dissolved in a mixture of 37 ml toluene, 15 ml water and 8 ml ethanol. 129 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 60 ml ether were added and the mixture was washed three times with 60 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 23 ml hydrochloric acid (5 wt.%) each time

and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 14 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 25 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.43 g of crude base (90.7% of theory) were obtained, from which 1.34 g (75.6% of theory) [2-(4'-chloro-3'-methoxybiphenyl-2-yl)ethyl]dimethylamine hydrochloride with a melting point of 227°C were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 36:

4-Chloro-2'-(2-dimethylaminoethyl)biphenyl-3-ol hydrochloride

0.58 g (2.01 mmol) of the base of the [2-(4'-chloro-3'-methoxybiphenyl-2-yl)ethyl]dimethylamine hydrochloride prepared according to example 35 were heated under reflux (bath temperature 145°C) with 58 ml hydrogen bromide solution (48 wt.% in water) for two hours.
For working up, the mixture was poured into 700 ml sodium bicarbonate solution (1 M) (pH 7-8) and extracted three times with 100 ml ether each time, the combined organic extracts were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). 0.54 g of crude base (98.0% of theory) was obtained, from which 0.51 g (93.5% of theory) 4-chloro-2'-(2-dimethylaminoethyl)biphenyl-3-ol hydrochloride with a melting point of 164°C was obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 37:
Dimethyl-(3'-nitrobiphenyl-2-ylmethyl)amine hydrochloride

1.04 g (6.20 mmol) 3'-nitrobenzeneboronic acid, 1.21 g (5.64 mmol) of the (2-bromobenzyl)dimethylamine prepared according to example 1 (2nd stage) and 1.99 g (18.8 mmol) sodium carbonate were dissolved in a mixture of 40 ml toluene, 16 ml water and 8 ml ethanol. 134 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 65 ml ether were added and the mixture was washed three times with 65 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 25 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 15 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 25 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 714 mg of crude base (49.3% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v:v) gave 330 mg of base, from which 262 mg (15.9% of theory) dimethyl-(3'-nitrobiphenyl-2-ylmethyl)amine hydrochloride with a melting point of 147°C were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 38:
4-Amino-2'-dimethylaminomethylbiphenyl-3-ol dihydrochloride

2.40 g (6.17 mmol) of the base of the *N*-(2'-dimethylaminomethyl-3-trifluoromethoxybiphenyl-4-yl)acetamide hydrochloride (22) prepared according to example 22 were heated under reflux (bath temperature 160°C) with 110 ml hydrogen bromide solution (33 wt.% in glacial acetic acid) for six hours.
For working up, the mixture was poured into 1,000 ml ether and the supernatant was decanted off. The residue was dissolved in water, the solution was washed three times with 20 ml ether each time, brought to pH 7-8 with sodium bicarbonate solution (1 M) and extracted three times with 40 ml ether each time, the combined organic extracts were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). 1.94 g of crude base (130% of theory) were obtained and were introduced on to a 3 x 30 cm column packed with silica gel. Elution with ether/n-hexane 2:1 (v:v) gave, in addition to 1.72 g of largely unchanged educt, 178 mg of crude base, from which 177 mg (7.5% of theory) 4-amino-2'-dimethylaminomethylbiphenyl-3-ol dihydrochloride, which decomposes on heating from 120°C, were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 39:
(3',5'-Difluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.71 g (8.26 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.06 g (5.51 mmol) bromo-3,5-difluorobenzene and 1.94 g (18.3 mmol) sodium carbonate were dissolved in a

mixture of 38 ml toluene, 15 ml water and 7.5 ml ethanol. 131 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.

For working up, 60 ml ether were added and the mixture was washed three times with 60 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 24 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 25 ml ether and rendered alkaline (pH approx. 12) with 14 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 25 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 1.19 g of crude base (87.6% of theory) were obtained and were introduced on to a 3 x 25 cm column packed with silica gel. Elution with ether/n-hexane 1:3 (v:v) gave 990 mg of base, from which 1.06 g (37.2% of theory) (3',5'-difluorobiphenyl-2-ylmethyl)dimethylamine hydrochloride which decomposes on heating from 190°C were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 40:
(2',5'-Dimethoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride

1.61 g (7.79 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 1.13 g (5.20 mmol) 2-bromo-1,4-dimethoxy-benzene and 1.83 g (17.3 mmol) sodium carbonate were dissolved in a mixture of 35 ml toluene, 14 ml water and 7 ml ethanol. 123 mg tetrakis(triphenylphosphine)palladium(0) were added

under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 55 ml ether were added and the mixture was washed three times with 55 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 22 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 10 ml ether and rendered alkaline (pH approx. 12) with 13 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 20 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 770 mg of crude base (61.0% of theory) were obtained, from which 777 mg (49.7% of theory) (2',5'-dimethoxybiphenyl-2-ylmethyl)dimethylamine hydrochloride with a melting point of 169°C were obtained according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 41:
2'-Dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-ylamine dihydrochloride

6.24 g (30.1 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 5.14 g (20.1 mmol) 2-bromo-4-trifluoromethoxy-phenylamine and 7.09 g (66.9 mmol) sodium carbonate were dissolved in a mixture of 140 ml toluene, 55 ml water and 27 ml ethanol. 476 mg tetrakis(triphenylphosphine)-palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 220 ml ether were added and the mixture was washed three times with 220 ml potassium hydroxide solution

(0.5 M) each time. The organic solution was extracted three times with 90 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 90 ml ether and rendered alkaline (pH approx. 12) with 52 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 90 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary evaporator (500 - 10 mbar). 3.46 g of crude base (55.5% of theory) were obtained and were introduced on to a 4 x 30 cm column packed with silica gel. Elution with ether/n-hexane 1:1 (v:v) gave 1.73 g of base (27.8% of theory). 389 mg 2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-ylamine dihydrochloride with a melting point of 125°C were obtained from 316 mg of this base according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 42:
N-(2'-Dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-yl)acetamide hydrochloride

1.42 g (4.56 mmol) of the base of the 2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-ylamine prepared according to example 41 were heated (bath temperature 140°C) with 80 ml hydrogen bromide solution (33 wt.% in glacial acetic acid) for 24 hours.
For working up, the mixture was poured into 800 ml ether and the supernatant was decanted off. The residue was dissolved in water, the solution was washed three times with 50 ml ether each time, rendered alkaline (pH > 12) with potassium hydroxide solution (1 M) and extracted three times with 50 ml ether each time, the combined organic extracts were dried over anhydrous magnesium sulfate and

filtered and the filtrate was concentrated on a rotary evaporator (500 to 10 mbar). 1.94 g of crude base (130% of theory) were obtained and were introduced on to a 3 x 30 cm column packed with silica gel. Elution with ether gave 940 mg of base (85.1% of theory). 274 mg N-(2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-yl)acetamide hydrochloride with a melting point of 115°C were obtained from 303 mg of this base according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Example 43:
3,5-Dichloro-2'-dimethylaminomethyl-biphenyl-4-ylamine hydrochloride

6.14 g (29.7 mmol) of the dimethyl 2-(dimethylaminomethyl)-benzeneboronate prepared according to example 18 (1st stage), 10.0 g (41.5 mmol) 4-bromo-2,6-dichloroaniline and 10.5 g (98.7 mmol) sodium carbonate were dissolved in a mixture of 100 ml toluene, 40 ml water and 20 ml ethanol. 354 mg tetrakis(triphenylphosphine)palladium(0) were added under nitrogen and the mixture was heated under reflux (bath temperature 110°C) for 16 hours.
For working up, 200 ml ether were added and the mixture was washed three times with 130 ml potassium hydroxide solution (0.5 M) each time. The organic solution was extracted three times with 90 ml hydrochloric acid (5 wt.%) each time and the combined acid phases were washed with 50 ml ether and rendered alkaline (pH approx. 12) with 45 ml sodium hydroxide solution (32 wt.%). The mixture was extracted three times with 100 ml ether each time, the combined organic phases were dried over anhydrous magnesium sulfate and filtered and the filtrate was concentrated on a rotary

evaporator (500 - 10 mbar). 6.88 g of crude base (78.7% of theory) were obtained. 470 mg (54.8% of theory) 3,5-dichloro-2'-dimethylaminomethylbiphenyl-4-ylamine hydrochloride were obtained from 765 mg of this crude product according to example 1 (3rd stage) with chlorotrimethylsilane/water in 2-butanone.

Pharmacological studies

Writhing test in mice

The analgesic activity was investigated on phenylquinone-induced writhing in mice (modified by I.C. Hendershot, J. Forsaith, J. Pharmacol. Exp. Ther. 125, 237-240 (1959)). Male NMRI mice weighing 25-30 g were used for this. Groups of 10 animals per dose of substance received 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) as an intraperitoneal administration 10 minutes after intravenous administration of the test substances. The animals were placed individually in observation cages. The number of pain-induced extension movements (so-called writhing reactions = straightening of the body with stretching out of the hind extremities) 5 - 20 minutes after the administration of phenylquinone was counted by means of a push-button counter. Animals which receive only physiological saline solution were also run as a control. All the substances were tested in the standard dosage of 10 mg/kg. The percentage inhibition (% inhibition) of the writhing reaction by a substance was calculated in accordance with the following equation:

$$\% \text{ inhibition} = 100 - \frac{\text{writhing reactions of the treated animals}}{\text{writhing reactions of the control animals}} * 100$$

For some substances, the ED_{50} values with 95% confidence limits of the writhing reaction were calculated from the

dose-dependent decrease in the writhing reactions compared with phenylquinone control groups investigated in parallel by means of regression analysis (evaluation program of Martens EDV Service, Eckental).

All the compounds according to the invention investigated showed a pronounced analgesic action. The results are summarized in the following table.

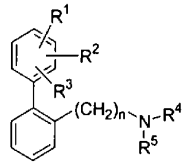
Table 1: Writhing test in mice

Example	% Inhibition of the writhing reaction with 10 mg/kg intravenously	ED_{50} (mg/kg intravenously)
(1)	53	
(2)	89	4.55
(3)	100	0.24
(4)	75	3.95
(5)	68	4.31
(6)	88	4.26
(7)	90	2.55
(8)	67	7.15
(9)	89	2.32
(10)	100	1.70
(11)	74	
(12)	89	1.74
(13)	81	5.30
(14)	100	2.28
(15)	52	3.66
(16)	89	4.59
(17)	90	
(18)	83	
(19)	86	
(20)	83	4.99

Example	% Inhibition of the writhing reaction with 10 mg/kg intravenously	ED_{50} (mg/kg intravenously)
(21)	53	6.78
(22)	76	6.05
(23)	97	
(24)	99	2.27
(25)	74	
(26)	100	0.75
(27)	89	
(28)	90	
(29)	83	5.71
(30)	89	
(31)	94	
(32)	98	
(33)	89	
(34)	80	
(35)	88	
(36)	93	
(37)	60	
(38)	65	
(39)	80	
(40)	57	
(41)	56	
(42)	44	
(43)	99	

The claims defining the invention are as follows:

1. Substituted 2-aminoalkylbiphenyl derivatives of the general formula I



I,

wherein

n is 1 or 2,

the radical R^1 represents CN, NO_2, SO_2CH_3, SO_2CF_3, -O-aryl, -O-C_{1-6}-alkylene-aryl, $NR^{6a}R^{7a}$, an aryl, an acetyl, an acetamidyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radical R^2 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

or R^1 and R^2 together in each case denote the group OCH_2O, OCH_2CH_2O, CH=CHO, $CH=C(CH_3)O$ or CH=CHNH,

the radical R^3 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radicals R^4, R^5, which are identical or different, represent H, or represent a C_{1-6}-alkyl radical,

the radicals R^6, R^7 which are identical or different, represent H, a C_{1-6}-alkyl, an aryl radical or an aryl radical bonded via a C_{1-6} alkylene group,

the radical R^{6a} represents H, a C_{1-6}-alkyl radical, an aryl radical or an aryl radical bonded via a C_{1-6} alkylene group,

the radical R^{7a} represents a C_{1-6}-alkyl radical, an aryl radical or an aryl radical bonded via a C_{1-6} alkylene group,

in the form of their bases and/or salts of physiologically tolerated acids, the compound 4-chloro-2'-dimethylaminomethylbiphenyl-2-carbonitrile being excluded.

2. Substituted 2-aminoalkylbiphenyl derivatives according to claim 1, wherein the radicals R^2 and/or R^3 represent a C_{1-3}-alkyl radical, and the other substituents and n have the meaning according to the general formula I.

3. Substituted 2-aminoalkylbiphenyl derivatives according to claim 1, wherein the radicals R^1, R^2 and/or R^3 represent an aryl radical bonded via a C_{1-3} alkylene group and the other substituents and n have the meaning according to the general formula I.

4. Substituted 2-aminoalkylbiphenyl derivatives according to any one of claims 1 to 3, wherein the radicals R^4 and/or R^5 represent a C_{1-3}-alkyl radical and the other substituents and n have the meaning according to the general formula I.

5. Substituted 2-aminoalkylbiphenyl derivatives according to any one of claims 1 to 4, wherein the radicals R^6 and/or R^7 represent a C_{1-3}-alkyl radical and the other substituents and n have the meaning according to the general formula I.

6. Substituted 2-aminoalkylbiphenyl derivatives according to any one of claims 1 to 4, wherein the radicals R^6 and/or R^7 represent an aryl radical bonded via a C_{1-3}-alkylene group and the other substituents and n have the meaning according to the general formula I.

7. Substituted 2-aminoalkylbiphenyl derivatives according to claim 1, selected from:

dimethyl-[2-(2-methylbenzofuran-4-yl)benzyl]amine and the corresponding hydrochloride;

dimethyl-(4'-nitro-3'-trifluoromethylbiphenyl-2-ylmethyl)-amine and the corresponding hydrochloride;

N-(2'-dimethylaminomethyl-3-trifluoromethoxybiphenyl-4-yl)acetamide and the corresponding hydrochloride;

[2-(1*H*-indol-5-yl)benzyl]dimethylamine and the corresponding hydrochloride;

(4'-methanesulfonylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2-benzo[1,3]dioxol-5-ylbenzyl)dimethylamine and the corresponding hydrochloride;

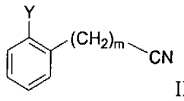
1-[2'-(2-dimethylaminoethyl)biphenyl-3-yl]ethanone and the corresponding hydrochloride;

dimethyl-(3'-nitrobiphenyl-2-ylmethyl)amine and the corresponding hydrochloride; and

N-(2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-yl)acetamide and the corresponding hydrochloride.

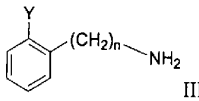
8. A substituted 2-aminoalkylbiphenyl derivative of general formula I as defined in claim 1, substantially as hereinbefore described with reference to any one of the examples.

9. A process for the preparation of substituted 2-aminoalkylbiphenyl derivatives of the general formula I according to any one of claims 1 to 7, wherein compounds of the general formula II



II

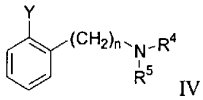
wherein Y denotes Cl, Br or I and m denotes 0 or 1, are reduced in solution with a reducing agent to give compounds of the general formula III,



III

wherein n denotes 1 or 2, and these are purified and isolated by conventional methods,

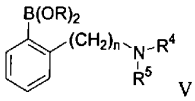
the compounds of the general formula III are reacted with aliphatic C_{1-6}-aldehydes in the presence of a reducing agent to give compounds of the general formula IV



IV

wherein R^4 and R^5 have the meaning according to the general formula I according to claim 1, and these are purified and isolated by conventional methods,

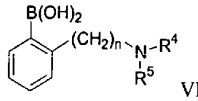
the compounds of the general formula IV are converted by halogen-metal exchange and subsequent reaction with a boric acid ester at a temperature of ≤ 0°C to give compounds of the general formula V,



V

wherein R denotes a C_{1-6} alkyl radical, and these are isolated and purified by conventional methods or employed in the following reaction step without further purification,

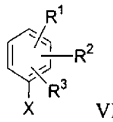
the compounds of the general formula V are reacted with aqueous acids to give compounds of the general formula VI



VI

and these are purified and isolated by conventional methods,

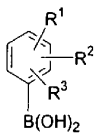
the compounds of the general formula V or VI are reacted in a transition metal-catalysed reaction in an aliphatic ether, a hydrocarbon, an alcohol, a chlorinated hydrocarbon, water or mixtures of these solvents at temperatures between 20 and 150°C with compounds of the general formula VII



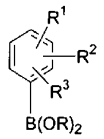
VII,

wherein X denotes Cl, Br, I or $OSO_2C_pF_{(2p+1)}$ and the radicals R^1 to R^3 have the meaning according to the general formula I according to claim 1, to give compounds of the general formula I, and these are purified and isolated by conventional methods, or

the compounds of the general formula VIII or IX



VIII



IX

wherein R^1 to R^3 have the meaning according to the general formula I according to claim 1, are reacted in a transition metal-catalysed reaction in an aliphatic ether, a hydrocarbon, an alcohol, a chlorinated hydrocarbon, water or mixtures of these solvents at temperatures between 20 and 150°C with compounds of the general formula III or IV to give compounds of the general formula I, and these are purified and isolated by conventional methods.

10. A process according to claim 9, wherein the compounds of the general formula II are reduced with lithium aluminium hydride and/or diisobutylaluminium hydride.

11. A process according to claim 9 or 10, wherein the compounds of the general formula III are reacted with aliphatic C_{1-6}-aldehydes in the presence of formic acid and/or sodium borohydride.

12. A process according to any one of claims 9 to 11, wherein the halogen-metal exchange is carried out with magnesium and/or butyllithium.

13. A process according to any one of claims 9 to 12, wherein the boric acid ester is a trialkyl borate.

14. A process according to claim 13, wherein the trialkyl borate is trimethyl borate.

15. A process according to any one of claims 9 to 14, wherein the compounds of the general formula V are reacted with hydrochloric acid to give compounds of the general formula VI.

16. A process according to any one of claims 9 to 15, wherein the compounds of the general formula V or VI are reacted in a reaction catalysed by palladium (0) compounds and/or by palladium (II) salts.

17. A process according to claim 16, wherein the reaction is catalysed by tetrakis(triphenylphosphine)palladium, bis(dibenzylideneacetone)palladium, elemental palladium on active charcoal, palladium(II) chloride and/or palladium(II) acetate.

18. A process according to any one of claims 9 to 15, wherein the compounds of the general formula VIII or IX are reacted in a reaction catalysed by palladium(0) compounds and/or by palladium(II) salts.

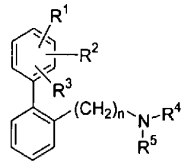
19. A process according to claim 18, wherein the reaction is catalysed by tetrakis(triphenylphosphine)palladium, bis(dibenzylideneacetone)palladium, elemental palladium on active charcoal, palladium(II) chloride and/or palladium(II) acetate.

20. A process according to any one of claims 9 to 19, wherein the transition metal-catalysed reaction is carried out in 1,4-dioxane, tetrahydrofuran, toluene, hexane, ethanol, isopropanol, chloroform, methylene chloride, water or mixtures of these solvents.

21. A process for preparing substituted 2-aminoalkylbiphenyl derivatives of formula I as defined in claim 1, substantially as hereinbefore described with reference to any one of the examples.

22. A substituted 2-aminoalkylbiphenyl derivatives of formula I as defined in claim 1 prepared according to the process of any one of claims 9 to 21.

23. Medicaments comprising, as the pharmaceutical active compound, at least one substituted 2-aminoalkylbiphenyl derivative of the general formula I



I,

wherein

n is 1 or 2,

the radical R^1 represents F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl radical, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radical R^2 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

or R^1 and R^2 together in each case denote the group OCH_2O, OCH_2CH_2O, CH=CHO, $CH=C(CH_3)O$ or CH=CHNH,

the radical R^3 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radicals R^4, R^5, which are identical or different, represent H, or represent a C_{1-6}-alkyl radical,

the radicals R^6, R^7 which are identical or different, represent H, a C_{1-6}-alkyl-, an aryl or an aryl radical bonded via a C_{1-6} alkylene group,

in the form of its base and/or salt of a physiologically tolerated acid and optionally further active compounds and/or auxiliary substances.

24. Medicament according to claim 23 comprising, as the pharmaceutical active compound, at leat one substituted 2-aminoalkylbiphenyl derivative of the general formula I selected from the group consisting of

(3'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-chlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-3-ol and the corresponding hydrochloride;

(2'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-chlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-chloro-4'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-methoxybiphenyl-2-ylethyl)dimethylamine and the corresponding hydrochloride;

dimethyl-[2-(2-methylbenzofuran-4-yl)benzyl]amine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-2-carbaldehyde and the corresponding hydrochloride;

(3'-difluoromethylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-3-carbaldehyde and the corresponding hydrochloride;

(3',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3',5'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

dimethyl-(4'-nitro-3'-trifluoromethylbiphenyl-2-ylmethyl)amine and the corresponding hydrochloride;

(3',4'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-fluoro-3'-trifluoromethylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-chloro-3'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

N-(2'-dimethylaminomethyl-3-trifluoromethoxybiphenyl-4-yl)acetamide and the corresponding hydrochloride;

(3'-isopropoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding and the corresponding hydrochloride;

2'-(2-dimethylaminoethyl)biphenyl-3-ol and the corresponding hydrochloride;

4-chloro-2'-dimethylaminomethylbiphenyl-3-ol and the corresponding hydrochloride;

[2-(1*H*-indol-5-yl)benzyl]dimethylamine and the corresponding hydrochloride;

(4'-methanesulfonylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',3'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',5'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2-benzo[1,3]dioxol-5-ylbenzyl)dimethylamine and the corresponding hydrochloride;

1-2'-(2-dimethylaminoethyl)biphenyl-3-yl]ethanone and the corresponding hydrochloride;

[2-(3'-4'-dimethoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride;

[2-(3'-isopropoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride;

[2-(4'-chloro-3'-methoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride;

4-chloro-2'-(2-dimethylaminoethyl)biphenyl-3-ol and the corresponding hydrochloride;

dimethyl-(3'-nitrobiphenyl-2-ylmethyl)amine and the corresponding hydrochloride;

4-amino-2'-dimethylaminomethylbiphenyl-3-ol and the corresponding dihydrochloride;

(3',5'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',5'-dimethoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

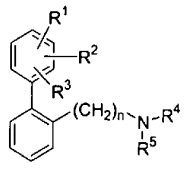
2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-ylamine and the corresponding dihydrochloride;

N-(2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-yl)acetamide and the corresponding hydrochloride; and

3,5-dichloro-2'-dimethylaminomethyl-biphenyl-4-ylamine and the corresponding hydrochloride.

25. Medicament according to claim 23 or 24 for the treatment/control of pain, inflammatory reactions, allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing mental illnesses or epilepsy.

26. Use of at least one substituted 2-aminoalkylbiphenyl derivative of the general formula I



I,

wherein

n is 1 or 2,

the radical R^1 represents F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl radical, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radical R^2 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

or R^1 and R^2 together in each case denote the group OCH_2O, OCH_2CH_2O, CH=CHO, $CH=C(CH_3)O$ or CH=CHNH,

the radical R^3 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radicals R^4, R^5, which are identical or different, represent H, or represent a C_{1-6}-alkyl radical,

the radicals R^6, R^7 which are identical or different, represent H, a C_{1-6}-alkyl-, an aryl or an aryl radical bonded via a C_{1-6} alkylene group,

in the form of their bases and/or salts or physiologically tolerated acids and optionally further active compounds and/or auxiliary substances,

for the preparation of a medicament for treatment/control for/of pain, inflammatory reactions, allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses or epilepsy.

27. The use according to claim 26, wherein one or more substituted 2-aminoalkylbiphenyl derivative of the general formula I are selected from the group consisting of

(3'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-chlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-3-ol and the corresponding hydrochloride;

(2'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-chlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-chloro-4'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-methoxybiphenyl-2-ylethyl)dimethylamine and the corresponding hydrochloride;

dimethyl-[2-(2-methylbenzofuran-4-yl)benzyl]amine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-2-carbaldehyde and the corresponding hydrochloride;

(3'-difluoromethylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-3-carbaldehyde and the corresponding hydrochloride;

(3',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3',5'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

dimethyl-(4'-nitro-3'-trifluoromethylbiphenyl-2-ylmethyl)amine and the corresponding hydrochloride;

(3',4'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-fluoro-3'-trifluoromethylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-chloro-3'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

N-(2'-dimethylaminomethyl-3-trifluoromethoxybiphenyl-4-yl)acetamide and the corresponding hydrochloride;

(3'-isopropoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding and the corresponding hydrochloride;

2'-(2-dimethylaminoethyl)biphenyl-3-ol and the corresponding hydrochloride;

4-chloro-2'-dimethylaminomethylbiphenyl-3-ol and the corresponding hydrochloride;

[2-(1*H*-indol-5-yl)benzyl]dimethylamine and the corresponding hydrochloride;

(4'-methanesulfonylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',3'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',5'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2-benzo[1,3]dioxol-5-ylbenzyl)dimethylamine and the corresponding hydrochloride;

1-2'-(2-dimethylaminoethyl)biphenyl-3-yl]ethanone and the corresponding hydrochloride;

[2-(3'-4'-dimethoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride;

[2-(3'-isopropoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride;

[2-(4'-chloro-3'-methoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride;

4-chloro-2'-(2-dimethylaminoethyl)biphenyl-3-ol and the corresponding hydrochloride;

dimethyl-(3'-nitrobiphenyl-2-ylmethyl)amine and the corresponding hydrochloride;

4-amino-2'-dimethylaminomethylbiphenyl-3-ol and the corresponding dihydrochloride;

(3',5'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

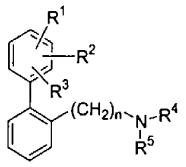
(2',5'-dimethoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-ylamine and the corresponding dihydrochloride;

N-(2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-yl)acetamide and the corresponding hydrochloride; and

3,5-dichloro-2'-dimethylaminomethyl-biphenyl-4-ylamine and the corresponding hydrochloride.

28. A method for treatment/control for/of pain, inflammatory reactions, allergic reactions, depressions, drug and/or alcohol abuse, gastritis, diarrhoea, urinary incontinence, cardiovascular diseases, respiratory tract diseases, coughing, mental illnesses or epilepsy in a subject, said method comprising administering to said subject at least one substituted 2-aminoalkylbiphenyl derivative of the general formula I



I,

wherein

n is 1 or 2,

the radical R^1 represents F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl radical, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radical R^2 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

or R^1 and R^2 together in each case denote the group OCH_2O, OCH_2CH_2O, CH=CHO, $CH=C(CH_3)O$ or CH=CHNH,

the radical R^3 represents H, F, Cl, Br, CN, NO_2, CHO, SO_2CH_3, SO_2CF_3, OR^6, NR^6R^7, a C_{1-6}-alkyl, an aryl, an acetyl, an acetamidyl, a benzoyl or an aryl radical bonded via a C_{1-6} alkylene group,

the radicals R^4, R^5, which are identical or different, represent H, or represent a C_{1-6}-alkyl radical,

the radicals R^6, R^7 which are identical or different, represent H, a C_{1-6}-alkyl-, an aryl or an aryl radical bonded via a C_{1-6} alkylene group,

in the form of their bases and/or salts or physiologically tolerated acids and optionally further active compounds and/or auxiliary substances,

or a medicament according to claim 23 or 24.

29. The method according to claim 28, wherein one or more substituted 2-aminoalkylbiphenyl derivative of the general formula I are selected from the group consisting of

(3'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-chlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-3-ol and the corresponding hydrochloride;

(2'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-chlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-chloro-4'-fluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3'-methoxybiphenyl-2-ylethyl)dimethylamine and the corresponding hydrochloride;

dimethyl-[2-(2-methylbenzofuran-4-yl)benzyl]amine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-2-carbaldehyde and the corresponding hydrochloride;

(3'-difluoromethylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethylbiphenyl-3-carbaldehyde and the corresponding hydrochloride;

(3',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(3',5'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

dimethyl-(4'-nitro-3'-trifluoromethylbiphenyl-2-ylmethyl)amine and the corresponding hydrochloride;

(3',4'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-fluoro-3'-trifluoromethylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(4'-chloro-3'-methoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

N-(2'-dimethylaminomethyl-3-trifluoromethoxybiphenyl-4-yl)acetamide and the corresponding hydrochloride;

(3'-isopropoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding and the corresponding hydrochloride;

2'-(2-dimethylaminoethyl)biphenyl-3-ol and the corresponding hydrochloride;

4-chloro-2'-dimethylaminomethylbiphenyl-3-ol and the corresponding hydrochloride;

[2-(1*H*-indol-5-yl)benzyl]dimethylamine and the corresponding hydrochloride;

(4'-methanesulfonylbiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',4'-dichlorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',3'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',5'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2-benzo[1,3]dioxol-5-ylbenzyl)dimethylamine and the corresponding hydrochloride;

1-2'-(2-dimethylaminoethyl)biphenyl-3-yl]ethanone and the corresponding hydrochloride;

[2-(3'-4'-dimethoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride;

[2-(3'-isopropoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride;

[2-(4'-chloro-3'-methoxybiphenyl-2-yl)ethyl]dimethylamine and the corresponding hydrochloride;

4-chloro-2'-(2-dimethylaminoethyl)biphenyl-3-ol and the corresponding hydrochloride;

dimethyl-(3'-nitrobiphenyl-2-ylmethyl)amine and the corresponding hydrochloride;

4-amino-2'-dimethylaminomethylbiphenyl-3-ol and the corresponding dihydrochloride;

(3',5'-difluorobiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

(2',5'-dimethoxybiphenyl-2-ylmethyl)dimethylamine and the corresponding hydrochloride;

2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-ylamine and the corresponding dihydrochloride;

N-(2'-dimethylaminomethyl-5-trifluoromethoxybiphenyl-2-yl)acetamide and the corresponding hydrochloride; and

3,5-dichloro-2'-dimethylaminomethyl-biphenyl-4-ylamine and the corresponding hydrochloride.

Dated 5 October, 2004

Grunenthal GmbH

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON