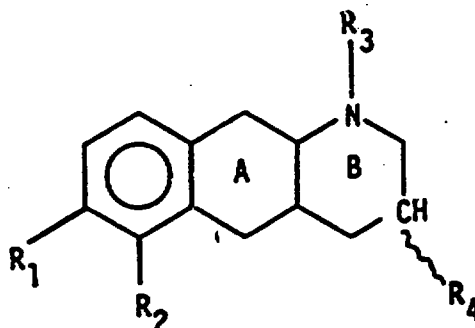


Description

The present invention relates to novel 1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline derivatives having valuable pharmaceutical properties, processes for the production of said derivatives, pharmaceutical compositions comprising said derivatives and the use of said derivatives as pharmaceuticals.

More particularly the present invention provides benzo[g]quinolines of formula I,



(I)

wherein the rings A and B are trans-fused and wherein

R_1 and R_2 are each independently hydrogen, hydroxy or methoxy, with the proviso that R_1 and R_2 may not both be hydrogen;

R_3 is hydrogen or C_{1-4} alkyl;

R_4 is $-\text{COOH}$, $-\text{CH}_2\text{OR}_8$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_9)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$.

R_5 is hydrogen or C_{1-3} alkyl,

R_6 is hydrogen or C_{1-3} alkyl and

R_7 is hydrogen, C_{1-3} alkyl, phenyl or pyridyl, said phenyl or pyridyl being optionally substituted by halogen, methyl or methoxy or

R_6 and R_7 together are $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$ or $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$,

R_8 is C_{1-4} alkyl or pyridyl, said pyridyl being optionally substituted by halogen, methyl or methoxy, and

R_9 and R_{10} are each independently hydrogen or C_{1-3} alkyl or together are $-(\text{CH}_2)_4-$ or $-(\text{CH}_2)_5-$,

as well as the physiologically-hydrolysable and -acceptable esters thereof.

"Halogen" as used herein means fluorine, chlorine or bromine. "Pyridyl" includes 2-, 3- and 4-pyridyl.

By the term "physiologically-hydrolysable and -acceptable esters" is meant esters with acids or alcohols which are hydrolysable under physiological conditions to yield acids and alcohols which are themselves physiologically acceptable, i.e. which are non-toxic at the desired dosage levels. Such esters may be obtained by acylation of benzo[g]quinolines in accordance with the invention bearing one or more hydroxy residues, e.g. hydroxy and/or hydroxymethyl groups at the 3-, 6- and/or 7-position and/or esterification of benzo[g]quinolines in accordance with the invention bearing an acidic residue, e.g. a carboxy group at the 3-position. Such esters include esters with mono- and di-carboxylic acids in particular carboxylic acids having 2 to 5 carbon atoms, as well as esters with aliphatic alcohols having 1 to 4 carbon atoms.

In formula I the following significances as well as combinations thereof are preferred:

1. R_1 and R_2 are independently hydrogen or hydroxy. Most preferably one is hydrogen and the other is hydroxy.

2. R_3 is C_{1-4} alkyl, especially n-propyl.

3. R_4 is other than $-\text{COOH}$; and is especially $-\text{CON}(\text{R}_9)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$, more especially $-\text{CH}_2\text{SR}_8$ or $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$, most especially $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$.

4. R_5 is hydrogen.

5. R_6 is hydrogen and R_7 is pyridyl optionally substituted by halogen, methyl, or methoxy; especially pyridyl optionally mono-substituted by halogen, methyl or methoxy; more especially 3-pyridyl mono-substituted in the para-position by methoxy.

6. R_8 is C_{1-4} alkyl, especially methyl.

7. R_9 is hydrogen or C_{1-4} alkyl; especially C_{1-4} alkyl; in particular ethyl, and R_{10} is hydrogen or C_{1-4} alkyl; especially C_{1-4} alkyl; in particular ethyl.

One group of compounds in accordance with the present invention comprises benzo[g]quinolines of formula I as illustrated above, wherein

R_1 and R_2 are both hydroxy or both methoxy or one of R_1 and R_2 is hydrogen and the other is hydroxy or methoxy,

R_3 is C_{1-4} alkyl,

R_4 is $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_9)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$,

R_5 is hydrogen or C_{1-3} alkyl,

R_7 is pyridyl optionally substituted by halogen, methyl or methoxy and

R_6 , R_9 and R_{10} have the meanings given for formula I,

as well as the physiologically-hydrolysable and -acceptable esters thereof.

A second group of compounds in accordance with the present invention comprises benzo[g]quinolines of formula I as illustrated above, wherein

R_1 , R_2 and R_3 have the meanings given for formula I,

R_4 is $-\text{COOH}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$, and

R_6 , R_7 , R_8 , R_9 and R_{10} have the meanings given for formula I,

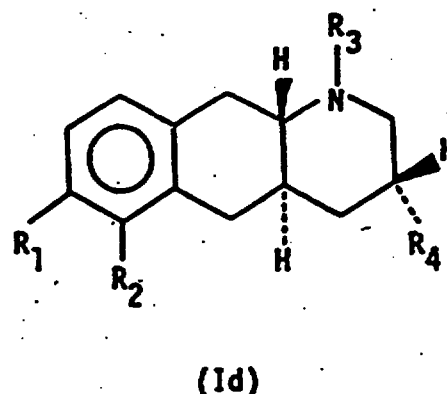
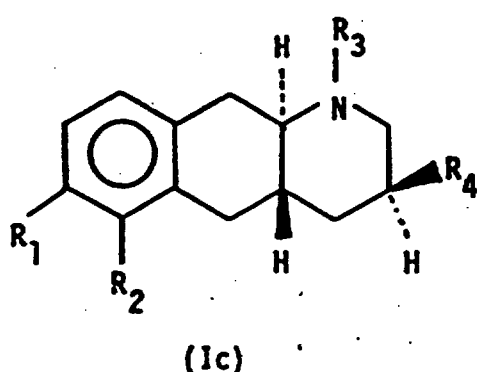
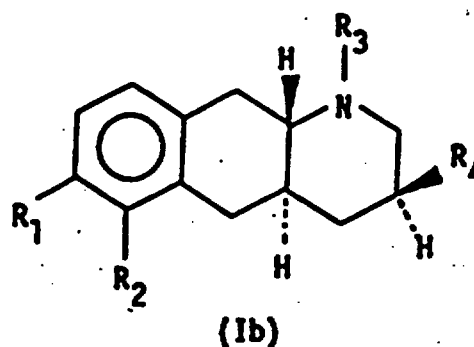
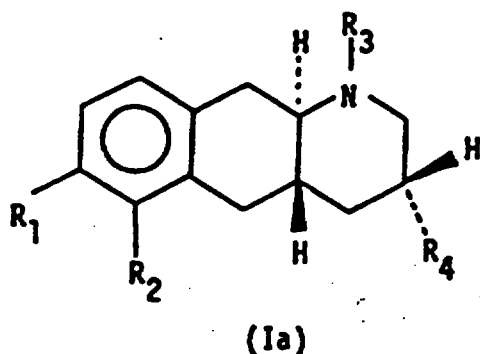
as well as the physiologically-hydrolysable and -acceptable esters thereof.

A further group of compounds in accordance with the present invention comprises benzo[g]quinolines of formula I as illustrated above, wherein one of R_1 and R_2 is hydrogen and the other is hydroxy or methoxy, and R_3 through R_{10} have the meanings given for formula I, as well as the physiologically-hydrolysable and -acceptable salts thereof.

The compounds of the present invention exist in free and in salt form, e.g. as acid addition salts or, when e.g. R_4 is carboxy, as salts with bases. The present invention includes both free and salt, in particular pharmaceutically acceptable salt, forms. Examples of appropriate pharmaceutically acceptable acid addition salt forms include e.g. the hydrochlorides and maleates. Pharmaceutically acceptable salts with bases include e.g. the sodium salts.

The substituent at the 3-position of the benzo[g]quinoline nucleus of the compound of the invention (R_4 in formula I) may be in the α - or β -position. Since the nucleus has the trans-configuration (i.e. the rings A and B in formula I are trans-fused, whereby hydrogen atoms at the 4a- and 10a-positions are also trans to each other) the compounds of the invention exist in four isomeric forms comprising two enantiomeric pairs. Where further substituents are present or where substituents themselves contain optically active centres, further isomeric forms will exist. It will be understood that the present invention includes both individual isomers, as well as racemates (i.e. mixtures comprising a single enantiomeric isomer pair) and other isomeric mixtures.

For formula I, the only optically active centres present in the nucleus are at positions 3, 4a and 10a, giving 4 isomeric forms. These may be represented as follows:



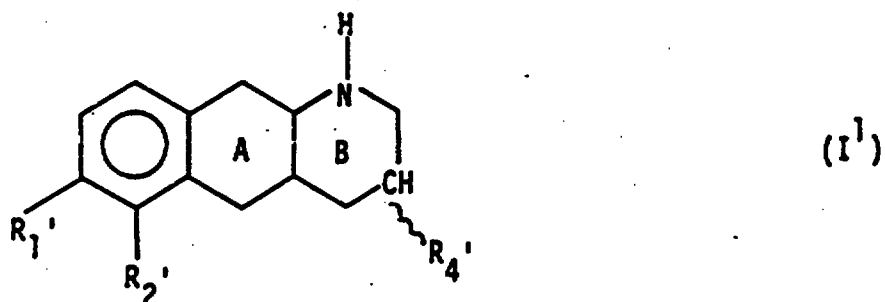
In relation to formula I the present invention includes the individual isomers, i.e. of formula Ia, Ib, Ic or Id, as well as mixtures thereof, especially racemates of formula Ia and Ib or Ic and Id.

For pharmaceutical application individual isomers and racemates of the compounds of the invention are preferred.

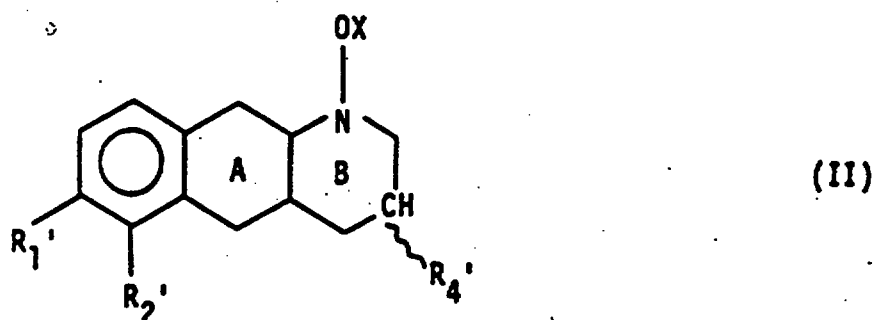
Racemic mixtures are identified throughout the present specification and claims by the name of one of the two enantiomers present (e.g. 3 α , 4 α , 10 $\alpha\beta$ or 3 β , 4 α , 10 $\alpha\beta$), followed by the designation "(Racemate)".

In addition to the foregoing there is also provided a process for the production of the compounds of the invention in free or in salt form which process comprises:

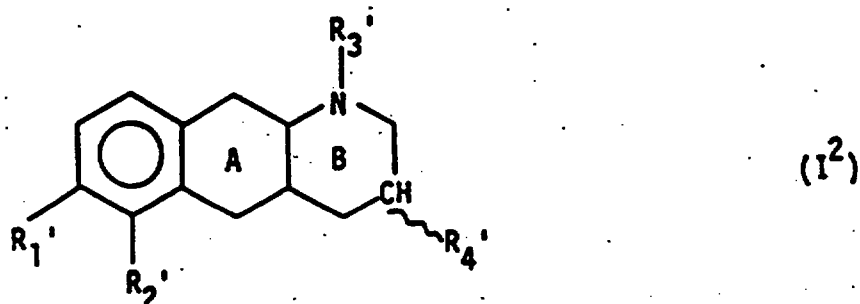
a) for the production of a compound of formula I¹,



15 wherein the rings A and B are trans-fused,
 R_1' and R_2' are each independently hydrogen or methoxy, with the proviso that R_1' and R_2' may not both be hydrogen,
 R_4' is $-\text{CH}_2\text{OR}_5$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$ or $-\text{CH}_2\text{SR}_8$ or esterified $-\text{COOH}$ or esterified $-\text{CH}_2\text{OH}$ and
 R_5 , R_6 , R_7 and R_8 have the meanings given for formula I, subjecting a compound of formula II,

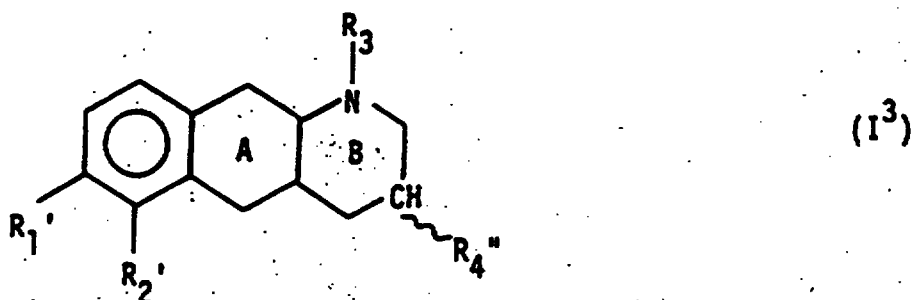


35 wherein the rings A and B are trans-fused, X is benzyl or C_{1-4} alkyl and R_1' , R_2' and R_4' have the meanings given for formula I¹, to cleavage, so as to split off the benzyloxy or C_{1-4} alkoxy group, e.g. the group $-\text{OX}$;
 b) for the production of a compound of formula I²,



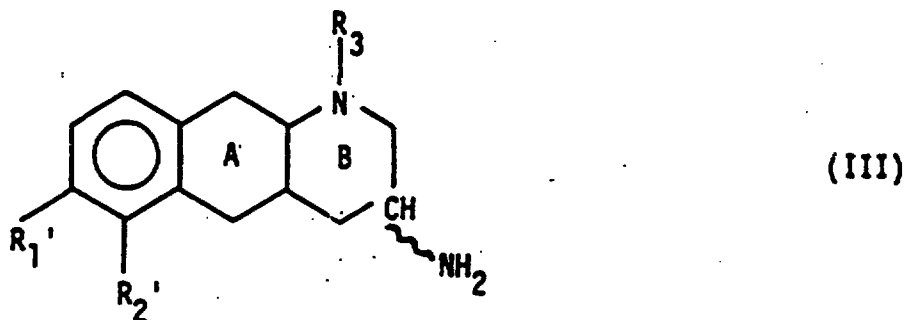
50 wherein the rings A and B are trans-fused, R_3' is C_{1-4} alkyl and R_1' , R_2' and R_4' have the meanings given for formula I¹,

alkylating a compound of formula I¹ as defined above to introduce a C_{1-4} alkyl group at the 1-position;
 c) for the production of a compound of formula I³,



65 wherein the rings A and B are trans-fused,

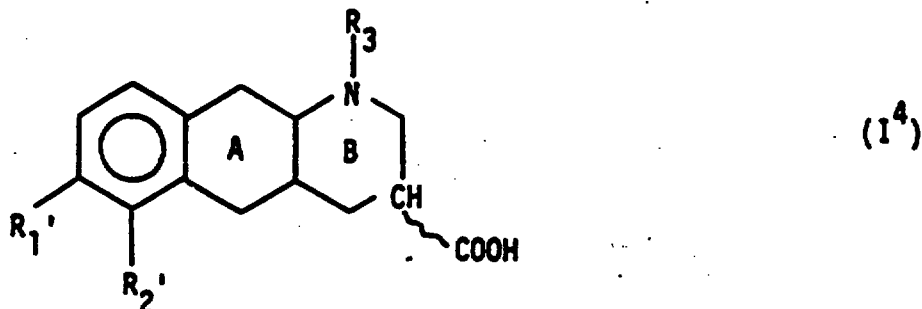
R_4'' is $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$,
 R_9 , R_9 and R_{10} have the meanings given for formula I and
 R_1' and R_2' have the meanings given for formula I',
 reacting a compound of formula III,



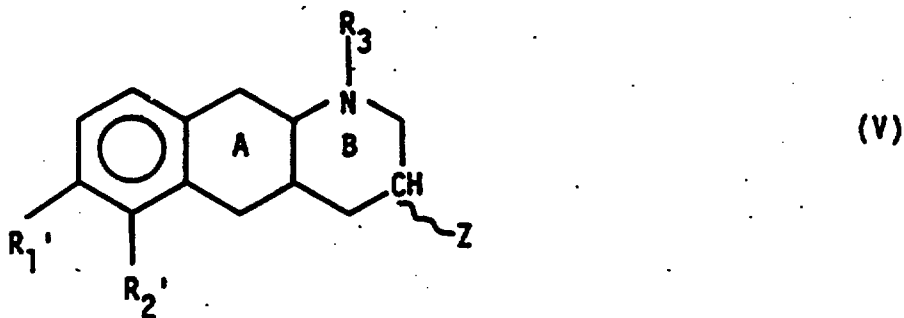
wherein the rings A and B are trans-fused and R_1' , R_2' and R_3 are as defined above for formula I', with an aminosulfonic or aminocarboxylic acid or reactive derivative thereof, e.g. with a compound of formula IVa or IVb,



wherein R_9 and R_{10} have the meanings given for formula I, or a reactive derivative thereof,
 d) for the production of a compound of formula I⁴,

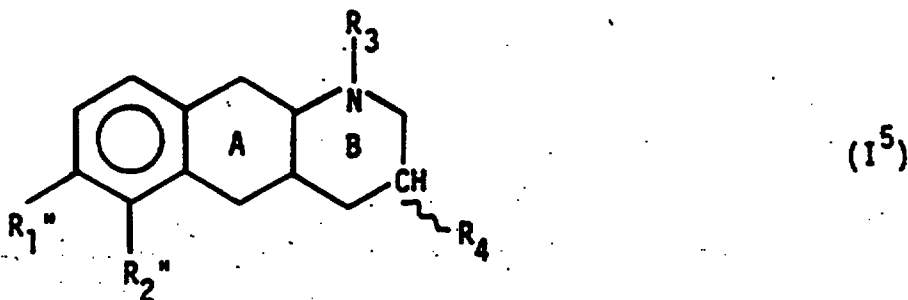


wherein the rings A and B are trans-fused and wherein R_1' and R_2' have the meanings given for formula I' and R_3 has the meaning given for formula I, hydrolysing a compound of formula V,



wherein the rings A and B are trans-fused, Z is an esterified carboxy group, and R_1' , R_2' and R_3 are as defined above for formula I⁴,

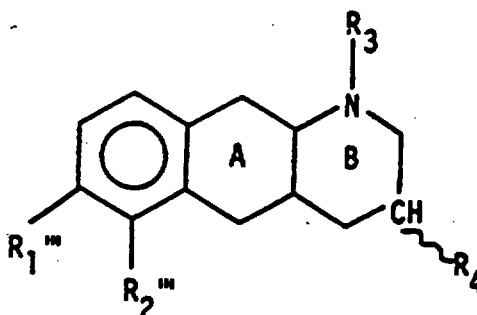
e) for the production of a compound of formula I⁵,



wherein the rings A and B are trans-fused,

R_1'' and R_2'' are each independently hydrogen, hydroxy or methoxy, with the proviso that at least one of R_1'' and R_2'' is hydroxy, and

R_3 and R_4 have the meanings given for formula I,
 5 subjecting a compound of formula VI,



wherein the rings A and B are trans-fused,

R_1''' and R_2''' are each independently hydrogen, hydroxy or methoxy, with the proviso that at least one of R_1''' and R_2''' is methoxy, and

R_3 and R_4 have the meanings given for formula I,
 to ether cleavage; or

f) reacting a benzo[g]quinoline of formula I as hereinbefore defined wherein R_4 is a carboxy group or a reactive derivative thereof with an amine of formula $\text{HN}(R_6)_2$, wherein R_6 and R_7 have the meanings given for formula I, to produce the corresponding amidated benzo[g]quinolines of formula I, or reacting a benzo[g]quinoline of formula I as hereinbefore defined wherein at least one of the residues R_1 , R_2 and R_4 is a hydroxy group (in the case of R_1 and R_2) or hydroxymethyl group (in the case of R_4), or a benzo[g]quinoline of formula I as hereinbefore defined wherein R_4 is a carboxy group or a reactive derivative thereof, with an appropriate acid or reactive derivative thereof, or with an appropriate alcohol, to produce the corresponding acylated or esterified benzo[g]quinoline of formula I; and, recovering the compound of formula I thus obtained in free or salt form.

Processes a) to f) above may be carried out in accordance with standard techniques known in the art.

For process a) benzyloxy and C_{1-4} alkoxy groups at the 1-position, e.g. the group $-\text{OX}$ of formula II, may be split off by reductive cleavage, e.g. by reduction in the presence of zinc and acetic acid.

Introduction of a substituent at the 1-position in accordance with process b) may be carried out e.g. by alkylation or acylation. Introduction of a C_{1-4} alkyl group may be effected e.g. by direct alkylation, reductive alkylation or by acylation followed by reduction of the obtained amide.

Direction alkylation may be effected e.g. by reaction with a compound of formula $\text{R}_3'-\text{Q}$, wherein Q is a leaving group and R_3' is C_{1-4} alkyl. Suitable leaving groups Q include chlorine, bromine and iodine as well as organic sulfonic acid residues such as methyl- and p-toluene-sulfonyloxy residues. The reaction is preferably carried out in the presence of an acid-binding agent, for example an alkali-metal or alkaline-earth metal carbonate, and of an inert organic solvent or diluent such as dimethylformamide.

Reductive alkylation may be effected e.g. by reaction with an aldehyde of formula $\text{R}_3''\text{CHO}$, wherein R_3'' is hydrogen or C_{1-3} alkyl and with concomitant hydrogenation e.g. in the presence of an appropriate catalyst such as palladium on charcoal. The reaction is suitably carried out in the presence of an inert, organic solvent or diluent, for example the corresponding alcohol of formula $\text{R}_3''-\text{CH}_2\text{OH}$, with normal or slightly elevated pressure.

Alkylation by acylation and reduction can be effected e.g. by reaction with an acid halide of the formula $\text{R}_3''\text{COHal}$, wherein R_3'' has the meaning given above and Hal is chlorine or bromine, followed by reduction for example using LiAlH_4 or diborane as reducing agent.

Process c) is carried out by acylation with an appropriate sulfamic or carbamic acid, for example a compound of formula IVa or IVb as defined above, or a reactive derivative thereof. Suitable reactive derivatives include the corresponding acid chlorides and bromides. The reaction is suitably carried out in the presence of an organic base such as triethylamine and in an inert, organic solvent or diluent such as chloroform, at normal or slightly elevated temperature.

Hydrolysis in accordance with process d) may be effected by treatment with an appropriate alkali, or by acid hydrolysis for example in the presence of trifluoroacetic acid.

Ether cleavage in accordance with process e) may be effected e.g. by reaction with HBr , BBr_3 or NaSCH_3 , in the presence of an inert, organic solvent or diluent such as methylene dichloride or DMF. The reaction is suitably carried out at temperatures of from e.g. -70° to 0°C (HBr or BBr_3) or from 100° to reflux (NaSCH_3). Obtained hydroxy groups may readily be converted into other oxy substituents by techniques known in the art, e.g. by acylation in accordance with the following process f).

Amidation or ester formation in accordance with process f) may be carried out using any of the techniques known in the art, for example, where hydroxy groups are to be acylated, by reaction with a

reactive derivative, e.g. the chloride or anhydride, of the selected acid or, where a carboxy group at the 3-position is to be amidated or esterified by reaction of e.g. a corresponding 3-carbonyl-halide or anhydride with the selected amide or alcohol.

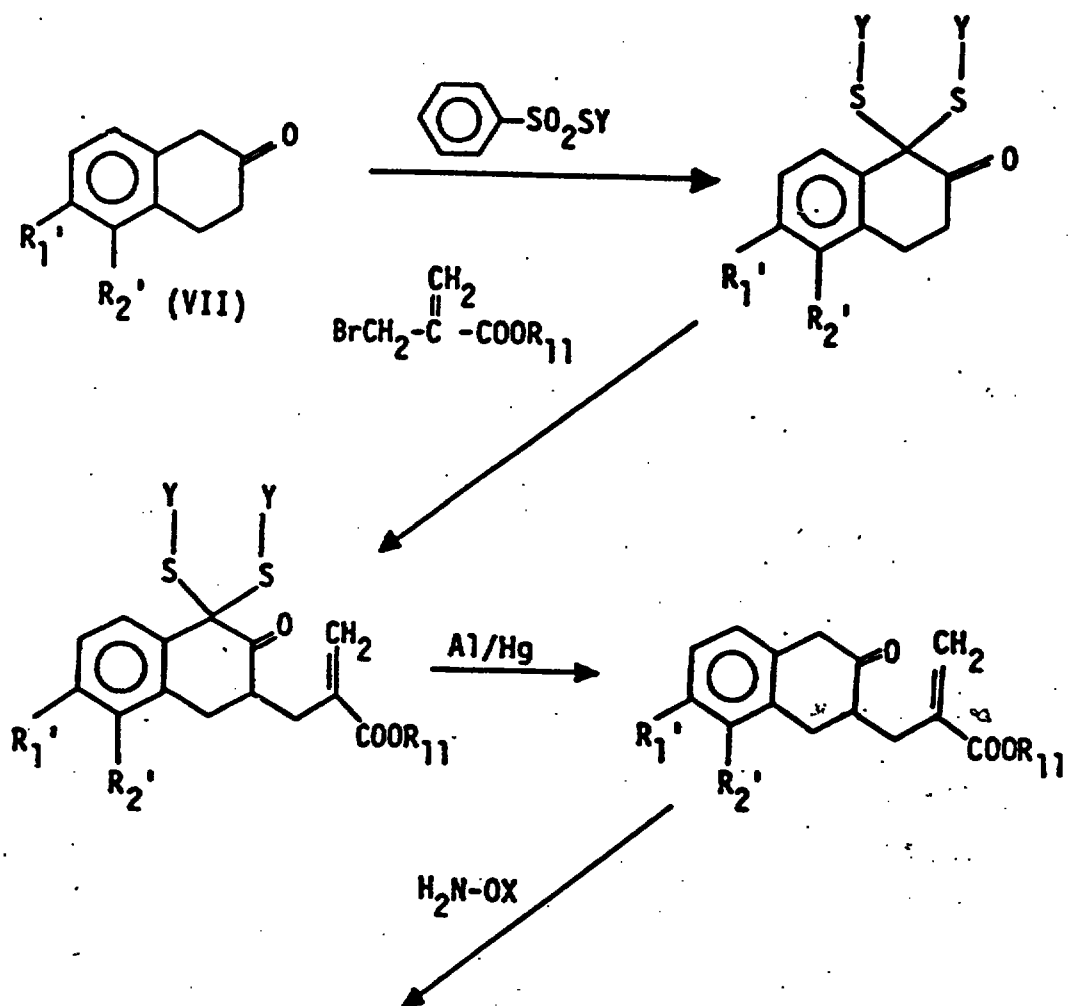
The starting materials for use in the above processes, e.g. the compounds of formulae II, III, V and VI, exist in various isomeric forms corresponding to those hereinbefore described for the products of formula I. Each of the above processes may be carried out using starting materials in the form of one or other of the individual enantiomers, or in the form of mixtures, in particular racemic mixtures thereof. Conveniently the starting materials used are in racemic form. These may be produced in accordance with procedures as hereinafter described.

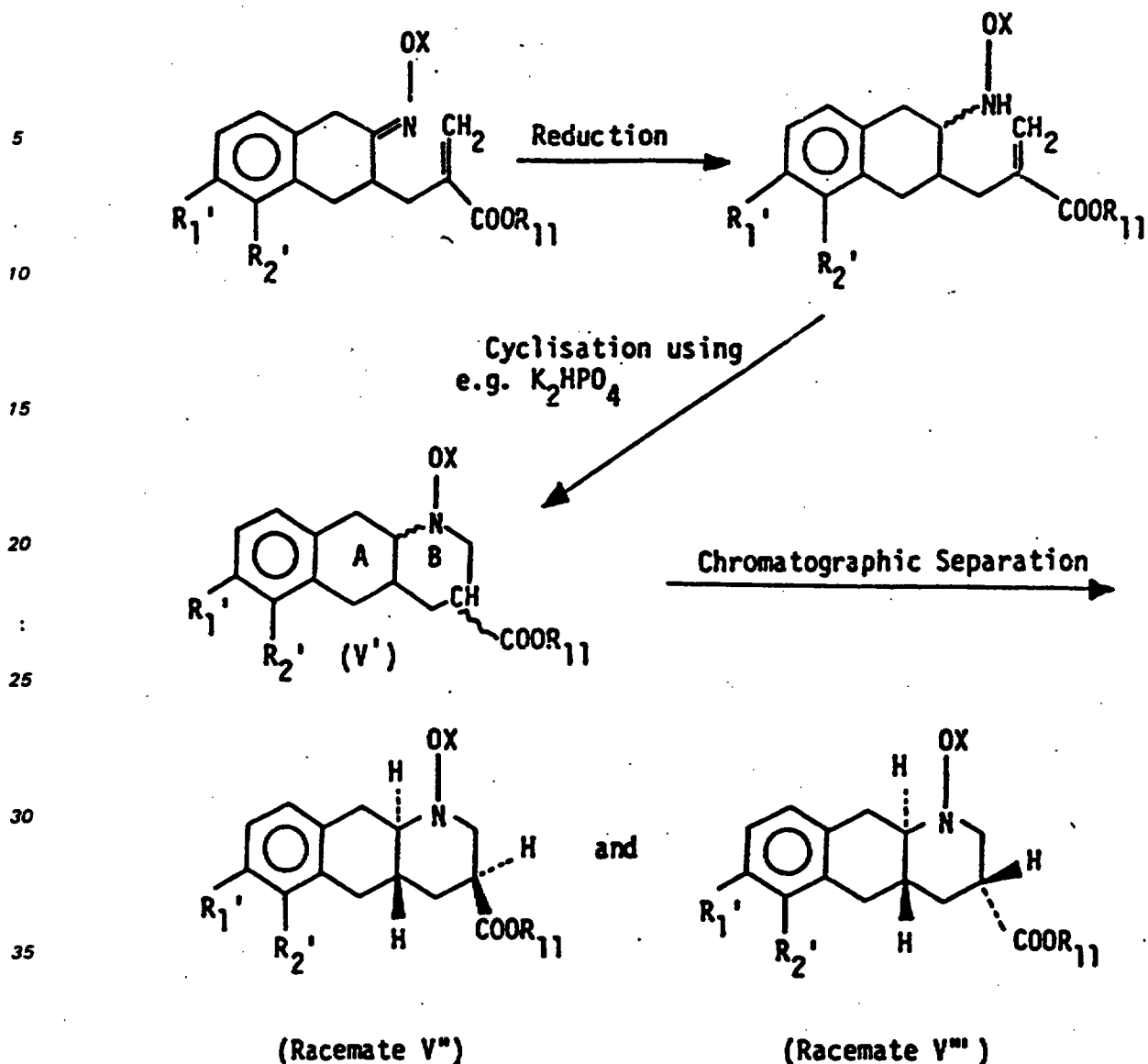
Where diastereomeric mixtures of the starting materials are used, the products too will be in the form of a diastereomeric mixture.

Diastereomers may be separated, e.g. chromatographically to yield racemates free of diastereomeric contaminants. Obtained racemates may be resolved to obtain individual optically active enantiomers using known resolution techniques for example via formation of acid addition salts with optically active acids and resolution of the obtained diastereomeric salt.

The compounds of the invention may be recovered from the initially obtained reaction medium in free form or in salt form, e.g. an acid addition salt form. Alternatively initially obtained salts may be converted into the free form or vice versa.

Starting materials for process a) may be obtained in accordance with known techniques, e.g. for the production of compounds of formula II in accordance with the following reaction sequence.





In the above reaction scheme, R_1' , R_2' and X have the meanings given hereinbefore for formula I', each Y is C_{1-4} alkyl or aryl (in particular phenyl) or both Ys together represent a C_{3-4} alkylene residue and R_{11} is C_{1-4} alkyl (in particular methyl, iso-propyl or t-butyl).

Each step of the above reaction scheme may be carried out in accordance with known techniques e.g. as hereinafter described in the accompanying examples. The starting materials of formula VII are known or may be produced analogously to known procedures.

As explained in example 1f, the initial product of the penultimate step (the compound of formula V', in which the rings A and B are cis- or trans-fused) contains only trace amounts of Racemate V'''. However, the amount of Racemate V''' present can readily be increased by epimerisation, e.g. in an alkaline medium as described e.g. in the following example 5a). For epimerisation R_{11} is preferably methyl.

It will be appreciated that although isolation of racemates is conveniently carried out at the formula V' stage, isolation may be effected at a later stage in synthesis, if desired. Similarly Racemates V'' and V''' can be used directly for further reaction or can be resolved to yield individual enantiomers and further reactions carried out using the enantiomeric forms.

Compounds of formula V', wherein the rings A and B are trans-fused are compounds of formula V as hereinbefore defined. When the residue $-COOR_{11}$ is a physiologically-hydrolysable and -acceptable ester residue, these compounds fall within the scope of formula II, as hereinbefore defined. The further compounds of formula II may be obtained from compounds of formula V by:

- i) reduction to obtain compounds of formula II, wherein R_4' is $-CH_2OH$;
- ii) etherification of compounds obtained in accordance with i) to obtain compounds of formula II, wherein R_4' is $-CH_2OR_5$ and R_5 is C_{1-4} alkyl;
- iii) mesylation of compounds obtained in accordance with i) to obtain corresponding compounds, wherein the substituent at the 3-position is $CH_2SO_2OCH_2-$ and reaction of these with a compound of formula R_6SH to obtain compounds of formula II, wherein R_4' is $-CH_2SR_6$;

- iv) mesylation in accordance with iii) and reaction of the product with an alkali-metal cyanide to obtain compounds of formula II, wherein R_4' is $-\text{CH}_2\text{CN}$;
 v) amidation to obtain compounds of formula II, wherein R_4' is $-\text{CON}(R_5)R_7$;
 vi) trans-esterification to obtain further compounds of formula II, wherein R_4' is esterified $-\text{COOH}$; and
 5 vii) acylation of compounds obtained in accordance with i) to obtain compounds of formula II, wherein R_4' is esterified $-\text{CH}_2\text{OH}$.

All of the reactions i) to vii) may be carried out in accordance with standard procedures e.g. as described in the accompanying examples.

Compounds of formula III as hereinbefore defined can be obtained from compounds of formula V in accordance with standard procedures, e.g. via Curtius reaction.

With the exception of the compounds of formula VII, all the intermediates hereinbefore described are new.

It will further be appreciated that in addition to their pharmaceutical utility as hereinafter described, various of the compounds of formula I are also useful as intermediates for the production of further compounds of formula I. Thus the compounds of formula I¹, I² and I³ may be used as starting materials for process e) and the compounds of formula I⁴ as starting materials for process f).

The following examples are illustrative of the above described processes for the preparation of the compounds of the invention. In these examples, the following abbreviations are used:

20	DMF	= Dimethylformamide
	HMPT	= Hexamethylphosphotriamide
	MeOH	= Methanol
	EtOH	= Ethanol
	THF	= Tetrahydrofuran
25	MS	= Mass spectroscopy.

Example 1

3 α -Methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

17 g of powdered zinc are added to a solution of 3.5 g 1-methoxy-3 α -methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate) in 35 ml of acetic acid and 18 ml H_2O . The reaction mixture is stirred for ca. 15 hours at room temperature, and then filtered and concentrated. The residue is taken up in CH_2Cl_2 , re-filtered and the residue washed with CH_2Cl_2 . The filtrate is extracted using 1N $\text{KHCO}_3/\text{H}_2\text{O}$, the organic phase dried over Na_2SO_4 and evaporated, whereupon the title compounds is obtained as a yellow oil. This crystallises on standing: M.P. = 66–68°C.

The starting material for the above process is obtained as follows:

a) 1,1-Bis(phenylthio)-5-methoxy-2-tetralone

70 g of 5-methoxy-2-tetralone, 150 g benzenesulfonic acid S-phenyl ester and 120 g sodium acetate are stirred for 24 hours in 1.1 litre methanol at room temperature. The title compound precipitates out during the course of reaction and is recovered by concentrating the reaction mixture to 1/2 volume, cooling to 10°C and filtering: M.P. = 139–141°C.

b) β -(1,2,3,4-Tetrahydro-1,1-bis(phenylthio)-2-oxo-5-methoxy-3-naphthyl)- α -methylidene-propionic acid t.butylester

12.6 ml diisopropylamine in 240 ml diethylether are added at -70°C to 53 ml of a 1.6 N solution of n-butyl-lithium in hexane. The mixture is left to warm for 15 minutes to -20°C and is recooled to -90°C . 23.4 g of the product of step a) dissolved in 250 ml THF/25 ml HMTP are then added drop-wise, so that the temperature does not rise above -70°C . After completion of addition, the reaction mixture is allowed to stand for 60 minutes at -70°C and 19.8 g 2-bromo-methylacrylic acid t.-butyl ester in 50 ml THF are added. The temperature is allowed to rise to -20°C and an excess of 2 N HCl is added. The obtained mixture is extracted by partitioning between $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ and the organic phase dried over Na_2SO_4 and evaporated to yield the title compound as a yellow oil, which is crystallised at -20°C from diethyl ether/hexane: M.P. = 120–121°C.

c) β -(1,2,3,4-Tetrahydro-2-oxo-5-methoxy-3-naphthyl)- α -methylidene-propionic acid t.butyl ester

140 g of freshly amalgated aluminium filings are added to 100 g of the product of step b) in 2.7 litres of THF and 300 ml H_2O . The reaction mixture is warmed to 50°C with stirring for 2 hours. The mixture is allowed to cool, and after addition of CH_2Cl_2 , is filtered. The residue is washed several times with CH_2Cl_2 , the filtrate evaporated and the residue extracted by partitioning between $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$. The organic phase is dried over Na_2SO_4 and evaporated. The residue is recrystallised at -20°C from diethyl ether/hexane (preferably with seeding using previously obtained crystals) to yield the title compound: M.P. = 95–96°C.

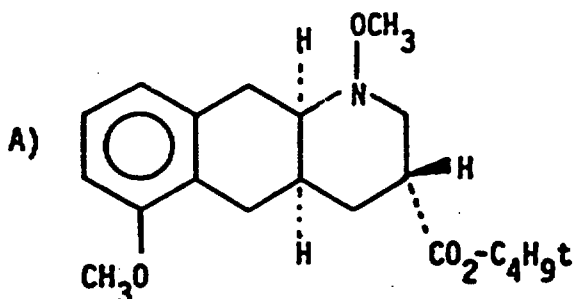
d) β -(1,2,3,4-Tetrahydro-2-methoxyimino-5-methoxy-3-naphthyl)- α -methylidene-propionic acid t.butyl ester

79 g of the product of step c), 41.5 g O-methylhydroxylamine hydrochloride and 44.5 g di-sodium-

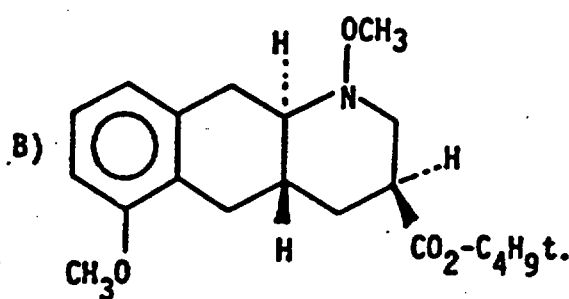
hydrogenphosphate bis-hydrate are stirred for 4 hours at room temperature in 1.6 litres methanol. The reaction mixture is evaporated and the residue extracted by partitioning between $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$. The organic phase is dried over Na_2SO_4 , evaporated and the title compound re-crystallised from hexane: M.P. = 72–73°C.

e) β -(1,2,3,4-Tetrahydro-2-methoxyamino-5-methoxy-3-naphtyl)- α -methylidene-propionic acid t.butyl ester
52 g sodium cyanoborohydride are added to 60 g of the product of step d) dissolved in 2.2 litres methanol. 7.5 N HCl in methanol are added drop-wise, the pH being maintained during the course of reaction at 3 to 4. Reaction is completed after 22 hours. The pH is adjusted to 7 by the addition of buffer and the reaction mixture evaporated and extracted with CH_2Cl_2 . The organic phase is dried over Na_2SO_4 and evaporated, whereupon the title compound is obtained as a diastereomeric mixture. Thin layer chromatographic analysis indicates that minor quantities of the step f) products are already present

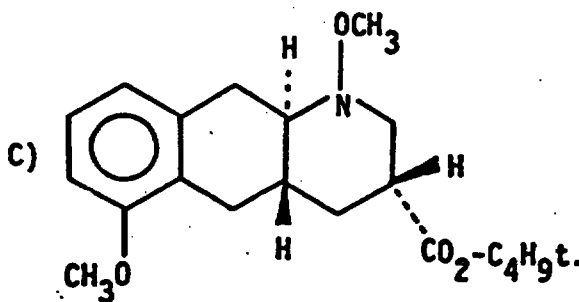
f) 1-Methoxy-3-t.-butyloxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline
90 g potassium hydrogen phosphate are added to a solution of 61.0 g of the product of step e) in 1.2 litres methanol. The reaction mixture is stirred for 3 days at room temperature, evaporated and the residue extracted by partitioning between $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$. The organic phases are dried over Na_2SO_4 and evaporated to yield the title compound as a brown oil. Thin layer chromatography indicates that the product is a diastereomeric mixture comprising four enantiomeric pairs. These are represented by the formulae A to D below, each of the four racemates being represented by the structure for one of the two enantiomers present:



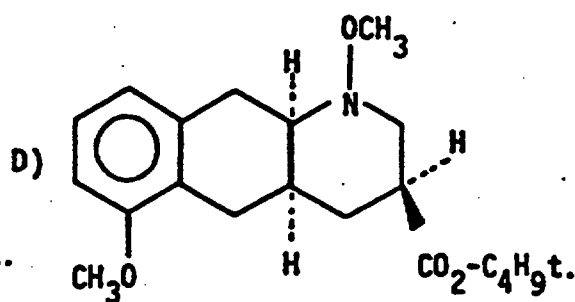
(Racemate) M.P. = 100–101° C



(Racemate) M.P. = 104–105° C



(Racemate) M.P. = 115–117° C



(Racemate) M.P. = 83–84° C

The initially obtained diastereomeric mixture consists chiefly of racemates B and D, with only minor quantities of racemate A and only trace amounts of racemate C. The 4 racemates A through D are readily separated by medium pressure liquid chromatography.

g) 1-Methoxy-3 α -carboxy-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

4 g of racemate B obtained from step f) are dissolved in 40 ml trifluoroacetic acid and the solution is allowed to stand for 75 minutes at room temperature. The reaction mixture is then concentrated and dried under high vacuum to yield the title compound as a grey solid which is then re-crystallised: M.P. = 196–197°C.

h) 1-Methoxy-3 α -methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

An excess of diazomethane in diethylether is added to a solution of 6.6 g of the raw-product obtained in step g) in 50 ml CH_2Cl_2 . After concentration and evaporation of the obtained reaction mixture under high

vacuum; the title compound is obtained as a brown solid. The raw product is employed directly for further reaction as hereinabove described. On re-crystallisation it has an M.P. of 111—112°C.

Example 2

1-n-Propyl-3 α -methoxycarbonyl-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

3.0 g 3 α -methoxycarbonyl-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate) (produced in accordance with example 1) are dissolved in 30 ml n-propanol. 3 ml n-propionaldehyde are added and hydrogenation is effected employing 1.2 g 10% palladium on charcoal with a reaction period of ca. 15 hours. The reaction mixture is filtered and evaporated, whereupon the title compound is obtained as a yellow oil which slowly solidifies. M.P. = 81—83°C.

Example 3

1-n-Propyl-3 α -diethylsulfamoylamino-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

1.5 g of 1-n-propyl-3 α -amino-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate) and 3.0 ml triethylamine are added to a solution of 1.9 g diethylsulfamoyl chloride in 50 ml chloroform, and the reaction mixture is stirred for ca. 15 hours at 50°C. 50 ml 1 N Na₂CO₃ solution are added and the mixture is stirred for 2 hours at room temperature, and extracted by partitioning between CH₂Cl₂/H₂O. The organic phase is dried over Na₂SO₄, evaporated and purified chromatographically, to yield the title compound as a yellow oil, which is crystallised from diethyl ether/hexane at -20°C: M.P. = 88—89°C.

The starting material for the above process is obtained as follows:

a) 1-n-Propyl-3 α -carbazoyl-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

18.5 ml hydrazine hydrate are added to a solution of 3.5 g 1-n-propyl-3 α -methoxycarbonyl-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate) (produced in accordance with example 2) in 60 ml methanol and the reaction mixture is stirred for ca. 15 hours at 50°C. After concentration and drying under high vacuum, the residue is taken up in diethylether, dried over Na₂SO₄ and evaporated to yield the title compound as a yellow oil, which crystallises on standing: M.P. = 84—86°C.

b) 1-n-Propyl-3 α -amino-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

8 ml of 1 N solution of nitrosyl chloride in THF are added at -30°C to a solution of 2.5 g of the product of step a) in 80 ml THF. Reaction is completed within 5 minutes. The obtained reaction mixture is boiled under reflux for 1 hour, 50 ml 2 N HCl are added, the solution is boiled for a further 2 hours under reflux, cooled, concentrated, the residue adjusted to pH 12 by the addition of 2 N NaOH, and extracted with CH₂Cl₂. The organic phase is dried over K₂CO₃ and evaporated to yield the title compound as a brown oil. The product is used directly for further reaction as hereinabove described.

Example 4

1-n-Propyl-3 α -diethylsulfamoylamino-6-hydroxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

2.7 ml borontribromide in 30 ml CH₂Cl₂ are added drop-wise at -30°C to a solution of 1.9 g 1-n-propyl-3 α -diethylsulfamoylamino-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate) (obtained in accordance with example 3) in 70 ml CH₂Cl₂. The reaction mixture is stirred for 4.5 hours at a temperature of from -30°C to -10°C, 100 ml 1 N KHCO₃ are added, the pH adjusted to 12 with 1 N NaOH and the obtained mixture extracted several times with methylene chloride. The organic phases are washed until neutral with H₂O, dried over Na₂SO₄ and concentrated, whereupon a brown foam develops. This is taken up in 80 ml CH₂Cl₂/MeOH (1:1), 9 ml 7N HCl in CH₃OH are added and the whole boiled for 15 minutes under reflux. The product is concentrated, extracted by partitioning between CH₂Cl₂/1N NaOH, the organic phase washed until neutral with H₂O, dried over Na₂SO₄ and evaporated. The solid residue is digested in boiling diethyl ether/hexane, cooled and filtered to yield the title compound as a beige powder: M.P. = 122.5—124°C.

Example 5

3 β -Methylthiomethyl-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

11.6 g zinc powder are added to a solution of 2.4 g 1-methoxy-3 β -methylthiomethyl-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate) in 24 ml acetic acid and 12 ml H₂O. The reaction mixture is stirred for ca. 15 hours at room temperature, filtered and the filtrate concentrated. The residue is taken up in CH₂Cl₂ and filtered again. The filtrate is extracted with 1 N KHCO₃ in H₂O, the organic phase dried and evaporated to yield the title compound: M.P. = 107.5—108.5°C.

The starting material is obtained as follows:

a) 1-Methoxy-3 β -methoxycarbonyl-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

8.5 g of 1-methoxy-3 α -methoxycarbonyl-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]-

quinoline (obtained in accordance with example 1h) are allowed to react for 2 days in a 1 N solution of NaOH in MeOH/H₂O (9:1) at room temperature. Reaction results in hydrolysis of the methoxycarbonyl group as well as partial epimerisation at the 3-position. The reaction mixture is concentrated, adjusted to pH 1—2 by addition of 4 N HCl and extracted several times with CH₂Cl₂/CH₃OH (95:5). The organic phase is dried and evaporated and the raw product reacted with an excess of diazomethane and evaporated. Epimerisation is completed by repeating the above procedure 2x, to yield the title compound, which is finally crystallised from ether/hexane: M.P. = 108—109°C.

b) 1-Methoxy-3β-hydroxymethyl-6-methoxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoline (Racemate)

A solution of 3.1 g of the product of step a) in 50 ml THF is added to a suspension of 0.57 g lithium aluminium hydride in 50 ml THF at room temperature. The reaction mixture is stirred for a further 2 hours at room temperature and 0.6 ml H₂O, and 0.6 ml 20% NaOH followed by a further 2 ml H₂O are added carefully. After 10 minutes the mixture is filtered and the filtrate evaporated to yield the title compound as a white powder: M.P. = 149—151°C.

c) 1-Methoxy-3β-mesyloxymethyl-6-methoxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoline (Racemate)

2.8 g of the product of step b) in 40 ml pyridine are added to 1.6 ml methanesulfonyl chloride at 0°C. The mixture is allowed to stand for ca. 15 hours at room-temperature, whereupon 20 ml of a 1 N NaHCO₃ solution is added and the whole stirred for 30 minutes. The reaction mixture is concentrated and extracted by partitioning between CH₂Cl₂/H₂O. The organic phase is dried and evaporated and the residue crystallised from ethyl acetate to yield the title compound: M.P. = 188—189°C.

d) 1-Methoxy-3β-methylthiomethyl-6-methoxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoline (Racemate)

2.5 g sodium hydride (50% dispersion in oil) are added with ice-cooling to 4 ml methylmercaptan in 20 ml DMF. 3 g of the product of step c) suspended in 30 ml DMF are then added to 0°C and the reaction mixture stirred for a further 2 hours with ice-cooling. The reaction mixture is concentrated under high vacuum and the residue extracted by partitioning between CH₂Cl₂/H₂O. The organic phase is dried and evaporated whereupon the title compound is obtained. The product is used directly for further reaction as hereinabove described.

Example 6

1-n-Propyl-3β-methylthiomethyl-6-methoxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoline (Racemate)

0.87 ml n-propyl iodide and 1.9 g K₂CO₃ are added to 1.9 g of 3β-methylthiomethyl-6-methoxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoline (Racemate) (obtained in accordance with the process of example 5) dissolved in 20 ml DMF and the reaction mixture is stirred for ca. 15 hours at room-temperature, filtered and concentrated under high vacuum. The residue is extracted by partitioning between CH₂Cl₂/H₂O and the organic phase dried and evaporated, whereupon the title compound is obtained as a yellow oil which crystallises on standing: M.P. = 74—75°C.

Example 7

1-n-Propyl-3β-methylthiomethyl-6-hydroxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoline (Racemate)

2.0 g of 1-n-propyl-3β-methylthiomethyl-6-methoxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoline (Racemate) (obtained in accordance with the process of example 6) are dissolved in 100 ml CH₂Cl₂ and a solution of 3.6 ml boron tribromide in 30 ml CH₂Cl₂ are added drop-wise at -30°C. The reaction mixture is stirred for 5 hours at a temperature of from -30° to -10°C. 125 ml KHCO₃ are added, the pH adjusted to 12 by the addition of 2 N NaOH, and the obtained mixture extracted several times with methylene chloride. The organic phases are washed until neutral with H₂O, dried over Na₂SO₄ and concentrated, whereupon a yellow precipitate develops. This is taken up in 100 ml CH₂Cl₂/MeOH (1:1), 10 ml of a 7 N solution of HCl in CH₃OH are added and the obtained mixture boiled for 10 minutes under reflux. The product is concentrated and extracted by partitioning between CH₂Cl₂/1 N NaOH. The organic phase is washed until neutral, dried and evaporated. The solid residue is digested in diethylether and filtered off to yield the title compound as a beige powder: M.P. = 173—174°C.

Example 8

3a-Methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoline (Racemate)

The title compound is obtained analogously to example 1, proceeding via the following intermediates:

a) 1,1-Bis(phenylthio)-6-methoxy-2-tetralone: M.P. = 97—99°C.

b) β-[1,2,3,4-Tetrahydro-1,1-bis(phenylthio)-2-oxo-6-methoxy-3-naphthyl]-α-methylidene-propionic acid t.butyl ester: M.P. = 118—119°C.

c) β-[1,2,3,4-Tetrahydro-2-oxo-6-methoxy-3-naphthyl]-α-methylidene-propionic acid t.butyl ester: M.P. = 58—60°C.

d) β -(1,2,3,4-Tetrahydro-2-methoxyimino-6-methoxy-3-naphthyl)- α -methylidene-propionic acid t.butyl ester: yellow oil.

e) β -(1,2,3,4-Tetrahydro-2-methoxyamino-6-methoxy-3-naphthyl)- α -methylidene-propionic acid t.butyl ester.

f) 1-Methoxy-3-t.butyloxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline is a diastereomeric mixture comprising 4 enantiomeric pairs as follows:

A) 1-Methoxy-3 β -t.butyloxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate): M.P. = 75°C.

B) 1-Methoxy-3 α -t.butyloxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate): M.P. = 94°C.

C) 1-Methoxy-3 β -t.butyloxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate): M.P. = 118°C.

D) 1-Methoxy-3 α -t.butyloxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate): M.P. = 91°C.

The initial diastereomeric mixture consists mainly of racemates B and D, with only minor quantities of A and trace amounts of C.

Individual racemates may readily be separated by medium pressure liquid chromatography.

Racemate B is used for further synthesis as follows:

g) 1-Methoxy-3 α -carboxy-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate).

h) 1-Methoxy-3 α -methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate). M.P. = 101—103°C. (Starting material).

Example 9

1-n-Propyl-3 α -methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

The title compound is produced analogously to example 2 starting from the product of example 8: MS: M⁺ = 317.

Example 10

1-n-Propyl-3 α -diethylsulfamoylamino-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

The title compound is obtained as an oil analogously to example 3, starting from the product of example 9 via the following intermediates:

a) 1-n-Propyl-3 α -carbazoyle-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate): Oil.

b) 1-n-Propyl-3 α -amino-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate).

Example 11

1-n-Propyl-3 α -diethylsulfamoylamino-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

The title compound is obtained analogously to example 4, starting from the product of example 10: M.P. for the hydrochloride = 210—211°C.

Example 12

3 β -Methylthiomethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

The title compound is obtained analogously to example 5 as an oil via the following intermediates starting from the product of example 8h):

a) 1-Methoxy-3 β -methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate): M.P. = 74—76°C.

b) 1-Methoxy-3 β -hydroxymethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate).

c) 1-Methoxy-3 β -mesyloxymethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate).

d) 1-Methoxy-3 β -methylthiomethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate): M.P. = 92—94°C.

Example 13

1-n-Propyl-3 β -methylthiomethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

The title compound is obtained analogously to example 6, starting from the product of example 12: M.P. for the hydrochloride = 236—238°C.

Example 14

1-n-Propyl-3 β -methylthiomethyl-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

4 g of a 50% dispersion of sodium hydride in oil are washed several times with hexane and suspended

in 50 ml DMF. 12 ml methylmercaptan are then added portion-wise, followed by 3.5 g of 1-n-propyl-3 β -methylthiomethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (obtained in accordance with example 13), dissolved in a little DMF.

- 5 The reaction mixture is stirred for 5 hours at 160°C, cooled and the DMF removed under high vacuum. The residue is taken up in methylene chloride and extracted 2 $\times$, first using 2 N HCl and then saturated NaHCO₃. the obtained solution is dried over Na₂SO₄, evaporated, purified chromatographically and the main fraction re-crystallised from CH₂Cl₂/hexane to yield the title compound: M.P. = 132—134°C.

Example 15

- 10 3 β -Methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)
60 g of zinc powder are added to a solution of 12.2 g 1-methoxy-3 β -methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate) (Example 5a) in 180 ml acetic acid/H₂O (1:1) and the reaction mixture is stirred for 3 days at room temperature. Isolation of the product is carried out analogously to example 1 to yield the title compound.

Example 16

- 1-Methyl-3 β -methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)
56 ml aqueous formaldehyde solution (35%) are added to a solution of 10 g of the product of example 15 in 180 ml methanol and the reaction mixture is hydrogenated for ca. 15 hours using 2 g Pd on charcoal as catalyst. The product is filtered, the filtrate concentrated and the residue extracted by partitioning between CH₂Cl₂/1N KHCO₃ solution. The organic phase is dried over Na₂SO₄ and evaporated to yield the title compound: M.P. subsequent to re-crystallisation = 93—94°C.

Example 17

- 25 1-Methyl-3 β -methoxycarbonyl-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)
A solution of 2.4 ml boron tribromide in 20 ml CH₂Cl₂ are added dropwise at -20°C to a solution of 1.2 g of the product of example 16 in 100 ml CH₂Cl₂, and the reaction mixture is stirred for 8 hours at -5 to -10°C. 50 ml H₂O are added and the temperature allowed to rise to room temperature. The obtained suspension is filtered, the residue boiled for 1 hour in 50 ml of a 1N solution of HCl in MeOH and evaporated. The residue is partitioned between CH₂Cl₂/2N Na₂CO₃ solution, the organic phase washed with water until neutral, dried over Na₂SO₄ and evaporated to yield the title compound as an amorphous powder: M.P. = 182°C.

Example 18

- 35 1-Methyl-3 β -carboxy-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)
7.5 ml of a 1N solution of KOH in EtOH is added to a solution of 0.7 g of the product of example 17 in 10 ml EtOH and the reaction solution boiled for 1 hour under reflux. After cooling the reaction mixture is neutralised by the addition of 7.5 ml of a 1N HCl solution in MeOH and evaporated. The residue is suspended in 2 ml H₂O. The non-soluble portion is separated by filtration to yield the title compound M.P. = 250—260°C (with decomposition).

Example 19

- 40 6-Hydroxy-N-(2-methoxy-5-pyridyl)-1-methyl-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline-3 β -carboxamide (Racemate)
A solution of 1.35 ml trifluoroacetic acid anhydride and 0.6 ml trifluoroacetic acid in 7 ml acetonitrile are added at -20°C to a suspension of 1.4 g of the product of example 18 in 35 ml acetonitrile, whereupon dissolution of the suspended material occurs. The reaction mixture is stirred for 40 minutes at 0°C, re-cooled to -20°C and 1.4 g 5-amino-2-methoxypyridine dissolved in 12 ml pyridine are added. The obtained reaction mixture is then stirred for a further 4 hours at 0°C. The obtained solution is partitioned between CH₂Cl₂/H₂O, the organic phases dried over Na₂SO₄ and evaporated (insoluble, unreacted starting material being recovered subsequent to partitioning by filtration). The residue is purified chromatographically to yield the title compound: M.P. = 209—211°C.

Example 20

- 55 3 β -Methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)
The title compound is obtained analogously to example 15 starting from the product of example 12a): M.P. = 110°C.

Example 21

- 60 1-Methyl-3 β -methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)
The title compound is obtained analogously to example 16 starting from the product of example 20.

Example 22

- 65 1-Methyl-3 β -methoxycarbonyl-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)
The title compound is obtained analogously to example 17 starting from the product of example 21: M.P. = 197—199°C.

Example 23

1-Methyl-3 β -carboxy-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate)

The title compound is obtained analogously to example 18 starting from the product of example 22:
M.P. = 194—196°C.

Example 24

7-Hydroxy-N-(2-methoxy-5-pyridyl)-1-methyl-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline-3 β -carboxamide (Racemate)

The title compound is obtained analogously to example 19 starting from the product of example 23:
M.P. = 244—246°C.

Example 25

1-n-Propyl-3 α -diethylsulfamoylamino-6-benzoyloxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline... (Racemate)

4.4 ml benzoylchloride are added drop-wise at 0°C to a solution of 1.5 g of the product of example 4 in 200 ml pyridine. The reaction mixture is stirred for 1 hour with ice-cooling, and then concentrated, and the residue partitioned between CH₂Cl₂/H₂O. The organic phase is dried over Na₂SO₄ and evaporated and the residue recrystallised in the form of the hydrochloride salt from ether: M.P. = 166—168°C.

The benzo[g]quinolines of formula I, as well as the pharmaceutically acceptable salts thereof possess valuable pharmaceutical properties as indicated in animal tests.

In particular they exhibit prolactin secretion-inhibiting activity as indicated by inhibition of pregnancy (ovum implantation) on administration to female rats on the 5th day after insemination, at dosages of from e.g. 0.01 to 3.0 mg/kg s.c., as well as by reduction of serum prolactin levels as measured by RIA, 4 hours after administration to male rats at dosages of from e.g. 0.001 to 0.1 mg/kg s.c. [both tests carried out in accordance with the methods described in *Experientia* 34, 1330 (1978)].

The said benzo[g]quinolines and salts are accordingly indicated for use as prolactin secretion inhibitors, e.g. in the treatment of conditions or disorders for which reduction of prolactin secretion levels is indicated, for example for the treatment of galactorrhoea including post-partum galactorrhoea, for the treatment of prolactin-dependent menstrual disorders including amenorrhoea, for the inhibition of lactation including post-partum lactation and morbid lactation as well as for the treatment of hyperprolactinaemic hypogonadism in males and females and of prolactinoma.

For this use as indicated daily dosage is in the range of from about 0.25 to about 10 mg conveniently administered in divided doses 2 to 4 times a day or in sustained release form. Suitable unit dosage forms, e.g. for oral administration, comprise from about 0.05 to about 5 mg of active ingredient in free or pharmaceutically acceptable salt form together with a pharmaceutically acceptable diluent or carrier therefor.

In addition to the foregoing the benzo[g]quinolines of formula I, as well as the pharmaceutically acceptable salts thereof also exhibit dopaminergic activity as indicated by elicited contralateral rotation on administration at dosages of from e.g. 0.05 to 2.0 mg/kg i.p. to rats in which unilateral damage of the nigro-neostriatal dopamine pathway has been induced by injection of 6-hydroxydopamine into the substantia nigra [test carried out in accordance with the method of U. Ungerstedt, *Acta physiol. scand. Suppl.* 367, 69—93 (1973)]. The said compounds also exhibit stereotypy in the apomorphine stereotypy test on administration at dosages of e.g. about 10 mg/kg i.p.

The said benzo[g]quinolines and salts are accordingly indicated for use as dopaminergic agents e.g. for the treatment of Morbus Parkinson. For this use an indicated daily dosage is in the range of from about 1 to about 40 mg conveniently administered in divided doses 2 to 4 times a day or in sustained release form. Suitable unit dosage forms, e.g. for oral administration, comprise from about 0.25 to about 20 mg of active ingredient in free or pharmaceutically acceptable salt form together with a pharmaceutically acceptable diluent or carrier therefor.

The benzo[g]quinolines of formula I, as well as the pharmaceutically acceptable acid addition salts thereof also exhibit dopamine receptor stimulating activity as indicated by induction of decreased blood pressure and decreased superior mesenteric and renal vascular resistance in the anaesthetised dog. For this test dogs are employed which have been anaesthetised with nembutal. Blood pressure is measured by means of a catheter inserted in the femoral artery and heart-frequency is monitored by means of an electrocardiogram. A sub-maximal isoprenaline dosage (0.5 μ g/mg) is administered 3 $\times$ i.v. and blood pressure and heart frequency is measured. The test substance is administered by injection into the femoral vein 10 minutes after the 3rd isoprenaline dosage and the inhibition of isoprenaline induced tachycardia is determined following repeated isoprenaline administrations at the same dosage after a further 5, 15, 35, 75, 155 and 315 minutes, with a follow-up measurement of heart frequency and blood pressure. The said compounds of the invention cause a decrease in blood pressure as well as a decrease in superior mesenteric and renal vascular resistance on administration in the above test at doses of from e.g. 2.5 to 100 μ g/kg i.v.

The said benzo[g]quinolines and salts are accordingly indicated for use as dopamine receptor stimulators e.g. for the treatment or prophylaxis of coronary disease, e.g. of congestive heart failure, as well as of hypertension and oliguric renal failure. For this use an indicated daily dosage is in the range of

from about 1 to 500 mg conveniently given in divided doses 2 to 4 times a day or in sustained release form. Suitable unit dosage forms, e.g. for oral administration, comprise from about 0.25 to 250 mg of active ingredient in free or pharmaceutically acceptable salt form together with a pharmaceutically acceptable diluent or carrier therefor.

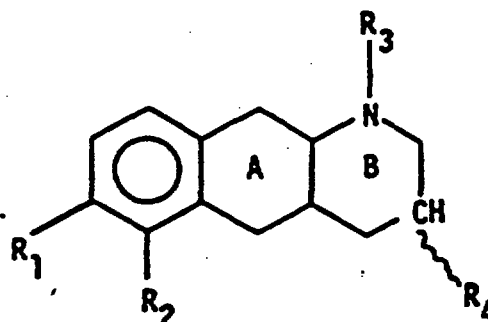
As indicated above for administration the benzo[g]quinolines may be in free or in pharmaceutically acceptable salt form, in particular pharmaceutically acceptable acid addition salt form. Such salt forms exhibit the same order of activity as the free forms.

In accordance with the foregoing the present invention also provides:

1. A benzo[g]quinoline of formula I as hereinbefore defined, or a physiologically-hydrolysable and -acceptable ester thereof, in free or pharmaceutically acceptable salt form for use as:
 - 1.1 A prolactin secretion inhibitor, in particular
 - 1.1.1 for use in the treatment of galactorrhoea, premenstrual disorders, hyperprolactinaemia, hypogonadism or prolactinoma or for use as a lactation inhibitor;
 - 1.2 A dopaminergic agent, in particular
 - 1.2.1 for use as in the treatment of Morbus Parkinson; and
 - 1.3 as a dopamine receptor stimulating agent, in particular
 - 1.3.1 for the treatment or prophylaxis of coronary disease, especially congestive heart failure, as well as for the treatment of hypertension or oliguric renal failure;
2. Use of a benzo[q]quinoline, ester or salt as defined under 1. above for the manufacture of a medicament suitable for treating conditions or disorders having an aetiology comprising a condition or disorder associated with prolactin secretion, in particular a condition or disorder as specified under 1.1.1 above, or treating Morbus Parkinson, or the prophylaxis or treatment of a condition or disorder as specified under 1.3.1 above, in other conditions to be treated by a dopaminergic agent; as well as
3. A pharmaceutical composition comprising a benzo[q]quinoline, ester or salt as defined under 1. above, together with a pharmaceutically acceptable diluent or carrier therefore.

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

1. A benzo[g]quinoline of formula I



wherein the rings A and B are trans-fused and wherein

R_1 and R_2 are each independently hydrogen, hydroxy or methoxy, with the proviso that R_1 and R_2 may not both be hydrogen;

R_3 is hydrogen or C_{1-4} alkyl;

R_4 is $-\text{COOH}$, $-\text{CH}_2\text{OR}_6$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_8)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$;

R_5 is hydrogen or C_{1-3} alkyl;

R_6 is hydrogen or C_{1-3} alkyl and

R_7 is hydrogen, C_{1-3} alkyl, phenyl or pyridyl, said phenyl or pyridyl being optionally substituted with halogen, methyl or methoxy or

R_8 and R_7 together are $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$ or $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$;

R_9 is C_{1-4} alkyl or pyridyl, said pyridyl being optionally substituted by halogen, methyl or methoxy, and

R_9 and R_{10} are each independently hydrogen or C_{1-3} alkyl or together are $-(\text{CH}_2)_4-$ or $-(\text{CH}_2)_5-$, or physiologically-hydrolysable and -acceptable ester thereof, in free or in salt form.

2. A compound according to claim 1 in the form of a racemate.

3. A benzo[g]quinoline of formula I as illustrated in claim 1, wherein

R_1 and R_2 are both hydroxy or both methoxy or one of R_1 and R_2 is hydrogen and the other is hydroxy or methoxy,

R_3 is C_{1-4} alkyl

R_4 is $-\text{CH}_2\text{OH}$, CH_2CN , $-\text{CON}(\text{R}_8)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$;

R_5 is hydrogen or C_{1-3} alkyl

R_7 is pyridyl optionally substituted by halogen, methyl or methoxy and

R_8 , R_9 and R_{10} have the meanings given in claim 1,

or a physiologically-hydrolysable and -acceptable ester thereof, in free or in acid addition salt form.

from about 1 to 500 mg conveniently given in divided doses 2 to 4 times a day or in sustained release form. Suitable unit dosage forms, e.g. for oral administration, comprise from about 0.25 to 250 mg of active ingredient in free or pharmaceutically acceptable salt form together with a pharmaceutically acceptable diluent or carrier therefor.

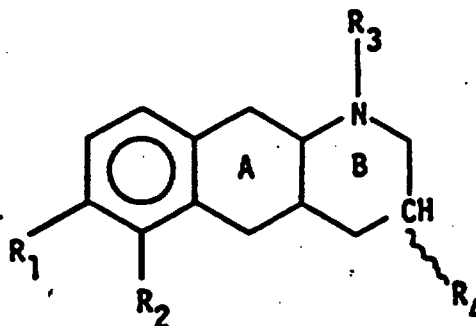
5 As indicated above for administration the benzo[g]quinolines may be in free or in pharmaceutically acceptable salt form, in particular pharmaceutically acceptable acid addition salt form. Such salt forms exhibit the same order of activity as the free forms.

In accordance with the foregoing the present invention also provides:

- 10 1. A benzo[g]quinoline of formula I as hereinbefore defined, or a physiologically-hydrolysable and -acceptable ester thereof, in free or pharmaceutically acceptable salt form for use as:
 - 1.1 A prolactin secretion inhibitor, in particular
 - 1.1.1 for use in the treatment of galactorrhoea, premenstrual disorders, hyperprolactinaemic hypogonadism or prolactinoma or for use as a lactation inhibitor;
 - 1.2 A dopaminergic agent, in particular
 - 1.2.1 for use as in the treatment of Morbus Parkinson; and
 - 1.3 as a dopamine receptor stimulating agent, in particular
 - 1.3.1 for the treatment or prophylaxis of coronary disease, especially congestive heart failure, as well as for the treatment of hypertension or oliguric renal failure;
- 20 2. Use of a benzo[q]quinoline, ester or salt as defined under 1. above for the manufacture of a medicament suitable for treating conditions or disorders having an aetiology comprising or associated with prolactin secretion, in particular a condition or disorder as specified under 1.1.1 above, or treating Morbus Parkinson, or the prophylaxis or treatment of a condition or disorder as specified under 1.3.1 above, in other conditions to be treated by a dopaminergic agent; as well as
3. A pharmaceutical composition comprising a benzo[q]quinoline, ester or salt as defined under 1. above, together with a pharmaceutically acceptable diluent or carrier therefore.

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

1. A benzo[g]quinoline of formula I



wherein the rings A and B are trans-fused and wherein

45 R_1 and R_2 are each independently hydrogen, hydroxy or methoxy, with the proviso that R_1 and R_2 may not both be hydrogen;

R_3 is hydrogen or C_{1-4} alkyl;

R_4 is $-\text{COOH}$, $-\text{CH}_2\text{OR}_6$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_8)\text{R}_7$, $-\text{CH}_2\text{SR}_6$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$;

R_5 is hydrogen or C_{1-3} alkyl,

R_6 is hydrogen or C_{1-3} alkyl and

50 R_7 is hydrogen, C_{1-3} alkyl, phenyl or pyridyl, said phenyl or pyridyl being optionally substituted by halogen, methyl or methoxy or

R_8 and R_7 together are $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$ or $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$,

R_9 is C_{1-4} alkyl or pyridyl, said pyridyl being optionally substituted by halogen, methyl or methoxy, and

R_9 and R_{10} are each independently hydrogen or C_{1-3} alkyl or together are $-(\text{CH}_2)_4-$ or $-(\text{CH}_2)_5-$,

55 or physiologically-hydrolysable and -acceptable ester thereof, in free or in salt form.

2. A compound according to claim 1 in the form of a racemate.

3. A benzo[g]quinoline of formula I as illustrated in claim 1, wherein

R_1 and R_2 are both hydroxy or both methoxy or one of R_1 and R_2 is hydrogen and the other is hydroxy or methoxy,

60 R_3 is C_{1-4} alkyl

R_4 is $-\text{CH}_2\text{OH}$, CH_2CN , $-\text{CON}(\text{R}_8)\text{R}_7$, $-\text{CH}_2\text{SR}_6$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$,

R_5 is hydrogen or C_{1-3} alkyl

R_7 is pyridyl optionally substituted by halogen, methyl or methoxy and

R_8 , R_9 and R_{10} have the meanings given in claim 1,

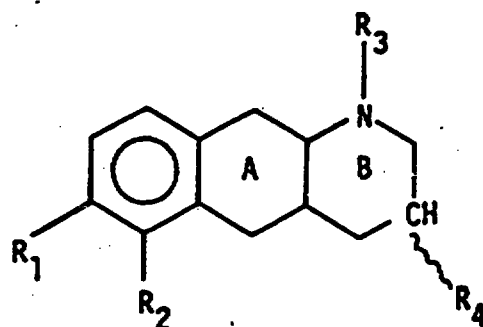
65 or a physiologically-hydrolysable and -acceptable ester thereof, in free or in acid addition salt form.



4. A compound according to claim 3 in the form of a racemate.
5. A benzo[g]quinoline of formula I as illustrated in claim 1, wherein
 R_1 , R_2 and R_3 have the meanings given in claim 1,
 R_4 is $-\text{COOH}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_9)\text{R}_{10}$, $-\text{CH}_2\text{SR}_9$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$, and
 R_5 , R_7 , R_8 , R_9 and R_{10} have the meanings given in claim 1,
 or physiologically-hydrolysable and -acceptable ester thereof, in free or in acid addition salt form.
6. A compound according to claim 5, in the form of a racemate.
7. A benzo[g]quinoline of formula I as illustrated in claim 1 wherein one of
 R_1 and R_2 is hydrogen and the other is hydroxy,
 R_3 is n-propyl,
 R_4 is $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$,
 R_9 is ethyl and
 R_{10} is ethyl,
 or a physiologically-hydrolysable and -acceptable ester thereof, in free or in salt form.
8. 1-n-Propyl-3 α -diethylsulfamoylamino-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate), in free or in acid addition salt form.
9. A compound selected from the group comprising
 3 β -Methylthiomethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-n-Propyl-3 β -methylthiomethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate); and
 1-n-Propyl-3 β -methylthiomethyl-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 said compound being in free or in acid addition salt form.
10. A compound selected from the group comprising:
 3 α -Methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-n-Propyl-3 α -methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-n-Propyl-3 α -diethylsulfamoylamino-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 3 β -Methylthiomethyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-n-Propyl-3 β -methylthiomethyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-n-Propyl-3 β -methylthiomethyl-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 3 α -Methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-n-Propyl-3 α -methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-n-Propyl-3 α -diethylsulfamoylamino-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-n-Propyl-3 α -diethylsulfamoylamino-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate); and
 7-Hydroxy-N-(2-methoxy-5-pyridyl)-1-methyl-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline-3 β -carboxamide (Racemate);
 said compound being in free or acid addition salt form.
11. A compound selected from the group comprising:
 3 β -Methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-Methyl-3 β -methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-Methyl-3 β -methoxycarbonyl-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-Methyl-3 β -carboxy-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 6-Hydroxy-N-(2-methoxy-5-pyridyl)-1-methyl-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline-3 β -carboxamide (Racemate);
 3 β -Methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-Methyl-3 β -methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-Methyl-3 β -methoxycarbonyl-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-Methyl-3 β -carboxy-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 1-n-Propyl-3 β -diethylsulfamoylamino-6-benzoyloxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate);
 said compound being in free or in salt form.



12. Process for the production of a benzo[g]quinoline of formula I,



(I)

wherein the rings A and B are trans-fused and wherein

R_1 and R_2 are each independently hydrogen, hydroxy or methoxy, with the proviso that R_1 and R_2 may not both be hydrogen;

R_3 is hydrogen or C_{1-4} alkyl;

R_4 is $-\text{COOH}$, $-\text{CH}_2\text{OR}_5$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ or $-\text{NHCON}(\text{R}_9)\text{R}_{10}$,

R_5 is hydrogen or C_{1-3} alkyl,

R_6 is hydrogen or C_{1-3} alkyl and

R_7 is hydrogen, C_{1-3} alkyl, phenyl or pyridyl, said phenyl or pyridyl being optionally substituted by halogen, methyl or methoxy or

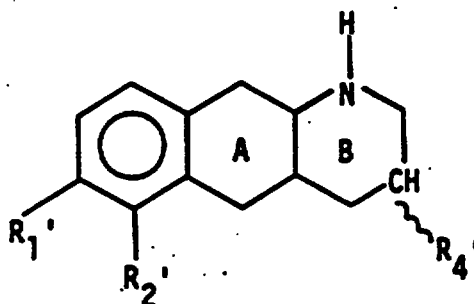
R_8 and R_9 together are $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$ or $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$,

R_{10} is C_{1-4} alkyl or pyridyl, said pyridyl being optionally substituted by halogen, methyl or methoxy, and

R_5 and R_{10} are each independently hydrogen or C_{1-3} alkyl or together are $-(\text{CH}_2)_4-$ or $-(\text{CH}_2)_5-$, or physiologically-hydrolysable and -acceptable ester thereof, in free or in salt form,

which process comprises:

a) for the production of a compound of formula I',



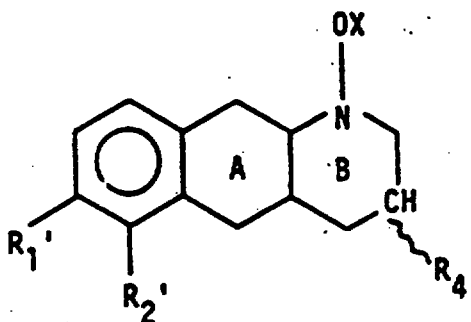
(I')

wherein the rings A and B are trans-fused,

R_1' and R_2' are each independently hydrogen or methoxy, with the proviso that R_1' and R_2' may not both be hydrogen;

R_4' is $-\text{CH}_2\text{OR}_5$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$ or CH_2SR_8 or esterified $-\text{COOH}$ or esterified $-\text{CH}_2\text{OH}$ and

R_5 , R_6 , R_7 and R_8 have the meanings given for formula I, subjecting a compound of formula II,

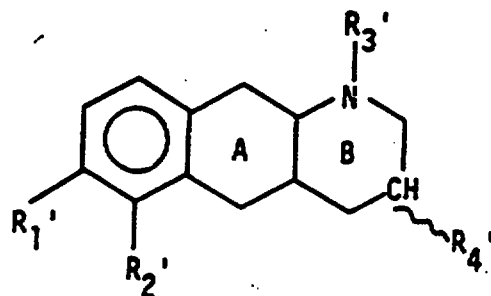


(II)

wherein the rings A and B are trans-fused, X is benzyl or C_{1-4} alkyl and R_1' , R_2' and R_4' have the meanings given for formula I', to cleavage, so as to split off the benzyloxy or C_{1-4} alkoxy group,



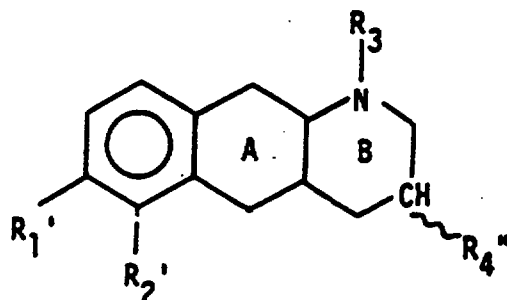
b) for the production of a compound of formula I²,



wherein the rings A and B are trans-fused, R₃' is C₁₋₄alkyl and R₁', R₂' and R₄' have the meanings given for formula I¹,

alkylating a compound of formula I¹ as defined above to introduce a C₁₋₄alkyl group at the 1-position;

c) for the production of a compound of formula I³,



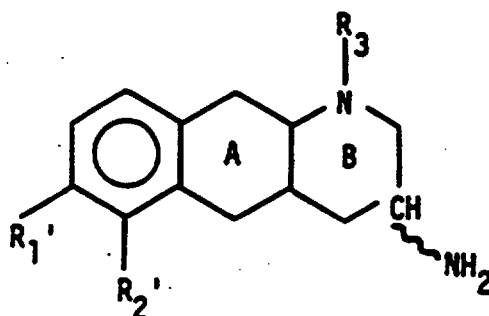
wherein the rings A and B are trans-fused,

R₄'' is —NHSO₂N(R₉)R₁₀ or NHCON(R₉)R₁₀,

R₃, R₉ and R₁₀ have the meanings given for formula I and

R₁' and R₂' have the meanings given for formula I¹,

reacting a compound of formula III,

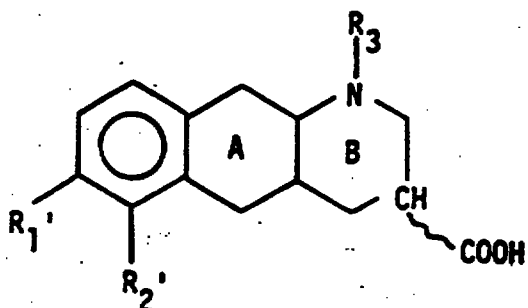


wherein the rings A and B are trans-fused and R₁', R₂' and R₃ are as defined above for formula I³, with an aminosulfonic or aminocarboxylic acid or reactive derivative thereof, e.g. with a compound of formula IVa or IVb,

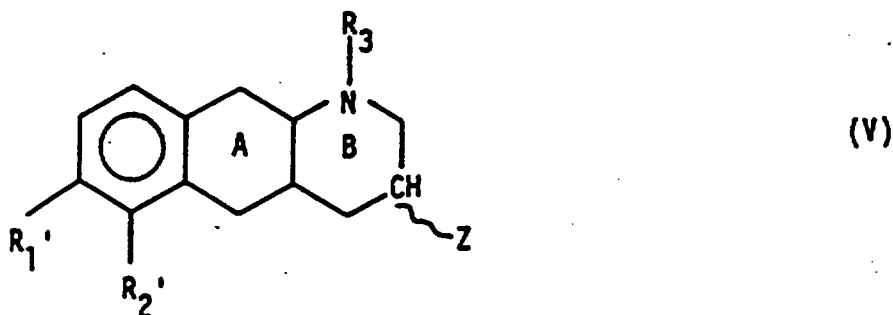


wherein R₉ and R₁₀ have the meanings given for formula I, or a reactive derivative thereof,

d) for the production of compound of formula I⁴,

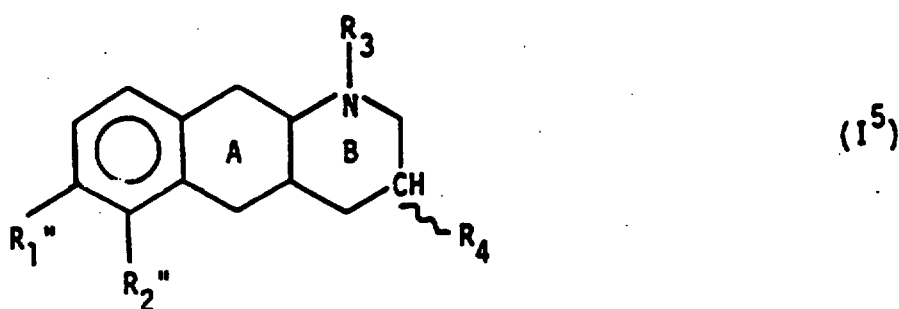


wherein the rings A and B are trans-fused and wherein R_1' and R_2' have the meanings given for formula I' and R_3 has the meaning given for formula I, hydrolysing a compound of formula V,



wherein the rings A and B are trans-fused, Z is an esterified carboxy group, and R_1' , R_2' and R_3 are as defined above for formula I',

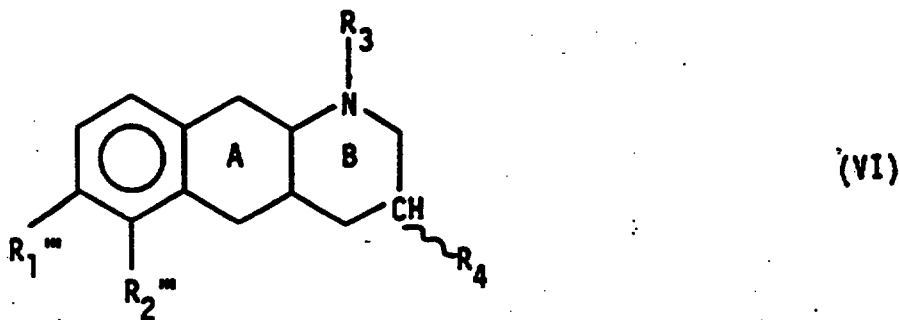
e) for the production of compound of formula I⁵,



wherein the rings A and B are trans-fused,

R_1'' and R_2'' are each independently hydrogen, hydroxy or methoxy, with the proviso that at least one of R_1'' and R_2'' is hydroxy, and

R_3 and R_4 have the meanings given for formula I, subjecting a compound of formula VI,



wherein the rings A and B are trans-fused,

R_1''' and R_2''' are each independently hydrogen, hydroxy or methoxy, with the proviso that at least one of R_1''' and R_2''' is methoxy, and

R_3 and R_4 have the meanings given for formula I, to ether cleavage;

f) reacting a benzo[g]quinoline of formula I as hereinbefore defined wherein R_4 is a carboxy group or a reactive derivative thereof with an amine of formula $HN(R_6)_2$, wherein R_6 and R_7 have the meanings given for formula I, to produce the corresponding amidated benzo[g]quinolines of formula I, or reacting a benzo[g]quinoline of formula I as hereinbefore defined wherein at least one of the residues R_1 , R_2 and R_4 is a hydroxy group (in the case of R_1 and R_2) or hydroxymethyl group (in the case of R_4), or a benzo[g]quinoline of formula I as hereinbefore defined wherein R_4 is a carboxy group or a reactive derivative thereof, with an appropriate acid or reactive derivative thereof, or with an appropriate alcohol, to produce the corresponding acylated or esterified benzo[g]quinoline of formula I; and, recovering the compound of formula I thus obtained in free or salt form.

13. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 11 in free or in pharmaceutically acceptable salt form, together with a pharmaceutically acceptable diluent or carrier therefor.



14. A compound as claimed in any one of claims 1 to 11 in free or in pharmaceutically acceptable salt form for use as a pharmaceutical.

15. A compound as claimed in any one of claims 1 to 11 in free or in pharmaceutically acceptable salt form for use as a prolactin secretion inhibitor, as a dopaminergic agent or as a dopamine receptor stimulating agent.

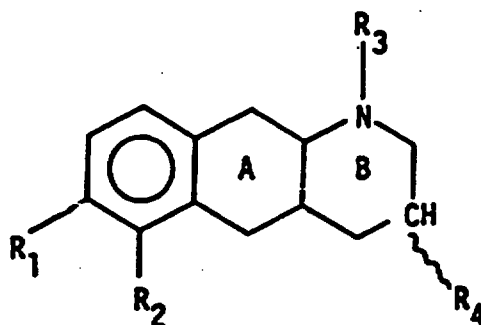
16. Use of a compound of any one of claims 1 to 11 for the manufacture of a medicament suitable for treating conditions or disorders having an aetiology comprising or associated with prolactin secretion, or treating Morbus Parkinson, or other conditions to be treated with a dopaminergic agent.

17. Use of a compound of any one of claims 1 to 11 for the manufacture of a medicament suitable for use as a prolactin secretion inhibitor.

18. Use of a compound for any one of claims 1 to 11 for the manufacture of a medicament suitable for use in the treatment of galactorrhoea, premenstrual disorders, hyperprolactinaemic hypogonadism or prolactinoma or for use as a lactation inhibitor.

Claims for the Contracting State: AT

1. Process for the production of a benzo[g]quinoline of formula I,



(I)

wherein the rings A and B are trans-fused and wherein

R_1 and R_2 are each independently hydrogen, hydroxy or methoxy, with the proviso that R_1 and R_2 may not both be hydrogen;

R_3 is hydrogen or C_{1-4} alkyl;

R_4 is $-COOH$, $-CH_2OR_5$, $-CH_2CN$, $-CON(R_6)R_7$, $-CH_2SR_6$, $-NHSO_2N(R_9)R_{10}$ or $-NHCON(R_9)R_{10}$,

R_5 is hydrogen or C_{1-3} alkyl,

R_6 is hydrogen or C_{1-3} alkyl and

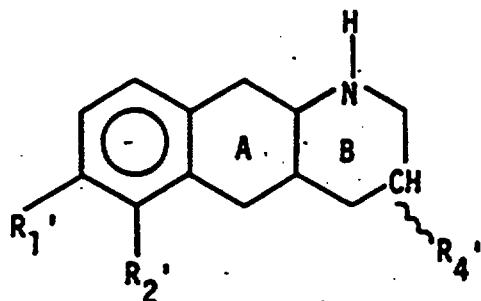
R_7 is hydrogen, C_{1-3} alkyl, phenyl or pyridyl, said phenyl or pyridyl being optionally substituted by halogen, methyl or methoxy or

R_6 and R_7 together are $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_2-O-(CH_2)_2-$,

R_8 is C_{1-4} alkyl or pyridyl, said pyridyl being optionally substituted by halogen, methyl or methoxy, and

R_9 and R_{10} are each independently hydrogen or C_{1-3} alkyl or together are $-(CH_2)_4-$ or $-(CH_2)_5-$, or physiologically-hydrolysable and -acceptable ester thereof, in free or in salt form, which process comprises:

a) for the production of a compound of formula I',



(I')

wherein the rings A and B are trans-fused,

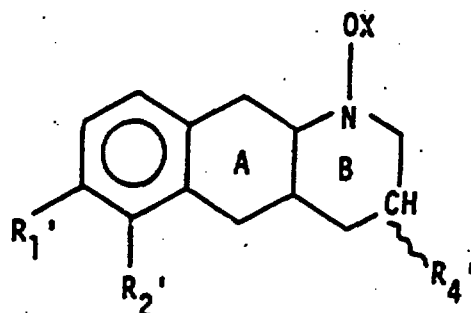
R_1' and R_2' are each independently hydrogen or methoxy, with the proviso that R_1' and R_2' may not both be hydrogen;

R_4' is $-CH_2OR_5$, $-CH_2CN$, $-CON(R_6)R_7$ or CH_2SR_6 or esterified $-COOH$ or esterified $-CH_2OH$ and

R_5 , R_6 , R_7 and R_8 have the meanings given for formula I,

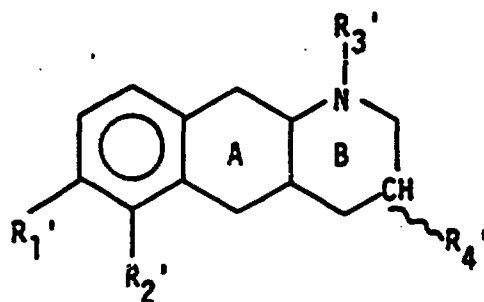
subjecting a compound of formula II,





(II)

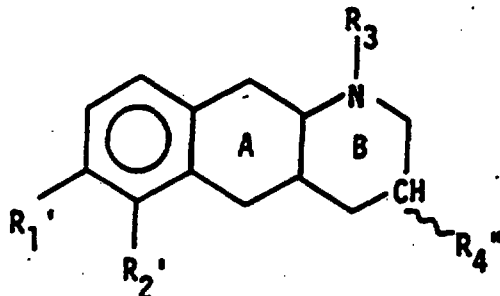
wherein the rings A and B are trans-fused, X is benzyl or C₁₋₄alkyl and R₁', R₂' and R₄' have the meanings given for formula I', to cleavage, so as to split off the benzyloxy or C₁₋₄alkoxy group,
b) for the production of a compound of formula I²,



(I²)

wherein the rings A and B are trans-fused, R₃' is C₁₋₄alkyl and R₁', R₂' and R₄' have the meanings given for formula I',

alkylating a compound of formula I' as defined above to introduce a C₁₋₄alkyl group at the 1-position;
c) for the production of a compound of formula I³,



(I³)

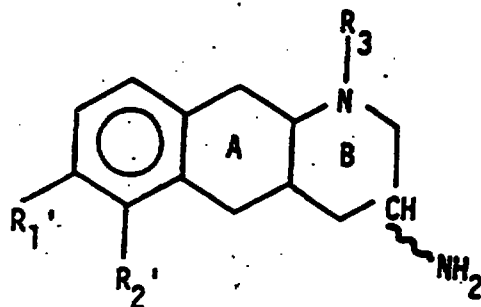
wherein the rings A and B are trans-fused,

R₄'' is —NHSO₂N(R₉)R₁₀ or —NHCON(R₉)R₁₀,

R₃, R₉ and R₁₀ have the meanings given for formula I and

R₁' and R₂' have the meanings given for formula I',

reacting a compound of formula III,



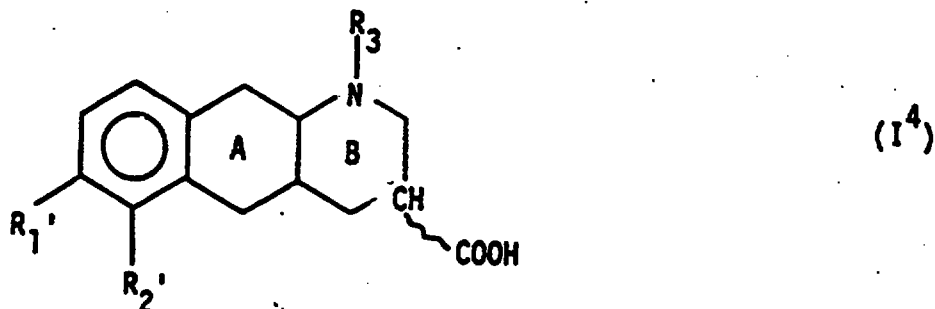
(III)

wherein the rings A and B are trans-fused and R₁', R₂' and R₃ are as defined above for formula I³, with an aminosulfonic or aminocarboxylic acid or reactive derivative thereof, e.g. with a compound of formula IVa or IVb,

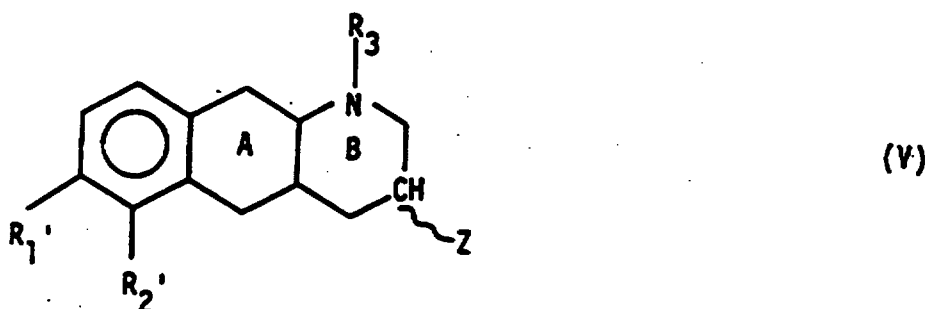




wherein R_9 and R_{10} have the meanings given for formula I, or a reactive derivative thereof,
d) for the production of compound of formula I⁴,

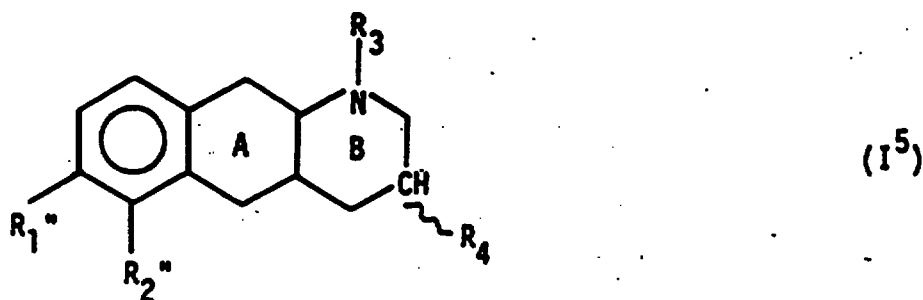


wherein the rings A and B are trans-fused and wherein R_1' and R_2' have the meanings given for formula I¹ and R_3 has the meaning given for formula I, hydrolysing a compound of formula V,



wherein the rings A and B are trans-fused, Z is an esterified carboxy group, and R_1' , R_2' and R_3 are as defined above for formula I⁴,

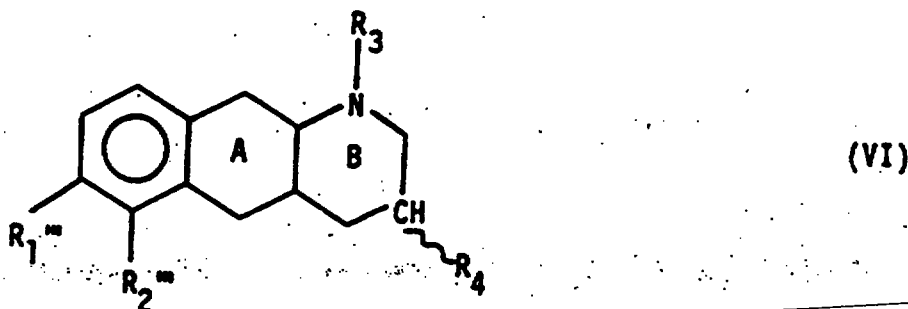
e) for the production of compound of formula I⁵,



wherein the rings A and B are trans-fused,

R_1'' and R_2'' are each independently hydrogen, hydroxy or methoxy, with the proviso that at least one of R_1'' and R_2'' is hydroxy, and

R_3 and R_4 have the meanings given for formula I, subjecting a compound of formula VI,



wherein the rings A and B are trans-fused,

R_1 , R_2 and R_3 are each independently hydrogen, hydroxy or methoxy, with the proviso that at least one of R_1 , R_2 and R_3 is methoxy, and

R_4 and R_5 have the meanings given for formula I, to ether cleavage;

f) reacting a benzo[g]quinoline of formula I as hereinbefore defined wherein R_4 is a carboxy group or a reactive derivative thereof with an amine of formula $\text{HN}(R_6)_2$, wherein R_6 and R_7 have the meanings given for formula I, to produce the corresponding amidated benzo[g]quinolines of formula I, or reacting a benzo[g]quinoline of formula I as hereinbefore defined wherein at least one of the residues R_1 , R_2 and R_4 is a hydroxy group (in the case of R_1 and R_2) or hydroxymethyl group (in the case of R_4), or a benzo[g]quinoline of formula I as hereinbefore defined wherein R_4 is a carboxy group or a reactive derivative thereof, with an appropriate acid or reactive derivative thereof, or with an appropriate alcohol, to produce the corresponding acylated or esterified benzo[g]quinoline of formula I; and, recovering the compound of formula I thus obtained in free or salt form.

2. Process according to claim 1 for the production of a benzo[g]quinoline of formula I as illustrated in claim 1 wherein one of

R_1 and R_2 is hydrogen and the other is hydroxy,

R_3 is n-propyl,

R_4 is $-\text{NHSO}_2\text{N}(R_9)R_{10}$,

R_9 is ethyl and

R_{10} is ethyl,

or a physiologically-hydrolysable and -acceptable ester thereof, in free or in salt form.

3. Process according to claim 1 for the production of 1-n-Propyl-3 α -diethylsulfamoylamino-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate), which process comprises subjecting 1-n-propyl-3 α -diethylsulfamoylamino-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline to ether cleavage.

4. A process for the production of a pharmaceutical composition which comprises mixing a compound of formula I, I¹, I², I³, I⁴, I⁵ as defined in claim 1, in free or in pharmaceutically acceptable salt form, with a pharmaceutical carrier or diluent.

5. A process according to claim 4 wherein the benzo[g]quinoline is 1-n-Propyl-3 α -diethylsulfamoylamino-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoline (Racemate) in free or pharmaceutically acceptable salt form.

6. Use of a compound of formula I, I¹, I², I³, I⁴, I⁵ as defined in claim 1, in free or in pharmaceutically acceptable salt form, for the manufacture of a medicament suitable for treating conditions or disorders having an aetiology comprising or associated with prolactin secretion, treating Morbus Parkinson, or other conditions to be treated with a dopaminergic agent.

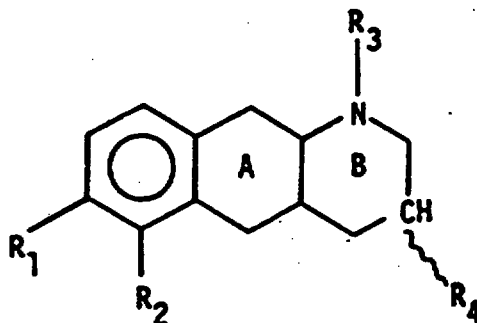
7. Use according to claim 6 wherein the benzo[g]quinoline is as defined in claim 5.

8. Use of a compound specified in claim 4 or 5 for the manufacture of a medicament suitable for use as a prolactin secretion inhibitor.

9. Use of a compound specified in claim 4 or 5 for the manufacture of a medicament suitable for use in the treatment of galactorrhoea, premenstrual disorders, hyperprolactinaemic hypogonadism or prolactinoma or for use as a lactation inhibitor.

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

1. Benzo[g]chinolin der Formel I,



(I)

worin die Ringe A und B trans-kondensiert sind und worin

R_1 und R_2 jeweils unabhängig voneinander Wasserstoff, Hydroxy oder Methoxy bedeuten, mit der Massgabe, dass R_1 und R_2 beide nicht für Wasserstoff stehen können;

R_3 Wasserstoff oder C_{1-4} Alkyl ist;

R_4 $-\text{COOH}$, $-\text{CH}_2\text{OR}_5$, $-\text{CH}_2\text{CN}$, $-\text{CON}(R_6)R_7$, $-\text{CH}_2\text{SR}_6$, $-\text{NHSO}_2\text{N}(R_9)R_{10}$ oder $-\text{NHCON}(R_9)R_{10}$ ist,

R_5 Wasserstoff oder C_{1-3} Alkyl ist,



R_6 Wasserstoff oder C_{1-3} -Alkyl ist, und
 R_7 Wasserstoff, C_{1-3} -Alkyl, Phenyl oder Pyridyl, wobei das Phenyl oder Pyridyl gegebenenfalls durch Halogen, Methyl oder Methoxy substituiert ist, oder

R_8 und R_7 zusammen $-(CH_2)_4-$, $(CH_2)_5-$ oder $-(CH_2)_2-O-(CH_2)_2-$ sind,

R_9 C_{1-4} -Alkyl oder Pyridyl, wobei das Pyridyl gegebenenfalls durch Halogen, Methyl oder Methoxy substituiert ist, und

R_9 und R_{10} jeweils unabhängig voneinander Wasserstoff oder C_{1-3} -Alkyl oder zusammen $-(CH_2)_4-$ oder $(CH_2)_5-$ sind,

oder ein physiologisch annehmbares und physiologisch hydrolysierbares Ester hiervon, in freier Form oder in Salzform.

2. Eine Verbindung gemäss Anspruch 1, in der Razematform.

3. Ein Benzo[g]chinolin der Formel I wie in Anspruch 1 veranschaulicht, worin

R_1 und R_2 beide Hydroxy oder beide Methoxy oder ein der Symbole R_1 und R_2 Wasserstoff und das andere Hydroxy oder Methoxy sind,

R_3 C_{1-4} -Alkyl ist,

R_4 $-CH_2OH$, $-CH_2CN$, $-CON(R_6)R_7$, $-CH_2SR_8$, $-NHSO_2N(R_9)R_{10}$ oder $-NHCON(R_9)R_{10}$ ist,

R_6 Wasserstoff oder C_{1-3} -Alkyl ist,

R_7 gegebenenfalls durch Halogen, Methyl oder Methoxy substituiertes Pyridyl ist, und

R_8 , R_9 und R_{10} die in Anspruch 1 angegebenen Bedeutungen haben,

oder ein physiologisch annehmbares und physiologisch hydrolysierbares Ester hiervon, in freier Form oder in Säureadditionssalzform.

4. Eine Verbindung gemäss Anspruch 3 in der Razematform.

5. Ein Benzo[g]chinolin der Formel I wie in Anspruch 1 veranschaulicht, worin

R_1 , R_2 und R_3 die in Anspruch 1 angegebenen Bedeutungen haben,

R_4 $-COOH$, $-CH_2OH$, $-CH_2CN$, $-CON(R_6)R_7$, $-CH_2SR_8$, $-NHSO_2N(R_9)R_{10}$ oder $-NHCON(R_9)R_{10}$, und

R_6 , R_7 , R_8 , R_9 und R_{10} die in Anspruch 1 angegebenen Bedeutung haben,

oder ein physiologisch annehmbares und physiologisch hydrolysierbares Ester hiervon, in freier Form oder in Säureadditionssalzform.

6. Eine Verbindung gemäss Anspruch 5, in Razematform.

7. Ein Benzo[g]chinolin der Formel I wie in Anspruch 1 veranschaulicht, worin ein der Symbole

R_1 und R_2 Wasserstoff und das andere Hydroxy ist,

R_3 n-Propyl ist,

R_4 $-NHSO_2N(R_9)R_{10}$ ist,

R_9 Ethyl ist, und

R_{10} Ethyl ist,

oder ein physiologisch annehmbares und physiologisch hydrolysierbares Ester hiervon, in freier Form oder in Salzform.

8. 1-n-Propyl-3 α -diethylsulfamoylamino-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat), in freier oder in Säureadditionssalzform.

9. Eine Verbindung ausgewählt aus der Gruppe enthaltend

3 β -Methylthiomethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

1-n-Propyl-3 β -methylthiomethyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat); und

1-n-Propyl-3 β -methylthiomethyl-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

wobei diese Verbindung in freier oder in Säureadditionssalzform ist.

10. Eine Verbindung ausgewählt aus der Gruppe enthaltend:

3 α -Methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

1-n-Propyl-3 α -methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin

(Razemat);

1-n-Propyl-3 α -diethylsulfamoylamino-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

3 β -Methylthiomethyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

1-n-Propyl-3 β -methylthiomethyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

1-n-Propyl-3 β -methylthiomethyl-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

3 α -Methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

1-n-Propyl-3 α -methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin

(Razemat);

1-n-Propyl-3 α -diethylsulfamoylamino-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

1-n-Propyl-3 α -diethylsulfamoylamino-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat); und



7-Hydroxy-N-(2-methoxy-5-pyridyl)-1-methyl-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin
(Razemat);

wobei diese Verbindung in freier oder in Säureadditionssalzform ist.

11. Eine Verbindung ausgewählt aus der Gruppe enthaltend

3 β -Methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

1-Methyl-3 β -methoxycarbonyl-6-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin

(Razemat);

1-Methyl-3 β -methoxycarbonyl-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin

(Razemat);

1-Methyl-3 β -carboxy-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

6-Hydroxy-N-(2-methoxy-5-pyridyl)-1-methyl-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin-3 β -
carboxamid (Razemat);

3 β -Methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

1-Methyl-3 β -methoxycarbonyl-7-methoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin

(Razemat);

1-Methyl-3 β -methoxycarbonyl-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin

(Razemat);

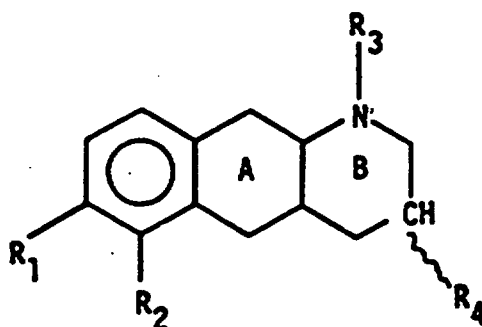
1-Methyl-3 β -carboxy-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin (Razemat);

1-n-Propyl-3 β -diethylsulfamoylamino-6-benzoyloxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]chinolin

(Razemat);

wobei diese Verbindung in freier Form oder in Salzform ist.

12. Verfahren zur Herstellung eines Benzo[g]chinolins der Formel I,



(I)

worin die Ringe A und B trans-kondensiert sind und worin

R₁ und R₂ jeweils unabhängig voneinander Wasserstoff, Hydroxy oder Methoxy bedeuten, mit der
Massgabe, dass R₁ und R₂ beide nicht für Wasserstoff stehen können;

R₃ Wasserstoff oder C₁₋₄Alkyl ist;

R₄ —COOH, —CH₂OR₅, —CH₂CN, —CON(R₆)R₇, —CH₂SR₈, —NHSO₂N(R₉)R₁₀ oder —NHCON(R₉)R₁₀ ist,

R₅ Wasserstoff oder C₁₋₃Alkyl ist,

R₆ Wasserstoff oder C₁₋₃Alkyl ist, und

R₇ Wasserstoff, C₁₋₃Alkyl, Phenyl oder Pyridyl, wobei das Phenyl oder Pyridyl gegebenenfalls durch
Halogen, Methyl oder Methoxy substituiert ist, oder

R₈ und R₉ zusammen —(CH₂)₄—, (CH₂)₅— oder —(CH₂)₂—O—(CH₂)₂— sind,

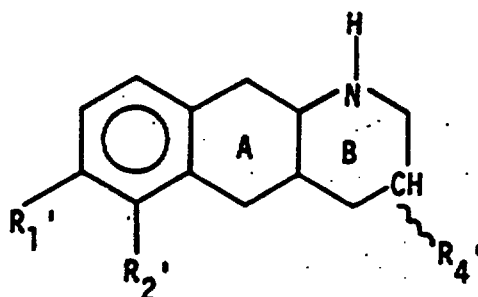
R₈ C₁₋₄Alkyl oder Pyridyl, wobei das Pyridyl gegebenenfalls durch Halogen, Methyl oder Methoxy
substituiert ist, und

R₉ und R₁₀ jeweils unabhängig voneinander Wasserstoff oder C₁₋₃Alkyl oder zusammen —(CH₂)₄—
oder (CH₂)₅— sind,

oder ein physiologisch hydrolysierbaren und physiologisch annehmbares Esters hiervon, in freier Form
oder in Salzform,

wobei das Verfahren umfasst:

a) zur Herstellung einer Verbindung der Formel I',



(I')

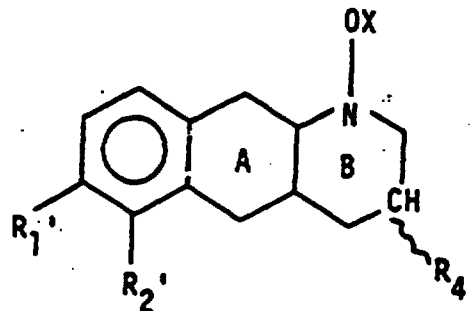


worin die Ringe A und B trans-kondensiert sind,

R_1' und R_2' jeweils unabhängig voneinander Wasserstoff oder Methoxy bedeuten, mit der Massgabe, dass R_1' und R_2' nicht beide Wasserstoff sein können,

$R_4' - CH_2OR_5$, $-CH_2CN$, $-CON(R_6)R_7$ oder $-CH_2SR_8$ oder verestertes $-COOH$ oder verestertes $-CH_2OH$ ist und

R_5 , R_6 , R_7 und R_8 die für Formel I angegebenen Bedeutungen haben, wird eine Verbindung der Formel II,

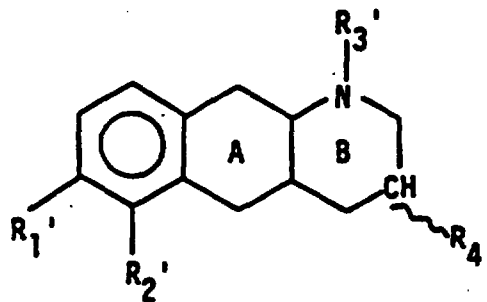


(II)

worin die Ringe A und B trans-kondensiert sind, X für Benzyl oder C_{1-4} Alkyl steht und R_1' , R_2' und R_4' die für Formel I¹ angegebenen Bedeutungen haben,

einer Spaltung unterworfen, so dass die Benzyloxy- oder C_{1-4} Alkoxygruppe abgespalten wird,

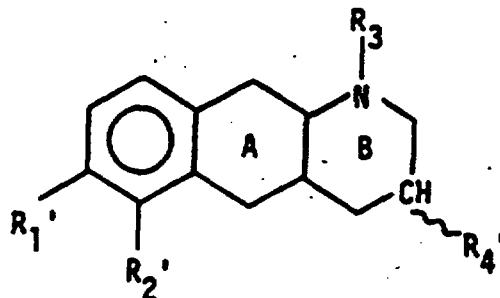
b) zur Herstellung einer Verbindung der Formel I²,

(I²)

worin die Ringe A und B trans-kondensiert sind, R_3' C_{1-4} Alkyl ist und R_1' , R_2' und R_4' die für Formel I¹ angegebenen Bedeutungen haben,

wird eine Verbindung der Formel I¹ wie oben definiert alkyliert, um eine C_{1-4} Alkylgruppe in Stellung 1 einzuführen;

c) zur Herstellung einer Verbindung der Formel I³,

(I³)

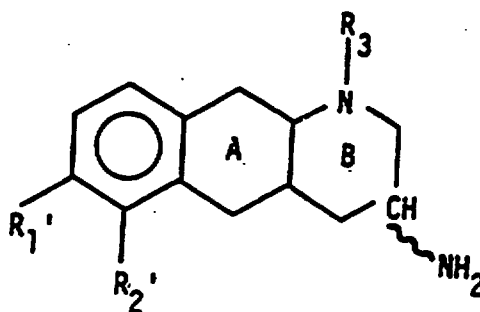
worin die Ringe A und B trans-kondensiert sind, $R_3' - NHSO_2N(R_9)R_{10}$ oder $-NHCON(R_9)R_{10}$ ist,

R_3 , R_9 und R_{10} die für Formel I angegebenen Bedeutungen haben und

R_1' und R_2' die für Formel I¹ angegebenen Bedeutungen haben,

wird eine Verbindung der Formel III,





(III)

worin die Ringe A und B trans-kondensiert sind und R_1' , R_2' und R_3 wie oben für Formel I³ definiert sind, mit einer Aminosulfonsäure oder Aminocarbonsäure oder einem reaktiven Derivat hiervon, z.B. mit einer Verbindung der Formel IVa oder IVb,



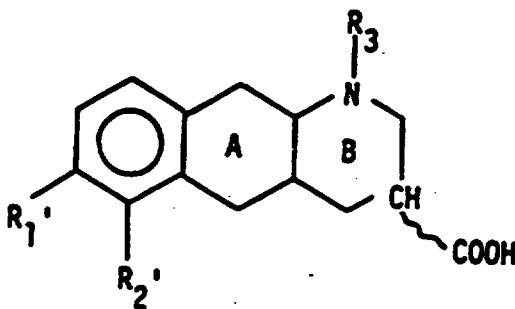
(IVa)



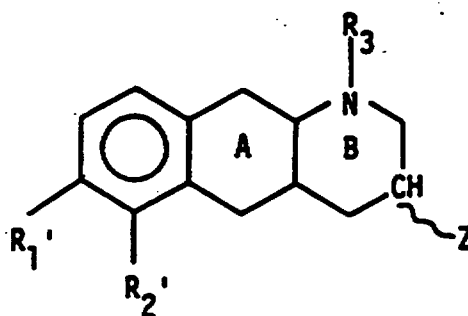
(IVb)

worin R_9 und R_{10} die für Formel I angegebenen Bedeutungen haben, oder einem reaktiven Derivat hiervon, umgesetzt,

d) zur Herstellung einer Verbindung der Formel I⁴,

(I⁴)

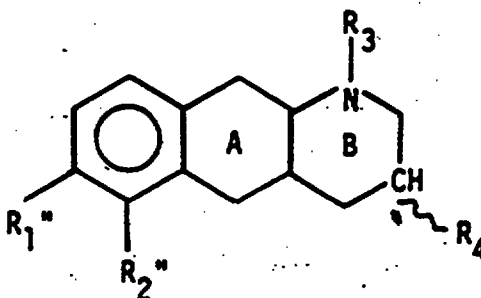
worin die Ringe A und B trans-kondensiert sind und worin R_1' und R_2' die für Formel I³ angegebenen Bedeutungen haben und R_3 die für Formel I angegebene Bedeutung hat, wird eine Verbindung der Formel V hydrolysiert,



(V)

worin die Ringe A und B trans-kondensiert sind, Z eine veresterte Carboxygruppe und R_1' , R_2' und R_3 wie oben für die Formel I⁴ definiert sind,

e) zur Herstellung einer Verbindung der Formel I⁵,

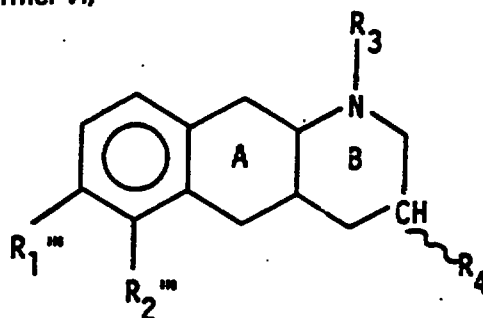
(I⁵)

worin die Ringe A und B trans-kondensiert sind,

R''_1 und R''_2 jeweils unabhängig voneinander Wasserstoff, Hydroxy oder Methoxy sind, mit der Massgabe dass mindestens ein der Symbole R''_1 und R''_2 Hydroxy ist; und

R_3 und R_4 die für die Formel I angegebenen Bedeutungen haben,

wird eine Verbindung der Formel VI,



(VI)

worin die Ringe A und B trans-kondensiert sind,

R'''_1 und R'''_2 jeweils unabhängig voneinander Wasserstoff, Hydroxy oder Methoxy sind, mit der Massgabe, dass mindestens ein der Symbole R'''_1 und R'''_2 Methoxy ist, und

R_3 und R_4 die für Formel I angegebenen Bedeutungen haben.

einer Etherspaltung unterworfen,

f) ein Benzo[g]chinolin der Formel I wie vorstehend definiert, worin R_4 eine Carboxygruppe, oder ein reaktives Derivat hiervon, wird mit einem Amin der Formel $HN(R_6)R_7$, worin R_6 und R_7 die für Formel I angegebenen Bedeutungen haben, umgesetzt zur Herstellung der entsprechend amidierten Benzo[g]chinoline der Formel I oder

ein Benzo[g]chinolin der Formel I wie vorstehend definiert, worin mindestens ein der Reste R_1 , R_2 und R_4 eine Hydroxygruppe (im Fall von R_1 und R_2) oder eine Hydroxymethylgruppe ist (im Fall von R_4) oder ein Benzo[g]chinolin der Formel I wie vorstehend definiert, worin R_4 eine Carboxygruppe oder ein reaktives Derivat hiervon ist, wird mit einer geeigneten Säure oder einem reaktiven Derivat hiervon, oder mit einem geeigneten Alkohol umgesetzt, zur Herstellung der entsprechenden acylierten oder veresterten Benzo[g]chinoline der Formel I;

und die so erhaltene Verbindung der Formel I in freier Form oder in Salzform gewonnen wird.

13. Ein pharmazeutisches Präparat enthaltend eine Verbindung gemäss einem der Ansprüche 1 bis 11 in freier Form oder in pharmazeutisch annehmbarer Salzform, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Carrier hierfür.

14. Eine Verbindung gemäss einem der Ansprüche 1 bis 11 in freier Form oder in pharmazeutisch annehmbarer Salzform zur Anwendung als Pharmazeutikum.

15. Eine Verbindung gemäss einem der Ansprüche 1 bis 11 in freier Form oder in pharmazeutisch annehmbarer Salzform zur Verwendung als Prolaktinsekretionshemmer, dopaminergisches Mittel oder Dopaminrezeptor-stimulierendes Mittel.

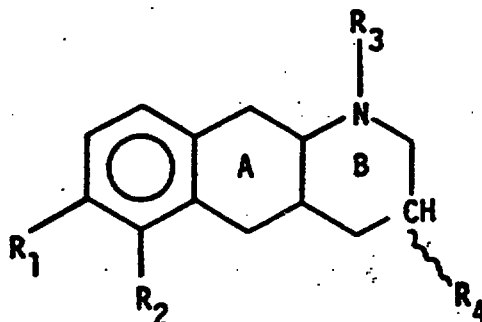
16. Verwendung einer Verbindung gemäss einem der Ansprüche 1 bis 11 zur Herstellung eines Arzneimittels geeignet für die Behandlung von Zuständen und Störungen, welche mit Prolaktinsekretion zusammenhängen, die Behandlung von Morbus Parkinson, oder von anderen Störungen, die mit einem dopaminergischen Mittel zu behandeln sind.

17. Verwendung einer Verbindung gemäss einem der Ansprüche 1 bis 11 zur Herstellung eines Arzneimittels geeignet für die Verwendung als Prolaktinsekretionshemmer.

18. Verwendung einer Verbindung gemäss einem der Ansprüche 1 bis 11 zur Herstellung eines Arzneimittels geeignet für die Verwendung zur Behandlung von Galaktorrhoe, prämenstruellen Beschwerden, hyperprolaktinemischen Hypogonadismus oder Prolaktinoma oder für die Anwendung als Laktationshemmer.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines Benzo[g]chinolins der Formel I,



(I)



worin die Ringe A und B trans-kondensiert sind und worin

R_1 und R_2 jeweils unabhängig voneinander Wasserstoff, Hydroxy oder Methoxy bedeuten, mit der Massgabe, dass R_1 und R_2 beide nicht für Wasserstoff stehen können;

R_3 Wasserstoff oder C_{1-4} Alkyl ist;

R_4 $-\text{COOH}$, $-\text{CH}_2\text{OR}_5$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ oder $-\text{NHCON}(\text{R}_9)\text{R}_{10}$ ist,

R_5 Wasserstoff oder C_{1-3} Alkyl ist,

R_6 Wasserstoff oder C_{1-3} Alkyl ist, und

R_7 Wasserstoff, C_{1-3} Alkyl, Phenyl oder Pyridyl, wobei das Phenyl oder Pyridyl gegebenenfalls durch Halogen, Methyl oder Methoxy substituiert ist, oder

R_6 und R_7 zusammen $-(\text{CH}_2)_4-$, $(\text{CH}_2)_5-$ oder $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ sind,

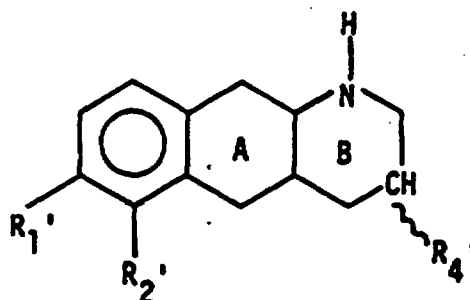
R_8 C_{1-4} Alkyl oder Pyridyl, wobei das Pyridyl gegebenenfalls durch Halogen, Methyl oder Methoxy substituiert ist, und

R_9 und R_{10} jeweils unabhängig voneinander Wasserstoff oder C_{1-3} Alkyl oder zusammen $-(\text{CH}_2)_4-$ oder $(\text{CH}_2)_5-$ sind,

oder eines physiologisch hydrolysierbaren und physiologisch annehmbaren Esters hiervon, in freier Form oder in Salzform,

wobei das Verfahren umfasst:

a) zur Herstellung einer Verbindung der Formel I¹,

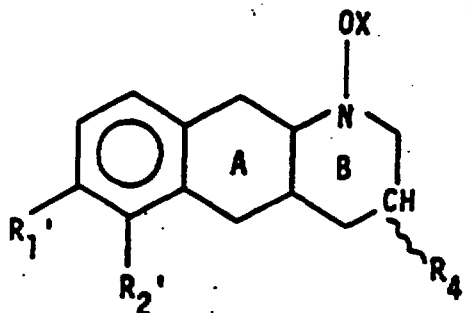
(I¹)

worin die Ringe A und B trans-kondensiert sind,

R_1' und R_2' jeweils unabhängig voneinander Wasserstoff oder Methoxy bedeuten, mit der Massgabe, dass R_1' und R_2' nicht beide Wasserstoff sein können,

R_4' $-\text{CH}_2\text{OR}_5$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$ oder $-\text{CH}_2\text{SR}_8$ oder verestertes $-\text{COOH}$ oder verestertes $-\text{CH}_2\text{OH}$ ist und

R_5 , R_6 , R_7 und R_8 die für Formel I angegebenen Bedeutungen haben, wird eine Verbindung der Formel II,

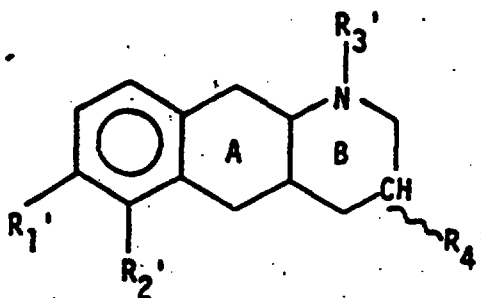


(II)

worin die Ringe A und B trans-kondensiert sind, X für Benzyl oder C_{1-4} Alkyl steht und R_1' , R_2' und R_4' die für Formel I¹ angegebenen Bedeutungen haben,

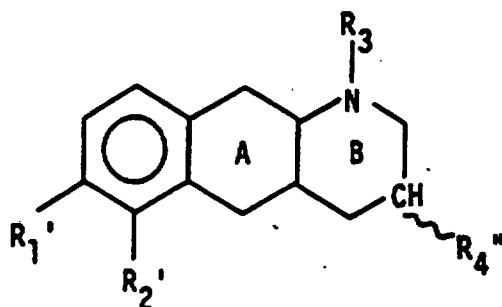
einer Spaltung unterworfen, so dass die Benzyloxy- oder C_{1-4} Alkoxygruppe abgespalten wird,

b) zur Herstellung einer Verbindung der Formel I²,

(I²)

worin die Ringe A und B trans-kondensiert sind, R_3 C_{1-4} Alkyl ist und R_1' , R_2' und R_4'' die für Formel I³ angegebenen Bedeutungen haben, wird eine Verbindung der Formel I³ wie oben definiert alkyliert, um eine C_{1-4} Alkylgruppe in Stellung 1 einzuführen;

c) zur Herstellung einer Verbindung der Formel I³,

(I³)

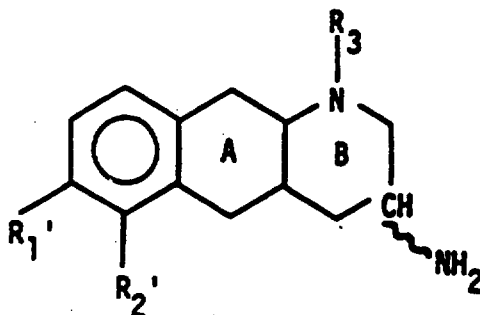
worin die Ringe A und B trans-kondensiert sind,

R''_4 -NHSO₂N(R₉)R₁₀ oder —NHCON(R₉)R₁₀ ist,

R_3 , R_9 und R_{10} die für Formel I angegebenen Bedeutungen haben und

R_1' und R_2' die für Formel I¹ angegebenen Bedeutungen haben,

wird eine Verbindung der Formel III,



(III)

worin die Ringe A und B trans-kondensiert sind und R_1' , R_2' und R_3 wie oben für Formel I³ definiert sind, mit einer Aminosulfonsäure oder Aminocarbonsäure oder einem reaktiven Derivat hiervon, z.B. mit einer Verbindung der Formel IVa oder IVb,



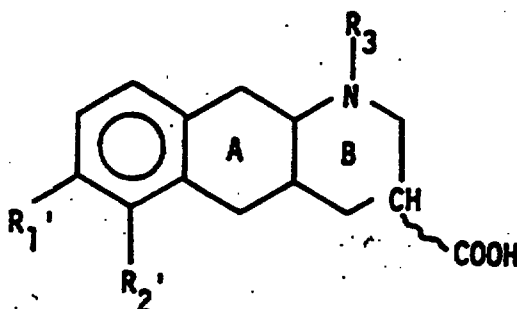
(IVa)



(IVb)

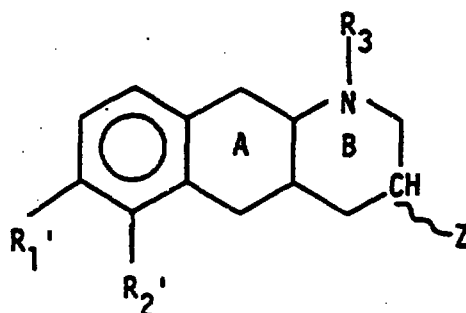
worin R_9 und R_{10} die für Formel I angegebenen Bedeutungen haben, oder einem reaktiven Derivat hiervon, umgesetzt,

d) zur Herstellung einer Verbindung der Formel I⁴,

(I⁴)

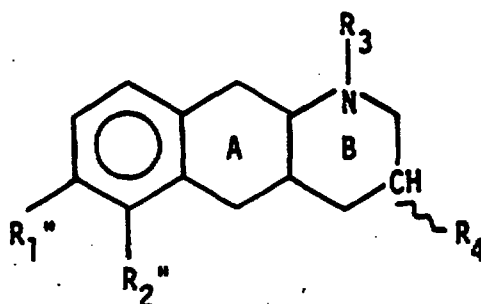
worin die Ringe A und B trans-kondensiert sind und worin R_1' und R_2' die für Formel I¹ angegebenen Bedeutungen haben und R_3 die für Formel I angegebene Bedeutung hat, wird eine Verbindung der Formel V hydrolysiert,



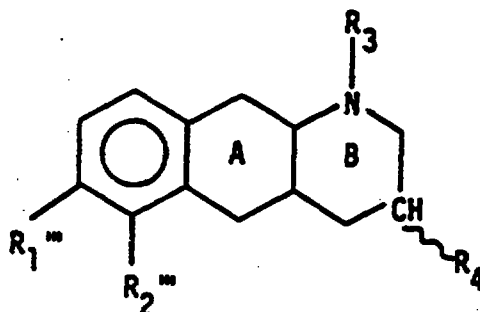


(V)

worin die Ringe A und B trans-kondensiert sind, Z eine veresterte Carboxygruppe und R_1' , R_2' und R_3 wie oben für die Formel I⁴ definiert sind,
e) zur Herstellung einer Verbindung der Formel I⁵,

(I⁵)

worin die Ringe A und B trans-kondensiert sind,
 R_1'' und R_2'' jeweils unabhängig voneinander Wasserstoff, Hydroxy oder Methoxy sind, mit der Massgabe dass mindestens ein der Symbole R_1'' und R_2'' Hydroxy ist, und
 R_3 und R_4 die für die Formel I angegebenen Bedeutungen haben,
wird eine Verbindung der Formel VI,



(VI)

worin die Ringe A und B trans-kondensiert sind,
 R_1''' und R_2''' jeweils unabhängig voneinander Wasserstoff, Hydroxy oder Methoxy sind, mit der Massgabe, dass mindestens ein der Symbole R_1''' und R_2''' Methoxy ist, und
 R_3 und R_4 die für Formel I angegebenen Bedeutungen haben,
einer Etherspaltung unterworfen,

f) ein Benzo[g]chinolin der Formel I wie vorstehend definiert, worin R_4 eine Carboxygruppe oder ein reaktives Derivat hiervon, wird mit einem Amin der Formel $\text{HN}(R_6)R_7$, worin R_6 und R_7 die für Formel I angegebenen Bedeutungen haben, umgesetzt zur Herstellung der entsprechend amidierten Benzo[g]chinoline der Formel I oder

ein Benzo[g]chinolin der Formel I wie vorstehend definiert, worin mindestens ein der Reste R_1 , R_2 und R_4 eine Hydroxygruppe (im Fall von R_1 und R_2) oder eine Hydroxymethylgruppe ist (im Fall von R_4) oder ein Benzo[g]chinolin der Formel I wie vorstehend definiert, worin R_4 eine Carboxygruppe oder ein reaktives Derivat hiervon ist, wird mit einer geeigneten Säure oder einem reaktiven Derivat hiervon, oder mit einem geeigneten Alkohol umgesetzt, zur Herstellung der entsprechenden acylierten oder veresterten Benzo[g]chinoline der Formel I;

und die so erhaltene Verbindung der Formel I in freier Form oder in Salzform gewonnen wird.

2. Verfahren gemäß Anspruch 1 zur Herstellung eines Benzo[g]chinolins der Formel I wie in Anspruch 1 veranschaulicht, worin ein der Symbole R_1 und R_2 Wasserstoff und das andere Hydroxy ist,



R_3 n-Propyl ist,
 R_4 —NHSO₂N(R_9) R_{10} ist,
 R_9 Ethyl ist, und
 R_{10} Ethyl ist,

5 oder ein physiologisch annehmbares und physiologisch hydrolysierbares Ester hiervon, in freier Form oder in Salzform.

3. Verfahren gemäss Anspruch 1 zur Herstellung von 1-n-Propyl-3 α -diethylsulfamoylamino-6-hydroxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]chinolin (Razemat), wobei das Verfahren das Unterwerfen von 1-n-Propyl-3 α -diethylsulfamoylamino-6-methoxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]chinolin einer
 10 Aetherabspaltung umfasst.

4. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, das das Beimengen einer Verbindung der Formel I, I¹, I², I³, I⁴, I⁵ wie im Anspruch 1 definiert, in freier Form oder in pharmazeutisch annehmbarer Salzform, mit einem pharmazeutischen Träger oder Verdünnungsmittel umfasst.

5. Verfahren gemäss Anspruch 4, wobei das Benzo[g]chinolin 1-n-Propyl-3 α -diethylsulfamoylamino-6-hydroxy-1,2,3,4,4a α ,5,10,10a β -octahydro-benzo[g]chinolin (Razemat) in freier Form oder in pharmazeutisch annehmbarer Salzform ist.

6. Verwendung einer Verbindung der Formel I, I¹, I², I³, I⁴, I⁵ wie in Anspruch 1 definiert, in freier oder in pharmazeutisch annehmbarer Salzform, zur Herstellung eines Arzneimittels geeignet für die Behandlung von Zuständen und Störungen, welche mit Prolaktinsekretion zusammenhängen, die Behandlung von
 20 Morbus Parkinson, oder von anderen Störungen, die mit einem dopaminergischen Mittel zu behandeln sind.

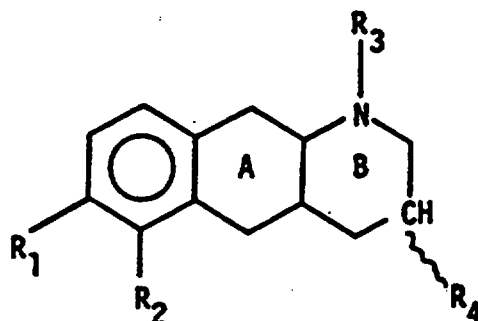
7. Verwendung gemäss Anspruch 6, wobei das Benzo[g]chinolin wie in Anspruch 5 definiert ist.

8. Verwendung einer in Anspruch 4 oder 5 angegebenen Verbindung zur Herstellung eines Arzneimittels geeignet für die Verwendung als Prolaktinsekretionshemmer.

9. Verwendung einer in Anspruch 4 oder 5 angegebenen Verbindung zur Herstellung eines
 25 Arzneimittels geeignet für die Verwendung zur Behandlung von Galaktorrhoe, prämenstruellen Beschwerden, hyperprolaktinemischen Hypogonadismus oder Prolaktinoma oder für die Anwendung als Laktationshemmer.

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

1. Une benzo[g]quinoléine de formule I



(I)

dans laquelle les cycles A et B sont condensés trans et dans laquelle

R_1 et R_2 signifient chacun indépendamment l'hydrogène ou un groupe hydroxy ou méthoxy, avec la condition que R_1 et R_2 ne signifient pas tous les deux l'hydrogène,

50 R_3 signifie l'hydrogène ou un groupe alkyle en C₁₋₄.

R_4 signifie —COOH, —CH₂OR₈, —CH₂CN, —CON(R_6) R_7 , —CH₂SR₈, —NHSO₂N(R_9) R_{10} ou —NHCON(R_9) R_{10} .

R_5 signifie l'hydrogène ou un groupe alkyle en C₁₋₃.

R_6 signifie l'hydrogène ou un groupe alkyle en C₁₋₃ et

55 R_7 signifie l'hydrogène ou un groupe alkyle en C₁₋₃, phényle ou pyridyle, lesdits groupes phényle ou pyridyle étant éventuellement substitués par de l'halogène ou des groupes méthyle ou méthoxy, ou bien R_6 et R_7 signifient ensemble —(CH₂)₄—, —(CH₂)₅— ou —(CH₂)₂—O—(CH₂)₂—,

R_8 signifie un groupe alkyle en C₁₋₄ ou pyridyle, ledit groupe pyridyle étant éventuellement substitué par de l'halogène ou des groupes méthyle ou méthoxy et

60 R_9 et R_{10} signifient chacun indépendamment l'hydrogène ou un groupe alkyle en C₁₋₃ ou signifient ensemble —(CH₂)₄— ou —(CH₂)₅—,

ou un ester physiologiquement hydrolysable et physiologiquement acceptable de ce composé, sous forme libre ou sous forme d'un sel.

2. Un composé selon la revendication 1, sous forme d'un racémique.

65 3. Une benzo[g]quinoléine de formule I comme illustré à la revendication 1, dans laquelle



R_1 et R_2 signifient tous les deux un groupe hydroxy ou tous les deux un groupe méthoxy, ou bien l'un de R_1 et R_2 signifie l'hydrogène et l'autre signifie un groupe hydroxy ou méthoxy,

R_3 signifie un groupe alkyle en C_{1-4} ,

R_4 signifie $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ ou $-\text{NHCON}(\text{R}_9)\text{R}_{10}$,

R_5 signifie l'hydrogène ou un groupe alkyle en C_{1-3} ,

R_7 signifie un groupe pyridyle éventuellement substitué par de l'halogène ou des groupes méthyle ou méthoxy et

R_6 , R_9 et R_{10} ont les significations indiquées à la revendication 1, ou un ester physiologiquement hydrolysable et physiologiquement acceptable de ce composé, sous forme libre ou sous forme d'un sel d'addition d'acide.

4. Un composé selon la revendication 3, sous forme d'un racémique.

5. Un benzo[g]quinoléine de formule I comme illustré à la revendication 1, dans laquelle R_1 , R_2 et R_3 ont les significations indiquées à la revendication 1,

R_4 signifie $-\text{COOH}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ ou $\text{NHCON}(\text{R}_9)\text{R}_{10}$,

et R_6 , R_7 , R_8 , R_9 et R_{10} ont les significations indiquées à la revendication 1, ou un ester physiologiquement hydrolysable et physiologiquement acceptable de ce composé, sous forme libre ou sous forme d'un sel d'addition d'acide.

6. Un composé selon la revendication 5, sous forme d'un racémique.

7. Une benzo[g]quinoléine de formule I comme illustré à la revendication 1, dans laquelle l'un de R_1 et R_2 signifie l'hydrogène et l'autre signifie un groupe hydroxy,

R_3 signifie un groupe n-propyle,

R_4 signifie $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$,

R_5 signifie un groupe éthyle et

R_{10} signifie un groupe éthyle,

ou un ester physiologiquement hydrolysable et physiologiquement acceptable de ce composé, sous forme libre ou sous forme d'un sel.

8. La 1-n-propyl-3 α -diéthylsulfamoylamino-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (racémique), sous forme libre ou sous forme d'un sel d'addition d'acide.

9. Un composé choisi dans le groupe comprenant

la 3 β -méthylthiométhyl-7-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (racémique),

la 1-n-propyl-3 β -méthylthiométhyl-7-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (racémique); et

la 1-n-propyl-3 β -méthylthiométhyl-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (racémique),

ledit composé étant sous forme libre ou sous forme d'un sel d'addition d'acide.

10. Un composé choisi dans le groupe comprenant

la 3 α -Méthoxycarbonyl-6-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-n-Propyl-3 α -méthoxycarbonyl-6-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-n-Propyl-3 α -diéthylsulfamoylamino-6-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 3 β -Méthylthiométhyl-6-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-n-Propyl-3 β -méthylthiométhyl-6-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-n-Propyl-3 β -méthylthiométhyl-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 3 α -Méthoxycarbonyl-7-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-n-Propyl-3 α -méthoxycarbonyl-7-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-n-Propyl-3 α -diéthylsulfamoylamino-7-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-n-Propyl-3 α -diéthylsulfamoylamino-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

le 7-Hydroxy-N-(2-méthoxy-5-pyridyl)-1-méthyl-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine-3 β -carboxamide (Racémique);

ledit composé étant sous forme libre ou sous forme d'un sel d'addition d'acide.

11. Un composé choisi dans le groupe comprenant

la 3 β -Méthoxycarbonyl-6-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-Méthyl-3 β -méthoxycarbonyl-6-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-Méthyl-3 β -methoxycarbonyl-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-Méthyl-3 β -carboxy-6-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

le 6-Hydroxy-N-(2-méthoxy-5-pyridyl)-1-méthyl-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine-



3 β -carboxamide (Racémique);

la 3 β -Méthoxycarbonyl-7-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-Méthyl-3 β -méthoxycarbonyl-7-méthoxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

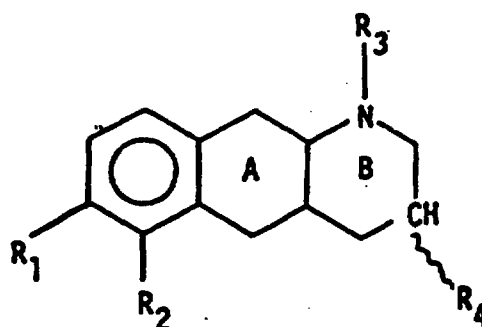
la 1-Méthyl-3 β -méthoxycarbonyl-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-Méthyl-3 β -carboxy-7-hydroxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

la 1-n-Propyl-3 β -diéthylsulfamoylamino-6-benzoyloxy-1,2,3,4,4a,5,10,10a β -octahydro-benzo[g]quinoléine (Racémique);

ledit composé étant sous forme libre ou sous forme d'un sel.

12. Procédé de préparation d'une benzo[g]quinoléine de formule I



(I)

dans laquelle les cycles A et B sont condensés trans et dans laquelle

R₁ et R₂ signifient chacun indépendamment l'hydrogène ou un groupe hydroxy ou méthoxy, avec la condition que R₁ et R₂ ne signifient pas tous les deux l'hydrogène,

R₃ signifie l'hydrogène ou un groupe alkyle en C₁₋₄,

R₄ signifie —COOH, —CH₂OR₆, —CH₂CN, —CON(R₆)R₇, —CH₂SR₈, —NHSO₂N(R₉)R₁₀ ou —NHCON(R₉)R₁₀,

R₅ signifie l'hydrogène ou un groupe alkyle en C₁₋₃,

R₆ signifie l'hydrogène ou un groupe alkyle en C₁₋₃ et

R₇ signifie l'hydrogène ou un groupe alkyle en C₁₋₃, phényle ou pyridyle, lesdits groupes phényle ou pyridyle étant éventuellement substitués par de l'halogène ou des groupes méthyle ou méthoxy, ou bien

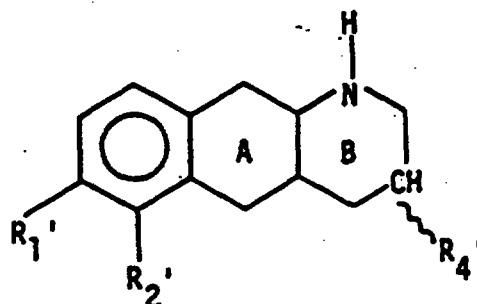
R₈ et R₉ signifient ensemble —(CH₂)₄—, —(CH₂)₅— ou —(CH₂)₂—O—(CH₂)₂—,

R₁₀ signifie un groupe alkyle en C₁₋₄ ou pyridyle, ledit groupe pyridyle étant éventuellement substitué par de l'halogène ou des groupes méthyle ou méthoxy et

R₅ et R₁₀ signifient chacun indépendamment l'hydrogène ou un groupe alkyle en C₁₋₃ ou signifient ensemble —(CH₂)₄— ou —(CH₂)₅—,

ou d'un ester physiologiquement hydrolysable et physiologiquement acceptable de ce composé, sous forme libre ou sous forme d'un sel, lequel procédé comprend

a) pour la préparation d'un composé de formule I'



(I')

dans laquelle les cycles A et B sont condensés trans,

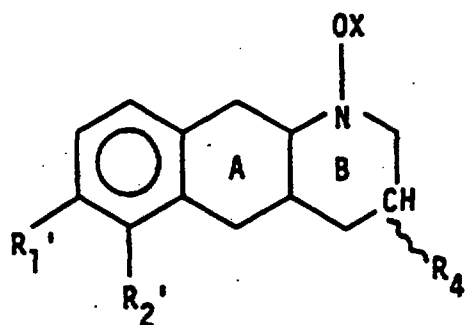
R₁' et R₂' signifient chacun indépendamment l'hydrogène ou un groupe méthoxy, avec la condition que R₁' et R₂' ne signifient pas tous les deux l'hydrogène,

R₄' signifie —CH₂OR₅, —CH₂CN, —CON(R₆)R₇ ou —CH₂SR₈ ou —COOH estérifié ou —CH₂OH estérifié et

R₅, R₆, R₇ et R₈ ont les significations indiquées pour la formule I,

le fait de soumettre un composé de formule II

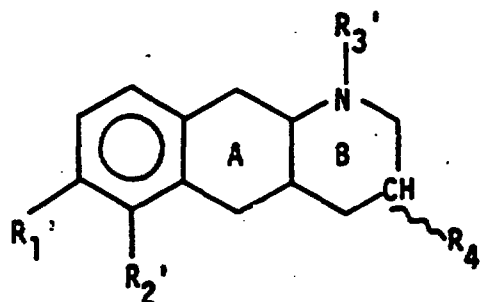




(II)

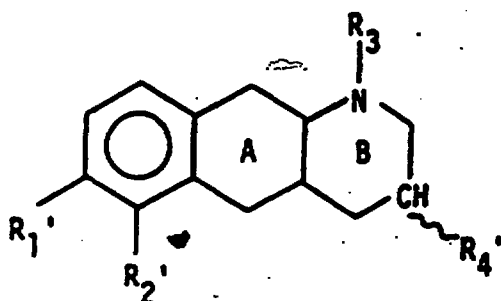
dans laquelle les cycles A et B sont condensés trans, X signifie un groupe benzyle ou alkyle en C₁₋₄ et R₁, R₂' et R₄' ont les significations indiquées pour la formule I¹, à un clivage afin d'éliminer le groupe benzyloxy ou alcoxy en C₁₋₄.

b) pour la préparation d'un composé de formule I²

(I²)

dans laquelle les cycles A et B sont condensés trans, R₃' signifie un groupe alkyle en C₁₋₄ et R₁', R₂' et R₄' ont les significations indiquées pour la formule I¹, l'alkylation d'un composé de formule I¹ comme défini plus haut pour introduire un groupe alkyle en C₁₋₄ en position 1.

c) pour la préparation d'un composé de formule I³

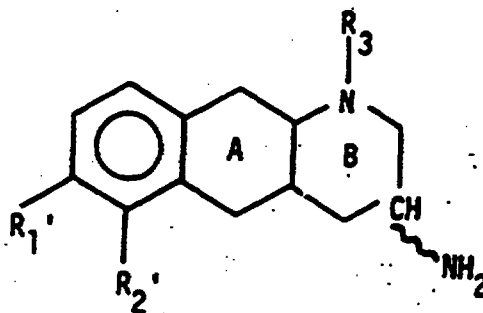
(I³)

dans laquelle les cycles A et B sont condensés trans,

R₄'' signifie —NHSO₂N(R₉)R₁₀ ou —NHCON(R₉)R₁₀.

R₃, R₉ et R₁₀ ont les significations indiquées pour la formule I et

R₁' et R₂' ont les significations indiquées pour la formule I¹, la réaction d'un composé de formule III

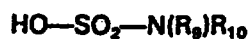


(III)

dans laquelle les cycles A et B sont condensés trans et R₁', R₂' et R₃ sont tels que définis plus haut pour la



formule I³, avec un acide aminosulfonique ou aminocarboxylique ou un dérivé réactif de ce composé, par exemple avec un composé de formule IVa ou IVb



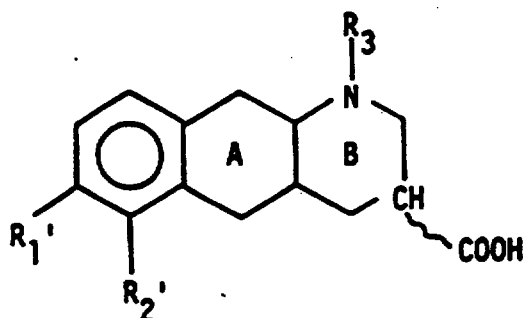
(IVa)



(IVb)

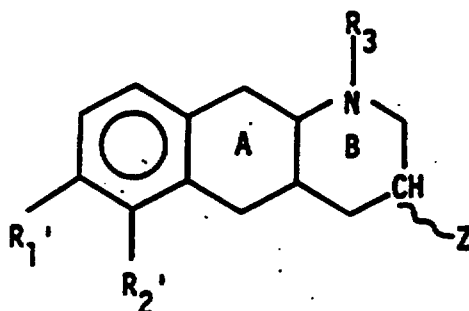
dans lesquelles R₉ et R₁₀ ont les significations indiquées pour la formule I, ou un dérivé réactif de ce composé,

d) pour la préparation d'un composé de formule I⁴



(I⁴)

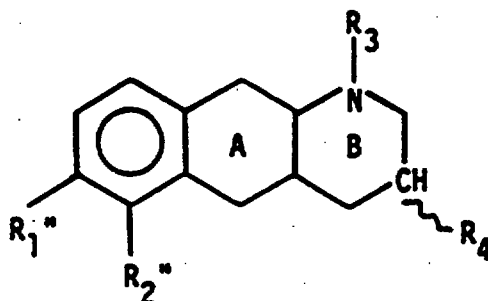
dans laquelle les cycles A et B sont condensés trans et dans lesquelles R₁' et R₂' ont les significations indiquées pour la formule I¹ et R₃ a la signification indiquée pour la formule I, l'hydrolyse d'un composé de formule V



(V)

dans laquelle les cycles A et B sont condensés trans, Z signifie un groupe carboxy estérifié et R₁', R₂' et R₃ sont tels que définis plus haut pour la formule I¹,

e) pour la préparation d'un composé de formule I⁵



(I⁵)

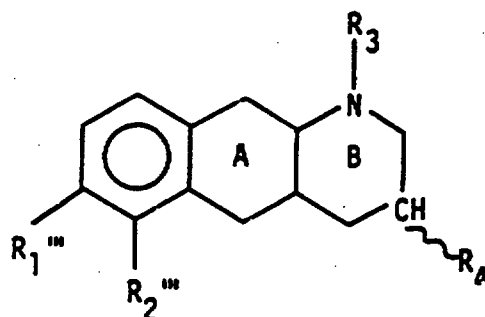
dans laquelle les cycles A et B sont condensés trans,

R₁'' et R₂'' signifient chacun indépendamment l'hydrogène ou un groupe hydroxy ou méthoxy, avec la condition qu'au moins un de R₁'' et R₂'' signifie un groupe hydroxy, et

R₃ et R₄ ont les significations indiquées pour la formule I,

la fait de soumettre un composé de formule VI





(VI)

dans laquelle les cycles A et B sont condensés trans,

R_1''' et R_2''' significant chacun indépendamment l'hydrogène ou un groupe hydroxy ou méthoxy, avec la condition qu'au moins un de R_1''' et R_2''' , signifie un groupe méthoxy et

R_3 et R_4 ont les significations indiquées pour la formule I, à un clivage du groupe éther,

f) la réaction d'une benzo[g]quinoléine de formule I comme définie plus haut dans laquelle R_4 signifie un groupe carboxy ou un dérivé réactif de ce composé, avec une amine de formule $HN(R_5)_2$, où R_5 et R_7 ont les significations indiquées pour la formule I, pour préparer les benzo[g]quinoléines ar. les correspondantes de formule I, ou la réaction d'une benzo[g]quinoléine de formule I telle que définie plus haut dans laquelle au moins un des restes R_1 , R_2 et R_4 signifie un groupe hydroxy (dans le cas de R_1 et R_2) ou un groupe hydroxyméthyle (dans le cas de R_4), ou d'une benzo[g]quinoléine de formule I telle que définie plus haut dans laquelle R_4 signifie un groupe carboxy ou un dérivé réactif de ce composé, avec un acide approprié ou un dérivé réactif de ce composé, ou avec un alcool approprié, pour préparer la benzo[g]quinoléine acylée ou estérifiée correspondante de formule I, et la récupération du composé de formule I ainsi obtenu sous forme libre ou sous forme d'un sel.

13. Une composition pharmaceutique comprenant un composé tel que revendiqué à l'une quelconque des revendications 1 à 11, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable, ensemble avec un diluant ou un véhicule pharmaceutiquement acceptable.

14. Un composé tel que revendiqué à l'une quelconque des revendications 1 à 11, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable, pour l'utilisation comme médicament.

15. Un composé tel que revendiqué à l'une quelconque des revendications 1 à 11, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable, pour l'utilisation comme inhibiteur de la sécrétion de la prolactine, comme agent dopaminergique ou comme agent stimulant les récepteurs de la dopamine.

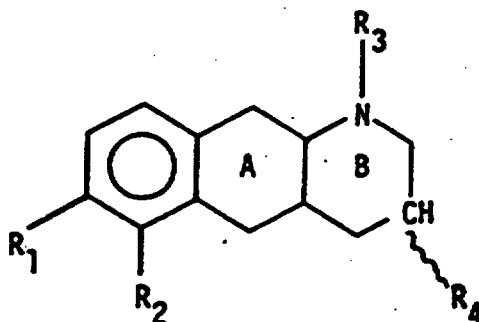
16. Utilisation d'un composé selon l'une quelconque des revendications 1 à 11, pour la préparation d'un médicament approprié pour le traitement de conditions ou de troubles ayant une étiologie comprenant ou associée à la sécrétion de la prolactine, ou pour le traitement de la maladie de Parkinson, ou d'autres conditions devant être traitées par un agent dopaminergique.

17. Utilisation d'un composé selon l'une quelconque des revendications 1 à 11, pour la préparation d'un médicament approprié pour l'utilisation comme inhibiteur de la sécrétion de la prolactine.

18. Utilisation d'un composé selon l'une quelconque des revendications 1 à 11, pour la préparation d'un médicament approprié pour l'utilisation dans le traitement de la galactorrhée, des troubles prémenstruels, de l'hypogonadisme hyperprolactinémique ou de la prolactinémie ou pour l'utilisation comme inhibiteur de la lactation.

Revendications pour l'Etat contractant : AT

1. Procédé de préparation d'une benzo[g]quinoléine de formule I



(I)

dans laquelle les cycles A et B sont condensés trans et dans laquelle

R_1 et R_2 signifient chacun indépendamment l'hydrogène ou un groupe hydroxy ou méthoxy, avec la condition que R_1 et R_2 ne signifient pas tous les deux l'hydrogène,



R_3 signifie l'hydrogène ou un groupe alkyle en C_{1-4} .

R_4 signifie $-\text{COOH}$, $-\text{CH}_2\text{OR}_5$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$, $-\text{CH}_2\text{SR}_8$, $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ ou $-\text{NHCON}(\text{R}_9)\text{R}_{10}$.

R_5 signifie l'hydrogène ou un groupe alkyle en C_{1-3} .

R_6 signifie l'hydrogène ou un groupe alkyle en C_{1-3} et

R_7 signifie l'hydrogène ou un groupe alkyle en C_{1-3} , phényle ou pyridyle, lesdits groupes phényle ou pyridyle étant éventuellement substitués par de l'halogène ou des groupes méthyle ou méthoxy, ou bien

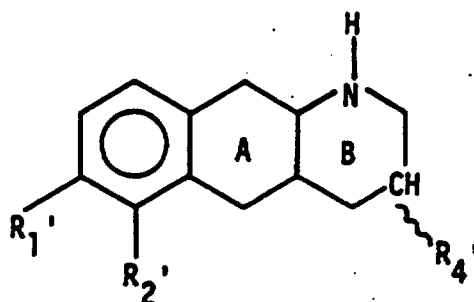
R_6 et R_7 signifient ensemble $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$ ou $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$.

R_8 signifie un groupe alkyle en C_{1-4} ou pyridyle, ledit groupe pyridyle étant éventuellement substitué par de l'halogène ou des groupes méthyle ou méthoxy et

R_9 et R_{10} signifient chacun indépendamment l'hydrogène ou un groupe alkyle en C_{1-3} ou signifient ensemble $-(\text{CH}_2)_4-$ ou $-(\text{CH}_2)_5-$.

ou d'un ester physiologiquement hydrolysable et physiologiquement acceptable de ce composé, sous forme libre ou sous forme d'un sel, lequel procédé comprend:

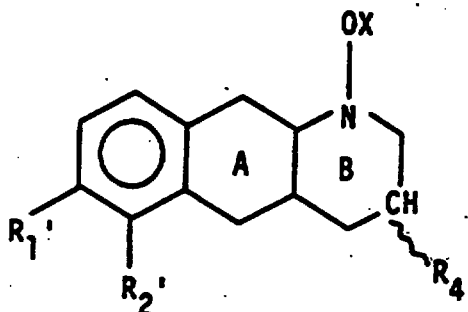
a) pour la préparation d'un composé de formule I'



dans laquelle les cycles A et B sont condensés trans,

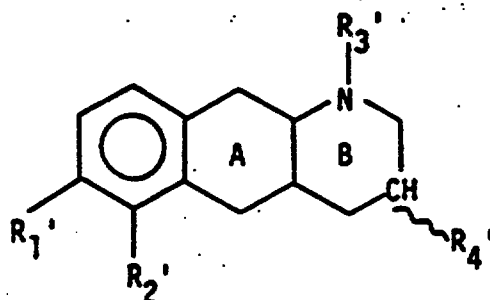
R_1' et R_2' signifient chacun indépendamment l'hydrogène ou un groupe méthoxy, avec la condition que R_1' et R_2' ne signifient pas tous les deux l'hydrogène.

R_4' signifie $-\text{CH}_2\text{OR}_5$, $-\text{CH}_2\text{CN}$, $-\text{CON}(\text{R}_6)\text{R}_7$ ou $-\text{CH}_2\text{SR}_8$ ou $-\text{COOH}$ estérifié ou $-\text{CH}_2\text{OH}$ estérifié et R_5 , R_6 , R_7 et R_8 ont les significations indiquées pour la formule I, le fait de soumettre un composé de formule II



dans laquelle les cycles A et B sont condensés trans, X signifie un groupe benzyle ou alkyle en C_{1-4} et R_1' , R_2' et R_4' ont les significations indiquées pour la formule I', à un clivage afin d'éliminer le groupe benzyloxy ou alcoxy en C_{1-4} .

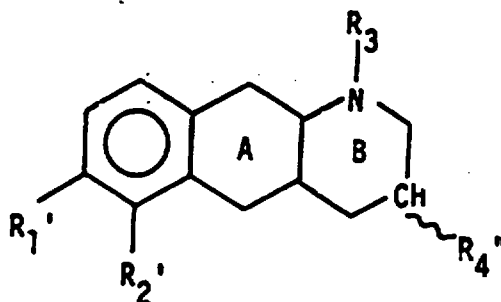
b) pour la préparation d'un composé de formule I²



dans laquelle les cycles A et B sont condensés trans, R_3' signifie un groupe alkyle en C_{1-4} et R_1' , R_2' et R_4' ont les significations indiquées pour la formule I', l'alkylation d'un composé de formule I' comme défini plus haut pour introduire un groupe alkyle en C_{1-4} en position 1.

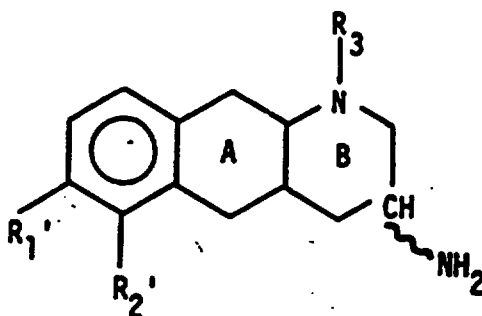


c) pour la préparation d'un composé de formule I³



(I³)

dans laquelle les cycles A et B sont condensés trans,
 R_4'' signifie $-\text{NHSO}_2\text{N}(\text{R}_9)\text{R}_{10}$ ou $-\text{NHCON}(\text{R}_9)\text{R}_{10}$,
 R_3 , R_9 et R_{10} ont les significations indiquées pour la formule I et
 R_1' et R_2' ont les significations indiquées pour la formule I',
 la réaction d'un composé de formule III



(III)

dans laquelle les cycles A et B sont condensés trans et R_1' , R_2' et R_3 sont tels que définis plus haut pour la
 formule I³, avec un acide aminosulfonique ou aminocarboxylique ou un dérivé réactif de ce composé, par
 exemple avec un composé de formule IVa ou IVb



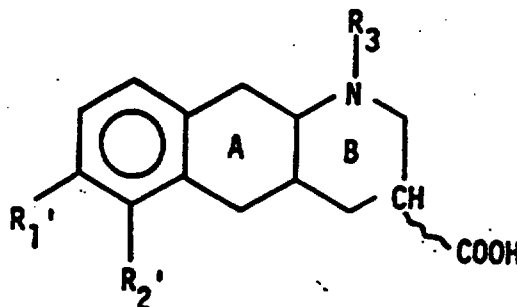
(IVa)



(IVb)

dans lesquelles R_9 et R_{10} ont les significations indiquées pour la formule I, ou un dérivé réactif de ce
 composé,

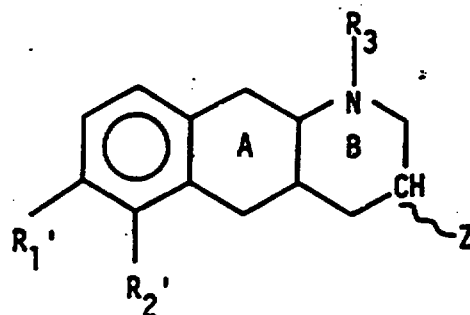
d) pour la préparation d'un composé de formule I⁴



(I⁴)

dans laquelle les cycles A et B sont condensés trans et dans lesquelles R_1' et R_2' ont les significations
 indiquées pour la formule I' et R_3 a la signification indiquée pour la formule I, l'hydrolyse d'un composé de
 formule V

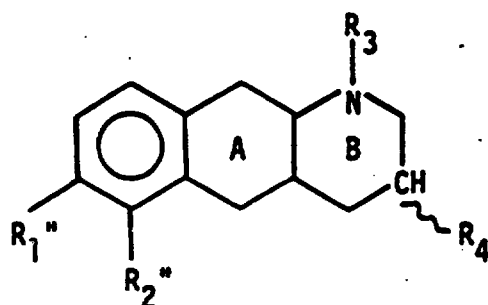




(V)

dans laquelle les cycles A et B sont condensés trans, Z signifie un groupe carboxy estérifié et R_1' , R_2' et R_3 sont tels que définis plus haut pour la formule I⁴,

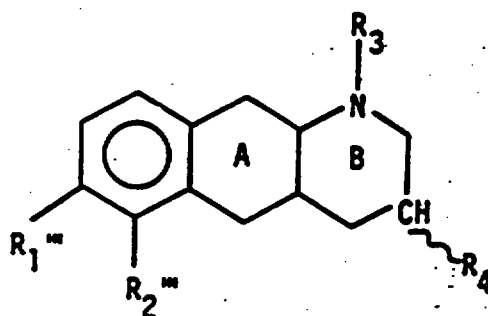
e) pour la préparation d'un composé de formule I⁵

(I⁵)

dans laquelle les cycles A et B sont condensés trans,

R_1'' et R_2'' signifient chacun indépendamment l'hydrogène ou un groupe hydroxy ou méthoxy, avec la condition qu'au moins un de R_1'' et R_2'' signifie un groupe hydroxy, et

R_3 et R_4 ont les significations indiquées pour la formule I, la fait de soumettre un composé de formule VI



(VI)

dans laquelle les cycles A et B sont condensés trans,

R_1''' et R_2''' signifient chacun indépendamment l'hydrogène ou un groupe hydroxy ou méthoxy, avec la condition qu'au moins un de R_1''' et R_2''' signifie un groupe méthoxy et

R_3 et R_4 ont les significations indiquées pour la formule I, à un clivage du groupe éther,

f) la réaction d'une benzo[g]quinoléine de formule I comme définie plus haut dans laquelle R_4 signifie un groupe carboxy ou un dérivé réactif de ce composé, avec une amine de formule $HN(R_6)_2$, où R_6 et R_7 ont les significations indiquées pour la formule I, pour préparer les benzo[g]quinoléines amidées correspondantes de formule I, ou la réaction d'une benzo[g]quinoléine de formule I telle que définie plus haut dans laquelle au moins un des restes R_1 , R_2 et R_4 signifie un groupe hydroxy (dans le cas de R_1 et R_2) ou un groupe hydroxyméthyle (dans le cas de R_4), ou d'une benzo[g]quinoléine de formule I telle que définie plus haut dans laquelle R_4 signifie un groupe carboxy ou un dérivé réactif de ce composé, avec un acide approprié ou un dérivé réactif de ce composé, ou avec un alcool approprié, pour préparer la benzo[g]quinoléine acylée ou estérifiée correspondante de formule I,

et la récupération du composé de formule I ainsi obtenu sous forme libre ou sous forme d'un sel.

2. Procédé selon la revendication 1, pour la préparation d'une benzo[g]quinoléine de formule I comme illustré à la revendication 1, dans laquelle l'un de R_1 et R_2 signifie l'hydrogène et l'autre signifie un groupe hydroxy,



R₃ signifie un groupe n-propyle,

R₄ signifie —NHSO₂N(R₉)R₁₀,

R₉ signifie un groupe éthyle et

R₁₀ signifie un groupe éthyle,

ou un ester physiologiquement hydrolysable et physiologiquement acceptable de ce composé, sous forme libre ou sous forme d'un sel.

3. Procédé selon la revendication 1 pour la préparation de la 1-n-propyl-3α-diéthylsulfamoylamino-6-hydroxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoléine (racémique), lequel procédé comprend la fait de soumettre la 1-n-propyl-3α-diéthylsulfamoylamino-6-méthoxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoléine à un clivage du groupe éther.

4. Un procédé de préparation d'une composition pharmaceutique qui comprend le mélange d'un composé de formule I, I¹, I², I³, I⁴, I⁵ comme défini à la revendication 1, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable, avec un véhicule ou un diluant pharmaceutique.

5. Un procédé selon la revendication 4, dans lequel la benzo[g]quinoléine est la 1-n-propyl-3α-diéthylsulfamoylamino-6-hydroxy-1,2,3,4,4a,5,10,10aβ-octahydro-benzo[g]quinoléine (racémique) sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable.

6. Utilisation d'un composé de formule I, I¹, I², I³, I⁴, I⁵ comme défini à la revendication 1, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable, pour la préparation d'un médicament approprié pour le traitement de conditions ou de troubles ayant une étiologie comprenant ou associée à la sécrétion de la prolactine, le traitement de la maladie de Parkinson, ou d'autres conditions devant être traitées par un agent dopaminergique.

7. Utilisation selon la revendication 6, où la benzo[g]quinoléine est telle que définie à la revendication 5.

8. Utilisation d'un composé spécifié à la revendication 4 ou 5, pour la préparation d'un médicament approprié pour l'utilisation comme inhibiteur de la sécrétion de la prolactine.

9. Utilisation d'un composé spécifié à la revendication 4 ou 5 pour la préparation d'un médicament approprié pour l'utilisation dans le traitement de la galactorrhée, des troubles pré-menstruels, de l'hypogonadisme hyperprolactinémique ou de la prolactinémie ou pour l'utilisation comme inhibiteur de la lactation.

