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(54) Title
OCTAHYDROBENZO(G) QUINOL-3-YL-CARBONYL UREAS

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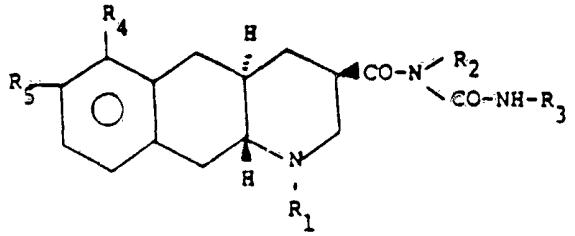
(57) Claim

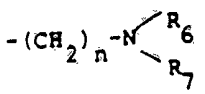
1. A compound of formula I



I

wherein

R_1 is alkyl of 1 to 4 C-atoms, allyl or 2-propinyl, one of groups R_2 and R_3 is alkyl of 1 to 4 C-atoms and the other of these groups R_2 and R_3 is a group of formula



wherein

R_6 and R_7, independently of one another, are CH_3 or

.../2

C_2H_5,

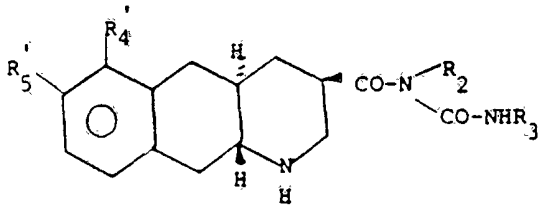
n is 2, 3 or 4,

R_4 and R_5, independently of one another, are hydrogen, hydroxy, methoxy, alkanoyloxy of 1 to 4 C-atoms or benzoyloxy, with the proviso that both cannot simultaneously be hydrogen,

in free base form or in acid addition salt form, in (3R,4aR,10aR) or (3S,4aS,10aS) optical isomer form, or in the form of a mixture of these isomers.

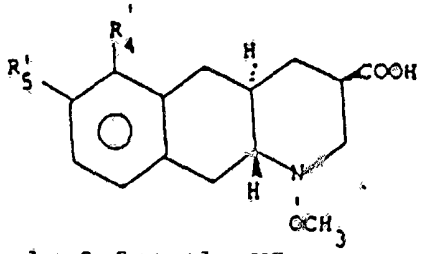
11. A method of inducing prolactin secretion inhibiting activity or dopaminergic receptor agonist activity in a subject which comprises administering a compound of claim 1 in free base form or pharmaceutically acceptable acid addition salt form to a subject in need of such treatment.

12. A compound of formula II



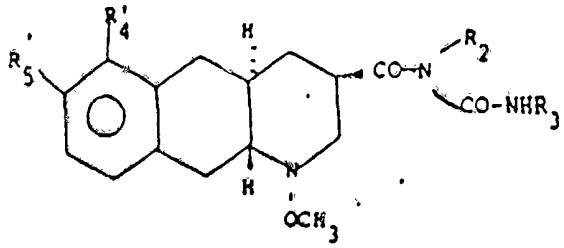
II

a compound of formula IV



IV

or a compound of formula VI



VI

wherein R_2 and R_3 are as defined in claim 1 and wherein R_4' and/or R_5' are methoxy.

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COMPLETE SPECIFICATION 604512

(ORIGINAL)

FOR OFFICE USE

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COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

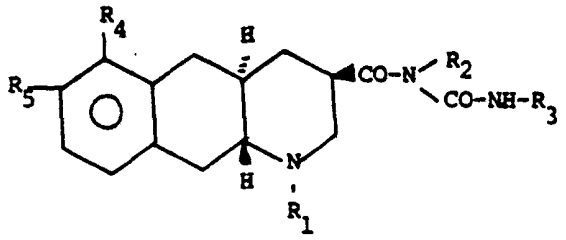
"Octahydrobenzo[g]quinoline-3β-carbonyl-urea derivatives useful as dopamine receptor stimulating and prolactin secretion inhibiting agents".

The following statement is a full description of this invention, including the best method of performing it known to us :-

"Octahydrobenzo[g]quinoline-3β-carbonyl-urea derivatives useful as dopamine receptor stimulating and prolactin secretion inhibiting agents".

This invention relates to octahydrobenzo[g]quinolines.

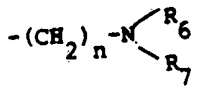
The present invention provides a compound of formula I



I

wherein

R_1 is alkyl of 1 to 4 C-atoms, allyl or 2-propinyl, one of groups R_2 and R_3 is alkyl of 1 to 4 C-atoms and the other of these groups R_2 and R_3 is a group of formula



wherein

R_6 and R_7, independently of one another, are CH_3 or C_2H_5,

n is 2, 3 or 4,

R_4 and R_5, independently of one another, are hydrogen, hydroxy, methoxy, alkanoyloxy of 1 to 4 C-atoms or benzoyloxy, with the proviso that both cannot simultaneously be hydrogen,

in free base form or in acid addition salt form, in (3R,4aR,10aR) or (3S,4aS,10aS) optical isomer form, or in the form of a mixture of these isomers.

In the above formula, as well as in the following description and inthe claims, the formulae of the octahydrobenzo-[g]quinolines cover not just the single stereoisomer shown, but also optical antipodes thereof and mixtures of the optical isomers, e.g. racemates.

The preferred optical isomers are the (3R,4aR,10aR) isomers.

The compounds of formula I may exist in the free base form or in acid addition salt form. The free base forms can be converted in conventional manner into their acid addition salt forms, and vice versa. Thus, the compounds of formula I may form acid addition salt forms, e.g. with inorganic acids such as hydrochloric acid or with organic acids such as maleic acid.

In formula I the following individual definitions and their combinations are preferred:-

R_1 is n-propyl or allyl

R_2 is $-(CH_2)_n-N\begin{matrix}R_6\\R_7\end{matrix}$ especially $-(CH_2)_3-N\begin{matrix}CH_3\\CH_3\end{matrix}$

R_3 alkyl, especially ethyl

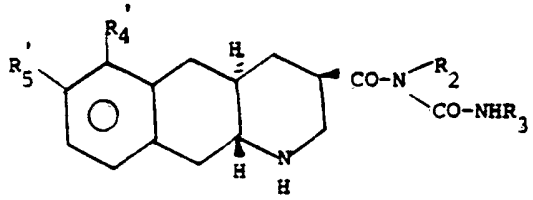
R_4 is OH or OCH_3

R_5 is hydrogen.

The present invention also provides a process for the production of a compound of formula I

wherein

a) in order to produce a compound of formula I, wherein R_4 and R_5, independently of one another are hydrogen or methoxy, with the proviso that both cannot simultaneously be hydrogen, a compound of formula II



II

wherein R_4' and/or R_5' are methoxy, is N-alkylated in position 1, or

b) in order to produce a compound of formula I, wherein R_4 and R_5, independently of one another, are hydrogen or hydroxy, with the proviso that both cannot simultaneously be hydrogen,
a compound of formula I, wherein R_4 and/or R_5 are methoxy, undergoes ether cleavage, or

c) in order to produce a compound of formula I, wherein R_4 and R_5, independently of one another, are hydrogen, alkanoyloxy of 1 to 4 C-atoms or benzoyloxy, with the proviso that both cannot simultaneously be hydrogen,

a compound of formula I, wherein R_4 and/or R_5 are hydroxy, is reacted with an alkanoic acid of 1 to 4 C-atoms or with benzoic acid or with a reactive derivative of such an acid and the compound of formula I is isolated in free base form or acid addition salt form.

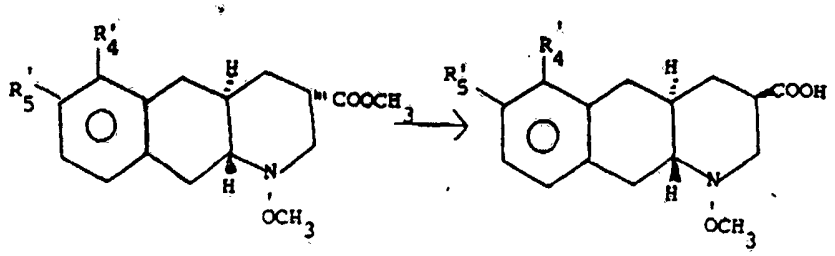
Process a) may be effected in conventional manner for an N-alkylation process. It may take place, e.g. by means of a reaction with a compound of formula R_1Z, wherein Z is a leaving group. Z preferably signifies Cl, Br, I or the acid group of an organic sulphonic acid, e.g. methanesulphonyloxy or p-toxyloxy. The reaction is preferably carried out in the presence of an acid-binding agent, e.g. Na_2CO_3 or an organic base.

The ether cleavage of process b) may take place in conventional manner, e.g. using reactive derivatives of the above-mentioned acids, preferably acid halides or acid anhydrides.

The acylation of process c) may be effected in conventional manner, e.g. using reactive derivatives of the above-mentioned acids, preferably acid halides or acid anhydrides.

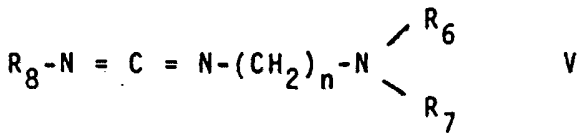
The starting compounds of formula II may be produced for example as follows:-

1) a compound of formula III is isomerized in a basic medium to form a compound of formula IV, with simultaneously hydrolysis of the ester group to a carboxyl group:-



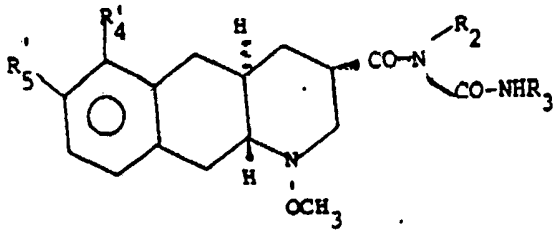
III IV

2) a compound of formula IV is reacted with a carbodiimide of formula V



V

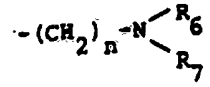
wherein R_8 is alkyl of 1 to 4 C-atoms,
to form a compound of formula VI

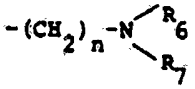


VI

This process may be carried out using processes which are known in general for the production of ureides from carboxylic acids and carbodiimides.

It is preferably to allow the compounds of formula IV and V to react together under reflux for several hours in an inert solvent, e.g. tetrahydrofuran.
If required, an organic base such as N-ethyl-diisopropylamine can be added. In this reaction there may be produced both compounds of formula VI wherein R_2 is

 and R_3 is alkyl, and

those wherein R_2 is alkyl and R_3 is  .

These two compounds can be separated from one another in conventional manner, e.g. by selective crystallisation or by chromatography.

3) the OCH_3- group in position 1 of a compound of formula VI is cleaved to produce a compound of formula II.

This cleavage may preferably take place by reduction, e.g.using zinc and acetic acid.

Compounds of formula II, IV, V and VII are new and form per se part of the invention.

Insofar as the production of any particular compound is not particularly described, e.g. compounds of formula III, these are known or may be produced in conventional manner or in analogous manner to those described in the literature or those described in the examples.

Individual optical isomers may be produced from pure optically active starting materials, e.g. an optically active compound of formula III.

Racemic mixtures may be separated into individual optical isomers, e.g. by using chromatography through supports bearing optically active compounds.

In the following examples all temperatures are given in degrees Celsius and are uncorrected.

In the examples hereinafter the racemates are characterised with the name in the α/β system (e.g. 3β,4aα,10aβ) followed by the designation (racemate).

EXAMPLE 1: 1-ethyl-3-(3-dimethylaminopropyl)-3-(1-allyl-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]-quinoline-3β-carbonyl)-urea (racemate)

900 mg of 1-ethyl-3-(3-dimethylaminopropyl)-3-(6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]quinoline-3β-carbonyl)-urea (racemate) are dissolved in 9 ml of dimethylformamide, then mixed with 34[illegible] mg of Na_2CO_3 and 0.18 ml of allyl bromide, and stirred for 6 hours at room temperature. The reaction mixture is then poured onto water and extracted with ethyl acetate.

After drying and evaporation, the title compound is obtained as a brown resin. This is dissolved in a little CH_2Cl_2 and is flash chromatographed over basic silica gel with CH_2Cl_2 + 0.5% CH_3OH + 5% ammonia solution (25%). The dihydrochloride of the title compound obtained melts at 185° (with foaming).

The starting material may be produced as follows:-

a) 1-methoxy-3β-carboxy-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]quinoline (racemate)

2.0 g of 1-methoxy-3α-methoxycarbonyl-6-methoxy-1,2,3,4,-4aα,5,10,10aβ-octahydrobenzo[g]quinoline (racemate), 40 ml of ethanol, 5 ml of water and 2.0 g of KOH are added together and refluxed overnight. In the morning, the mixture is concentrated, poured onto 2N HCl and the precipitated white solid is filtered off by suction. M.p. of the title compound, ca. 215°C.

b) 1-ethyl-3-(3-dimethylaminopropyl)-3-(1-methoxy-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]quinoline-3β-carbonyl)-urea (racemate)

500 mg of the end product of stage a), 323 mg of N-ethyl-N'-(3'-dimethylaminopropyl)-carbodiimide, 0.36 ml of N-ethyldiisopropylamine and 10 ml of tetrahydrofuran are added together and boiled overnight under argon. In the morning, the mixture is concentrated by evaporation. The colourless resinous residue is dissolved in CH_2Cl_2 and is shaken twice with 2N NaOH. Subsequently, the CH_2Cl_2 solution is shaken twice with 2n HCl, the acidic phase is rendered alkaline with conc. NaOH and extracted with CH_2Cl_2. The organic phase is dried and concentrated by evaporation. The residue obtained is a colourless resin which is dissolved in a little CH_2Cl_2 and flash chromatographed with CH_2Cl_2 + 4% CH_3OH. The isomer 3-ethyl-1-(3-dimethylaminopropyl)-3-(1-methoxy-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]quinoline-3β-carbonyl)-urea is obtained as the second product.

c) 1-ethyl-3-(3-dimethylaminopropyl)-3-(6-methoxy-1,2,3,4,-4aα,5,10,10aβ-octahydrobenzo[g]quinoline-3β-carbonyl)-urea (racemate)

1.64 g of the end product of stage b) are suspended in 20 ml of acetic acid and 10 ml of water, and then 5.8 g of zinc dust are added in portions whilst stirring at room temperature, whereby an exothermic reaction is observed. After this addition, stirring continues for 6 hours at room temperature.

The mixture is subsequently filtered and washed with water and ethyl acetate. The filtrate is concentrated, mixed with $NaHCO_3$ solution and extracted with ethyl acetate. The organic phase is washed once with brine, dried and concentrated. The title compound is obtained.

EXAMPLE 2: 1-ethyl-3-(3-dimethylaminopropyl)-3-(1-propyl-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]-quinoline-3β-carbonyl)-urea (racemate)

The title compound is produced analogously to example 1. M.p. of the dihydrochloride (foam) ca. 140°C with decomposition.

EXAMPLE 3:

The (3R,4aR,10aR) optical isomer of the title compound of example 1 is obtained from the corresponding (-)(3S,4aR,10aR) 1-methoxy-3β-carboxy-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]quinoline.

The compounds of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, have interesting pharmacological properties and are therefore indicated for use in therapy.

In particular, the compounds of formula I possess dopaminergic activity (dopamine receptor stimulating activity) and prolactin (PRL) secretion inhibiting activity. This activity may be demonstrated e.g. by the inhibition of basal prolactin secretion of male rats using the method of E.Flückiger et al. (Experientia 34, 1330, 1978). In this test, the compounds are shown to be active at doses of from about 0.005 to about 0.1 mg/kg s.c.

In addition, when administered perorally at doses of ca. 0.03 to 0.5 mg/kg p.o. the compounds have long-lasting activity, e.g. when compared to bromocriptine.

The compound of example 1 is the preferred racemate compound. The 3R,4aR,10aR isomer is the preferred isomer.

Because of their PRL secretion inhibiting activity, the compounds of formula I in free base form or in pharmaceutically acceptable acid addition salt form are indicated for use as prolactin secretion inhibitors, e.g. the treatment of illnesses in which a reduction of the PRL level is desired, e.g. in the treatment of galactorrhoea, in the treatment of PRL-dependent menstrual disorders, e.g. amenorrhoea, to prevent lactation, and in the treatment of hyperprolactinemic hypogonadism of men and women, and in the treatment of prolactinomas. Because of their dopaminergic activity the compounds are also indicated for use in Morbus Parkinson.

The prolactin secretion inhibiting activity is the preferred indication.

An indicated daily dose is from about 0.5 to about 10 mg, conveniently administered once-a-day or if desired once up to 5 days.

Unit dosages may contain from about 0.5 to about 50 mg.

The compounds of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, may be administered enterally (for example as

tablets or capsules) or parenterally (e.g. as injection solutions or suspensions). If desired they may also be used in sustained release form.

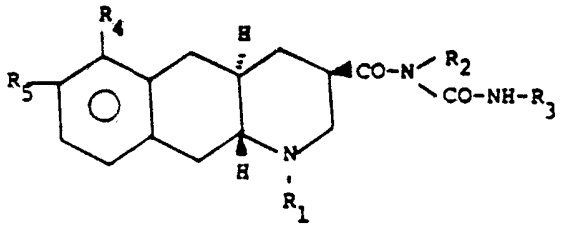
The invention also provides pharmaceutical compositions which comprise a compound of formula I in free base form or pharmaceutically acceptable acid addition salt form in association with a pharmaceutical diluent or tablet. These compositions, for example, a solution or a tablet, can be produced in conventional methods, using conventional adjuvants and carriers.

The invention also relates to the compounds of formula I in free base form or in pharmaceutically acceptable acid addition salt form for use in therapy, especially for use as prolactin inhibitors and dopaminergic agents, e.g. for any of the above indicated indications.

AUSTRALIA

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

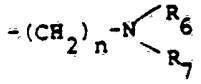
1. A compound of formula I



I

wherein

R_1 is alkyl of 1 to 4 C-atoms, allyl or 2-propinyl, one of groups R_2 and R_3 is alkyl of 1 to 4 C-atoms and the other of these groups R_2 and R_3 is a group of formula



wherein

R_6 and R_7, independently of one another, are CH_3 or C_2H_5,

n is 2, 3 or 4,

R_4 and R_5, independently of one another, are hydrogen, hydroxy, methoxy, alkanoyloxy of 1 to 4 C-atoms or benzoyloxy, with the proviso that both cannot simultaneously be hydrogen,

in free base form or in acid addition salt form, in (3R,4aR,10aR) or (3S,4aS,10aS) optical isomer form, or in the form of a mixture of these isomers.

2. A compound of claim 1 in free base form or in acid addition salt form, in individual isomer form, in free base form or in acid addition salt form.

3. A compound of claim 2 in free base form or in acid addition salt form, having the configuration shown in claim 1.

4. An antipode of a compound of claim 3 in free base form or in acid addition salt form.

5. A compound of claim 1 which is 1-ethyl-3-(3-dimethyl-aminopropyl)-3-(1-allyl-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]-quinoline-3β-carbonyl)-urea in free base form or in acid addition salt form.

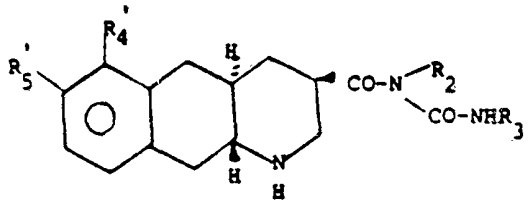
6. A compound of claim 5 in racemate form.

7. A compound of claim 5 in the form of the (3R,4aR,10aR) isomer.

8. A compound of claim 1 which is 1-ethyl-3-(3-dimethyl-aminopropyl)-3-(1-propyl-6-methoxy-1,2,3,4,4aα,5,10,10aβ-octahydrobenzo[g]-quinoline-3β-carbonyl)-urea in free base form or in acid addition salt form.

9. A process for the production of a compound of formula I as defined in claim 1 wherein

a) in order to produce a compound of formula I, wherein R_4 and R_5, independently of one another are hydrogen or methoxy, with the proviso that both cannot simultaneously be hydrogen, a compound of formula II



II

wherein R_4 and/or R_5 are methoxy, is N-alkylated in position 1, or

b) in order to produce a compound of formula I, wherein R_4 and R_5, independently of one another, are hydrogen or hydroxy, with the proviso that both cannot simultaneously be hydrogen, a compound of formula I, wherein R_4 and/or R_5 are methoxy, undergoes either cleavage, or

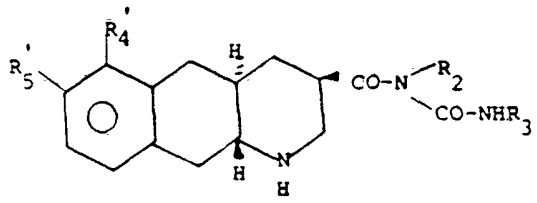
c) in order to produce a compound of formula I, wherein R_4 and R_5, independently of one another, are hydrogen, alkanoyloxy of 1 to 4 C-atoms or benzoyloxy, with the proviso that both cannot simultaneously be hydrogen, a compound of formula I, wherein R_4 and/or R_5 are hydroxy, is reacted with an alkanoic acid of 1 to 4 C-atoms or with benzoic acid or with a reactive derivative of such an acid and the compound of formula I is isolated in free base form or acid addition salt form.

10. A pharmaceutical composition comprising a compound of claim 1 in free base form or pharmaceutically

acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

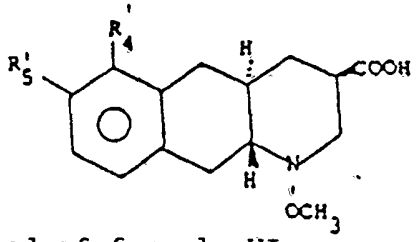
11. A method of inducing prolactin secretion inhibiting activity or dopaminergic receptor agonist activity in a subject which comprises administering a compound of claim 1 in free base form or pharmaceutically acceptable acid addition salt form to a subject in need of such treatment.

12. A compound of formula II



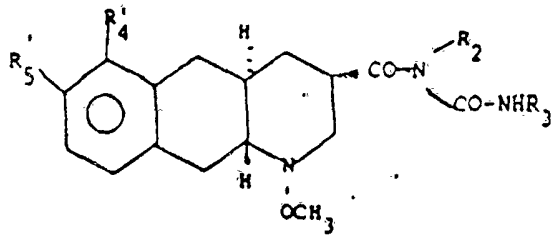
II

a compound of formula IV



IV

or a compound of formula VI



VI

wherein R_2 and R_3 are as defined in claim 1 and wherein R_4' and/or R_5' are methoxy.

DATED this 14th day of September, 1990
Sandoz Ltd.
By Its Patent Attorneys
DAVIES & COLLISON