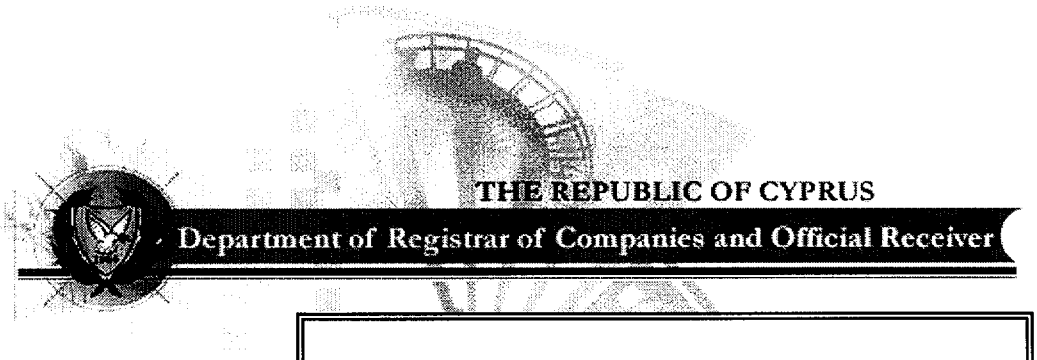

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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(54) **Dibenz[cd,f]indole derivatives, their preparation and pharmaceutical compositions containing them**

(57) A 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof is a useful anti-parkinson agent.

GB 2 118 185 A

SPECIFICATION

Dibenz[cd,f]indole derivatives, their preparation and pharmaceutical compositions containing them

The present invention relates to dibenz[cd,f]indole derivatives, their preparation and pharmaceutical compositions containing them.

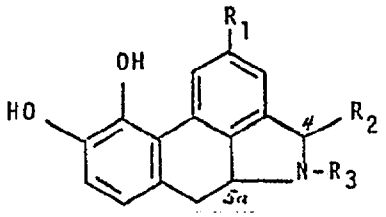
Belgian Patent No. 877 169 describes a class of 4,5,5a,6-tetrahydro-dibenz[cd,f]indole derivatives having at least one oxy substituent in one or both of the fused benzene rings and having stimulant activity on central dopaminergic receptors. All the compounds specifically exemplified contain only oxy substituents in one fused benzene ring, i.e. in positions 9 and 10, and no substituent in the other fused benzene ring. It has now been surprisingly found that a group of 4,5,5a,6-tetrahydro-dibenz[cd,f]indole derivatives substituted by alkyl in the 2 position and by oxy substituents in the 9 and 10 positions the dibenz[cd,f]indole nucleus, which are nowhere specifically described or suggested in this patent, exhibit particularly interesting pharmacological properties, e.g. a specific central dopaminergic activity and are well tolerated, e.g. in rats.

In accordance with the invention, there are thus provided 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indoles and acid addition salts thereof hereinafter referred to as "the compounds of the invention".

The oxy substituent may be for example a hydroxy group or a group which is hydrolysable under physiological conditions to an hydroxy group, e.g. an acyloxy group. Alternatively it may be an ether group.

The compounds of the invention may be if desired substituted in the other positions of the dibenz[cd,f]indole nucleus, preferably in the 5 position and conveniently in the 4 position.

More particularly the present invention provides a (4R*,5aS*) compound of formula I



(I)

wherein

R_1 is (C_{1-4})alkyl,

R_2 is hydrogen, (C_{1-10})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl (C_{1-4})alkyl, and

R_3 is (C_{1-5})alkyl,

or a physiologically hydrolysable and acceptable ester thereof, and acid addition salts of the compound or ester.

The term (4R*,5aS*) according to the usual convention indicates that the compound may be in the form of the racemate or optically isomer wherein the hydrogen atoms in positions 4 and 5a of the dibenz[cd,f]indole nucleus are cis to each other. The optical isomers having the absolute configuration 4S,5aR are preferred.

Any alkyl radicals preferably are straight chain radicals.

R_1 is preferably methyl.

When R_2 is an alkyl radical, this contains preferably 1 to 4 carbon atoms, and is especially *n*-propyl.

Conveniently, R_3 has preferably 2 or 3 carbon atoms, and is especially ethyl.

One group of compounds in accordance with the present invention comprises the compounds of formula I as defined above, wherein R_2 is (C_{1-4})alkyl and R_3 is (C_{1-3})alkyl as the racemate or (4S,5aR) optical isomer.

Physiologically hydrolysable and acceptable esters are esters which are hydrolysable under physiological conditions to yield the corresponding 9,10-dihydroxy-dibenz[cd,f]indole. Such esters include esters of monocarboxylic acids, in particular aliphatic or monoaromatic carboxylic acids of formula

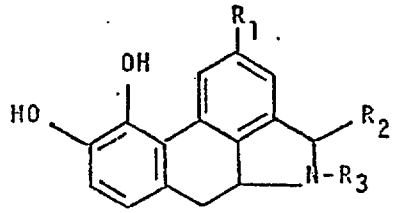
R'COOH

wherein R' is (C_{1-17})alkyl, (C_{3-6})cycloalkyl, phenyl, phenyl mono- or independently di-substituted by chlorine, fluorine, trifluoromethyl, (C_{1-4})alkyl or (C_{1-4})alkoxy, unsubstituted benzyl or benzyl mono-, or independently, di-substituted by chlorine, fluorine, (C_{1-4})alkyl or (C_{1-4})alkoxy.

The present invention provides also a process for the production of a compound of the invention or an acid addition salt thereof, which includes the steps of obtaining a 2-alkyl-9,10-di-hydroxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof, by splitting the ether groups in a corresponding 2-alkyl-4,5,5a,6-tetrahydro-dibenz[cd,f]indole having splittable ether groups in the 9 and 10 positions, or a precursor thereof, or interconverting an 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-

dibenz[cd,f]indole or an acid addition salt thereof into another 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof, and recovering the desired 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole as such as or as an acid addition salt thereof.

More particularly, the invention provides a process for the production of a (4R*,5aS*) compound of formula I



(I)

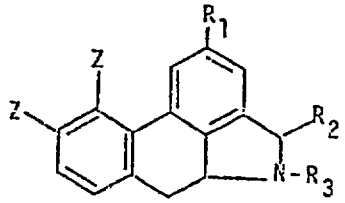
wherein

R_1 is (C_{1-4})alkyl,

R_2 is hydrogen, (C_{1-10})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl, and

R_3 is (C_{1-5})alkyl, or a physiologically hydrolysable and acceptable ester thereof, or an acid addition salt of the compound or ester, which comprises

a) obtaining a (4R*,5aS*) compound of formula I or an acid addition salt thereof, by splitting the ether groups in a (4R*,5aS*) compound of formula II



(II)

wherein R_1 to R_3 are as defined above, and the Z radicals are the same or different and are splittable ether groups, or a precursor thereof, or

b) obtaining a physiologically hydrolysable and acceptable ester of a (4R*,5aS*) compound of formula I or an acid addition salt thereof, by acylating a corresponding (4R*,5aS*) compound of formula I, and recovering the (4R*,5aS*) compound of formula I or a physiologically hydrolysable and acceptable ester as such or as an acid addition salt of the compound or ester.

The ether splitting process may be effected in conventional manner for splitting ether groups. For example the reaction may be carried out by treatment with a strong mineral acid, e.g. aqueous hydrobromic or hydroiodic acid. Suitable temperatures may be from 100°C or higher, preferably from 100°C to the boiling point of the reaction mixture, especially at about 130°C.

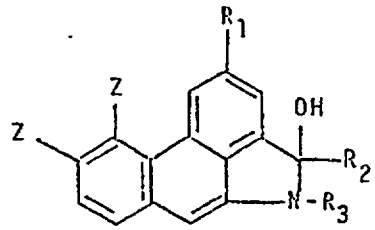
The ether group Z is preferably (C_{1-4})alkyl.

One compound of the invention may be converted into another compound of the invention in conventional manner. For example hydroxy groups in the 9, 10 positions may be acylated.

The acylation may be effected in conventional manner for the selective acylation of phenolic groups in the presence of an amine function. For example there may be used as acylating agent a functional derivative of an acid such as an acid chloride, acid bromide or an acid anhydride. Conveniently the reaction is carried out by reacting an acid chloride in the presence of trifluoroacetic acid at temperatures from 20°C to the boiling point of the reaction mixture or in the presence of pyridine at temperatures from 0°C to room temperature.

The 2-alkyl-4,5,5a,6-tetrahydro-dibenz[cd,f]indoles containing splittable ether groups in the 9 and 10 positions and acid addition salts thereof, which are also compounds of the invention, may be produced by a process which includes the steps of reducing an appropriate 2-alkyl-4-hydroxy-4,5-dihydro-dibenz[cd,f]indole having splittable ether groups in the 9 and 10 positions, or a precursor thereof and recovering the desired 2-alkyl-4,5,5a,6-tetrahydro-dibenz[cd,f]indole having splittable ether groups on the 9 and 10 positions as such or as an acid addition salt thereof.

In particular the (4R*,5aS*) compound of formula II and acid addition salts thereof, may be prepared by reducing compounds of formula III



(III)

wherein Z, R_1, R_2 and R_3 are as defined above, or a precursor thereof, and recovering the desired (4R*,5aS*) compound of formula II as such or as an acid addition salt thereof.

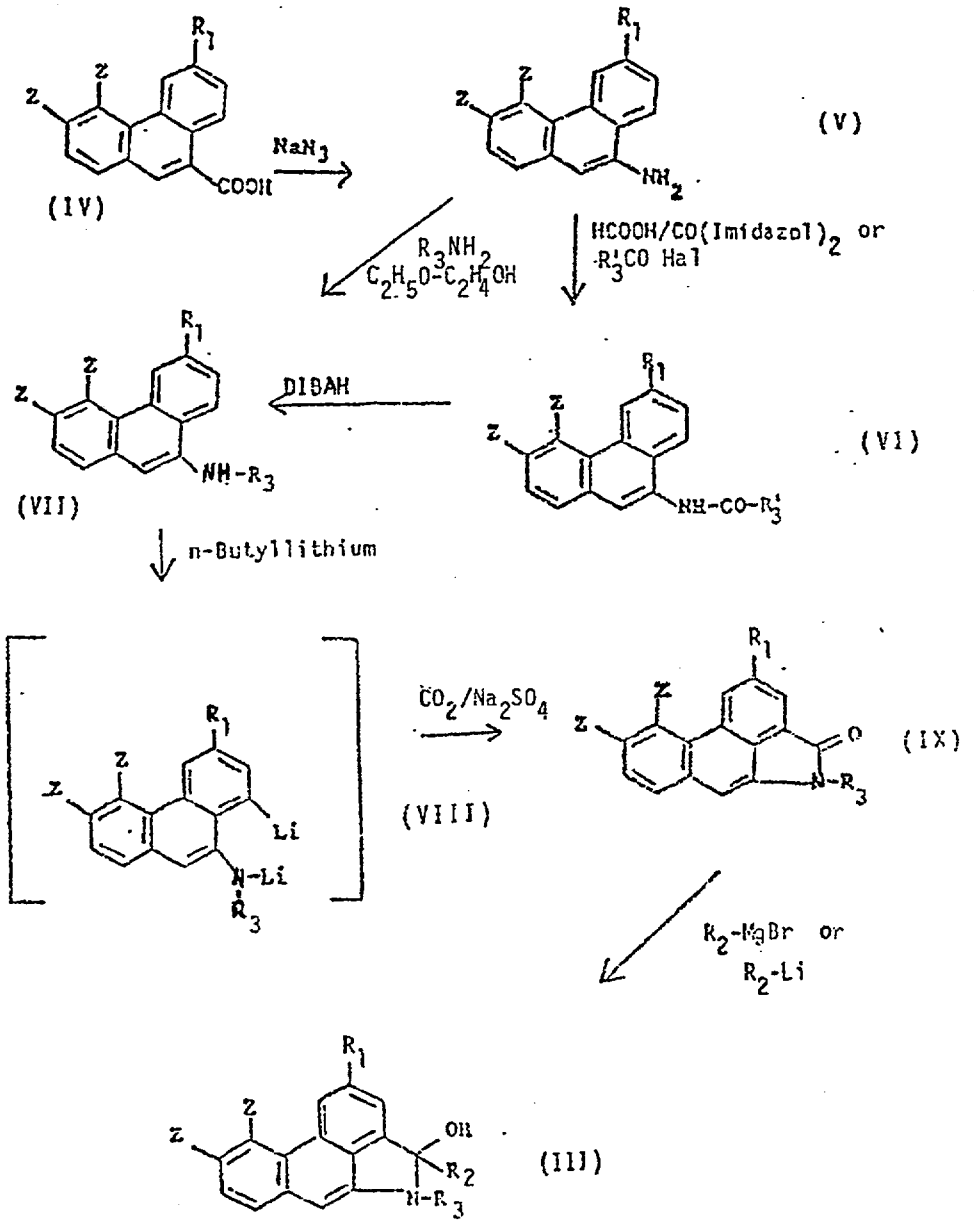
The reduction may be effected in conventional manner, conveniently under acidic conditions suitable for the acidic reduction of enamines or imines, for example with zinc in an aqueous mineral acid, preferably hydrochloric acid, conveniently in the presence of a mercury (II) salt, for example mercury (II) chloride. The reaction may suitably be effected in the presence of for example ethanol. Suitable temperatures may be from 50°C to the boiling point of the reaction mixture.

As used herein the term precursor refers to compounds which are capable of being converted into the starting materials in conventional manner, e.g. temporarily protected compounds.

The resulting compounds of the invention may be recovered from the reaction mixture and purified in known manner. The free base forms of the compounds of the invention, including the compounds of formula I and esters thereof and compounds of formula II, and including compounds specifically exemplified hereinafter may be converted into acid addition salt forms in conventional manner and *vice versa*. Suitable acids for salt formation include, for example, hydrochloric acid.

Racemic compounds of the invention may be obtained from racemic starting materials. Optically active isomers may be obtained from optically active precursors or from the racemate. The enantiomers may be obtained from the racemate by known methods, for example by fractional crystallization of diastereoisomeric salts, e.g. their salts with (+)-di-O,O-p-toluoyl-D-tartaric acid or (—)-di-O,O-p-toluoyl-L-tartaric acid. Racemic resolution into the optically active isomers may be effected at the final stage or at an earlier stage in the synthesis, e.g. before splitting of the ether groups, e.g. in a compound of formula II.

The starting materials 2-alkyl-4,5,5a,6-tetrahydro-dibenz[cd,f]indoles may be prepared according known methods, for example as described in the above Belgian patent No. 877,169. For example starting materials of formula III may be prepared according the following reaction scheme:



The compounds of formulae V to IX and III per se also form part of the present invention.

In the reaction scheme the radicals R_1, R_2, R_3 and Z are as defined above, R_3' is hydrogen or methyl or ethyl and Hal is chlorine or bromine.

The reactions may be carried out in conventional manner and the products of the above reactions may be isolated and purified in known manner.

In the above intermediates the ether groups Z are preferably methoxy.

Insofar the preparation or any particular starting material is not particularly described, this may be effected in conventional manner or in analogous manner to that described hereinafter for analogous compounds.

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

Example 1:
(±)(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-2-methyl-4-n-propyl-dibenz[cd,f]indole

a) 9-amino-3,4-dimethoxy-6-methyl-phenanthrene (compound of formula V)

A mixture of 400 ml (2.87 M) of trifluoroacetic anhydride and 400 ml (5.22 M) of trifluoroacetic acid is added at room temperature under a nitrogen atmosphere to 61.1 g (0.206 M) of 3,4-dimethoxy-6-methyl-phenanthrene-9-carboxylic acid and the mixture is stirred for 10 minutes. After the mixture has been cooled to −5°, 16.08 g (0.247 M) sodium azide are carefully added in solid form. The mixture is stirred for 2 hours at 0°, poured onto ice, extracted three times with methylene chloride and washed with a solution 1N of sodium hydroxide. The aqueous phases are extracted twice with methylene chloride 2-propanol 8:2. The organic phases are combined, dried and evaporated, to give white crystals. 86 g of the resultant mixed anhydride are warmed for 2 hours under reflux in 800 ml of a solution 2N of sodium hydroxide and 800 ml ethanol and the mixture is evaporated. The residue is washed with water/ice and extracted three times with methylene chloride. The organic phases are combined, dried and evaporated to give the title compound as an oil.

b) 9-acetylamino-3,4-dimethoxy-6-methyl-phenanthrene (compound of formula VI)

105.7 ml (0.750 M) of N-ethyl-N,N-diisopropyl-amine are added to a solution of 100.2 g (0.375 M) of 9-amino-3,4-dimethoxy-6-methyl-phenanthrene in 1000 ml methylene chloride. To the resulting mixture is added dropwise over 30 minutes a solution of 34.5 ml (0.450 M) of acetyl chloride in 250 ml methylene chloride. During the addition, the temperature of the reaction mixture is maintained at 20° by cooling with ice. The reaction mixture is stirred for 2 hours at room temperature and extracted with methylene chloride. The organic phases are washed with ice cooled 2N hydrochloric acid, water and 2N sodium bicarbonate, dried over sodium sulfate and evaporated, to give the title compound. M.pt. 190—192° after crystallisation from acetone/ether.

c) 9-ethylamino-3,4-dimethoxy-6-methyl-phenanthrene (compound of formula VII)

1700 ml (2.05 M) of a 20% solution of diisobutylaluminium hydride in toluene are added at room temperature over a period of 45 minutes to a suspension of 105.7 g (0.342 M) of 9-acetylamino-3,4-dimethoxy-6-methyl-phenanthrene in 1500 ml anhydrous tetrahydrofuran. The mixture is then warmed with stirring under a nitrogen atmosphere for 2 hours at 80°. The reaction mixture is then cooled at 0° and under nitrogen atmosphere and a mixture of 2500 ml 2N hydrochloric acid/ice, cooled at −10°, is added by portions at such a rate that the gas evolution is maintained. The acid solution is made alkaline to pH 10 by addition at 0° of 3 litres 2N sodium hydroxide and the mixture is extracted three times with methylene chloride/2-propanol 7:3. The organic phases are combined, washed, dried and evaporated to give the title compound. M.pt. 100—102° after crystallisation from acetone/ether.

d) 5-ethyl-4,5-dihydro-9,10-dimethoxy-2-methyl-4-oxo-dibenz[cd,f]indole (compound of formula IX)

661.4 ml (1.084 M) of a 15% solution of *n*-butyl-lithium in hexane are added at 0°, over a period of 20 minutes and under a nitrogen atmosphere, to a solution of 97 g (0.328 M) of 9-ethylamino-3,4-dimethoxy-6-methyl-phenanthrene in 1000 ml anhydrous tetrahydrofuran; the reaction mixture becomes dark red. After stirring for 30 minutes at 0°, the mixture is transferred in portions with a teflon tube with nitrogen pressure at −50° onto a mixture of 500 g sodium sulfate and 500 g dry ice in 1500 ml tetrahydrofuran. After the temperature of the mixture has reached room temperature, the mixture is poured onto water/ice, extracted three times with methylene chloride. The combined organic phases are dried over sodium sulfate and evaporated to give the title compound. M.pt. 158—160° (decomp.) after crystallisation from ether/petroleum ether.

e) 5-ethyl-4,5-dihydro-4-hydroxy-9,10-dimethoxy-2-methyl-4-n-propyl-dibenz[cd,f]indole (compound of formula III)

A solution of 377 ml (4.1 M) of *n*-propyl bromide in 4 litres tetrahydrofuran is added over a period of 90 minutes at reflux to 99.8 g (4.1 M) of magnesium turnings and the mixture is stirred for one hour

at reflux. To the resultant mixture is added dropwise over 30 minutes and under a nitrogen atmosphere a solution of 880 g (2.73 M) of 5-ethyl-4,5-dihydro-9,10-dimethoxy-2-methyl-4-oxo-dibenz[cd,f]indole in 6 litres tetrahydrofuran. The reaction mixture is warmed for 2 hours at reflux and then extracted with methylene chloride. The organic phase is washed with a saturated solution of potassium bicarbonate and with water, dried over sodium sulfate and evaporated to give the title compound in the form of a red-brown oil [IR Spectrum (CH_2Cl_2):3450 cm^{-1} (OH)]. The crude product is directly used for the next step.

f) (±)-(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-2-methyl-4-n-propyl-dibenz[cd,f]indole (compound of formula II)

A suspension of 100 g (0.273 M) of 5-ethyl-4,5-dihydro-4-hydroxy-9,10-dimethoxy-2-methyl-4-*n*-propyl-dibenz[cd,f]indole in 2000 ml ethanol is added with stirring to a suspension of 322 g (4.928 M) of zinc dust and 74.3 g (0.273 M) of mercury(II) chloride in 2000 ml distilled water. The reaction mixture is refluxed, 450 ml of 18% hydrochloric acid are added dropwise over a period of 15 minutes and the mixture is refluxed overnight with stirring. The mixture is then cooled to room temperature, filtered and the zinc amalgam is washed with 500 ml methylene chloride. The filtrate is made alkaline with 1 litre of concentrated NH_4OH and extracted three times with methylene chloride (700 ml each time). The combined organic phases are washed with water, dried and evaporated. The resultant oil is chromatographed on silica gel using methylene chloride with 2% methanol to give the title compound as an oil.

g) (±)-(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-2-methyl-4-n-propyl-dibenz[cd,f]indole

100 g of (±)-(4R*,5aS*)-5-ethyl-4,5,5a-6-tetrahydro-9,10-dimethoxy-2-methyl-4-*n*-propyl-dibenz[cd,f]indole in 1 litre of a 47% aqueous solution of hydrobromic acid are warmed for 6 hours at reflux at a bath temperature of 150°. After evaporation of the mixture to dryness, the crystalline residue is stirred in acetone and filtered. The precipitate is washed with acetone then with ether and dried under high vacuum, to give the hydrobromide of the title compound. M.pt. 200° with decomposition. The hydrochloride melts at 185° with decomposition.

Example 2:
(—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-2-methyl-4-n-propyl-dibenz[cd,f]indole

a) (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-2-methyl-4-n-propyl-dibenz[cd,f]indole

74.3 g (211 mM) of (±)-(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-2-methyl-4-*n*-propyl-dibenz[cd,f]indole are dissolved in 600 ml acetone and a solution of 81.67 g (211 mM) of (—)-di-O,O'-p-toluoyl-L-tartaric acid monohydrate in 300 ml acetone is added with stirring. The mixture is further stirred for one hour at room temperature, a total of 1 litre ether being added in portions during this period. The resultant precipitate is filtered of, washed with ethyl acetate until it remains light yellow, and dried.

114.7 g of the crystals obtained from the first crystallisation are dissolved in 1 litre CH_2Cl_2/methanol 7:3 at reflux and the solution is filtered and concentrated until a major part of the product crystallizes out. The mixture is stirred for about 15 minutes, the product is filtered off, washed with ethyl acetate until it remains colourless and dried.

48 g of the resulting product is recrystallised in the same manner by using 700 ml CH_2Cl_2/methanol 50:50 to give colourless crystals.

The resulting crystals are recrystallised in the same manner by using 1.2 litres acetone and 60 ml methanol. There is thus obtained (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-2-methyl-4-*n*-propyl-dibenz[cd,f]indole (—)-di-O.O-p-toluoyl-L-tartrate in form of colourless crystals which melt at 185—198°; $[\alpha]_D^{20}$=—150° (c=0.5 in methanol).

b) (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-2-methyl-4-n-propyl-dibenz[cd,f]indole

Proceeding as described in Example 1g), (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-2-methyl-4-*n*-propyl-dibenz[cd,f]indole hydrobromide is obtained from the tartrate obtained above under a). The corresponding hydrochloride melts at above 160° with decomposition; $[\alpha]_D^{20}$=—94° (c=0.5 in methanol).

Example 3:
(4R*,5aS*)-4,5,5a,6-tetrahydro-9,10-dihydroxy-2-methyl-4,5-di-n-propyl-dibenz[cd,f]indole

(±)(4R*,5aS*)-4,5,5a,6-tetrahydro-9,10-dimethoxy-2-methyl-4,5-di-*n*-propyl-dibenz[cd,f]indole, (oil), is obtained in analogous manner to Example 1a to f). This compound is converted into the (—)-(4S,5aR) isomer form. Sintering of the hydrochloride at 210° and melting at 222—224°; $[\alpha]_D^{20}$=—127° (c=0.5 in methanol).

In analogous manner to Example 2 there is obtained (—)-(4S,5aR)-4,5,5a,6-tetrahydro-9,10-dihydroxy-2-methyl-4,5-di-*n*-propyl-dibenz[cd,f]indole hydrochloride. M.pt. above 145° with decomposition; $[\alpha]_D^{20}$=—82.2° (c=0.45 in methanol).

It is also to be appreciated that 9-amino-3,4-dimethoxy-6-methyl-phenanthene may be converted directly into 9-ethylamino-3,4-dimethyloxy-6-methyl-phenanthrene by heating with ethylamine in 2-ethoxyethanol.

The compounds of the invention, in particular the compounds of formulae I and II, and their pharmaceutically acceptable acid addition salts thereof possess pharmacological activity in animals and are therefore indicated for use as pharmaceuticals. In particular, the compounds are indicated for use as central dopaminergic stimulant agents, as indicated by standard tests, for example according to the method of U. Ungerstedt et al [Acta Physiol. Scand. Suppl. (1971), *387*, Suppl. 66—93], by induction of contralateral turning of notable duration in rats (whose substantia nigra has been lesioned by a microinjection of 6-hydroxydopamine one week previously) after i.p. and p.o. administration in an amount of 0.03 to about 10 mg/kg animal body weight. The activity is confirmed by induction of dose dependent stereotyped sniffing, licking and biting behaviour in the rat according to the following test, after i.p. administration in an amount of 1 to 30 mg/kg animal body weight.

Rats, 180—222 g, are placed in perspex cylinders of 30 cm diameter on a wire grid floor. After 30 minutes to allow acclimatisation to the cage, the rats are injected with the compound under investigation. The behaviour of the rats is observed for 2 minutes at 30 minutes intervals for 2 hours and then at 60 minute intervals for a total of up to 7 hours. The degree of stereotyped behaviour observed is assessed using a scoring system based on that described by Costall, Nayler and Olley [Europ. J. Pharmac. *18*, 83—94, (1972)].

The score and criteria are as follows:—

1. Intermittent sniffing
2. Persistent sniffing, occasional licking
3. Licking, occasional biting
4. Intense and persistent biting.

The central dopaminergic activity is also confirmed by an inhibition of catalepsy induced by reserpine in mice on s.c. administration of about 0.01 mg to about 2 mg/kg of the compounds.

It is to be appreciated that the compounds of the invention having carboxylic acyloxy substituents may hydrolyse under physiological conditions to give the corresponding active compounds of the invention wherein the oxy substituents are hydroxy.

Moreover for the compounds of the invention especially the Example 2 compound, this central dopaminergic activity is specific as indicated in in vitro tests by non-affinity for clonidine receptors using the method described by A. Closse et al in "Psychopharmacology and Biochemistry of Neurotransmitter Receptors", H. I. Yamanura, R. V. Olsen and E. Usdin, Edition, Elsevier North Holland Inc., Amsterdam, 1980, pages 463—465. This specifity is confirmed by a weak prolactin secretion inhibition activity and insignificant emesis in the dog at doses suitable for central dopaminergic activity.

The compounds are therefore indicated for use as central dopaminergic agents, e.g. for treating Morbus Parkinson. An indicated daily dose is from about 4 to about 30 mg conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 1 to about 15 mg of the compound, or in sustained release form.

The compounds of the invention, in particular the compounds of formula I, are furthermore indicated for use as anti-depressant agents, as indicated by the inhibition of catalepsy induced by reserpine in mice on s.c. administration of about 0.01 mg to about 2 mg/kg of the compounds and by the inhibition of the catalepsy induced by tetrabenazine in rats on p.o. administration of about 5 to about 20 mg/kg of the compounds.

An indicated dose for this indication is from about 0.05 to about 2 mg conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 1 to about 15 mg of the compound, or in sustained release form.

The preferred indication is the anti-Parkinson indication. The preferred compound is the compound of Example 2.

The compounds may be administered in pharmaceutically acceptable acid addition salt form. These salt forms exhibit the same order of activity as the free base form.

The present invention also provides a pharmaceutical composition comprising a compound of the invention, e.g. a compound of formula I, a physiologically hydrolysable and acceptable ester thereof, or a compound of formula II, or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable diluent or carrier.

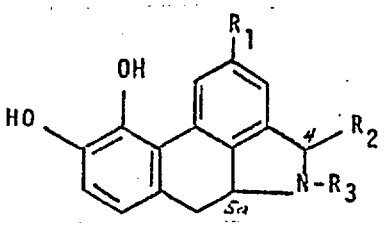
These compositions may be formulated in conventional manner so as to be for example a solution, a capsule or tablet.

Claims

1. A process for the production of a 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof, which includes the steps of obtaining a 2-alkyl-9,10-dihydroxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof, by splitting the ether groups in a

corresponding 2-alkyl-4,5,5a,6-tetrahydro-dibenz[cd,f]indole having splittable ether groups in the 9 and 10 positions or a precursor thereof, or interconverting an 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof into another 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof, and recovering the desired 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole as such or as an acid addition salt thereof.

2. A process according to claim 1 for the production of a (4R*,5aS*) compound of formula I



(I)

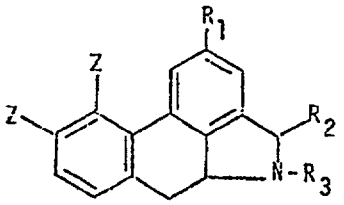
wherein

R_1 is (C_{1-4})alkyl,

R_2 is hydrogen, (C_{1-10})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl, and

R_3 is (C_{1-5})alkyl, or a physiologically hydrolysable and acceptable ester thereof, or an acid addition salt of the compound or ester, which comprises

a) obtaining a (4R*,5aS*) compound of formula I or an acid addition salt thereof, by splitting the ether groups in a (4R*,RaS*) compound of formula II



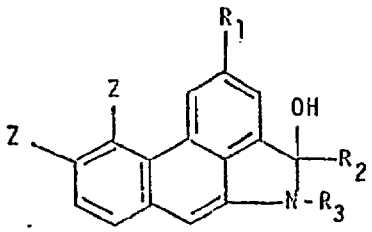
(II)

wherein R_1 to R_3 are as defined above, and the Z radicals are the same or different and are splittable ether groups, or a precursor thereof, or

b) obtaining a physiologically hydrolysable and acceptable ester of a (4R*,5aS*) compound of formula I or an acid addition salt thereof, by acylating a corresponding (4R*,5aS*) compound of formula I, and recovering the (4R*,5aS*) compound of formula I or a physiologically hydrolysable and acceptable ester as such or as an acid addition salt of the compound or ester.

3. A process for the production of a 2-alkyl-4,5,5a,6-tetrahydro-dibenz[cd,f]indole having splittable ether groups in the 9 and 10 positions, or an acid addition salt thereof, which includes the steps of reducing an appropriate 2-alkyl-4-hydroxy-4,5-dihydro-dibenz[cd,f]indole having splittable ether groups in the 9 and 10 positions, or a precursor thereof, and recovering the desired 2-alkyl-4,5,5a,6-dibenz[cd,f]indole having splittable ether groups in the 9 and 10 positions as such or as an acid addition salt thereof.

4. A process according to claim 3 for the production of a (4R*,5aS*) compound of formula II as defined in claim 3 or an acid addition salt thereof, which comprises reducing a compound of formula III



(III)

wherein R_1, R_2, R_3 and Z as as defined in claim 3, or a precursor thereof, and recovering the desired (4R*,5aS*) compound of formula II as such or as an acid addition salt thereof.

5. A 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof, whenever produced by a process substantially as hereinbefore described with reference to any one of the Examples If or Ig or 2.

6. A 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof whenever produced by a process according to any one of claims 1 to 5.

7. A 2-alkyl-9,10-dioxy-4,5,5a,6-tetrahydro-dibenz[cd,f]indole or an acid addition salt thereof.

8. A compound of claim 7 having splittable ether groups in the 9 and 10 positions, or an acid addition salt thereof.

9. A (4R*,5aS*) compound of formula I as defined in claim 2 or a physiologically hydrolysable and acceptable ester thereof, or an acid addition salt of the compound or ester.

10. A compound of claim 9 wherein R_2 is (C_{1-4})alkyl and R_3 is (C_{1-3})alkyl, as a racemate or as the (4S,5aR) optical isomer, or an acid addition salt of the racemate or isomer.

11. A compound of claim 7 which is (4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-2-methyl-4-n-propyl-dibenz[cd,f]indole or an acid addition salt thereof.

12. A compound of claim 7 which is (4R*,5aS*)-4,5,5a,6-tetrahydro-2-methyl-9,10-dihydroxy-4,5-di-*n*-propyl-dibenz[cd,f]indole or an acid addition salt thereof.

13. A (4R*,5aS*) compound of formula II as defined in claim 2 or an acid addition salt thereof.

14. A compound of claim 13 wherein R_2 is (C_{1-4})alkyl and R_3 is (C_{1-3})alkyl as a racemate or as the (4S,5aR) optical isomer, or an acid addition salt of the racemate or optical isomer.

15. A compound of claim 13 or 14 wherein Z is (C_{1-4})alkoxy or an acid addition salt thereof.

16. A compound of claim 15 which is (4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-2-methyl-4-*n*-propyl-dibenz[cd,f]indole or an acid addition salt thereof.

17. A compound of claim 15 which is (4R*,5aS*)-4,5,5a,6-tetrahydro-9,10-dimethoxy-2-methyl-4,5-*n*-propyl-dibenz[cd,f]indole or an acid addition salt thereof.

18. A compound of any one of claims 6 to 17 in racemic form or an acid addition salt of the compound.

19. A compound of any one of claims 6 to 17 in the form of an optical isomer, or an acid addition salt of the compound.

20. A compound of claim 19 in the form of the (4S,5aR) optical isomer or an acid addition salt thereof.

21. A compound of claim 7 which is (4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydro-2-methyl-4-*n*-propyl-dibenz[cd,f]indole, or an acid addition salt thereof.

22. A compound of claim 7 which is (4S,5aR)-4,5,5a,6-tetrahydro-9,10-dihydroxy-2-methyl-4,5-di-*n*-propyl-dibenz[cd,f]indole, or an acid addition salt thereof.

23. A compound of claim 7 which is (4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-2-methyl-4-*n*-propyl-dibenz[cd,f]indole, or an acid addition salt thereof.

24. A compound of claim 7 which is (4S,5aR)-4,5,5a,6-tetrahydro-9,10-dimethoxy-2-methyl-4,5-di-*n*-propyl-dibenz[cd,f]indole, or an acid addition salt thereof.

25. A compound according to any one of claims 6 to 24, or a pharmaceutically acceptable acid addition salt of the compound for use as a pharmaceutical.

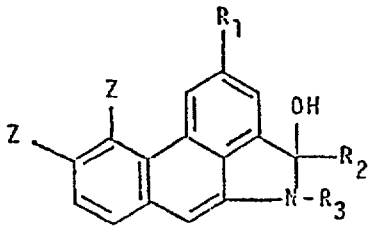
26. A compound according to any one of claims 6 to 24, or a pharmaceutically acceptable acid addition salt of the compound for use as an anti-parkinson agent.

27. A compound according to any one of claims 6 to 24, or a pharmaceutically acceptable acid addition salt of the compound for use as an anti-depressant agent.

28. A pharmaceutical composition comprising a compound according to any one of claims 6 to 24, or a pharmaceutically acceptable acid addition salt of the compound, in association with a pharmaceutical carrier or diluent.

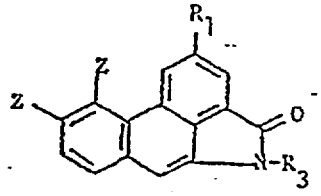
29. A compound of any one of the following formulae:

a compound of formula III



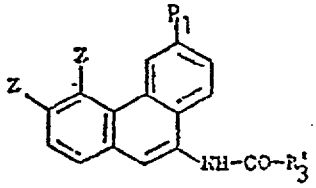
(III)

a compound of formula IX



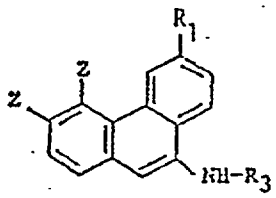
(IX)

a compound of formula VI



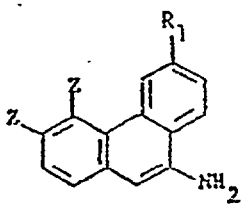
(VI)

a compound of formula VII



(VII)

a compound of formula V



(V)

wherein R_1, R_2, Z and R_3 are as defined in claim 2.

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