

PATENT SPECIFICATION

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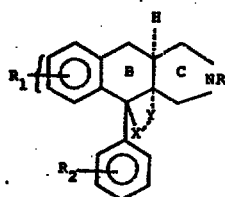


(54) BENZOISOINDOLINE DERIVATIVES

(71) We, SANDOZ LTD., of 35
Lichtstrasse, CH4002 Basle, Switzerland, a
Swiss Body Corporate, do hereby declare the
invention, for which we pray that a patent
may be granted to us, and the method by
which it is to be performed, to be particu-
larly described in and by the following state-
ment:—

The present invention relates to new hydro-
4-phenyl-benz[f]isoindoline derivatives.

The present invention provides compounds
of formula I,



I

wherein

- 15 R is (i) hydrogen, (ii) alkyl of 1 to 5
carbon atoms, (iii) alkenyl or alkynyl of
3 to 5 carbon atoms, the multiple bond
thereof being in other than the α -position,
20 (iv) alkyl of 1 to 4 carbon atoms substituted
by cycloalkyl of 3 to 6 carbon atoms, (v)
hydroxyalkyl of 2 to 5 carbon atoms, (vi)
phenylalkyl of 7 to 11 carbon atoms in the
aggregate thereof, (vii) phenylalkyl of 7
25 to 11 carbon atoms in the aggregate thereof
monosubstituted in the phenyl thereof by
halogen, alkoxy of 1 to 4 carbon atoms
or alkyl of 1 to 4 carbon atoms, or (viii)
A—CO—R₃,

wherein

A is alkylene of 1 to 4 carbon atoms, and
R₃ is alkyl of 1 to 5 carbon atoms, alkoxy
of 1 to 4 carbon atoms, hydroxy, phenyl or
phenyl substituted by halogen,

R₁ and R₂ are identical or different and
each is hydrogen, halogen or alkyl of 1 to
4 carbon atoms, and either (i) each of
X and Y is hydrogen, and the rings
B and C are cis to each other, or (ii)

X and Y together are an additional bond.

Substituted as used herein preferably signi-
fies monosubstituted. The term lower with
reference to a carbon-containing radical and
where not particularly defined otherwise,
refers to up to 4 carbon atoms.

When the radical R or R₃ is lower alkyl
of 1 to 5 carbon atoms, then this especially
has 1 to 4 preferably 1 to 3, e.g. 1 or 2
carbon atoms.

When R is an alkyl group of 1 to 4 carbon
atoms substituted by a cycloalkyl group of
3 to 6 carbon atoms, then the alkyl group
thereof especially has 1 to 3, e.g. 1 or 2
carbon atoms and the cycloalkyl group thereof
especially has 3 to 5, e.g. 3 carbon atoms.
An example of a preferred substituent of this
series is the cyclopropylmethyl group.

When the radical is a hydroxyalkyl group
of 2 to 5 carbon atoms, then this especially has
2 to 4, preferably 2 or 3 carbon atoms.

When the radical R is a phenylalkyl radical
of 7 to 11 carbon atoms or a phenylalkyl
radical of 7 to 11 carbon atoms monosubsti-
tuted by halogen, alkoxy of 1 to 4 or alkyl of
1 to 4 carbon atoms, then this phenylalkyl
radical especially has 7 to 9, preferably 7 or

8 carbon atoms. A halogen substituent which may be present in this radical especially denotes fluorine, chlorine or bromine, preferably fluorine or chlorine. An alkoxy or alkyl substituent of 1 to 4 carbon atoms which may be present in this radical especially has 1 to 3, preferably 1 or 2 carbon atoms.

When the radical R is a group $A-CO-R_3$, preferably when R_3 is other than phenyl or halophenyl then A especially has 1 to 3, preferably 1 or 2 carbon atoms.

When R_3 is phenyl substituted by halogen, then the halogen substituent especially signifies fluorine, chlorine or bromine, preferably fluorine or chlorine.

When the radical R_3 is an alkoxy group of 1 to 4 carbon atoms, then this especially has 1 or 2, preferably 1 carbon atom.

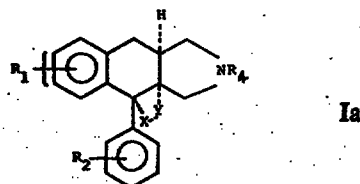
When the radical R_1 or R_2 is halogen, then this especially signifies fluorine, chlorine or bromine, especially fluorine or chlorine.

When the radical R_1 or R_2 is an alkyl group of 1 to 4 carbon atoms, then this especially has 1 or 2, preferably 1 carbon atom.

X when hydrogen, may be cis or trans to the hydrogen atom in the 9α -position.

Further, in accordance with the invention, a compound of formula Ia,

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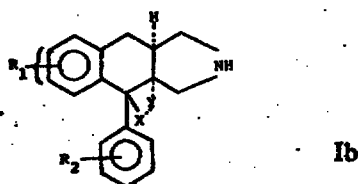


wherein

R_1 , R_2 , X and Y are as defined above, and R_4 is (i) alkyl of 1 to 5 carbon atoms, (ii) alkenyl or alkynyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α -position thereof, (iii) alkyl of 1 to 4 carbon atoms substituted by cycloalkyl of 3 to 6 carbon atoms, (iv) hydroxyalkyl of 2 to 5 carbon atoms, (v) phenylalkyl of 7 to 11 carbon atoms in the aggregate thereof, (vi) phenylalkyl of 7 to 11 carbon atoms in the aggregate thereof monosubstituted in the phenyl thereof by halogen, alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms, or (vii) $A-CO-R_3$, wherein R and R_3 are as defined above,

may be obtained by a process comprising a) alkylating a compound of formula Ib,

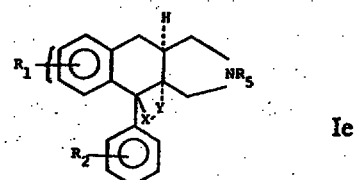
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wherein

R_1 , R_2 , X and Y are as defined above, or b) reductively alkylating a compound of formula Ib, to produce a compound of formula Ic,

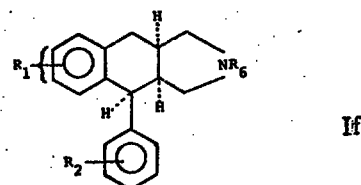
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wherein

R_1 , R_2 , X and Y are as defined above and R_5 is a primary or secondary alkyl of 1 to 5 carbon atoms, or c) epimerising a compound of formula If,

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wherein

R_1 and R_2 are as defined above, and R_6 is (i) alkyl of 1 to 5 carbon atoms, (ii) alkenyl or alkynyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α -position thereof, (iii) alkyl of 1 to 4 carbon atoms substituted by cycloalkyl of 3 to 6 carbon atoms, (iv) hydroxyalkyl of 2 to 5 carbon atoms, (v) phenylalkyl of 7 to 11 carbon atoms in the aggregate thereof, (vi) phenylalkyl of 7 to 11 carbon atoms in the aggregate thereof monosubstituted in the phenyl thereof by halogen, alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms, or (vii) $A-CO-R_3'$,

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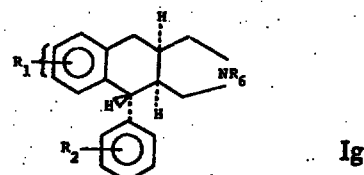
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wherein

A is as defined above, and R_3' is alkyl of 1 to 5 carbon atoms, phenyl or phenyl substituted by halogen, under strong alkaline conditions to produce a compound of formula Ig,

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wherein

R_1 , R_2 and R_6 are as defined above, or d) hydrogenating a compound of formula Ih,

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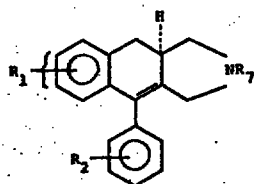
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Ig

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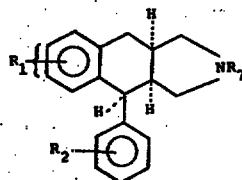
Ih

wherein

R₁ and R₂ are as defined above, and
R₇ is (i) alkyl of 1 to 5 carbon atoms, (ii)
alkyl of 1 to 4 carbon atoms substituted
by cycloalkyl of 3 to 6 carbon atoms, (iii)
phenylalkyl of 7 to 11 carbon atoms in
the aggregate thereof, (iv) phenylalkyl of
7 to 11 carbon atoms in the aggregate
thereof by halogen or alkyl of 1 to 4 carbon
atoms, or (iv) A-CO-R₃,

wherein

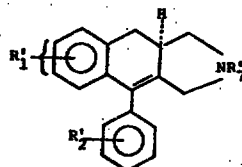
A and R₃ are as defined above, with
hydriodic acid and red phosphorus to
produce a compound of formula II,



II

wherein

R₁, R₂ and R₇ are as defined above, or
a) catalytically hydrogenating a compound of
formula Ij,

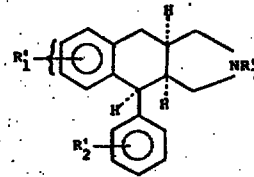


Ij

wherein

R₁' and R₂' are identical or different and
each is hydrogen, fluorine or alkyl of 1 to
4 carbon atoms, and
R₇' is (i) alkyl of 1 to 5 carbon atoms, (ii)
alkyl of 1 to 4 carbon atoms substituted
by cycloalkyl of 3 to 6 carbon atoms, (iii)
hydroxyalkyl of 2 to 5 carbon atoms, (iv)
phenylalkyl of 8 to 11 carbon atoms, (iv)
the aggregate thereof, the phenyl thereof
being in other than the α -position of the
alkyl moiety or (v) phenylalkyl of 8 to 11
carbon atoms in the aggregate thereof
monosubstituted in the phenyl thereof by
halogen, alkoxy of 1 to 4 carbon atoms
or alkyl of 1 to 4 carbon atoms, the phenyl
thereof being in other than the α -position
of the alkyl moiety,

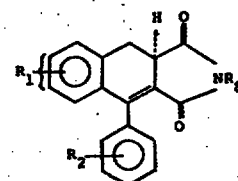
to produce a compound of formula Ik,



Ik

wherein

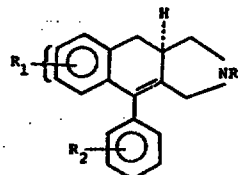
R₁', R₂' and R₇' are as defined above, or
f) reducing with a metal hydride a compound
of formula II,



II

wherein

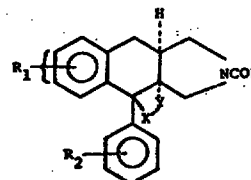
R₁ and R₂ are as defined above, and
R₈ is (i) alkyl of 1 to 5 carbon atoms, (ii)
alkyl of 1 to 4 carbon atoms substituted by
cycloalkyl of 3 to 6 carbon atoms, (iii)
hydroxyalkyl of 2 to 5 carbon atoms, (iv)
phenylalkyl of 7 to 11 carbon atoms in
the aggregate thereof, (v) phenylalkyl of
7 to 11 carbon atoms in the aggregate
thereof monosubstituted on the phenyl
thereof by halogen, alkoxy of 1 to 4 carbon
atoms or alkyl of 1 to 4 carbon atoms,
to produce a compound of formula Iu,



Iu

wherein

R₁, R₂ and R₈ are as defined above, or
g) reducing a compound of formula IV,



IV

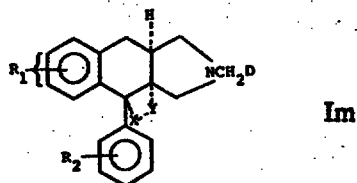
wherein

R₁, R₂, X and Y are as defined above, and
D is (i) hydrogen, (ii) alkyl of 1 to 4
carbon atoms, (iii) cycloalkyl of 3 to 6
carbon atoms, (iv) alkyl of 1 to 3 carbon
atoms substituted by cycloalkyl of 3 to 6
carbon atoms, (v) hydroxyalkyl of 1 to 4
carbon atoms, (vi) phenyl, (vii) phenyl-

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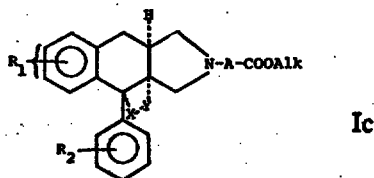
- alkyl of 7 to 10 carbon atoms in the aggregate thereof, (viii) phenyl mono-substituted by halogen, alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms, or (ix) phenylalkyl of 7 to 10 carbon atoms in the aggregate thereof monosubstituted on the phenyl thereof by halogen, alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms,
- 10 to produce a compound of formula Im,



wherein

R₁, R₂, X, Y and D are as defined above, with a metal hydride, or

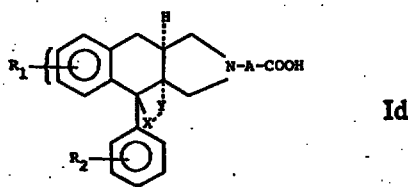
- 15 h) hydrolyzing a compound of formula Ic,



wherein

R₁, R₂, X, Y and A are as defined above, and

- 20 Alk is alkyl of 1 to 4 carbon atoms, to produce a compound of formula Id,



wherein

R₁, R₂, X, Y and A are as defined above.

- 25 Process variants a) to h) may for example be effected as follows:—

a) N-alkylation of a compound of formula Ib may, for example, be effected with a compound of formula V

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ER₄

V

wherein

R₄ is as defined above, and

E is the acid radical of a reactive ester.

- 35 In the compounds of formula V, E may, for example, signify halogen such as chlorine, bromine or iodine or the acid radical of an organic sulphonyl acid, e.g. an alkylsulphonyl radical preferably of 1 to 4 carbon atoms such as methylsulphonyl or an aryl-

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sulphonyloxy radical such as phenylsulphonyloxy or *p*-tolylsulphonyloxy. 40

The N-alkylation of a compound of formula Ib with a compound of formula V is conveniently effected in an organic solvent, e.g. an amide of an aliphatic carboxylic acid preferably of 1 to 4 carbon atoms, e.g. dimethylformamide. The reaction is conveniently affected in the presence of a basic condensation agent such as sodium carbonate or N-ethyl-N,N-diisopropylamine. 45

The reaction temperature may be from room temperature to about 100°C. 50

Suitable reactive derivatives corresponding to a compound of formula V may alternatively be employed, *inter alia*, α,β -unsaturated carbonyl compounds for the introduction of a radical A¹—CO—R₃, wherein A¹ is ethylene or alkyl substituted ethylene and R₃ is as defined above, and e.g., ethylene oxide for the introduction of a e.g. hydroxyethyl group. 55

The reaction of a compound of formula Ib with an α,β -unsaturated carbonyl compound such as methylvinylketone or an acrylic acid alkyl ester, the alkoxy group thereof being of 1 to 4 carbon atoms, is conveniently effected in a suitable organic solvent, e.g. methanol or ethanol. The reaction temperature may be from room temperature to the reflux temperature of the reaction mixture, preferably at about 40 to 80°C. Benzyl trimethyl ammonium hydroxide may conveniently be present. 60

The reaction of a compound of formula Ib with ethylene oxide may be effected in a manner analogous to known methods and is illustrated in Example 5. The reaction may be effected in an inert solvent, e.g. ethanol. 65

b) The reductive alkylation of a compound of formula Ib to a compound of formula Ic may be effected in a manner analogous to known methods, for example, by alkylating a compound of formula Ib with an aldehyde or ketone in the presence of formic acid (Leuckart-Wallach method). Alternatively the reductive alkylation may be effected hydrogenolytically, i.e. with hydrogen gas in the presence of a suitable metal catalyst such as raney-nickel or palladium. However, under catalytic hydrogenation, any chlorine, bromine or iodine substituents present in the compounds of formula Ib and any additional bond in the 3a,4-position of the compounds of formula Ib may also be at least partially reduced. Therefore, it is convenient to use the Leuckart-Wallach method indicated above for the reductive alkylation of such compounds, for the production of compounds of formula Ic having chlorine, bromine or iodine substituents. 70

The reaction in accordance with Leuckart-Wallach may be effected in a suitable organic solvent, preferably an excess of formic acid, 75

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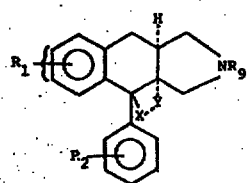
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oxylic acid 45
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at e.g. an elevated temperature, conveniently
at reflux.
The catalytic reductive alkylation may be
effected in a suitable organic solvent, e.g.
an alkanol such as methanol, conveniently at
room temperature.
c) The conversion of a compound of formula
If into a compounds of formula Ig may be
effected under strong alkaline conditions, e.g.
with a strong base, for example potassium
tert.-butoxide. An elevated temperature may
be employed, e.g. 100 to 200°C.
Especially suitable reaction media for this
conversion are a saturated solution of potas-
sium hydroxide (e.g. 40%) in *n*-butanol (e.g.
1 to 7 days at reflux temperature) or of
potassium tert.butoxide in dimethylsulphoxide
(e.g. 1 to 7 days at 25—80°C), as illustrated
in the Examples hereinafter.
Process c) is especially suited for produc-
tion of compounds of formula Ig, wherein the
radical R₃ is alkyl of 1 to 5 carbon atoms,
alkynyl or alkenyl of 4 to 5 carbon atoms
and wherein the multiple bond is not in an
 α - or β -position to the nitrogen atom to which
R₃ is bound, alkyl of 1 to 4 carbon atoms
substituted by cycloalkyl of 3 to 6, preferably
5 or 6 carbon atoms, hydroxyalkyl of 2 to 5
carbon atoms, phenylalkyl of 7 to 11 carbon
atoms, phenylalkyl of 7 to 11 carbon atoms
monosubstituted on the phenyl radical by
halogen, alkoxy of 1 to 4 carbon atoms or
alkyl of 1 to 4 carbon atoms, or a radical
A—CO—R₃, wherein A is as defined above
and R₃ is phenyl or phenyl substituted by
halogen.
d) The hydrogenolysis of a compound of
formula Ih to a compound of formula Ii
with hydroiodic acid and red phosphorus
may be effected in a manner analogous to
known methods. For example, by adding
dropwise an aqueous solution of hydroiodic
acid to a solution or suspension of a mixture
of a compound of formula Ih with red
phosphorus in a suitable solvent or suspension
agent such as glacial acetic acid. The resulting
reaction mixture may then conveniently be
heated, e.g. to 80—120°C.
e) The catalytic hydrogenation of a com-
pound of formula Ij to a compound of for-
mula Ik may be effected in a manner anala-
gous to known methods.
Suitable catalysts are metal catalysts such
as palladium and Raney-nickel. The hydro-
genation may be effected in an organic solvent,
e.g. methanol or ethanol.
The reaction is preferably effected at a
slight excess pressure, e.g. about 2 to 6
atmospheres and preferably at an elevated
temperature, e.g. from about 40 to about
80°C.
In accordance with a preferred method,
the hydrogenation is effected in the presence
of a palladium catalyst produced *in situ* from

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palladium (II)-chloride and sodium boro-
hydride.
f) The reduction of a compound of formula
II with a metal hydride may be effected in
a manner analogous to the methods known
for the reduction of amides.
This may, for example, be effected by
adding a solution of aluminium hydride or
a dialkyl aluminium hydride to an inert
organic solvent, e.g. a cyclic or open chain
ether such as tetrahydrofuran, to a solution
of a compound of formula II in preferably
the same inert organic solvent and conveni-
ently at room or elevated temperature. The
reduction may, for example, also be effected
with a lithium aluminium hydride/aluminium
chloride mixture. When the compounds of
formula II do not have a chlorine, bromine
or iodine substituent, then the reduction may
also be effected with a complex hydride, e.g.
a complex aluminium hydride such as lithium
aluminium hydride or with a complex lithium
aluminium hydride-aluminium chloride. This
process variant may be effected under process
conditions analogous to those described for
the reduction with aluminium hydride.
g) The reduction of an amide of formula IV
with a metal hydride may also be effected in
a manner analogous to known methods. Suit-
able metal hydrides are, for example, alumi-
nium hydride and dialkyl aluminium hydride
and, when the compounds of formula IV do
not have a chlorine, bromine or iodine sub-
stituent, then also lithium aluminium hydride
or lithium aluminium hydride/aluminium
chloride. Suitable solvents are inert solvents
e.g. cyclic or open chain ether such as tetra-
hydrofuran.
The reduction may be effected at room
temperature.
h) A hydrolysis of a compound of formula
Ic may be effected under acid conditions,
e.g. with 2N hydrochloric acid, conveniently
at an elevated temperature, preferably at
reflux temperature.
However, a compound of formula Ic may
be hydrolyzed to a compound of formula Id
under alkaline conditions. The alkaline
hydrolysis is preferably effected in an aqueous
alcoholic solution of an alkaline metal or
alkaline earth metal hydroxide, especially in
an aqueous, methanolic or ethanolic solution
of sodium, potassium or barium hydroxide,
conveniently at room temperature or at a
slightly elevated temperature.
The compounds of formula Ia obtained
in accordance with the above processes may
be isolated and purified in accordance with
known methods.
Further, in accordance with the invention,
a compound of formula Ib may be obtained
by a process comprising
a) replacing the group R₃ by a hydrogen
atom in a compound of formula VI,

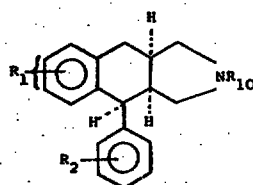


VI

wherein

R₁, R₂, X and Y are as defined above, and R₉ is an electron attracting group, or

- 5 b¹) epimerising a compound of formula VII,

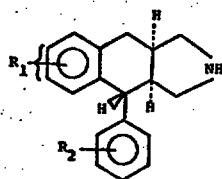


VII

wherein

R₁ and R₂ are as defined above, and R₁₀ is the radical R₉, defined above, under strong alkaline conditions, to produce a compound of formula In

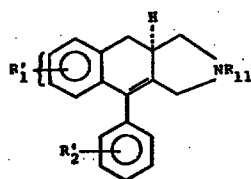
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In

wherein

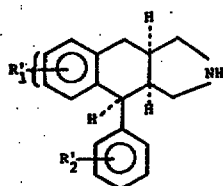
- 15 R₁ and R₂ are as defined above, or c¹) catalytically hydrogenating a compound of formula Io



Io

wherein

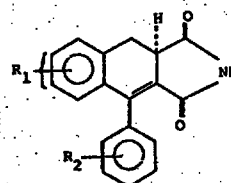
- 20 R₁' and R₂' are as defined above, and R₁₁ is hydrogen or the benzyl group, to produce a compound of formula Ip,



Ip

wherein

R₁' and R₂' are as defined above, or d¹) reducing a compound of formula VIII

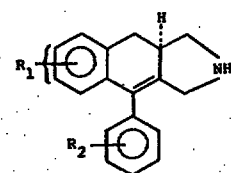


VIII

wherein

R₁ and R₂ are as defined above, with a metal hydride to produce a compound of formula Iq,

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Iq

wherein

R₁ and R₂ re as defined above.

Process variants a¹) to d¹) may be effected as follows:—

a¹) Examples of suitable electron-attracting groups R₉ are acyl groups such as the trifluoroacetyl group, the benzoyl group, an aliphatic or aromatic sulphonyl group, e.g. a tosyl radical, a lower alkoxy-carbonyl radical such as the methoxy- or ethoxy-carbonyl group, or the phenoxycarbonyl group.

The removal of the group R₉ may, for example, be effected by hydrolysis with a 1 to about 5N-solution of an alkali metal hydroxide such as sodium or potassium hydroxide in preferably methanol or ethanol.

When R₉ is an acyl group which can be readily split off, e.g. the trifluoroacetyl group, then hydrolysis may be effected at room temperature or at a slightly elevated temperature.

When R₉ is an acyl group which is less readily split off, e.g. the phenoxy carbonyl group, then the reaction is conveniently effected with heating, preferably at the reflux temperature of the reaction mixture.

When R₉ is an aliphatic or aromatic sulphonyl group, then this group may be split off under reductive conditions, in a manner analogous to known methods, e.g. with sodium ammonia or phenol in e.g. 40% hydrobromic acid.

The hydrolysis of a compound of formula VI may also be effected under acid conditions, e.g. with 2N-hydrochloric acid, conveniently at an elevated temperature, preferably at the reflux temperature of the reaction mixture.

b¹) The conversion of a compound of formula VII into a compound of formula In may

70

bove, or
formula VIII 25

VIII

bove, with a
compound of 30

Iq

be effected 35
m-attracting
as the tri-
group, an
roup, e.g. a
onyl radical
xy-carbonyl
oup.
may, for
with a 1 to
tal hydrox-
hydroxide 45

ich can be
etyl group,
at room
d tempera- 50

ich is less
y carbonyl
nveniently
the reflux
e.
matic sul-
y be split
a manner 60
e.g. with
e.g. 40%

f formula
acid con- 65
acid, con-
e, prefer-
e reaction

f formula 70
In may

be effected as described for the conversion of a compound of formula If into a compound of formula Ig (see process c).

Any group R₁ which may be present, will be split off in the presence of nucleophilic anions, e.g. OH⁻, O⁻(lower)alkyl⁻.

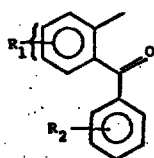
cⁱ) The catalytic hydrogenation of a compound of formula Io may be effected as described for the catalytic hydrogenation of a compound of formula Ij (see process e).

When R₁₁ is the benzyl group, then this may be also removed.

dⁱ) The reduction of a compound of formula VIII with a metal hydride may be effected as described for the reduction of a compound of formula II to a compound of formula Iu (process f).

The compounds of formulae II, IV, VI and VIII are also new.

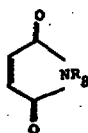
20 A compound of formula II may, for example, be obtained by condensing a compound of formula X,



X

wherein

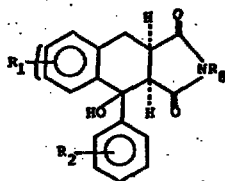
25 R₁ and R₂ are as defined above, with a compound of formula XI,



XI

wherein

30 R₁ is as defined above, to produce a compound of formula XII



XII

wherein

35 R₁, R₂ and R₃ are as defined above, and dehydrating the resulting compound of formula XII.

40 The condensation of a compound of formula X with a compound of formula XI may be effected, e.g. by irradiation of a solution of these compounds in an inert solvent such as acetone or a chlorinated aliphatic hydrocarbon such as methylene chloride, at e.g. room temperature.

The compounds of formula XII may be

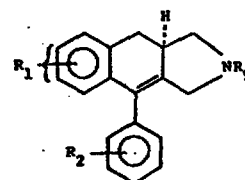
dehydrated in accordance with known methods with an organic or inorganic acid. 45 Examples of suitable acids are aliphatic or aromatic sulphonic acid, trifluoroacetic acid, trichloroacetic acid and formic acid and examples of suitable inorganic acids are sulphuric acid, hydrochloric acid, perchloric acid and phosphoric acid. 50

While the removal of water generally proceeds smoothly at room temperature when a concentrated strong acid, such as sulphuric acid or trifluoroacetic acid is used, it is advisable to heat the reaction mixture when a dilute or weaker acid is used. 55

Dehydration may be effected, e.g. by dissolving the compound of formula XII in an organic acid such as trifluoroacetic acid and stirring the reaction mixture at a temperature of e.g. about 20 to 40°C. 60

The compounds of formula IV and the compounds of formula VI may be produced in accordance with known methods by acylating the corresponding compounds of formula Ib, e.g. with a corresponding acid halide, preferably a corresponding chlorine or bromide, or with a corresponding acid anhydride. N-formylation may be alternatively effected in accordance with known methods. Most of the compounds of formula VI may be synthesized directly, as described below, by cyclisation of a suitable amide. 65

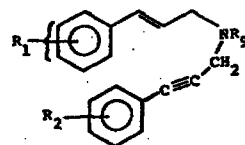
aⁱⁱ) A compound of formula VIa 70 75



VIa

wherein

R₁, R₂ and R₃ are as defined above, may be obtained by thermic cyclization of a compound of formula XIII 80



XIII

wherein

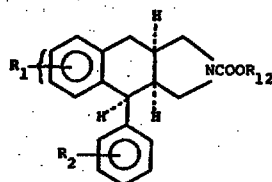
R₁, R₂ and R₃ are as defined above.

85 The thermic cyclization of a compound of formula XIII may be effected in an inert organic solvent, preferably having a high boiling point, e.g. dichloro-benzene. The reaction is conveniently effected in the absence of oxygen and the reaction mixture is heated to about 160—190°C. 90

The resulting compound of formula VIa may be de-acylated to the corresponding NH-

compound, as described above, and, if desired, subjected to catalytic hydrogenation. In the latter case, any chlorine, bromine or iodine substituent which may be present, may also

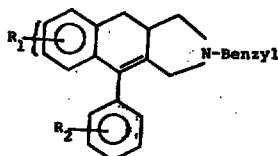
- 5 bⁱⁱ) A compound of formula VIb



VIb

wherein

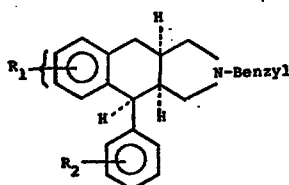
- 10 R₁ and R₂ are as defined above, and R₁₂ is lower alkyl or a phenyl group, may, for example, be produced by reduction of a compound of formula Ir



Ir

wherein

- 15 R₁ and R₂ are as defined above, with hydriodic acid and red phosphorus, and subsequent replacement of the benzyl group in the resulting compound of formula Is



Is

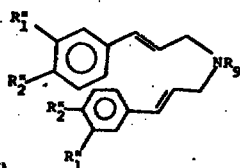
- 20 wherein

R₁ and R₂ are as defined above, by a —COOR₁₂ group wherein R₁₂ is as defined above.

- 25 The substitution of the benzyl group in the compound of formula Is may be effected in accordance with known methods, e.g. by reaction of the compound of formula Is with a corresponding chloro-carbonic acid ester.

- 30 The resulting compound of formula VIb may be converted, as described (process aⁱ or bⁱ) into the corresponding tetrahydro compound of formula VII (R₁₀=H), or into a compound of formula In.

- 35 cⁱⁱ) Thermic cyclization of a compound of formula XIV



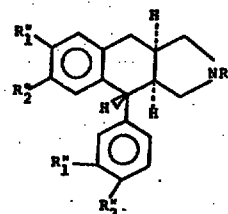
XIV

wherein

R₃ is as defined above, and

R₁^{''} is hydrogen, and

- 40 R₂^{''} is halogen or an alkyl group of 1 to 4 carbon atoms or R₁^{''} is halogen or alkyl of 1 to 4 carbon atoms, and R^{''} is hydrogen, yields a compound of formula VIc



VIc

wherein

R₁^{''}, R₂^{''} and R₃ are as defined above.

The thermic cyclisation of a compound of formula XIV may be effected under the conditions described for process aⁱⁱ.

A compound of formula VIII may be produced as described for the production of compounds of formula II, from a compound of formula X and using maleic imide in place of a compound of formula XI.

The compounds of formula Ir are included in the general formula Iu. A process for their production is described *inter alia* in process f.

The compounds produced in accordance with the above processes may be isolated in the usual manner and purified in accordance with known methods.

Insofar as the production of the starting materials is not described, these are known or may be produced in accordance with known processes or in a manner analogous to the processes described herein or to known processes. For example a compound of formula XIV may be prepared as described in Example 6 in conventional manner.

Free base forms of the compounds of formula I may be converted into acid addition salt forms in conventional manner, and *vice versa*. Suitable acids for salt formation include hydrochloric acid, naphthalene-1,5-disulphuric acid, maleic acid, fumaric acid, hydrobromic acid and sulphuric acid.

Similar considerations apply to other free bases mentioned above.

The compounds of formulae I, II, IV, VI to VIII and XII may be in racemic form or individual optical isomer form, e.g. owing to the presence of an asymmetric carbon atom at the 4-position. An individual optical isomer may be obtained from the corresponding racemic mixture in conventional manner, for example by fractional crystallization of salts of the racemic acids with optically active acids.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade and are uncorrected.

EXAMPLE 1.
(3aRS,4SR,9aSR) - 2 - acetonil - 3a,4,9,9a-tetrahydro - 4 - phenyl - benz[f]isoindoline [process a)].

5 A solution of 3.76 g of chloroacetone in 35 cc of dimethyl formamide is added dropwise at 100° with stirring to a mixture of 10 g of (3aRS,4SR,9aSR)-3a,4,9,9a-tetrahydro-4-phenyl-benz[f]isoindoline, 8.5 g of sodium carbonate, 0.2 g of sodium iodide and 80 cc of dimethyl formamide. The reaction mixture is stirred at 100° for 2 hours and is then concentrated by evaporation in a high vacuum. The residue is shaken with methylene chloride/2N caustic soda solution. 15 The organic phase is dried and concentrated by evaporation, active charcoal is added to the residue in ether, the solution is filtered and concentrated by evaporation, and the residue is crystallized from ether/pentane, whereby the title compound, having a M.P. of 106—108°, is obtained.

20 The production of (3aRS,4SR,9aSR)-3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline is described *inter alia* in Example 6.

25 The following compounds of formula Ia are obtained in a manner analogous to that described in Example 1, with the use of the corresponding starting materials, by alkylation of compounds of formula Ib [in accordance with process a)]:

30 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 207—209°;

35 (3aRS,4SR,9aSR) - 2 - allyl - 3a,4,9,9a-tetrahydro - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 187—190°;

40 (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline, M.P. 65—68°;

45 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - isopropyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrogen maleate salt form 150—158°;

50 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-4 - phenyl - 2 - (2 - propenyl)benz[f]isoindoline, M.P. 93—95°;

55 (3aRS,4SR,9aSR) - 2 - (o - chlorophenethyl) - 3a,4,9,9a - tetrahydro - 4 - phenyl-benz[f]isoindoline, M.P.P. of the hydrogen maleate form 178—179°;

60 (3aRS,4SR,9aSR) - 2 - (3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindolin - 2-yl)acetophenone, M.P. 120—130°;

65 (3aRS,4SR,9aSR) - p - fluoro - 4-(3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindolin - 2 - yl)butyrophene, M.P. 81—84°;

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - (p - methylbenzyl) - 4 - phenyl - benz[f]isoindoline, M.P. 120—121°;

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-

2 - (p - methoxy - benzyl) - 4 - phenyl-benz[f]isoindoline, M.P. 95—100°;

(3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a-tetrahydro - 2 - methyl - 4 - (4 - chlorophenyl)benz[f]isoindoline, M.P. 133—135°;

70 (3aRS,4SR,9aSR) - 6 - chloro - 4 - (4-chlorophenyl) - 2 - cyclo - propylmethyl-3a,4,9,9a - tetrahydro - benz[f]isoindoline, M.P. 124—126°;

75 (3aRS,4SR,9aSR) - 2 - acetonil - 6 - chloro - 4 - (4 - chlorophenyl) - 3a,4,9,9a-tetrahydro-benz[f]isoindoline, M.P. of the bis(base)naphthalene - 1,5 - disulphonate salt form 305—307°;

80 (3aRS,4SR,9aSR) - 7 - chloro - 4 - (m-chlorophenyl) - 3a,4,9,9a - tetrahydro - 2-methyl - benz[f]isoindoline, M.P. of the bis-(base)naphthalene - 1,5 - disulphonate salt form 244—248°;

85 (3aRS,4SR,9aSR) - 2 acetonil - 7-chloro - 4 - (m - chlorophenyl) - 3a,4,9,9a-tetrahydro - benz[f]isoindoline, M.P. of the bis(base)naphthalene - 1,5 - disulphonate salt form 266—269°;

90 (3aRS,4SR,9aSR) - 7 - chloro - 4 - (m-chlorophenyl) - 2 - cyclo - propylmethyl-3a,4,9,9a - tetrahydro - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 243—247°;

95 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,6 - dimethyl - 4 - (p - tolyl)benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 195—198°;

100 (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-3a,4,9,9a - tetrahydro - 6 - methyl - 4 - (p-tolyl)benz[f]isoindoline, M.P. 98—100°;

105 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-6 - methyl - 2 - (3 - methyl - but - 2 - enyl)-4-(p-tolyl)benz[f]isoindoline, M.P. of the hydrochloride salt form 197—207° (decomp.);

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,6 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 280—283°;

110 (3aRS,4SR,9aSR) - 2 - acetonil - 3a,4,9,9a-tetrahydro - 6 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 295—301°;

115 (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-3a,4,9,9a - tetrahydro - 6 - methyl - 4 - phenyl-benz[f]isoindoline, M.P. of the hydrochloride salt form 198—204°;

120 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,7 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form, 244—248°;

125 (3aRS,4SR,9aSR) - 2 - acetonil - 3a,4,9,9a-tetrahydro - 7 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 295—299°;

(3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-3a,4,9,9a - tetrahydro - 7 - methyl - 4-phenyl-benz[f]isoindoline, M.P. 79—82°;

2 - (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-

up of 1. to 40
n or alkyl
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VIc

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- hydro - 7 - methyl - 4 - phenyl - benz[f]isoindolin - 2 - yl) - *p* - fluoroacetophenone M.P. of the hydrogen maleate salt form 164—166°;
(3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a-tetrahydro - 2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 231—233°;
(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2 - (3 - methylbut - 2 - enyl) - 4 - phenyl - benz[f]isoindoline (M.P. of the hydrogen maleate: 163—168°);
(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 6 - methyl - 2 - (3 - methylbut - 2 - enyl) - 4 - phenyl - benz[f]isoindoline;
(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 6 - methyl - 4 - phenyl - 2 - (2 - propinyl) - benz[f]isoindoline;
(3aRS,4SR,9aSR) - 6 - chloro - 2 - cyclopropylmethyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
(3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a-tetrahydro - 4 - phenyl - 2 - (2 - propinyl) - benz[f]isoindoline;
(3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a-tetrahydro - 2 - (3 - methylbut - 2 - enyl) - 4 - phenyl - benz[f]isoindoline;
(3aRS,4SR,9aSR) - 6 - chloro - 2 - ethyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
(3aRS,4SR,9aSR) - 2 - *n* - butyl - 6 - chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
(3aRS,4SR,9aSR) - 6 - chloro - 2 - isopropyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
(3aRS,4SR,9aSR) - 2 - (but - 2 - inyl) - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 297—303°;
(3aRS,4SR,9aSR) - 2 - acetonyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 265—269°;
(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2,6 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 183—187°;
(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2,7 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 204—207°;
(3aRS,4SR,9aSR) - 2 - benzyl - 6 - chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline, M.P. 115—117°;
(9aRS) - 2 - benzyl - 9,9a - dihydro - 6 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. 139—143°;
(9aRS) - 9,9a - dihydro - 2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrogen maleate salt form 158—162° (decomp.);
(9aRS) - 2 - benzyl - 9,9a - dihydro - 7 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. 139—142°;
(9aRS) - 2 - benzyl - 9,9a - dihydro - 4 - phenyl - benz[f]isoindoline, M.P. 113—115°;
(9aRS) - 2 - benzyl - 6 - chloro - 9,9a - dihydro - 4 - phenyl - benz[f]isoindoline, M.P. 266—268°.
Examples 6, 9, 10, 11, 12, 13 and 20. illustrate processes for the production of the required starting materials.
The following Examples illustrate further process variants in accordance with process a):
- EXAMPLE 2.**
(3aRS,4SR,9aSR) - 4 - (3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindolin-2-yl)-2-butanone [variant of process a)].
A solution of 7.4 g of (3aRS,4SR,9aSR)-3a,4,9,9a-tetrahydro - 4 - phenyl - benz[f]isoindoline in 60 cc of ethanol is heated to the boil at reflux for 1½ hours after the addition of 3 cc of methylvinyl-ketone, and is subsequently concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate. After concentrating by evaporation, the filtrate yields the title compound as oily residue. Hydrogen maleate salt form: M.P. 121—124° (after crystallization from ethanol).
- EXAMPLE 3.**
(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline - 2-propionic acid methyl ester [variant of process a)].
A mixture of 15 g of (3aRS,4SR,9aSR)-3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline, 5.9 g of acrylic acid methyl ester and 1 cc of a 40% solution of benzyl trimethyl ammonium hydroxide in methanol is stirred at 50° for 4 hours and is then concentrated by evaporation. The evaporation residue is reduced to a slime with silica gel in benzene/ethyl acetate (9:1) and filtration is effected. Upon concentrating the filtrate by evaporation, the title compound, having a M.P. of 75—76° (after crystallization from ether/petroleum ether), is obtained.
- EXAMPLE 4.**
(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline - 2-propionic acid [hydrolysis of ester—process h)].
10 g of (3aRS,4SR,9aSR)-3a,4,9,9a-tetrahydro - 4 - phenyl - benz[f]isoindoline - 2-propionic acid methyl ester are heated to the boil at reflux in 50 cc of 2 N hydrochloric acid for 5 hours. The solution is then concentrated by evaporation, the residue is dissolved in water, the pH of the solution is adjusted to 1 with caustic soda solution, and 1 equivalent of 1,5-naphthalene di-

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line, M.P. 65
dihydro - 4 -
P. 113—115°.
chloro - 9,9a -
line, M.P. 70
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5 sulphonic acid is added, whereby the bis-1,5-naphthalene-disulphonate salt form of the title compound is obtained in sticky form. The supernatant water is poured off and the resin is triturated with acetone, whereby it crystallizes. M.P. 193—195°.

EXAMPLE 5.

(3aRS,4SR,9aSR) - 2 - (2 - hydroxyethyl) - 3a,4,9,9a - tetrahydro - 6 - methyl - 4 - (p - tolyl) - 2 - benz[f]isindoline [variant of process a)].

1.3 g of ethylene oxide are passed, with stirring, at -15°, through a solution of 4 g of (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 6 - methyl 4 - (p - tolyl)benz[f]isindoline in 30 cc of ethanol. The mixture is allowed to stand at +5° for 16 hours and is then concentrated. The residue is chromatographed on 30 g of silica gel with methylene chloride/methanol/aqueous saturated ammonia (95:4.5:0.5), whereby the title compound, having a M.P. of 128—129° (after crystallization from methylene chloride/petroleum ether), is obtained.

25 The compounds described in Examples 2 to 5 may also be produced in a manner analogous to Example 1.

Produced in a manner analogous to Example 2: 4 - [(9aRS) - 9,9a - dihydro, 4 - phenyl - benz[f]isindolin - 2 - yl] - butan - 2 - one, M.P. of the hydrogen maleate salt form 132—134°.

35 Produced in a manner analogous to Examples 3 and 4: [(9aRS) - 9,9a - dihydro - 4 - phenyl - benz[f]isindolin - 2 - yl] - propionic acid, M.P. of the bis(base)naphthalene-1,5-disulphonate 206—210°.

EXAMPLE 6.

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isindoline [process a¹].

45 22.3 g of (3aRS,4SR,9aSR) - 2 - trifluoroacetyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isindoline are dissolved in a 3N caustic potash solution in methanol with heating. The mixture is stirred at room temperature for 30 minutes, is subsequently poured on water and extracted with methylene chloride. The extract is dried over sodium sulphate, the solution is concentrated by evaporation and the residue is crystallized from methylene chloride pentane, whereby the title compound, having a M.P. of 136—138°, is obtained.

55 The (3aRS,4SR,9aSR) - 2 - trifluoroacetyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isindoline required as starting material, may, for example, be obtained as follows:

60 A solution of 310 g of N,N-bis-(trans-cinnamyl)trifluoroacetamide in 6 liters of o-dichloro-benzene is heated to the boil at reflux for 16 hours in an atmosphere of argon

and is subsequently concentrated by evaporation. The residue is crystallized from 65 methylene chloride / pentane, whereby (3aRS,4SR,9aSR) - 2 - trifluoroacetyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isindoline, having a M.P. of 150—153°, is obtained. 70

IR (CH₂Cl₂) 1690, no band at 950 to 990 cm⁻¹.

The N,N-bis-(trans-cinnamyl)trifluoroacetamide, required as starting material, may be produced as follows: 75

A solution of 275 g of N-cinnamyl-trifluoroacetamide in 600 cc of hexamethyl phosphoric acid triamide is added dropwise, while cooling and stirring, to a suspension of 30.2 g of sodium hydride in 540 cc of hexamethyl phosphoric acid triamide. After gas evolution is complete, a solution of 248.5 g of cinnamyl bromide in 540 cc of hexamethyl phosphoric acid triamide is added dropwise, and the mixture is stirred at 25° for 16 hours. The reaction mixture is then poured on water and extracted with ether. The ether solution, which has been dried over sodium sulphate, is concentrated by evaporation, and the oily residue is chromatographed with toluene on 90 1.5 kg of silica gel.

Upon concentrating by evaporation, the filtrate yields N,N-bis(trans-cinnamyl)trifluoroacetamide as oily residue.

IR (CH₂Cl₂) 1690, 968 cm⁻¹. 95

The title compound may also be obtained under the usual conditions by reduction of (3aRS,4SR,9aSR) - 2 - tosyl - 3a,4,9,9a-tetrahydro - 4 - phenyl - benz[f]isindoline. The (3aRS,4SR,9aSR) - 2 - tosyl - 3a,4,9,9a-tetrahydro - 4 - phenyl - benz[f]isindoline, required as starting material, may, for example, be obtained as follows: 100

A solution of 2 g of N,N-bis-(trans-cinnamyl)-p-toluenesulphonic acid amide in 105 120 cc of o-dichlorobenzene is heated to the boil at reflux for 48 hours in an atmosphere of argon and is subsequently concentrated by evaporation, whereby (3aRS,4SR,9aSR)-2 - tosyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isindoline is obtained as residue. 110 M.P. 185—187° (after crystallization from ether/pentane).

The following compounds of formula Ib may be obtained in a manner analogous to that described in Example 6, using the corresponding starting materials and process a¹): 115

(3aRS,4SA,9aSR) - 6 - chloro - 4 - (4-chlorophenyl) - 3a,4,9,9a - tetrahydro - benz- 120 [f]isindoline, M.P. 133—134°;

(3aRS,4SR,9aSR) - 6 - fluoro - 4 - (p-fluorophenyl) - 3a,4,9,9a - tetrahydro - benz- [f]isindoline, M.P. of the hydrogen maleate salt form 134—136°;

(3aRS,4SR,9aSR) - 7 - chloro - 4 - (m-chlorophenyl) - 3a,4,9,9a - tetrahydro - benz- [f]isindoline, M.P. of the hydrogen maleate salt form 166—168°; 125

- (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-6 - methyl - 4 - (p - tolyl)benz[f]isoindoline, M.P. 129—132°;
- 5 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-6 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 174—176°;
- 10 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-7 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 225—227°;
- 15 (3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a-tetrahydro - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 205—207°;
- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro-4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 256—258°;
- 20 (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro-6 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 215—220°;
- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro-7 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 226—230°;
- 25 (3aRS,4RS,9aSR) - 6 - chloro - 3a,4,9,9a-tetrahydro - 4 - phenyl - benz[f]isoindoline, M.P. 144—145°;
- 30 (9aRS) - 9,9a - dihydro - 4 - phenyl-benz[f]isoindoline, M.P. of the hydrochloride salt form 238—243° decomp.).

EXAMPLE 7.

- 35 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - methyl - 4 - phenyl - 4 - phenyl-benz[f]isoindoline [process b)].
- A mixture of 8 g of (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline, 120 cc of a 40% aqueous solution of formaldehyde and 320 cc of methanol is stirred in an atmosphere of hydrogen after the addition of a catalytic amount of Raney nickel, until the take up of gas is complete. The filtered reaction mixture is then concentrated by evaporation, methanol is added to the residue, the insoluble material is filtered off and the solution is concentrated by evaporation, whereby the title compound is obtained as residue. The hydrochloride salt form of the title compound has a M.P. of 207—209° (ethanol/ether).
- 50

EXAMPLE 8.

- 55 (3aRS,4SR,9aSR) - 6 - chloro - 4 - (p-chlorophenyl) - 3a,4,9,9a - tetrahydro-2 - methyl - benz[f]isoindoline [process b)].
- A mixture of 1.5 g of (3aRS,4SR,9aSR) - 6 - chloro - 4 - (p - chlorophenyl) - 3a,4,9,9a-tetrahydro - benz[f]isoindoline, 10 cc of 100% formic acid and 10 cc of a 40% aqueous formaldehyde solution is heated to the boil at reflux for 2 hours in an atmosphere of nitrogen. The mixture is concentrated by
- 60

evaporation, the residue is taken up in water, the solution is made alkaline with concentrated caustic soda solution is extracted with methylene chloride. Ether is added to the dried extracts until they are turbid, filtration through Hyflo (Registered Trade Mark) and concentration by evaporation are effected, whereby the title compound is obtained as residue. M.P. 133—135° (after crystallization from ether).

The following compounds are obtained in a manner analogous to that described in Examples 7 and 8 from the corresponding starting materials and using process b):

- (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - isopropyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrogen maleate salt form 150—158°;
- (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,6 - dimethyl - 4 - (p - tolyl)benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 195—198°;
- (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,6 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 280—283°;
- (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,7 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 244—248°;
- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro-2,6 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 183—187°;
- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro-2,7 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 204—207°;
- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro-2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 297—303°.
- The following compounds are obtained in a manner analogous to that described in Example 8 from the corresponding starting materials and using process b):
- (3aRS,4SR,9aSR) - 7 - chloro - 4 - (m-chlorophenyl) - 3a,4,9,9a - tetrahydro - 2-methyl-benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 244—248°;
- (3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a-tetrahydro - 2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 231—233°;
- (3aRS,4SR,9aSR) - 2 - ethyl - 6 - chloro-3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
- (3aRS,4SR,9aSR) - 2 - n - butyl - 6-chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl-benz[f]isoindoline;
- (3aRS,4SR,9aSR) - 6 - chloro - 2 - isopropyl - 3a,4,9,9a - tetrahydro - 4 - phenyl-benz[f]isoindoline;
- (9aRS) - 9,9a - dihydro - 2 methyl - 4-

22

up in water, concentrated 65
with meth-
to the dried
ion enough
and concen-
ed, whereby 70
as residue.
zation from

obtained in a 75
scribed in
corresponding
ss b):

tetrahydro-
benz[f]iso-
maleate salt 80

tetrahydro-
benz[f]iso-
aphthalene-
198°; 85

tetrahydro-
benz[f]iso-
aphthalene-
283°; 90

tetrahydro-
benz[f]iso-
aphthalene-
248°; 95

tetrahydro-
benz[f]iso-
aphthalene-
87°; 100

tetrahydro-
benz[f]iso-
aphthalene-
17°; 105

tetrahydro-
isoindoline,
ene-1,5-di- 105

obtained in
scribed in
g starting

- 4 - (m- 110
ydro - 2-
the bis-
salt form

3a,4,9,9a- 115
yl - benz-
loride salt

- chloro-
benz[f]- 120

ityl - 6-
- phenyl-

2 - iso- 125
- phenyl-

thyl - 4-

phenyl-benz[f]isoindoline, M.P. of the hydro-
gen maleate salt form 158—162° (decomp.).

EXAMPLE 9.

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-
6 - methyl - 4 - phenyl - benz[f]iso-
indoline [process c,b¹]

A solution of 20.2 g of (3aRS,4SR,9aSR)-
3a,4,9,9a - tetrahydro - 6 - methyl - 4 -
phenyl-benz[f]isoindoline in 500 cc of n-
butanol saturated with solid potassium hy-
droxide is heated to the boil at reflux for 70
hours in an atmosphere of argon, and is
subsequently concentrated by evaporation.
The residue is divided between water/
methylene chloride, the organic phase is dried
and concentrated by evaporation, the residue
is taken up in an excess of hydrochloric acid
in methanol, the solution is concentrated by
evaporation, and after crystallization of the
residue from methanol/ether, the hydro-
chloride salt form of the title compound,
having a M.P. of 174—176° (decomp.), is
obtained.

EXAMPLE 10.

(3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a-
tetrahydro - 4 - phenyl - benz[f]iso-
indoline [process b¹].

6.4 g of (3aRS,4SR,9aSR) - 6 - chloro-
3a,4,9,9a - tetrahydro - 2 - phenoxycarbonyl-
4-phenyl-benz[f]isoindoline are heated to the
boil at reflux in 320 cc of a saturated solution
of potassium hydroxide in n-butanol for 70
hours in an atmosphere of nitrogen. The
reaction mixture is then concentrated, the
residue is taken up in water and extraction is
effected with methylene chloride. The washed
and dried methylene chloride solution is con-
centrated by evaporation, whereby the title
compound is obtained. M.P. of the hydro-
chloride salt form 205—207° (after crystal-
lization from methylene chloride/ether).

The following compounds are obtained in
a manner analogous to that described in
Example 9 or 10 from the corresponding
starting materials and using process b¹):

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-
4 - phenyl - benz[f]isoindoline, M.P. 136—
138°;

(3aRS,4SR,9aSR) - 6 - chloro - 4 - (4-
chlorophenyl) - 3a,4,9,9a - tetrahydro - benz-
[f]isoindoline, M.P. 133—134°;

(3aRS,4SR,9aSR) - 6 - fluoro - 4 - (p-
fluorophenyl) - 3a,4,9,9a - tetrahydro - benz-
[f]isoindoline, M.P. of the hydrogen maleate
salt form 134—136°;

(3aRS,4SR,9aSR) - 7 - chloro - 4 - (m-
chlorophenyl) - 3a,4,9,9a - tetrahydro - benz-
[f]isoindoline, M.P. of the hydrogen maleate
salt form 166—168°;

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-
6 - methyl - 4 - (p-tolyl)benz[f]isoindoline,
M.P. 129—132°;

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-
7 - methyl - 4 - phenyl - benz[f]isoindoline,
M.P. of the hydrochloride salt form 225—
227°.

The following compounds are obtained in
a manner analogous to that described in
Example 9 from the corresponding starting
materials and using process c):

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-
2 - methyl - 4 - phenyl - benz[f]isoindoline,
M.P. of the hydrochloride salt form 207—
209°;

(3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-
3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]-
isoindoline, M.P. 65—68°;

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-
2 - isopropyl - 4 - phenyl - benz[f]isoindoline.
M.P. of the hydrogen maleate salt form
150—158°;

(3aRS,4SR,9aSR) - 2 - (o - chlorophen-
ethyl) - 3a,4,9,9a - tetrahydro - 4 - phenyl-
benz[f]isoindoline, M.P. of the hydrogen
maleate salt form 178—179°;

(3aRS,4SR,9aSR) - 2 - (3a,4,9,9a - tetra-
hydro - 4 - phenyl - benz[f]isoindolin - 2-
yl)acetophenone, M.P. 120—130°;

(3aRS,4SR,9aSR) - p - fluoro - 4-
(3a,4,9,9a - tetrahydro - 4 - phenyl - benz-
[f]isoindolin - 2 - yl)butyropenone, M.P.
81—84°;

(3aRS,4SR,9aSR) - 6 - chloro - 4 - (4-
chlorophenyl) - 3a,4,9,9a - tetrahydro - 2-
methyl-benz[f]isoindoline, M.P. 133—135°;

(3aRS,4SR,9aSR) - 6 - chloro - 4 - (4-
chlorophenyl) - 2 - cyclopropyl - methyl-
3a,4,9,9a - tetrahydro - benz[f]isoindoline,
M.P. 124—126°;

(3aRS,4SR,9aSR) - 7 - chloro - 4 - (m-
chlorophenyl) - 3a,4,9,9a - tetrahydro - 2-
methyl-benz[f]isoindoline, M.P. of the bis-
(base)naphthalene-1,5-disulphonate salt form
244—248°;

(3aRS,4SR,9aSR) - 7 - chloro - 4 - (m-
chlorophenyl) - 2 - cyclopropyl - methyl-
3a,4,9,9a - tetrahydro - benz[f]isoindoline,
M.P. of the bis(base)naphthalene-1,5-di-
sulphonate salt form 243—247°;

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-
2,6 - dimethyl - 4 - (p - tolyl)benz[f]iso-
indoline, M.P. of the bis(base)naphthalene-
1,5-disulphonate salt form 195—198°;

(3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-
3a,4,9,9a - tetrahydro - 6 - methyl - 4 - (p-
tolyl)benz[f]isoindoline, M.P. 98—100°;

(3aRS,4SR,9aSR) - 2 - (2 - hydroxyethyl)-
3a,4,9,9a - tetrahydro - 6 - methyl - 4 - (p-
tolyl)-2-benz[f]isoindoline, M.P. 128—129°;

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-
2,6 - dimethyl - 4 - phenyl - benz[f]iso-
indoline, M.P. of the bis(base)naphthalene-
1,5-disulphonate 280—283°;

(3aRS,4SR,9aSR) - 6 - chloro - 2 - cyclo-
propylmethyl - 3a,4,9,9a - tetrahydro - 4-
phenyl-benz[f]isoindoline;

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- (3aRS,4SR,9aSR) - 2 - ethyl - 6 - chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
- 5 (3aRS,4SR,9aSR) - 2 - n - butyl - 6 - chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
- (3aRS,4SR,9aSR) - 6 - chloro - 2 - isopropyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
- 10 (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl - 3a,4,9,9a - tetrahydro - 6 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 198—204°;
- (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2,7 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 244—248°;
- 15 (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl - 3a,4,9,9a - tetrahydro - 7 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. 79—82°;
- 20 2 - [(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 7 - methyl - 4 - phenyl - benz[f]isoindolin-2-yl] - p - fluoroacetophenone, M.P. of the hydrogen maleate salt form 164—166°;
- 25 (3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a - tetrahydro - 2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 231—233°;
- 30 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2 - (p - methylbenzyl) - 4 - phenyl - benz[f]isoindoline, M.P. 120—121°;
- (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2 - (p - methoxybenzyl) - 4 - phenyl - benz[f]isoindoline, M.P. 95—100°.

EXAMPLE 11.

- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro - 6 - methyl - 4 - phenyl - benz[f]isoindoline [processes e), c¹].
- 40 A solution of 0.55 g of palladium-II-chloride and 0.39 g of common salt in 50 cc of water is added at 25° to a solution of 35.2 g of (9aRS)-2-benzyl-9,9a-dihydro-6-methyl-4-phenyl-benz[f]isoindoline in 300 cc
- 45 of ethanol. A solution of 2.0 g of sodium borohydride in 25 cc of water is added dropwise to the mixture at 0°, stirring is effected at 25° for 30 minutes, the pH of the solution is adjusted to 2 with aqueous concentrated
- 50 hydrochloric acid, and hydrogenation is finally effected at 60°C and a pressure of 4 atmospheres for 18 hours. The reaction mixture is filtered, the filtrate is concentrated, the residue is extracted with hot ethanol,
- 55 and the clear solution is allowed to cool, whereby the hydrochloride salt form of the title compound, having a M.P. of 215—220° (from methanol/ether), crystallizes.

EXAMPLE 12.

- 60 (3aRS,4RS,9aSR) - 2 - benzyl - 6 - chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline [processes d), c¹].
- 190 cc of 57% hydriodic acid are added

dropwise to a suspension of 30 g of (9aRS)-2 - benzyl - 6 - chloro - 9,9a - dihydro - 4 - phenyl-benz[f]isoindoline and 46.8 g of red phosphorus in 400 cc of glacial acetic acid, the mixture is subsequently heated to 110° for 5½ hours, is then poured on ice and made alkaline with caustic soda solution. After extraction with ethyl acetate, the organic phase is filtered through Celite (Registered Trade Mark), the filtrate is dried and concentrated by evaporation, whereby the title compound, having a M.P. of 115—117° (after crystallization from pentane), is obtained.

The following compounds are obtained in a manner analogous to that described in Examples 11 and 12, from the corresponding starting materials and using processes d) or e):

- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro - 2,6 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 183—187°;
- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro - 2,7 - dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate 204—207°;
- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro - 2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate 297—303°.

The following compounds are obtained in a manner analogous to that described in Example 11, from the corresponding starting materials and using process e) or c¹):

- (3aRS,4RS,9SR) - 3a,4,9,9a - tetrahydro - 7 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 226—230°;
- (3aRS,4RS,9aSR) - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 256—258°;

EXAMPLE 13.

- (3aRS,4RS,9aSR) - 6 - chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline [process a¹].

A mixture of 8.8 g of (3aRS,4RS,9aSR)-6 - chloro - 3a,4,9,9a - tetrahydro - 2 - phenoxyacetyl - 4 - phenyl - benz[f]isoindoline, 260 cc of methanol and 42 g of 50% caustic soda solution is heated to the boil at reflux for 15 hours in an atmosphere of nitrogen, is then concentrated and diluted with methylene chloride. The washed and dried organic phase is concentrated by evaporation, whereby the title compound, having a M.P. of 144—145° (after crystallization from ether/pentane), is obtained.

The (3aRS,4RS,9aSR) - 6 - chloro - 3a,4,9,9a - tetrahydro - 2 - phenoxyacetyl - 4-phenyl-benz[f]isoindoline, used as starting material, may be produced as follows:

3.65 cc of chloroformic acid phenyl ester, 125 are added at 0° to a solution of 9 g of (3aRS,4RS,9aSR) - 2 - benzyl - 6 - chloro -

30 g of (9aRS)-
a - dihydro - 4 -
d 46.8 g of red
acial acetic acid,
heated to 110°
on ice and made
solution. After
he organic phase
egistered Trade
nd concentrated
title compound,
(after crystal-
lized).

re obtained in a
described in
e corresponding
processes d) or

9a - tetrahydro-
l - benz[f]iso-
se)naphthalene-
3—187°;

9a - tetrahydro-
- benz[f]iso-
se)naphthalene-

9a - tetrahydro-
z[f]isoindoline,
thalene-1,5-di-

re obtained in
described in
onding starting
or c²):

1 - tetrahydro-
[f]isoindoline,
t form 226—

1 - tetrahydro-
; M.P. of the
58°;

o - 3a,4,9,9a-
- benz[f]iso-

3,4RS,9aSR)-
ahydro - 2 -
- benz[f]iso-

and 42 g of
eated to the
n atmosphere

l and diluted
washed and
ed by evapor-

nd, having a
lization from

6 - chloro-
oxycarbonyl-
l as starting

ollows:
phenyl ester,
of 9 g of

6 - chloro-

3a,4,9,9a - tetrahydro - 4 - phenyl - benz-
[f]isoindoline in 90 cc of methylene chloride,
stirring is effected at room temperature for
16 hours, washing is then effected with a
3 N caustic soda solution, 2 N hydrochloric
acid and water, drying and concentration by
evaporation are effected. The oily residue is
chromatographed with toluene/ethyl acetate
(1:1) on a 100-fold quantity of silica gel,
whereby (3aRS,4RS,9aSR) - 6 - chloro-
3a,4,9,9a - tetrahydro - 2 - phenoxycarbonyl-
4-phenyl-benz[f]isoindoline, having a M.P.
of 130—134° (after crystallization from
ether), is obtained.

EXAMPLE 14.

(9aRS) - 2 - benzyl - 9,9a - dihydro - 6-
methyl - 4 - phenyl - benz[f]isoindoline
[process f,d¹].

35 cc of 100% sulphuric acid are added
dropwise to a solution of 27 g of lithium
aluminium hydride in 400 cc of tetrahydro-
furan at -5° while stirring in an atmosphere
of nitrogen. The mixture is subsequently
stirred at room temperature for 30 minutes,
is again cooled to -5°, and a solution of
90 g of (9aRS)-2-benzyl-9,9a-dihydro-6-
methyl - 4 - phenyl - benz[f]isoindoline - 1,3-
dione in 1 liter of tetrahydrofuran is added
dropwise within 30 minutes. After stirring at
room temperature for 26 hours, the reaction
mixture is decomposed by the addition of
water and a 12% caustic soda solution, and
the resulting precipitate is filtered off. The
filtrate is concentrated by evaporation, the
residue is taken up in methylene chloride, the
filtered solution is concentrated and the residue
is crystallized from ether/pentane, whereby
the title compound, having a M.P. of 139—
143°, is obtained.

The (9aRS) - 2 - benzyl - 9,9a - dihydro-
6 - methyl - 4 - phenyl - benz[f]isoindoline-
1,3-dione, used as starting material, may be
produced as follows:

A solution of 35 g of 2,5-dimethylbenzo-
phenone and 31.5 g of N-benzylmaleimide in
500 cc of acetone or methylene chloride is
irradiated with a mercury high pressure lamp
through a Pyrex (Registered Trade Mark)
filter, until all the material has reacted (20
to 130 hours), filtration and concentration
by evaporation are then effected. After crystal-
lization from ether, the residue yields 35 g
2 - benzyl 3a,4,9,9a - tetrahydro - 6 - methyl-
4 - phenyl - benz[f]isoindolin - 4 - cl - 1,3-
dione, having a M.P. of 162—164°, which are
dissolved in 170 cc of trifluoroacetic acid.
The solution is stirred at 25° for 3 hours
and concentrated by evaporation. After crystal-
lization from methylene chloride/methanol,
the residue yield 30 g of (9aRS)-2-benzyl-
9,9a - dihydro - 6 - methyl - 4 - phenyl-
benz[f]isoindoline - 1,3 - dione, having a
M.P. of 156—158°.

The following compounds are obtained in

a manner analogous to that described in
Example 14, from the corresponding starting
materials and using process f) or d¹):

(9aRS) - 2 - benzyl - 9,9a - dihydro - 7-
methyl - 4 - phenyl - benz[f]isoindoline,
M.P. 139—142°;

(9aRS) - 2 - benzyl - 6 - chloro - 9,9a-
dihydro - 4 - phenyl - benz[f]isoindoline,
M.P. 266—268°;

(9aRS) - 2 - benzyl - 9,9a - dihydro - 4-
phenyl-benz[f]isoindoline, M.P. 113—115°;

(9aRS) - 9,9a - dihydro - 4 - phenyl-
benz[f]isoindoline. M.P. of the hydrochloride
salt form 238—243° (decomp.);

(9aRS) - 9,9a - dihydro - 2 - methyl - 4-
phenyl-benz[f]isoindoline, M.P. of the hydro-
gen maleate salt form 158—162° (decomp.).

EXAMPLE 15.

(3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-
3a,4,9,9a - tetrahydro - 4 - phenyl-
benz[f]isoindoline [process g)].

4.7 g of cyclopropylcarboxylic acid chlor-
ide are added dropwise at -5° to a mixture
of 7.5 g of (3aRS,4SR,9aSR)-3a,4,9,9a-
tetrahydro - 4 - phenyl - benz[f]isoindoline,
7.9 g of pyridine and 100 cc of methylene
chloride. The mixture is stirred at room
temperature of 1 hour, is then successively
shaken with a 10% aqueous citric acid solu-
tion and a sodium hydrogen carbonate solu-
tion, is dried over sodium sulphate and con-
centrated by evaporation, whereby
(3aRS,4SR,9aSR) - 2 - cyclopropylcarbonyl-
3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]-
isoindoline, having a M.P. of 149—151°
(after crystallization from ether), is obtained
as residue.

1 g of lithium aluminium hydride is added
portionwise to a warm solution of 8.6 g of
(3aRS,4SR,9aSR) - 2 - cyclopropylcarbonyl-
3a,4,9,9a - tetrahydro - 4 - phenyl - benz-
[f]isoindoline in 100 cc of tetrahydrofuran.
The mixture is stirred at room temperature
for 1 hour, is then decomposed with a 2N
caustic soda solution and filtered. The con-
centrated filtrate is reduced to a paste with
silica gel in benzene/ethyl acetate (1:1),
filtration and concentration by evaporation
are effected, whereby the title compound,
having a M.P. of 65—68° (after crystalliza-
tion from pentane), is obtained.

The following compounds of formula Im
are obtained in a manner analogous to that
described in Example 15 from the correspond-
ing starting materials and using process g):

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-
2 - methyl - 4 - phenyl - benz[f]isoindoline,
M.P. of the hydrochloride salt form 207—
209°;

(3aRS,4SR,9aSR) - 6 - chloro - 2 - cyclo-
propylmethyl - 3a,4,9,9a - tetrahydro - 4-
phenyl-benz[f]isoindoline;

(3aRS,4SR,9aSR) - 2 - (o - chlorophen-
ethyl) - 3a,4,9,9a - tetrahydro - 4 - phenyl-

- benz[f]isoindoline, M.P. of the hydrogen maleate salt form 178—179°;
 (3aRS,4SR,9aSR) - 6 - chloro - 4 - (4-chlorophenyl) - 3a,4,9,9a - tetrahydro - 2-methyl-benz[f]isoindoline, M.P. 133—135°;
 5 (3aRS,4SR,9aSR) - 6 - chloro - 4 - (4-chlorophenyl) - 2 - cyclopropylmethyl-3a,4,9,9a - tetrahydro - benz[f]isoindoline, M.P. 124—126°;
 10 (3aRS,4SR,9aSR) - 7 - chloro - 4 - (4-chlorophenyl) - 3a,4,9,9a - tetrahydro - 2-methyl-benz[f]isoindoline, M.P. of the bis-(base)naphthalene-1,5-disulphonate 244—248°;
 15 (3aRS,4SR,9aSR) - 7 - chloro - 4 - (4-chlorophenyl) - 2 - cyclopropylmethyl-3a,4,9,9a - tetrahydro - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 243—347°;
 20 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,6-dimethyl - 4 - (p-tolyl)benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate salt form 195—198°;
 (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-3a,4,9,9a - tetrahydro - 6 - methyl - 4 - (p-tolyl)benz[f]isoindoline, M.P. 98—100°;
 25 (3aRS,4SR,9aSR) - 2 - (2 - hydroxyethyl) - 3a,4,9,9a - tetrahydro - 6 - methyl-4 - (p-tolyl) - 2 - benz[f]isoindoline, M.P. 128—129°;
 30 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,6-dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate 280—283°;
 35 (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-3a,4,9,9a - tetrahydro - 6 - methyl - 4-phenyl-benz[f]isoindoline, M.P. of the hydrochloride salt form 198—204°;
 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,7-dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate 244—248°;
 40 (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl-3a,4,9,9a - tetrahydro - 7 - methyl - 4-phenyl-benz[f]isoindoline, M.P. 79—82°;
 45 (3RS,4SR,9aSR) - 2 - ethyl - 6 - chloro-3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline;
 (3aRS,4SR,9aSR) - 2 - n-butyl - 6-chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl-benz[f]isoindoline;
 50 (3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a-tetrahydro - 2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 231—233°;
 55 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - (p-methylbenzyl) - 4 - phenyl - benz[f]isoindoline, M.P. 120—121°;
 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 (p-methoxybenzyl) - 4 - phenyl - benz[f]isoindoline, M.P. 95—100°;
 60 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - methyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate form 297—303°;
 65 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,6-dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate 183—187°;
 (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,7-dimethyl - 4 - phenyl - benz[f]isoindoline, M.P. of the bis(base)naphthalene-1,5-disulphonate 204—207°;
 (3aRS,4SR,9aSR) - 2 - benzyl - 6 - chloro-3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline, M.P. 115—117°;
 (9aRS) - 9,9a - dihydro - 2 - methyl - 4-phenyl - benz[f]isoindoline, M.P. of the hydrogen maleate salt form 158—162° (decomp.);
 (9aRS) - 2 - benzyl - 9,9a - dihydro - 4-phenyl - benz[f]isoindoline, M.P. 265—269°;
 (9aRS) - 2 - benzyl - 9,9a - dihydro - 6-methyl - 4 - phenyl - benz[f]isoindoline, M.P. 139—143°;
 (9aRS) - 2 - benzyl - 9,9a - dihydro - 7-methyl - 4 - phenyl - benz[f]isoindoline, M.P. 139—142°;
 (9aRS) - 2 - benzyl - 6-chloro - 9,9a-dihydro - 4 - phenyl - benz[f]isoindoline, M.P. of the hydrochloride salt form 266—268°.
 The following are characteristic Examples which illustrate the described processes for the production of the required starting materials:
 EXAMPLE 16.
 (3aRS,4SR,9aSR) - 2 - trifluoroacetyl - 6-chloro - 4 - (p-chlorophenyl)-3a,4,9,9a - tetrahydro - benz[f]isoindoline.
 A solution of 30 g of N,N-bis-(trans-p-chlorocinnamyl)trifluoroacetamide in 600 cc of o-dichlorobenzene is heated to the boil at reflux for 16 hours in an atmosphere of argon and is subsequently concentrated by evaporation. The residue is chromatographed on 250 g of silica gel with benzene. The filtrate is concentrated by evaporation, where-by the title compound is obtained as residue. M.P. 107—112° (after crystallization from ether/pentane).
 The N,N-bis-(trans-p-chlorocinnamyl)-trifluoroacetamide, used as starting material, may be produced by alkylation of N-trans-p-chlorocinnamyl-trifluoroacetamide with trans-p-chlorocinnamyl bromide (in a manner analogous to Example 6).
 EXAMPLE 17.
 (3aRS,4SR,9aSR) - 2 - trifluoroacetyl - 6-fluoro - 4 - (p-trifluorophenyl)-3a,4,9,9a - tetrahydro - benz[f]isoindoline.
 The title compound, having a M.P. of 173—176° (after crystallization from ether), is produced in a manner analogous to that described in Example 6, by thermic cyclization of N,N-bis-(trans-p-fluorocinnamyl)-trifluoroacetamide.

- tetrahydro-
benz[f] iso-
naphthalene- 70

- tetrahydro-
benz[f] iso-
naphthalene- 75

1 - 6 - chloro-
enyl - benz- 75

- methyl - 4-
M.P. of the
158—162° 80

dihydro - 4-
265—269°;
dihydro - 6-
f]isindoline, 85

dihydro - 7-
f]isindoline, 85

loro - 9,9a-
f]isindoline. 90
form 266—

ic Examples
processes for
starting mat- 95

oacetyl - 6-
lorophenyl)-
benz[f]iso- 100

is-(trans-*p*-
in 600 cc
to the boil
mosphere of 105
entrated by
natalographed
nzene The
tion, where-
l as residue. 110
zation from

p - chloro-
l as starting
lkylation of 115
- trifluoro-
namyl bro-
example 6).

acetyl - 6- 120
orophenyl)-
t[f]isindo-

a M.P. of
rom ether), 125
ous to that
nic cycliza-
cinnamyl)-

The N,N - bis - (trans - *p* - fluorocinnamyl)-trifluoroacetamide, having a M.P. of 77—79° (after crystallization from chloroform), required as starting material, may be produced in a manner analogous to that described in Example 6 from N-*p*-fluorocinnamyl-trifluoroacetamide and *p* - fluorocinnamyl bromide.

EXAMPLE 18.

10 (3aRS,4SR,9aSR) - 2 - trifluoroacetyl - 7-chloro - 4 - (*m* - chlorophenyl) - 3,4,9,9a-tetrahydro - benz[f]isindoline.

15 The title compound is obtained as an oil by thermic cyclization of N,N-bis-(trans-*m*-chlorocinnamyl)-trifluoroacetamide in a manner analogous to that described in Example 6 and is purified by chromatography on silica gel (benzene/ethyl acetate 19:1). The N,N-bis - (trans - *m* - chlorocinnamyltrifluoroacetamide (oil), required as starting material, may be produced in a manner analogous to that described in Example 6 from N-*m*-chlorocinnamyl trifluoroacetamide and *m*-chlorocinnamyl bromide.

EXAMPLE 19.

25 (3aRS,4SR,9aSR) - 2 - trifluoroacetyl - 3a,4,9,9a - tetrahydro - 6 - methyl - 4 - (*p* - tolyl)benz[f]isindoline.

30 The title compound, having a M.P. of 110—113° (after crystallization from ether/pentane), is obtained in a manner analogous to that described in Example 6, by thermic cyclization of N,N-bis-trans-*p*-methylcinnamyl trifluoroacetamide.

35 The N,N - bis - (trans - *p* - methylcinnamyltrifluoroacetamide (oil), required as starting material, may be produced in a manner analogous to that described in Example 6 from N-*p*-methylcinnamyl trifluoroacetamide and *p*-methylcinnamyl bromide.

EXAMPLE 20.

40 (9aRS) - 2 - trifluoroacetyl - 9,9a - dihydro-4-phenyl-benz[f]isindoline.

45 A solution of 218 g of N-(trans-cinnamyl)-N - 3 - phenyl - 2 - propinyl trifluoroacetamide in 4.4 liters of *o*-dichlorobenzene is heated to the boil at reflux for 5 hours in an atmosphere of argon and is subsequently concentrated by evaporation. After crystallization from ether/pentane, the residue yields the title compound, having a M.P. of 195—197°.

50 The N - (trans - cinnamyl) - N - (3-phenyl - 2 - propinyl)trifluoroacetamide, used as starting material, may be produced by alkylation of N-(trans-cinnamyl)trifluoroacetamide with 1-bromo-3-phenyl-2-propine.

55 The compounds of formula I exhibit pharmacological activity, although the preferred utility for the compounds having the (3aRS,4RS,9aSR) configuration and those wherein X and Y form an additional bond,

is their use as intermediates for the preparation of the corresponding (3aRS,4SR,9aSR) compounds. In particular the compounds exhibit anti-depressant activity as indicated by, for example, an inhibition of tetrabenazine induced catalepsy in rats.

The compounds are therefore indicated for use as anti-depressant agents. For this use an indicated daily dosage is from 50 to 500 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 12 to 250 mg, or in sustained release form.

Furthermore the compounds exhibit analgesic activity as indicated by standard tests with mice, e.g. the phenylbenzoquinone syndrome test.

The compounds are therefore further indicated for use as analgesic agents. For this use an indicated daily dose is from 30 to 300 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 7 to 150 mg, or in sustained release form.

In general the anti-depressant activity is the preferred activity, especially for the compounds (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 6 - chloro - 2 - methyl - 4 - phenylbenz[f]isindoline, and also for

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - acetonyl - 4 - phenyl - benz[f]isindoline, (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-6 - methyl - 4 - phenyl - benz[f]isindoline, (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - cyclopropylmethyl - 7 - methyl - 4 - phenyl - benz[f]isindoline, and

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-6 - chloro - 2 - isopropyl - 4 - phenyl - benz[f]isindoline.

However, in respect of, for example, the compounds

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,6 - dimethyl - 4 - para - tolyl - benz[f]-isindoline,

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,6 - dimethyl - 4 - phenyl - benz[f]isindoline,

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - acetonyl - 6 - methyl - 4 - phenyl - benz[f]isindoline,

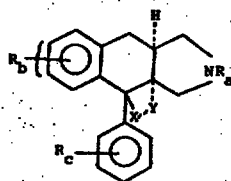
(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2,7 - dimethyl - 4 - phenyl - benz[f]isindoline,

(3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro-2 - acetonyl - 7 - methyl - 4 - phenyl - benz[f]isindoline, and compounds wherein R₁ is lower alkyl of 4 carbon atoms these tend to show more interesting activity in the above-mentioned analgesic test than in the above-mentioned anti-depressant test.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily pre-

pared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet.

A class of compounds of formula I comprises compounds of formula Iw



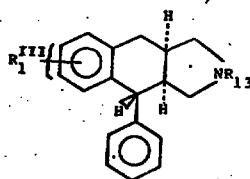
Iw

wherein

X and Y as defined in Claim 1, R_a is (i) hydrogen, (ii) alkyl of 1 to 3 carbon atoms, (iii) alkenyl or alkynyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α -position thereof, (iv) cyclopropylmethyl, (v) hydroxyethyl, (vi) phenylalkyl of 7 or 8 carbon atoms in the aggregate thereof, (vii) phenylalkyl of 7 or 8 carbon atoms in the aggregate thereof monosubstituted by fluorine, chlorine, methyl or methoxy, (viii) acetonyl, 3-oxobutyl, phenacyl, *p*-fluorophenacyl or 4 - (*p* - fluorophenyl) - 4 - oxobutyl and R_b and R_c are identical or different and each is hydrogen, chlorine, fluorine or methyl.

The (3aRS,4SR,9aSR) - tetrahydrobenzofuran derivatives of formula I, are especially interesting.

A class of preferred compounds comprises the compounds of formula Iaa

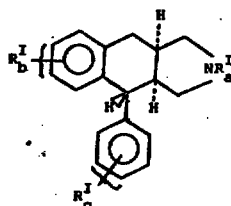


Iaa

wherein

$R_{1,13}$ is hydrogen, methyl or chlorine, and R_{13} is methyl, 2-propinyl, cyclopropylmethyl or acetonyl.

A further class comprises compounds of formula Iz



Iz

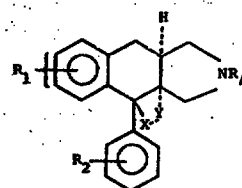
wherein

R_a is hydrogen, methyl, 2-propinyl, cyclopropylmethyl, acetonyl and R_b and R_c are independently hydrogen, methyl or chlorine.

A further class of compounds comprises compounds of formula I wherein X and Y are hydrogen, R_a is hydrogen and R is hydrogen, alkyl, alkenyl, hydroxyalkyl, phenylalkyl or $-A-CO-R_a$ wherein A is defined above and R_a is phenyl or phenyl substituted by halogen.

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula Ia,



Ia

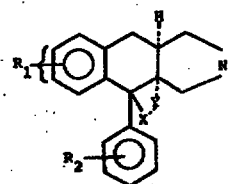
wherein

R_1 and R_2 are identical or different and each is hydrogen, halogen or alkyl of 1 to 4 carbon atoms, and either (i) each of X and Y is hydrogen, and the rings B and C are cis to each other, or (ii) X and Y together are an additional bond, R_1 is (i) alkyl of 1 to 5 carbon atoms, (ii) alkenyl or alkynyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α -position thereof, (iii) alkyl of 1 to 4 carbon atoms substituted by cycloalkyl of 3 to 6 carbon atoms, (iv) hydroxyalkyl of 2 to 5 carbon atoms, (v) phenylalkyl of 7 to 11 carbon atoms, in the aggregate thereof, (vi) phenylalkyl of 7 to 11 carbon atoms in the aggregate thereof monosubstituted in the phenyl thereof by halogen, alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms, or (vii) $A-CO-R_3$,

wherein

A is alkylene of 1 to 4 carbon atoms, and R_3 is alkyl of 1 to 5 carbon atoms, alkoxy of 1 to 4 carbon atoms, hydroxy, phenyl or phenyl substituted by halogen.

which comprises alkylating a compound of formula Ib,



Ib

wherein

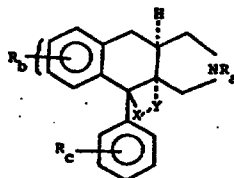
R_1 , R_2 , X and Y are as defined above.

2. A process for the production of a com-



pared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet.

A class of compounds of formula I comprises compounds of formula Iw



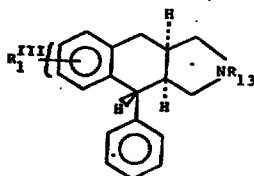
Iw

wherein

X and Y as as defined in Claim 1, R_1 is (i) hydrogen, (ii) alkyl of 1 to 3 carbon atoms, (iii) alkenyl or alkynyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α -position thereof, (iv) cyclopropylmethyl, (v) hydroxyethyl, (vi) phenylalkyl of 7 or 8 carbon atoms in the aggregate thereof, (vii) phenylalkyl of 7 or 8 carbon atoms in the aggregate thereof monosubstituted by fluorine, chlorine, methyl or methoxy, (viii) acetonyl, 3-oxobutyl, phenacyl, *p*-fluorophenacyl or 4 - (*p* - fluorophenyl) - 4 - oxobutyl and R_2 and R_3 are identical or different and each is hydrogen, chlorine, fluorine or methyl.

The (3aRS,4SR,9aSR) - tetrahydrobenzofuroindolines of formula I, are especially interesting.

A class of preferred compounds comprises the compounds of formula Iaa

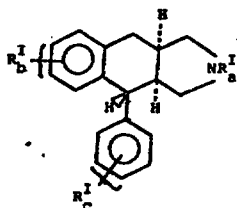


Iaa

wherein

R_1 is hydrogen, methyl or chlorine, and R_{13} is methyl, 2-propinyl, cyclopropylmethyl or acetonyl.

A further class comprises compounds of formula Iz



Iz

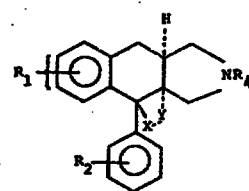
wherein

R_3 is hydrogen, methyl, 2-propinyl, cyclopropylmethyl, acetonyl and R_4 and R_5 are independently hydrogen, methyl or chlorine.

A further class of compounds comprises compounds of formula I wherein X and Y are hydrogen, R_2 is hydrogen and R is hydrogen, alkyl, alkenyl, hydroxyalkyl, phenylalkyl or $-A-CO-R_3$ wherein A is defined above and R_3 is phenyl or phenyl substituted by halogen.

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula Ia,



Ia

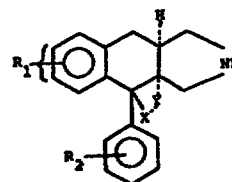
wherein

R_1 and R_2 are identical or different and each is hydrogen, halogen or alkyl of 1 to 4 carbon atoms, and either (i) each of X and Y is hydrogen, and the rings B and C are cis to each other, or (ii) X and Y together are an additional bond, R_3 is (i) alkyl of 1 to 5 carbon atoms, (ii) alkenyl or alkynyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α -position thereof, (iii) alkyl of 1 to 4 carbon atoms substituted by cycloalkyl of 3 to 6 carbon atoms, (iv) hydroxyalkyl of 2 to 5 carbon atoms, (v) phenylalkyl of 7 to 11 carbon atoms, in the aggregate thereof, (vi) phenylalkyl of 7 to 11 carbon atoms in the aggregate thereof monosubstituted in the phenyl thereof by halogen, alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms, or (vii) $A-CO-R_3$,

wherein

A is alkylene of 1 to 4 carbon atoms, and R_3 is alkyl of 1 to 5 carbon atoms, alkoxy of 1 to 4 carbon atoms, hydroxy, phenyl or phenyl substituted by halogen.

which comprises alkylating a compound of formula Ib,



Ib

wherein

R_1 , R_2 , X and Y are as defined above.

2. A process for the production of a com-



18

19

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19

opiny, cyclo-
tly hydrogen, 45
ds comprises
in X and Y
R is hydro-
phenylalkyl 50
defined above
substituted by

n of a com- 55

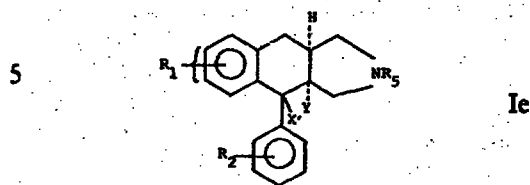
Ia

fferent and
kyl of 1 to 60
each of
rings
, or (ii)
onal bond,
atoms, (ii) 65
bon atoms,
g in other
) alkyl of
by cyclo-
) hydroxy- 70
) phenyl-
is, in the
yl of 7 to
te thereof
hereof by
atoms or 75
or (vii)

toms, and
s, alkoxy 80
y, phenyl
L
pound. of

Ib 85

pound of formula I defined in claim 1 which
comprises reductively alkylating a compound
of formula Ib as defined in claim 1, to
produce a compound of formula Ic,

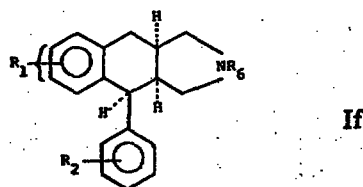


wherein

R₁, R₂, X and Y are as defined in claim 1
and

10 R₃ is a primary or secondary alkyl of 1
to 5 carbon atoms.

3. A process which comprises epimerising
a compound of formula If,



wherein

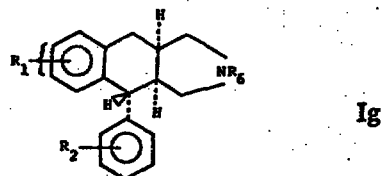
15 R₁ and R₂ are as defined in claim 1, and
R₃ is (i) alkyl of 1 to 5 carbon atoms, (ii)
alkenyl or alkynyl of 3 to 5 carbon atoms,
the multiple bond thereof being in other
than the α -position thereof, (iii) alkyl of
20 1 to 4 carbon atoms substituted by cyclo-
alkyl of 3 to 6 carbon atoms, (iv) hydroxy-
alkyl of 2 to 5 carbon atoms, (v) phenyl-
alkyl of 7 to 11 carbon atoms in the aggre-
gate thereof, (vi) phenylalkyl of 7 to 11
25 carbon atoms in the aggregate thereof
monosubstituted in the phenyl thereof by
halogen, alkoxy of 1 to 4 carbon atoms or
alkyl of 1 to 4 carbon atoms, or (vii)
A-CO-R₃,

30 wherein

A is as defined in claim 1, and

R₃' is alkyl of 1 to 5 carbon atoms, phenyl
or phenyl substituted by halogen,

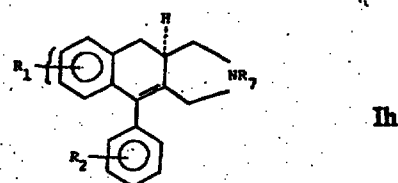
35 under strong alkaline conditions to produce
a compound of formula Ig,



wherein

R₁, R₂ and R₃ are as defined in claim 1.

40 4. A process which comprises hydrogen-
ating a compound of formula Ih,

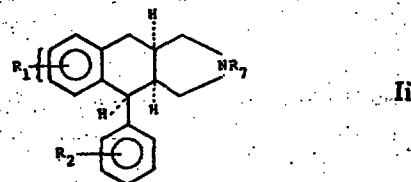


wherein

R₁ and R₂ are as defined in claim 1, and
R₃ is (i) alkyl of 1 to 5 carbon atoms, (ii)
alkyl of 1 to 4 carbon atoms substituted
by cycloalkyl of 3 to 6 carbon atoms, (iii)
phenylalkyl of 7 to 11 carbon atoms in the
aggregate thereof, (iv) phenylalkyl of 7 to
11 carbon atoms in the aggregate thereof
by halogen or alkyl of 1 to 4 carbon atoms,
or (iv) A-CO-R₃,

wherein

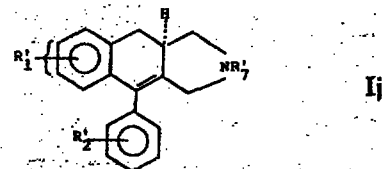
A and R₃ are as defined in claim 1,
with hydriodic acid and red phosphorus to
produce a compound of formula Ii,



wherein

R₁, R₂ and R₃ are as defined in claim 1.

5. A process which comprises catalytically
hydrogenating a compound of formula Ij,

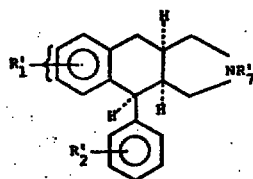


wherein

R₁' and R₂' are identical or different and
each is hydrogen, fluorine or alkyl of 1 to
4 carbon atoms, and

R₃' is (i) alkyl of 1 to 5 carbon atoms, (ii)
alkyl of 1 to 4 carbon atoms substituted
by cycloalkyl of 3 to 6 carbon atoms, (iii)
hydroxyalkyl of 2 to 5 carbon atoms, (iv)
phenylalkyl 8 to 11 carbon atoms in the
aggregate thereof, the phenyl thereof being
in other than the α -position of the alkyl
moiety or (v) phenylalkyl of 8 to 11 carbon
atoms in the aggregate thereof monosubsti-
tuted in the phenyl thereof by halogen,
alkoxy of 1 to 4 carbon atoms or alkyl of
1 to 4 carbon atoms, the phenyl thereof
being in other than the α -position of the
alkyl moiety

to produce a compound of formula Ik,

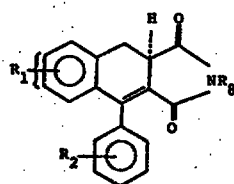


Ik

wherein

 R_1' , R_2' and R_3' are as defined above.

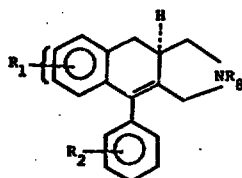
- 5 A process which comprises reducing with a metal hydride a compound of formula II,



II

wherein

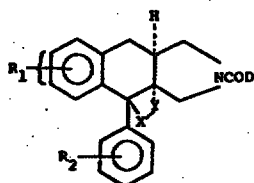
- 10 R_1 and R_2 are as defined in claim 1 and, R_8 is (i) alkyl of 1 to 5 carbon atoms, (ii) alkyl of 1 to 4 carbon atoms substituted by cycloalkyl of 3 to 6 carbon atoms, (iii) hydroxyalkyl of 2 to 5 carbon atoms, (iv) phenylalkyl of 7 to 11 carbon atoms in the aggregate thereof, (v) phenylalkyl of 7 to 11 carbon atoms in the aggregate thereof monosubstituted on the phenyl thereof by halogen, alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms, to produce a compound of formula Iu,



Iu

wherein

- 20 R_1 , R_2 and R_8 are as defined in claim 1. 7. A process which comprises reducing a compound of formula IV,



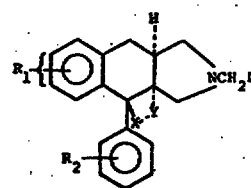
IV

wherein

- 30 R_1 , R_2 , X and Y are as defined in claim 1, and D is (i) hydrogen, (ii) alkyl of 1 to 4 carbon atoms, (iii) cycloalkyl of 3 to 6 carbon atoms, (iv) alkyl of 1 to 3 carbon atoms substituted by cycloalkyl of 3 to 6 carbon atoms, (v) hydroxyalkyl of 1 to 4

carbon atoms, (vi) phenyl, (vii) phenyl-alkyl of 7 to 10 carbon atoms in the aggregate thereof, (viii) phenyl monosubstituted by halogen alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms, or (ix) phenylalkyl of 7 to 10 carbon atoms in the aggregate thereof monosubstituted on the phenyl thereof by halogen, alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms,

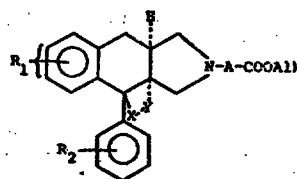
to produce a compound of formula Im,



Im

wherein

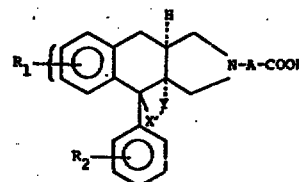
- 45 R_1 , R_2 , X and Y are as defined in claim 1 and D is as defined above, with a metal hydride, 8. A process which comprises hydrolyzing a compound of formula Ic,



Ic

wherein

- 50 R_1 , R_2 , X, Y and A are as defined in claim 1, and Alk is alkyl of 1 to 4 carbon atoms, to produce a compound of formula Id,



Id

wherein

- 60 R_1 , R_2 , X, Y and A are as defined in claim 1. 9. A process for the production of a compound of formula Ib, as defined in Claim 1, comprising a¹) replacing the group R_8 by a hydrogen atom in a compound of formula VI,

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(vii) phenyl-
in the aggre-
nosubstituted
carbon atoms
oms (ix)
atoms in the
tuted on the
koxy of 1 to
to 4 carbon

Ia Im,

Im

i in claim 1

hydrolyzing

Ic

ed in claim

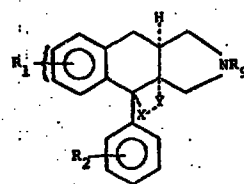
ms,
a Id,

Id

d in claim

of a com-
Claim 1,hydrogen
/I,

21



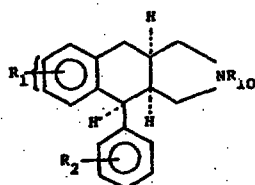
VI

wherein

R_1 , R_2 , X and Y are as defined in claim 1,
and

R_3 is an electron attracting group.

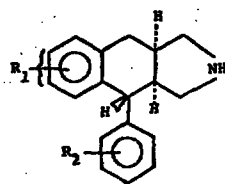
10. A process comprising epimerising a
compound of formula VII,



VII

wherein

10 R_1 and R_2 as as defined in claim 1, and
 R_{10} as the radical R_9 , defined in claim 9,
under strong alkaline conditions,
to produce a compound of formula In

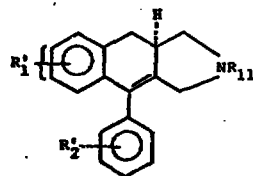


In

15 wherein

R_1 and R_2 are as defined in claim 1.

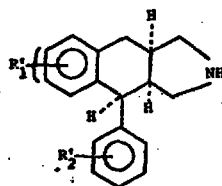
11. A process which comprises catalytically
hydrogenating a compound of formula Io



Io

20 wherein

R_1' and R_2' are as defined in claim 1, and
 R_{11} is hydrogen or the benzyl group, to
produce a compound of formula Ip,

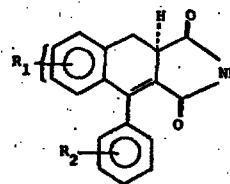


Ip

25 wherein

R_1' and R_2' are as defined in claim 5.

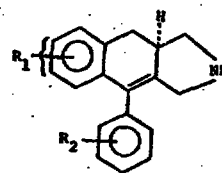
12. A process which comprises reducing a
compound of formula VIII



VIII

wherein

R_1 and R_2 are as defined in claim 1,
with a metal hydride to produce a compound
of formula Iq,



Iq.

wherein

R_1 and R_2 are as defined in claim 1.

13. A process for the production of a
compound of formula Ia and Ib, as stated
in Claim 1, substantially as hereinbefore
described with reference to any one of the
Examples 1 to 5, 7, 8 and 13, or Example 6
respectively.

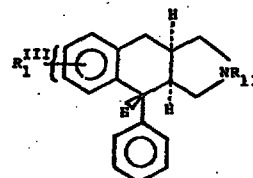
14. A process for the production of a
compound of formula Ia or Ib, as stated
in Claim 1, substantially as hereinbefore
described with reference to any one of the
Examples 10 to 12, 14 and 15 or any one
of Examples 9 to 14 respectively.

15. A compound of formula Ia, whenever
produced by a process according to any one
of Claims 1 or 8, 13 and 14.

16. A compound of formula Ib, whenever
produced by a process according to Claim
9 to 14.

17. A compound of formula Ia or Ib as
defined in Claim 1.

18. A compound of the formula Iaa:



Iaa

wherein

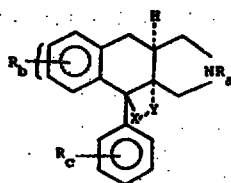
R_1^{III} is hydrogen, methyl or chlorine, and
 R_{13} is methyl, 2-propinyl, cyclopropyl-
methyl or acetyl.

19. A compound of the formula Iw:

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* C L M S *

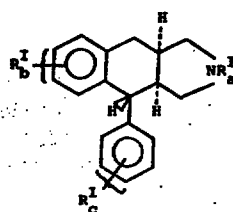


Ix.

wherein

X and Y are as defined in Claim 1, R_1 is (i) hydrogen, (ii) alkyl of 1 to 3 carbon atoms, (iii) alkenyl or alkynyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α -position thereof, (iv) cyclopropylmethyl, (v) hydroxethyl, (vi) phenylalkyl of 7 or 8 carbon atoms in the aggregate thereof, (vii) phenylalkyl of 7 or 8 carbon atoms in the aggregate thereof monosubstituted by fluorine, chlorine, methyl or methoxy, (viii) acetonyl, 3-oxobutyl, phenacyl, *p*-fluorophenacyl or 4-(*p*-fluorophenyl)-4-oxobutyl and R_b and R_c are identical or different and each is hydrogen, chlorine, fluorine or methyl.

20. A compound of the formula Iz:



Iz.

20 wherein

R_a is hydrogen, methyl, 2-propenyl, cyclopropylmethyl, acetonyl and R_b and R_c are independently hydrogen, methyl or chlorine.

25 21. A compound of Claim 17 wherein X and Y are hydrogen.

22. A compound of Claim 21 wherein R_1 and R_2 are hydrogen.

30 23. A compound of Claim 22, wherein R is hydrogen, alkyl, alkenyl, alkynyl, alkyl substituted by cycloalkyl, halophenylalkyl, or $-A-CO-R_3^{II}$ as defined in Claim 22.

35 24. A compound of Claim 22, wherein R_1 is $-A-CO-R_3^{III}$ wherein A is alkylene and R_3^{III} is hydroxy.

25. A compound of Claim 22, wherein R_1 is alkyl, alkenyl, alkynyl or hydroxyalkyl.

26. A compound of Claim 22, wherein R_1 is alkyl substituted by cycloalkyl.

40 27. A compound of Claim 22, wherein R_1 is phenylalkyl, wherein the phenyl moiety is substituted by halogen, alkoxy or alkyl.

28. A compound of Claim 22, wherein R_1 is $-A-CO-R_3^{IV}$ wherein A is alkylene and R_3^{IV} is alkyl or alkoxy.

45 29. A compound of Claim 22, wherein R_1 is $-A-CO-R_3^V$ wherein A is alkylene and R_3^V is phenyl or halophenyl.

30. A compound of Claim 22, wherein A is ethylene or alkyl substituted ethylene.

31. A compound of Claim 2 wherein R_3 is alkyl.

32. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2 - methyl - 4 - phenyl - benz[f]isoindoline.

33. (3aRS,4SR,9aSR) - 2 - allyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline.

34. (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline.

35. (aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2 - isopropyl - 4 - phenyl - benz[f]isoindoline.

36. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 4 - phenyl - 2 - (2 - propenyl)benz[f]isoindoline.

37. (3aRS,4SR,9aSR) - 2 - (o - chlorophenethyl) - 3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindoline.

38. (3aRS,4SR,9aSR) - 2 - (3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindolin-2-yl)acetophenone.

39. (3aRS,4SR,9aSR) - *p* - fluoro - 4 - (3a,4,9,9a - tetrahydro - 4 - phenyl - benz[f]isoindolin - 2 - yl)butyrophenone.

40. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2 - (p - methylbenzyl) - 4 - phenyl - benz[f]isoindoline.

41. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2 - (p - methoxy - benzyl) - 4 - phenyl - benz[f]isoindoline.

42. (3aRS,4SR,9aSR) - 6 - chloro - 3a,4,9,9a - tetrahydro - 2 - methyl - 4 - 4 - chlorophenylbenz[f]isoindoline.

43. (3aRS,4SR,9aSR) - 6 - chloro - 4 (4 - chlorophenyl - 2 - cyclopropylmethyl - 3a,4,9,9a - tetrahydro - benz[f]isoindoline.

44. (3aRS,4SR,9aSR) - 2 - acetonyl - 6 - chloro - 4 - (4 - chlorophenyl) - 3a,4,9,9a - tetrahydro - benz[f]isoindoline.

45. (3aRS,4SR,9aSR) - 7 - chloro - 4 - (m - chlorophenyl) - 3a,4,9,9a - tetrahydro - 2 - methyl - benz[f]isoindoline.

46. (3aRS,4SR,9aSR) - 2 - acetonyl - 7 - chloro - 4 - (m - chlorophenyl) - 3a,4,9,9a - tetrahydro - benz[f]isoindoline.

47. (3aRS,4SR,9aSR) - 7 - chloro - 4 - (m - chlorophenyl) - 2 - cyclopropylmethyl - 3a,4,9,9a - tetrahydro - benz[f]isoindoline.

48. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2,6 - dimethyl - 4 - (p - tolyl)benz[f]isoindoline.

49. (3aRS,4SR,9aSR) - 2 - cyclopropylmethyl - 3a,4,9,9a - tetrahydro - 6 - methyl - 4 - (p - tolyl)benz[f]isoindoline.

50. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 6 - methyl - 2 - (3 - methyl - but-2-enyl) - 4 - (p - tolyl)benz[f]isoindoline.

51. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetrahydro - 2,6 - dimethyl - 4 - phenyl - benz[f]isoindoline.

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22, wherein A
ethylene,
wherein R_s is

4,9,9a - tetra-
1 - benz[f]iso-

2 - allyl-
phenyl - benz-

- cyclopropyl-
- 4 - phenyl-

9,9a - tetra-
yl - benz[f]-

1,9,9a - tetra-
propinyl)benz-

- (o - chloro-
hydro - 4 -

- (3a,4,9,9a-
[f]isoindolin-

- fluoro - 4-
henyl - benz-
none.

1,9,9a - tetra-
- 4 - phenyl-

9,9a - tetra-
benzyl) - 4-

6 - chloro-
hyl - 4 - 4-

chloro - 4 (4-
propylmethyl-
oindoline.

acetonyl - 6-
- 3a,4,9,9a-

chloro - 4-
tetrahydro-

acetonyl - 7-
- 3a,4,9,9a-

chloro - 4-
opylmethyl-
oindoline.

9,9a - tetra-
tolyl)benz-

cyclopropyl-
6 - methyl-

9,9a - tetra-
thyl - but-
ine.

9a9 - tetra-
ayl - benz-

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52. (3aRS,4SR,9aSR) - 2 - acetonyl-
3a,4,9,9a - tetrahydro - 6 - methyl - 4-
phenyl-benz[f]isoindoline.

53. (3aRS,4SR,9aSR) - 2 - cyclopropyl-
methyl - 3a,4,9,9a - tetrahydro - 6 - methyl-
4-phenyl-benz[f]isoindoline.

54. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 2,7 - dimethyl - 4 - phenyl - benz-
[f]isoindoline.

55. (3aRS,4SR,9aSR) - 2 - acetonyl-
3,4,9,9a - tetrahydro - 7 - methyl - 4-
phenyl-benz[f]isoindoline.

56. (3aRS,4SR,9aSR) - 2 - cyclopropyl-
methyl - 3a,4,9,9a - tetrahydro - 7 - methyl-
4-phenyl-benz[f]isoindoline.

57. 2 - (3aRS,4SR,9aSR) - 3a,4,9,9a-
tetrahydro - 7 - methyl - 4 - phenyl - benz-
[f]isoindolin - 2 - yl) - p - fluoroaceto-
phenone.

58. (3aRS,4SR,9aSR) - 6 - chloro-
3a,4,9,9a - tetrahydro - 2 - methyl - 4-
phenyl-benz[f]isoindoline.

59. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 2 - (3 - methylbut - 2 - enyl) - 4-
phenyl-benz[f]isoindoline.

60. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 6 - methyl - 2 - (3 - methylbut - 2-
enyl) - 4-phenyl-benz[f]isoindoline.

61. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 6 - methyl - 4 - phenyl - 2 - (2-
propinyl) - benz[f]isoindoline.

62. (3aRS,4SR,9aSR) - 6 - chloro - 2-
cyclopropylmethyl - 3a,4,9,9a - tetrahydro - 4-
phenyl-benz[f]isoindoline.

63. (3aRS,4SR,9aSR) - 6 - chloro-
3a,4,9,9a - tetrahydro - 4 - phenyl - 2 - (2-
propinyl)-benz[f]isoindoline.

64. (3aRS,4SR,9aSR) - 6 - chloro-
3a,4,9,9a - tetrahydro - 2 - (3 - methylbut-
2-enyl)-4-phenyl-benz[f]isoindoline.

65. (3aRS,4SR,9aSR) - 6 - chloro - 2-
ethyl - 3a,4,9,9a - tetrahydro - 4 - phenyl-
benz[f]isoindoline.

66. (3aRS,4SR,9aSR) - 2 - n - butyl - 6-
chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl-
benz[f]isoindoline.

67. (3aRS,4SR,9aSR) - 6 - chloro - 2-
isopropyl - 3a,4,9,9a - tetrahydro - 4 - phenyl-
benz[f]isoindoline.

68. (3aRS,4SR,9aSR) - 2 - (but - 2 -
inyl) - 3a,4,9,9a - tetrahydro - 4 - phenyl-
benz[f]isoindoline.

69. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 2 - methyl - 4 - phenyl - benz[f]-
isoindoline.

70. (3aRS,4SR,9aSR) - 2 - acetonyl-
3a,4,9,9a - tetrahydro - 4 - phenyl - benz-
[f]isoindoline.

71. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 2,6 - dimethyl - 4 - phenyl - benz-
[f]isoindoline.

72. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 2,7 - dimethyl - 4 - phenyl - benz-
[f]isoindoline.

73. (3aRS,4SR,9aSR) - 2 - benzyl - 6-

chloro - 3a,4,9,9a - tetrahydro - 4 - phenyl-
benz[f]isoindoline.

74. (9aRS) - 2 benzyl - 9,9a - dihydro-
6-methyl-4-phenyl-benz[f]isoindoline.

75. (9aRS) - 9,9a - dihydro - 2 - methyl-
4 - phenyl - benz[f]isoindoline.

76. (9aRS) - 2 - benzyl - 9,9a - dihydro-
7-methyl-4-phenyl-benz[f]isoindoline.

77. (9aRS) - 2 - benzyl - 9,9 - dihydro-
4-phenyl-benz[f]isoindoline.

78. (9aRS) - 2 - benzyl - 6 - chloro-
9,9a-dihydro-4-phenyl-benz[f]isoindoline.

79. (3aRS,4SR,9aSR) - 4 - (3a,4,9,9a-
tetrahydro - 4 - phenyl - benz[f]isoindolin-
2-yl)-2-butanone.

80. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 4 - phenyl - benz[f]isoindoline - 2-
propionic acid methyl ester.

81. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 4 - phenyl - benz[f]isoindoline] - 2-
propionic acid.

82. (3aRS,4SR,9aSR) - 2 - (hydroxy-
ethyl) - 3a,4,9,9a - tetrahydro - 6 - methyl-
4-(p-tolyl)-benz[f]isoindoline.

83. 4 [(9aRS) - 9,9a - dihydro - 4 -
phenyl - benz[f]isoindolin - 2 - yl] - butan-
2-one.

84. [(9aRS) - 9,9a - dihydro - 4 - phenyl-
benz[f]isoindoline-2-yl]-propionic acid.

85. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro-4-phenyl-benz[f]isoindoline.

86. (3aRS,4SR,9aSR) - 6 - chloro - 4 - (4-
chlorophenyl) - 3a,4,9,9a - tetrahydro- benz-
[f]isoindoline.

87. (3aRS,4SR,9aSR) - 6 - fluoro - 4 -
(p - fluorophenyl) - 3a,4,9,9a - tetrahydro-
benz[f]isoindoline.

88. (3aRS,4SR,9aSR) - 7 - chloro - 4 -
(m - chlorophenyl) - 3a,4,9,9a - tetrahydro-
benz[f]isoindoline.

89. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 6 - methyl - 3 - (p-tolyl)benz[f]-
isoindoline.

90. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 6 - methyl - 4 - phenyl-benz[f]-
isoindoline.

91. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro - 7 - methyl - 4 - phenyl - benz[f]-
isoindoline.

92. (3aRS,4SR,9aSR) - 6 - chloro-
3a,4,9,9a - tetrahydro - 4 - phenyl - benz-
[f]isoindoline.

93. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro-4-phenyl-benz[f]isoindoline.

94. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro-6-methyl-4-phenyl-benz[f]isoindoline.

95. (3aRS,4SR,9aSR) - 3a,4,9,9a - tetra-
hydro-7-methyl-4-phenyl-benz[f]isoindoline.

96. (3aRS,4SR,9aSR) - 6 - chloro-
3a,4,9,9a - tetrahydro - 4 - phenyl - benz-
[f]isoindoline.

97. (9aRS) - 9,9a - dihydro - 4 - phenyl-
benz[f]isoindoline.

98. (3aRS,4SR,9aSR) - 2 - acetonyl-

70

75

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85

90

95

100

105

110

115

120

125



* C L N S *

34

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3a,4,9,9a - tetrahydro - 4 - phenyl - benz-[f]isoindoline.

99. A compound of claim 21, wherein R_1 and R_2 are independently hydrogen, halogen or methyl.

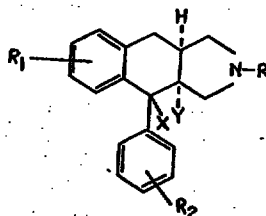
100. A compound of claim 99, wherein R_2 is hydrogen.

101. A compound of claim 99 or 100, wherein R_1 is in the 6 position.

102. A compound of claim 101, wherein R is hydrogen, alkyl or cycloalkyl, halophenyl-alkyl or $-A-CO-R_3$, wherein R_3 is halophenyl, and A is as defined in claim 1.

103. A compound of claim 102, wherein R is alkyl, cycloalkylalkyl or halophenylalkyl and R_1 is hydrogen or halogen.

104. A compound of claim 17 having the formula I,



I

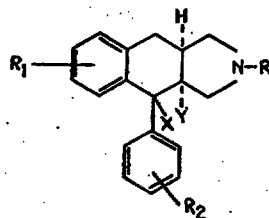
wherein

each of X and Y is hydrogen, R_1 is hydrogen, halogen or alkyl, R_2 is hydrogen, and

R is (i) hydrogen, (ii) alkyl of 1 to 5 carbon atoms, (iii) alkenyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α -position, (iv) hydroxy-alkyl of 2 to 5 carbon atoms, (v) phenyl-alkyl of 7 to 11 carbon atoms in the aggregate thereof, (vi) $-A-CO-R_3$ wherein A is alkylene or 1 to 4 carbon atoms, and R_3 is phenyl or phenyl substituted by halogen.

105. A compound of claim 104 with the proviso that when R_1 , R_2 , X and Y are hydrogen, R is other than methyl.

106. A compound of claim 17 having the formula I,



I

wherein

(i) each of X and Y is hydrogen, and the rings are cis to each other, or
(ii) X and Y together are an additional bond;

R_1 is hydrogen, halogen or alkyl of 1 to 4 carbon atoms;

(a) R_2 is hydrogen, halogen or alkyl, and R may be (i) alkenyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α position; (ii) alkyl of 1 to 4 carbon atoms substituted by cycloalkyl of 3 to 6 carbon atoms; (iii) phenyl-alkyl of 7 to 11 carbon atoms in the aggregate thereof monosubstituted in the phenyl thereof by halogen, alkoxy of 1 to 4 carbon atoms or alkyl of 1 to 4 carbon atoms; (iv) $-A-CO-R_3$ wherein A is alkylene of 1 to 4 carbon atoms, and R_3 is alkyl of 1 to 5 carbon atoms; alkoxy of 1 to 4 carbon atoms; or hydroxy; or (b) either R_2 is halogen or alkyl of 1 to 4 carbon atoms, or

X and Y together are an additional bond, and

R is a significance (i) to (iv) as defined above, or additionally may be (v) hydrogen, (vi) alkyl of 1 to 5 carbon atoms, (vii) alkenyl of 3 to 5 carbon atoms, the multiple bond thereof being in other than the α position, (viii) hydroxy-alkyl of 2 to 5 carbon atoms, (ix) phenylalkyl of 7 to 11 carbon atoms in the aggregate thereof, or (x) $-A-CO-R_3$ wherein A is alkylene or 1 to 4 carbon atoms; R_3 is phenyl or phenyl substituted by halogen.

107. A compound of claim 106, wherein X and Y are hydrogen, and R_1 and R_2 are hydrogen.

108. An (3aRS,4RS,9aSR) epimer of a compound according to any one of claims 34, 35, 37, 38, 39, 40-43, 45, 47 to 49, 53, 56 to 58, 65 to 67, 82, 86 to 89.

109. A bis-(3a,4)-dehydro analogue of a compound of any one of claims 70, 71, 72, 93, 94 or 95.

110. A compound according to any one of claims 15 to 73, 79 to 82, 85 to 86, 88 to 107 or an epimer thereof having the same configuration at the 3a, 4 and 9a positions as 3a,4,9,9a - tetrahydro - 4 phenyl - 2-trifluoroacetyl-benz[f]isoindoline produced according to the process described in Example 6.

111. A compound according to any one of claims 15 to 110 in free base form.

112. A compound according to any one of claims 15 to 110 in acid addition salt form.

113. A compound according to any one of claims 15 to 112 in individual optical isomer form.

114. A compound according to any one of claims 15 to 112 in racemic form.

115. A pharmaceutical composition comprising a compound of any one of claims 15 to 114 in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.



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alkyl of 1 to 4

or alkyl, and
1 to 5 carbon
thereof being 50

; (ii) alkyl of
ited by cyclo-

; (iii) phenyl-
atoms in the

stituted in the 55
alkoxy of 1 to

1 to 4 carbon
wherein A is

toms, and R₃
atoms; alkoxy 60

hydroxy; or
alkyl of 1 to

ditional bond, 65

(v) as defined
(v) hydrogen,

oms,
in atoms, the

in other than 70
y-alkyl of 2

carbon atoms
, or (x)

alkylene or 75
s phenyl or

l.
106, wherein

and R₂ are 80

primer of a
of claims 34,

o 49, 53, 56

atalogue of a 85
70, 71, 72,

any one of
o 86, 78 to

g the same 90
9a positions

phenyl - 2-
produced

in Example 95

any one of

n.
any one of

salt form.
o any one 100

ual optical

o any one
n.

tion com- 105
of claims

n pharma-
salt form,

cal carrier 110

116. A pharmaceutical composition of claim 115, wherein the compound is of any one of claims 99 to 103.

5 117. A pharmaceutical composition comprising a compound of any one of claims 21 to 31, 32 to 39, 79 to 81, 85, 98, 107, in free base form or in pharmaceutically accept-

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

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