PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 471/04, 491/048
A61K 31/435, C07D 495/04
A61K 31/495 // (C07D 471/04
C07D 221:00, 209:00)

A1

(11) International Publication Number: **WO 93/01186**

(43) International Publication Date: 21 January 1993 (21.01.93)

(21) International Application Number: PCT/EP92/01483

(22) International Filing Date: 1 July 1992 (01.07.92)

(30) Priority data:

MI91A001863	5 July 1991 (05.07.91)	IT
MI92A000563	11 March 1992 (11.03.92)	IT

(71) Applicant *(for all designated States except US):* DR. LO ZAMBELETTI S.P.A. [IT/IT]; Via Zambeletti, I-20021 Baranzate (IT).

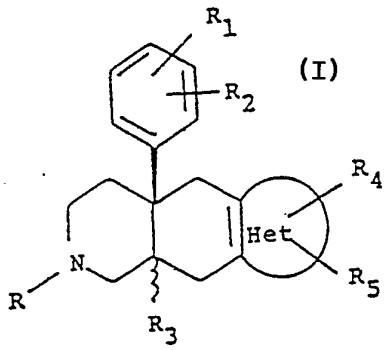
(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* COLLE, Roberto [IT/IT]; VECCHIETTI, Vittorio [IT/IT]; DONDIO, Giulio [IT/IT]; RONZONI, Silvano [IT/IT]; Dr. Lo Zambeletti S.p.A., Via Zambeletti, I-20021 Baranzate (IT).

(74) Agents: RUSSELL, Brian, John et al.; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).

Published
With international search report.

(54) Title: HYDROISOQUINOLINE DERIVATIVES



(57) Abstract

Compounds of formula (I) in which, R is linear or branched alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl, aralkyl or furan-2-yl alkyl; R_1 and R_2, which may be the same or different, are each hydrogen, hydroxy, alkoxy, or halogen; R_3 is hydrogen, hydroxy or alkoxy; "Het" is optionally substituted single or fused heteroxyclic ring, containing from 5 to 10 ring atoms and comprising up to four heteratoms in the or each ring, selected from oxygen, nitrogen and sulphur; R_4 and R_5, which may be the same or different, are each hydrogen alkyl, halogen, nitro, CF, cyano, alkoxy carbonyl, NH, alkylcarbonylamino, hydroxy, alkoxy, or benzyl, are selective delta receptor agonists and are useful in the treatment of pain.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		
ES	Spain	MG	Madagascar		

HYDROISOQUINOLINE DERIVATIVES

This invention is concerned with novel hydroisoquinoline derivatives, processes for their preparation, and their use in medicine.

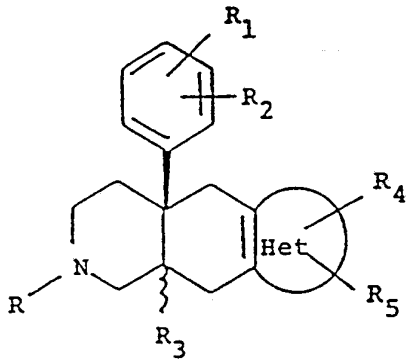
The presence of at least three populations of opioid receptors (mu, delta and kappa) is now well established and documented and all three appear to be present in the central and peripheral nervous system of many species including man (Lord J.A.H. et al, Nature 1977, 267, 495).

Activation of all 3 opioid receptor subtypes can lead to antinociception in animal models. In particular, studies with peptidic delta agonists have indicated that activation of the delta receptor produces antinociception in rodents and primates, and can induce clinical analgesia in man (Yaksh T.L. and Onofrio, B.M. Lancet 1983, 1386). Some experiments suggest that these delta analgesics may also lack the usual side-effects associated with mu and kappa activation (Galligan et al, J.Pharm. Exp. Ther. 1984, 229, 641).

WO/8900995 discloses heterocycle condensed epoxymorphinan derivatives which are said to be delta selective antagonists, and EP-A-295783 discloses codeine derivatives which are said to be analgesic agents acting predominantly on delta receptors.

We have now discovered a novel class of heterocycle condensed octahydroisoquinoline derivatives which are selective delta opioid receptor ligands which may therefore be of potential therapeutic utility as analgesics.

According to the present invention, there is provided a compound, or a solvate or salt thereof of formula (I):



(I)

in which,
R is linear or branched C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-5} alkenyl, aryl, aralkyl or furan-2-yl alkyl;
R_1 and R_2, which may be the same or different, are each hydrogen, hydroxy, C_{1-3} alkoxy, preferably methoxy, or halogen;
R_3 is hydrogen, hydroxy or C_{1-3} alkoxy, preferably methoxy;
"Het" is an optionally substituted single or fused heterocyclic ring, preferably having aromatic character, containing from 5 to 10 ring atoms and comprising up to four heteroatoms in the or each ring, selected from oxygen, nitrogen and sulphur;
R_4 and R_5, which may be the same or different, are each hydrogen, C_{1-3} alkyl, preferably methyl, halogen, nitro, CF_3, cyano, C_{1-3} alkoxy carbonyl, NH_2, C_{1-3} alkylcarbonylamino, hydroxy, C_{1-3} alkoxy, preferably methoxy, or benzyl.

When R is aryl, it is preferably phenyl, and when aralkyl, it is preferably phenyl C_{1-6} alkyl.

Examples of R are methyl, ethyl, cyclopropylmethyl, propyl and 2-phenylethyl.

Examples of R_1 and R_2 are hydrogen, hydroxy and methoxy, in all positions of the aromatic ring.

Examples of `Het' are indolo, N-methylindolo, N-ethylindolo, N-benzylindolo, benzofuro, benzothieno, quino and quinoxalino.

Examples of R_4 or R_5 are hydrogen, methyl, ethyl, fluorine, chlorine, hydroxy, methoxy, or benzyl.

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

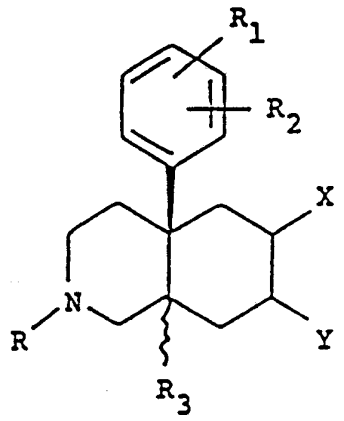
One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of pharmaceutically acceptable salts of a compound of formula (I) include acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Examples of pharmaceutically acceptable solvates of a compound of formula (I) include hydrates.

The compounds of formula (I) may exist as cis or trans isomers, and the invention extends to both such forms as well as to their single enantiomers and to mixtures thereof, including racemates.

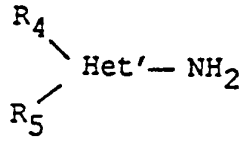
The present invention also provides a process for the preparation of a compound of formula (I) which comprises reacting a compound of formula (II):



(II)

in which, simultaneously, one of X and Y is oxo and the other is hydrogen or oximino, and R, R_1, R_2 and R_3 are as defined for formula (I), with a

compound of formula (III):



(III)

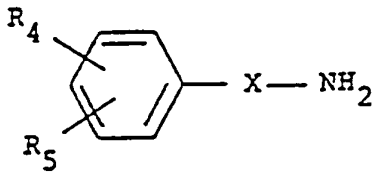
in which Het' is a ring-opened precursor of Het, as defined for formula (I), and R_4 and R_5 are as defined for formula (I), and optionally thereafter performing one or both of the following steps:

a) converting the obtained compound of formula (I) to a further compound of formula (I),

b) forming a salt and/or solvate of the obtained compound of formula (I).

Examples of the process of the invention are as follows:

i) To produce a compound of formula (I) in which Het is 2,3- or 3,2-indolo, 2,3- or 3,2-N-methylindolo, 2,3- or 3,2-benzofuro or 2,3- or 3,2-benzothieno, and R_1 and R_2 are other than hydroxy, a compound of formula (II) may be reacted with a compound of formula (IIIa):



(IIIa)

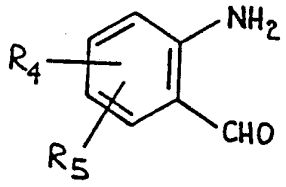
in which X is -NH-, -NMe-, -S-, or -O- and R_4 and R_5 are as defined for formula (I), under Fischer condensation conditions.

ii) To produce a compound of formula (I) in which Het is N-methylindolo, N-ethylindolo, or N-benzylindolo, and R_1 and R_2 are other than hydroxy, a corresponding compound of formula (I) in which Het is indolo may be reacted with a methyl, ethyl, or benzyl halide and a strong base (such as sodium or potassium hydride) in an aprotic solvent (such as

THF or DMF).

iii) To produce a compound of formula (I) in which R_1 or R_2 is hydroxy, a compound of formula (I) in which R_1 or R_2 is methoxy is demethylated using a Lewis acid (such as BBr_3) or concentrated aqueous HI or HBr at elevated temperature, for example 25° to 110°.

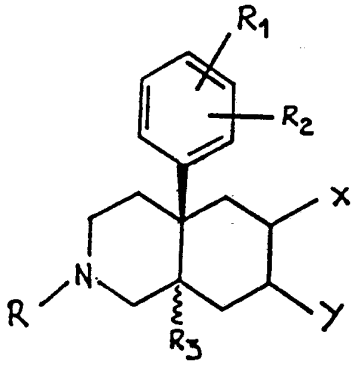
iv) To produce a compound of formula (I) in which Het is 2,3 or 3,2-quino and R_1 and R_2 are other than hydroxy, a compound of formula (II) may be reacted with a compound of formula (IIIb):



(IIIb)

in which R_4 and R_5 are as defined for formula (I), in the presence of methanesulfonic acid.

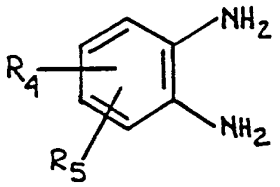
v) To produce a compound of formula (I) in which Het is 2,3 or 3,2-quinoxalino and R_1 and R_2 are other than hydroxy, a compound of formula (II) may be reacted with isoamyl nitrite and potassium tertbutoxide to obtain a compound of formula (IIa):



(IIa)

in which, simultaneously, one of X and Y is oxo and the other is oximino and R, R_1, R_2 and R_3 are as defined for formula (I).

The resulting compounds of formula (IIa) are thereafter condensed in refluxing DMF with a compound of formula (IIIc):



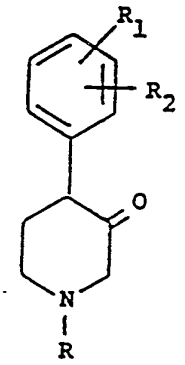
(IIIc)

in which R_4 and R_5 are as defined for formula (I).

Compounds of formula (II) in which X is oxo and Y is hydrogen are known compounds, or can be prepared from known compounds by known methods (Zimmerman D. et al, J. Org. Chem. 1989, 54, 1442).

Compounds of formula (II) in which X is hydrogen and Y is oxo are known compounds and can be prepared, for example, as described by Judd D. B. *et al.*, J. Med. Chem,. 1992, 35, 48.

Alternatively, they may be prepared by a Robinson cyclisation reaction between a piperidine derivative of formula (IV):



(IV)

in which R, R_1, and R_2 are as defined for formula (I), and methylvinylketone, and subsequent reduction with lithium in liquid ammonia, or catalytic hydrogenation.

Alternatively, these compounds of formula (II) can be prepared from compounds of formula (II) in which X is oxo and Y is hydrogen by using a 6,7-carbonyl shift technique according to methods known in the art.

Compounds of formula IV are known compounds or can be prepared from

known compounds by known methods. (J.C.S., Perk. Trans. I, 1989, 1187).

Compounds of formula (III) are commercially available compounds, or can be easily made from commercially available compounds.

As mentioned before, the compounds of formula (I) exist in more than one stereoisomeric form and the process of the invention produces mixtures thereof. The individual isomers may be obtained from the enantiomerically pure intermediate of formula (II).

The individual forms of the compounds of formula (II) may be separated one from another by resolution using an optically active acid such as tartaric acid or 0,0'-di-p-toluoyltartaric acid. Alternatively, an asymmetric synthesis would offer a route to the individual form.

The compounds of formula (I) may be converted into their pharmaceutically acceptable acid addition salts by reaction with the appropriate organic or mineral acids.

Solvates of the compounds of formula (I) may be formed by crystallization or recrystallization from the appropriate solvent. For example hydrates may be formed by crystallization or recrystallization from aqueous solutions, or solutions in organic solvents containing water.

Also salts or solvates of the compounds of formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or solvates. Accordingly such salts or solvates also form part of this invention.

The activity of the compounds of formula (I) in standard tests indicates that they are of potential therapeutic utility in the treatment of pain.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition

comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of pain.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known analgesic agents.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of pain.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as

a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

As mentioned earlier, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of pain in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

Compounds of this invention and their preparation are illustrated in the following Examples and their structures are summarised in Table I.

The preparation of novel intermediates is illustrated in the Descriptions.

Description 1

(-)-2-Ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline.

5.97 g (20.77 mmoles) of(±)-2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4, 4a,5,6,7,8,8a β-6-oxo-decahydroisoquinoline were dissolved in 80 ml of abs. ethanol. 8.02 g (20.77 mmoles) of (+)-di-0,0'-p-toluoyl-D-tartaric acid, dissolved in 80 ml of abs. ethanol, were added to the hot solution of the free base.
After a gentle warming,the solution was filtered and the less soluble diastereomeric salt crystallized on standing. The salt was recrystallized from abs. ethanol, up to a constant rotatory power, to give 5.62 of (+)-di-0,0'-p-toluoyl-D-tartrate.
M.P.=161-163°C.

$C_{38}H_{43}NO_{10}$

Elemental analysis: Calcd. C,67.74; H,6.43; N,2.08;
Found C,67.30; H,6.47;N,2.03.

$[\alpha]_D^{20}$ = +57.42 (C=2 in MeOH)

The tartrate salt was transformed into the free base by dissolving in 5% NaOH solution, extracting with CH_2Cl_2 and evaporating the solvent in vacuo to yield 2.3 g of the title compound (77% of the theoretical).

$[\alpha]_D^{20}$= -83.85 (C=2 in $CHCl_3$)

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

Description 2

(+)-2-Ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline.

The mother liquors obtained from the first crystallization of Description 1 were evaporated in vacuo to dryness. The residue was treated with 5% NaOH solution and extracted with CH_2Cl_2 to afford 2.75 g (9.6 mmoles) of the enriched free base which was

dissolved in 45 ml of abs. ethanol. 3.78 g (9.6 mmoles) of (-)-di-0-0'-p-toluoyl-L-tartaric acid, dissolved in 45 ml of abs. ethanol, were added to the hot solution of the free base and the diastereomeric salt crystallized on standing. The salt was recrystallized from abs. ethanol, up to a constant rotatory power, to give 5.82 g of (-)-di-0-0'-p-toluoyl-L-tartrate.

M.P.=162-163°C.

$C_{38}H_{43}NO_{10}$

Elemental analysis: Calcd. C,67.74; H,6.43; N,2.08;
Found C,67.42; H,6.41; N,2.05.

$[\alpha]_D^{20}$ = -55.36 (C=2 in MeOH)

The tartrate salt was transformed into the free base dissolving in 5% NaOH solution, extracting with CH_2Cl_2 and evaporating the solvent in vacuo to yield 2.4 g of the title compound (80% of the theoretical).

$[\alpha]_D^{20}$ = +82.20 (C=2 in $CHCl_3$)

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

Example 1

2-ethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro indolo[2,3-g]isoquinoline hydrochloride

To a stirred solution of 0.493 ml (5.22 mmoles) of boron tribromide in 15 ml of dry chloroform was added dropwise, under nitrogen at room temperature, a solution of 313 mg (0.868 mmoles) of 2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro indolo[2,3-g]isoquinoline in 3 ml of dry chloroform. After 30 min the solution was poured into 15 g of ice containing 1.5 ml of concentrated NH_4OH and stirred for 30 min. The precipitate was filtered and collected. The filtrate was extracted with CH_2Cl_2, dried over sodium sulphate, evaporated in vacuo and combined with the precipitate.
The solid residue was chromatographed by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 79:15:1 respectively, to yield 108 mg of solid which was taken up in 5 ml of methanol and brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried, to yield 60 mg of the title compound. M.P. = 277-278°C

$C_{23}H_{26}N_2O$ .HCl

Elemental analysis: Calcd C,72.14; H,7.11; N,7.32; Cl,9.26;
Found C,71.69; H,7.01; N,7.25; Cl,9.00.

I.R. (KBr) : 3450; 3260; 3200; 1600; 1450 cm^{-1}

Example 2

2-methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aα-octahydro indolo[2,3-g]isoquinoline

250 mg (0.72 mmoles) of 4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aα -octahydro indolo[2,3-g]isoquinoline were reacted with 0.4 ml (4.32 mmoles) of boron tribromide as described in Example 1.
The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH, 86:10:0.6 respectively, obtaining 180 mg of the title compound.
M.P. = 200-207°C

$C_{22}H_{24}N_2O$

Elemental analysis: Calcd. C, 79.48; H, 7.28; N, 8.43;
Found C, 79.09; H, 7.11; N, 8.21.

I.R. (KBr) : 3400; 3280; 2900; 1595; 1470 cm^{-1}

Example 3

2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro indolo[2,3-g]isoquinoline hydrocloride

532 mg (1.64 mmoles) of 2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline hydrochloride and 357 mg (2.47 mmoles) of phenylhydrazine hydrochloride were dissolved in 33 ml of methanol saturated with HCl. The solution was refluxed under a nitrogen atmosphere for 3 hours and then cooled at room temperature.
The reaction mixture was evaporated in vacuo, the residue was dissolved in ethyl acetate and treated with an excess of 1N sodium hydroxide, then the mixture was extracted with ethyl acetate. The combined extracts were dried over sodium sulphate and evaporated in vacuo.
The solid residue was chromatographed by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 94:5:0.5 respectively, to yield 457 mg of the free base which was taken up in 10 ml of acetone and brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried, to yield 400 mg of the title compound. M.P.= 168-171°C.

$C_{24}H_{28}N_2O$ .HCl

Elementai analysis: Calcd. C,72.61; H,7.36; N,7.06; Cl,8.93;
Found C,72.35; H,7.25; N,6.99; Cl,8.75.

I.R. (KBr): 3400; 3200; 1605; 1460 cm^{-1}

N.M.R. ($CDCl_3$) : δ 8.10 (s broad, 1H); 7.45 (m, 1H); 7.20
300 MHz (free base) (m, 1H); 7.08 (m, 5H); 6.62 (m, 1H);
3.68 (s, 3H); 2.85-3.10 (m, 6H); 2.58
(m, 2H); 2.45 (m, 3H); 2.00 (m, 2H);
1.10 (t, 3H).

Example 4

4aα-(3-methoxyphenyl)-2-methyl-1,2,3,4,4a,5,11,11aα-octahydro indolo[2,3-g]isoquinoline

500 mg (1.83 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aα-6-oxo-decahydroisoquinoline and 396 mg (2.74 mmoles) of phenylhydrazine hydrochloride were reacted as described in Example 3.
After the work-up, the solid residue was chromatographed by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 100:3:0.3 respectively, to yield 250 mg of the title compound. M.P.= 202-206°C.

$C_{23}H_{26}N_2O$

Elemental analysis: Calcd. C,79.73; H,7.56; N,8.09;
Found C,79.50; H,7.31; N,7.88.

I.R. (KBr): 3400; 3120; 2790; 1600; 1580 cm^{-1}

N.M.R. (CD_3OD) 300 MHz : δ 7.3-6.65 (m, 8H); 3.67 (s, 3H); 3.33 (m, 1H); 3.03 (m, 1H); 2.88 (m, 1H); 2.73 (m, 1H); 2.59 (m, 1H); 2.51 (m, 1H); 2.40-2.20 (m, 7H); 1.63 (m, 1H).

Example 5

2-Methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline hydrochloride.

1.92 g (5.54 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4, 4a, 5, 11, 11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 3.14 ml (33.24 mmoles) of boron tribromide as described in Example 1. The solid residue was taken up in MeOH and brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 1.4 g of the title compound. M.P.=>300°C.

$C_{22}H_{24}N_2O \cdot HCl$

Elemental analysis: Calcd. C,71.62; H,6.83; N,7.59; Cl,9.61;
Found C,66.94; H,6.53; N,6.92; Cl,8.96.

I.R. (KBr) : 3420; 3250; 2600; 1580; 1460 cm^{-1}

Example 6

2-Methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline hydrochloride hemihydrate.

6.0 g (19.36 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4, 4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline hydrochloride and 4.2 g (29.04 mmoles) of phenylhydrazine hydrochloride were reacted and worked-up as described in Example 3. The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 90:7:0.7 respectively,to afford 3.68 g of the free base which was taken up in a mixture of acetone/methanol 1:1 and brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 3.1 g of the title compound. M.P.=>300°C.

$C_{23}H_{26}N_2O \cdot HCl \cdot 1/2H_2O$

Elemental analysis: Calcd. C,70.48; H,7.20; N,7.15; Cl,9.05;
Found C,70.41; H,7.25; N,6.99; Cl,9.04.

I.R. (KBr) : 3410; 3150; 1605; 1580; 1465; 1040 cm^{-1}

N.M.R. (DMSO-d6) : δ 10.6 (s,1H); 7.4-6.8 (m,9H); 3.7 (s,3H);
80 MHz 3.5-2.6 (m,11H); 2.5 (s,3H).

Example 7

2,6-Dimethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline.

950 mg (2.63 mmoles) of 2,6-dimethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 1.5 ml (15.8 mmoles) of boron tribromide as described in Example 1. The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 86:10:0.6 respectively, to yield 130 mg of the title compound. M.P.=252-254°C.

$C_{23}H_{26}N_2O$

I.R. (KBr) : 3420; 1580; 1470; 1235 cm^{-1}

N.M.R. (CD_3OD): δ 7.5-6.4 (m,8H); 3.5 (s,3H); 3.4-2.1 (m,11H);
80 MHz 2.35 (s,3H).

Example 8

2,6-Dimethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline.

A solution of 200 mg (0.58 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline, dissolved in 2 ml of dimethylformamide, was added dropwise, under nitrogen atmosphere at 0°C, to a suspension of 26 mg (0,65 mmoles) of 60-65% NaH dispersion in mineral oil in 2 ml of dimethylformamide. The mixture was stirred 1 hour at 0°C, then 0.04 ml (0.65 mmoles) of methyl iodide were added dropwise and the reaction mixture was allowed to reach room temperature. After 40 minutes the solvent was evaporated in vacuo and the residue was taken-up in H_2O and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo to dryness.
The residue was purified by silica gel flash column chromatography, eluting with a mixture of $(i\text{-}Pr)_2O$/MeOH/conc. NH_4OH 85:15:0.4 respectively, to yield 50 mg of the title compound. M.P.=128-130°C.

$C_{24}H_{28}N_2O$

I.R. (KBr) : 2910; 1610; 1580; 1470; 1240 cm^{-1}

N.M.R. ($CDCl_3$): δ 7.4-6.9 (m,7H); 6.8-6.5 (m,1H); 3.65 (s,3H);
80 MHz 3.5 (s,3H); 3.3-2.1 (m,11H); 2.35 (s,3H).

Example 9

2-Methyl-4aα-phenyl-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g] isoquinoline.

873 mg (6.31 mmoles) of potassium carbonate and 798 mg (4.42 mmoles) of 1-phenyl-5-chlorotetrazole were added to a solution of 1.4 g (4.21 mmoles) of 2-methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a, 5, 11, 11aβ-octahydroindolo[2,3-g]isoquinoline in 20 ml of dimethylformamide under nitrogen atmosphere at room temperature. The reaction mixture was heated overnight a 70°C, the solvent was evaporated in vacuo and the residue was taken up in H_2O and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo ro dryness.

The crude product was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 86:10:0.6 respectively to yield 1.0 g of 2-methyl-4aα-[3-[(1-phenyl-tetrazol-5-yl)oxy]phenyl]-1,2,3,4,4a,5,11,11aβ-octahydroindolo [2,3-g]isoquinoline. M.P.=110-115°C.

$C_{29}H_{28}N_6O$

Elemental analysis: calcd. C,73.08; H,5.92; N,17.64;
Found C,71.68; H,5.97; N,17.21.

I.R. (KBr) : 3400; 3200; 3080; 1600; 1590; 1500; 1450 cm^{-1}

N.M.R. ($CDCl_3$) 80 MHz : δ 7.8-6.9 (m,13H); 3.1-2.0 (m,11H); 2.35 (s,3H).

This intermediate was dissolved in 35 ml of glacial acetic acid and hydrogenated at 60°C in a Parr apparatus at 60 psi in the presence of a catalytic amount of 10% Pd on charcoal, until the theoretical amount of H_2 was consumed. The catalyst was filtered off and the solvent was evaporated in vacuo. The residue was taken up in H_2O, brought to basic pH with an excess of 40% NaOH and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo to dryness. The crude product was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 90:8:0.5 respectively, to yield 100 mg of the title compound. M.P.=221-223°C.

$C_{22}H_{24}N_2$

I.R. (KBr) : 3200; 2940; 1470; 1455; 1280 cm^{-1}

N.M.R. ($CDCl_3$): 80 MHz 7.7 (s broad,1H); 7.45-6.85 (m,9H); 3.0-1.9 (m,11H); 2.35 (s,3H).

Example 10

2-Methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydrobenzofuro[2,3-g]isoquinoline.

900 mg (2.59 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11a β-octahydrobenzofuro[2,3-g]isoquinoline were reacted with 1.47 ml (15.5 mmoles) of boron tribromide as described in Example 1. The crude product was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 86:10:0.6 respectively, to yield 550 mg of the title compound. M.P.=258-261°C.

$C_{22}H_{23}NO_2$

Elemental analysis: Calcd. C,79.25; H,6.95; N,4.20;
Found C,76.81; H,6.86; N,4.05.

I.R. (KBr) : 3440; 2910; 1590; 1450; 1240; 1230 cm^{-1}

N.M.R. (DMSO-d6) : δ 9.1 (s,1H); 7.5-6.4 (m,8H); 3.5-2.1 (m,11H);
80 MHz 2.35 (s,3H).

Example 11

2-Methyl-4aα-(3-methoxyphenyl-1,2,3,4,4a,5,11,11aβ-octahydrobenzofuro[2,3-g]isoquinoline hydrochloride.

3.90 g (26.8 mmoles) of O-phenylhydroxylamine hydrochloride and 3.28 ml (50.64 mmoles) of methanesulfonic acid were added to a solution of 3.92 g (12.66 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline hydrochloride in 240 ml of absolute ethanol and refluxed for 2 hours under nitrogen atmosphere. The reaction mixture was evaporated in vacuo; the residue was taken up in H_2O, brought to basic pH with an excess of 20% NaOH and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo to dryness. The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 94.5:5:0.5

respectively, to yield 1.2 g of the free base, which was taken up in acetone and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 900 mg of the title compound. M.P.=246-248°C.

$C_{23}H_{25}NO_2 \cdot HCl$

Elemental analysis : Calcd. C,71.95; H,6.83; N,3.65; Cl, 9.24;
Found C,69.22; H,6.59; N,3.53; Cl,10.10.

I.R. (KBr) : 3430; 2400; 1600; 1580; 1450 cm^{-1}

MS (E.I.)(free base): : 347 (M+); 203.

N.M.R.($CDCl_3$)(free base): δ 7.3-6.5 (m,8H); 3.53 (s,3H); 3.15 (d,1H); 2.8-2.75 (m,4H); 2.65 (d,1H); 2.35-2.15 (m,3H); 2.25 (s,3H); 1.35 (m,2H).
300 MHz

Example 12

2,9-Dimethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline.

820 mg (2.07 mmoles) of 2,9-dimethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindole[2,3-g]isoquinoline were reacted with 1.2 ml (12.42 mmoles) of boron tribromide as described in Example 1.
The solid residue was crystallized from 40 ml of a mixture of acetone/MeOH 9:1 respectively.
The precipitate was filtered, washed and dried, to yield 288 mg of the title compound. M.P.=292-296°C.

$C_{23}H_{26}N_2O$

I.R. (KBr) : 3210; 1610; 1460 cm^{-1}

N.M.R. (DMSO-d6): δ 6.45-7.20 (m,8H); 3.95-4.45 (m,2H); 2.85
80 MHz (s,3H); 2.38 (s,3H); 2.00-3.80 (m,10H).

Example 13

2,9-Dimethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline hydrochloride.

1.5 g (4.84 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a, 5,6,7,8,8aβ-6-oxo-decahydroisoquinoline hydrochloride and 0.77 g (4.84 mmoles) of p-tolylhydrazine hydrochloride were reacted as described in Example 3.
The reaction mixture was evaporated in vacuo; the residue was dissolved in a mixture of CH_2Cl_2 and 1N NaOH and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo to dryness.
The solid residue was taken up in MeOH and brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 1.1 g of the title compound. M.P.=245-250°C.

$C_{24}H_{28}N_2O \cdot HCl$

Elemental analysis: Calcd. C,72.60; H,7.36; N,7.05;
Found C,70.69; H,7.45; N,6.73.

I.R. (KBr) : 3410; 3210; 1600; 1470; 1250 cm^{-1}

N.M.R. (CD_3OD) : δ 7.5-6.6 (m,8H); 3.6 (s,3H), 3.4-2.3 (m,11H);
80 MHz 2.7 (s,3H); 2.4 (s,3H).

Example 14

2-Methyl-4aα-(3-hydroxyphenyl)-9-fluoro-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline.

1.1 g (3.0 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-9-fluoro-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 1.7 ml (18.0 mmoles) of boron tribromide as described in Example 1.
The solid residue was crystallized from MeOH. The precipitate was filtered, washed and dried, to yield 580 mg of the title compound. M.P.=>300°C.

$C_{22}H_{23}FN_2O$

Elemental analysis: Calcd. C,75.40; H,6.61; N,7.99; F,5.42;
Found C,73.63; H,6.46; N,7.77; F,5.29.

I.R. (KBr) : 3280; 2940; 1595; 1460; 1255 cm^{-1}

Example 15

2-Methyl-4aα-(3-methoxyphenyl)-9-fluoro-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

1.5 g (4.84 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline hydrochloride and 0.79 g (4.84 mmoles) of 4-fluorophenylhydrazine hydrochloride were reacted as described in Example 3 to yield 1.47 g of the title compound which was recrystallized from MeOH. M.P.=>300°C.

$C_{23}H_{25}FN_2O \cdot HCl$

Elemental analysis: Calcd. C,68.90; H,6.53; N,6.98; Cl,8.84;
F,4.73;
Found C,68.81; H,6.56; N,6.83; Cl,8.83;
F,4.62.

I.R. (KBr) : 3440; 3200; 1605; 1455 cm^{-1}

Example 16

2-Methyl-4aα-(3-hydroxyphenyl)-7-chloro-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline.

600 mg (1.58 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-7-chloro-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 0.9 ml (9.48 mmoles) of boron tribromide as described in Example 1.
The solid residue was crystallized from MeOH. The precipitate was filtered, washed and dried to yield 200 mg of the title compound.
M.P.=>300°C.

$C_{22}H_{23}ClN_2O$

Elemental analysis: Calcd. C.72.02; H,6.32; N,7.64; Cl,9.66;
Found C,70.42; H,6.25; N,7.38; Cl,9.36.

I.R. (KBr) : 3250; 2850; 1590; 1450; 1245 cm^{-1}

Example 17

2-Methyl-4aα-(3-methoxyphenyl)-7-chloro-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

1.5 g (4.84 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline hydrochloride and 0.87 g (4.84 mmoles) of 2-chlorophenylhydrazine hydrochloride were reacted and worked-up as described in Example 3.
The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 86:10:0.6 respectively, to yield 1.2 g of the free base which was taken up in 50 ml of acetone and the solution brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried, to yield 920 mg of the title compound. M.P.=>300°C.

$C_{23}H_{25}ClN_2O \cdot HCl$

Elemental analysis: Calcd. C,66.18; H,6.28; N,6.71; Cl,16.99;
Found C,64.58; H,6.11; N,6.51; Cl,15.89.

I.R. (KBr) : 3420; 3205; 2480; 1600; 1470; 1250 cm^{-1}

N.M.R. (CD_3OD) : δ 7.4-6.6 (m,8H); 3.65 (s,3H); 3.6-2.5 (m,11H);
80 MHz 2.85 (s,3H).

Example 18

2-Methyl-4aα-(3-hydroxyphenyl)-9-chloro-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

960 mg (2.5 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-9-chloro-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 1.4 ml (15 mmoles) of boron tribromide as described in Example 1.
The solid residue was taken up in MeOH and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 410 mg of the title compound. M.P.=>300°C.

$C_{22}H_{23}ClN_2O \cdot HCl$

Elemental analysis: Calcd. C,65.50; H,5.99; N,6.94; Cl,17.50;
Found C,61.39; H,5.71; N,6.40; Cl,16.88.

I.R. (KBr) : 3410; 3210; 1580; 1460 cm-1

N.M.R. (DMSO-d6) : δ 6.50.7.60 (m,8H); 3.95-4.45 (m,2H); 2.95
80 MHz (s,3H); 1.90-3.90 (m,10H).

Example 19

2-Methyl-4aα-(3-methoxyphenyl)-9-chloro-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

1.5 g (4.84 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline hydrochloride and 0.87 g (4.84 mmoles) of 4-chlorophenylhydrazine hydrochloride were reacted as described in Example 3.
The solvent was evaporated in vacuo and the solid residue was recrystallized from MeOH. The precipitate was filtered, washed and dried to yield 1.2 g of the title compound. M.P.=>300°C.

$C_{23}H_{25}ClN_2O \cdot HCl$

Elemental analysis: Calcd. C,66.10; H,6.27; N,6.71; Cl,16.90;
Found C,64.52; H,6.11; N,6.59; Cl,16.58.

I.R (KBr) : 3340; 2920; 1600; 1500; 1330 cm^{-1}

N.M.R (CD_3OD) 80 MHz : δ 7.4-6.6 (m,8H); 4.0-2.4 (m,11H); 3.65 (s,3H); 2.75 (s,3H).

Example 20

2-Ethyl-6-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

900 mg (2.5 mmoles) of 2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline, 66 mg (2.8 mmoles) of 60-65% NaH and 0.171 ml(2.75 mmoles) of methyliodide were reacted as described in Example 8.
After the work-up the residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 94.5:5:0.5respectively,to yield 550 mg of the free base which was taken-up in acetone and brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 450 mg of the title compound.M.P.=234-240°C.

$C_{25}H_{30}N_2O \cdot HCl$

I.R. (KBr) : 3310, 2940, 2405, 1610, 1580, 1470 cm^{-1}

Elemental analysis: Calcd. C,73.06; H,7.60; N,8.63; Cl,6.82;
Found C,72.28; H,7.57; N,8,82; Cl,6.68.

Example 21

2-Ethyl-6-methyl-4aα-(3-hydroxyohenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

410 mg (1.13 mmoles) of 2-ethyl-6-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 0.64 ml (6.8 mmoles) of boron tribromide as described in Example 1. The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 86:10:0.6 respectively. The product was dissolved in MeOH and brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 200 mg of the title compound. M.P.=>300°C.

$C_{24}H_{28}N_2O.HCl$

I.R. free base (KBr): 3420; 1580; 1470; 1230 cm^{-1}

Example 22

2-Methyl-4aα-phenyl-9-methoxy-1,2,3,4,4a,5,11,11aβ-octahydroindolo [2,3-g]isoquinoline.

900 mg (3.22 mmoles) of 2-methyl-4aα-phenyl-1,2,3,4,4a,5,6,7,8, 8aβ-6-oxo-decahydroisoquinoline hydrochloride and 562 mg (3.22 mmoles) of 4-methoxyphenylhydrazine hydrochloride were reacted and worked-up as described in Example 3.
The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 93:7:0.5 respectively,to afford 600 mg of the pure free base which was crystallized from AcOEt. The precipitate was filtered, washed and dried to yield 400 mg of the title compound. M.P.=201-203°C.

$C_{23}H_{26}N_2O$

I.R. (KBr) : 3410; 2930; 1625; 1595; 1465 cm^{-1}

Elemental analysis: Calcd. C,79.73; H,7.56; N,8.09;
Found C,79.74; H,7.58; N,8.05.

Example 23

2-Methyl-4aα-phenyl-9-hydroxy-1,2,3,4,4a,5,11,11aβ-octahydroindolo [2,3-g]isoquinoline.

1.6 g (4.6 mmoles) of 2-methyl-4aα-phenyl-9-methoxy-1,2,3,4,4a,5, 11,11a β -octahydroindolo[2,3-g]isoquinoline were reacted with 2.6 ml (27.6 mmoles) of boron tribromide as described in Example 1. The solid residue was purified by silica gel flash column chromatography, eluting with CH_2Cl_2/MeOH/conc. NH_4OH 87:13:0.8 respectively. The product was dissolved in MeOH and brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 200 mg of the title compound. M.P.=>300°C.

$C_{22}H_{24}N_2O \cdot HCl$

I.R. (KBr) : 3470; 3250; 2940; 1630; 1595 cm^{-1}

Elemental analysis: Calcd. C,71.63; H,6.83; N,7.59; Cl,9.61;
Found C,66.73; H,6.32; N,7.01; Cl,8.98.

Example 24

2-Methyl-4aα-(2-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline hydrochloride.

4.0 g (12.91 mmoles) of 2-methyl-4aα-(2-methoxyphenyl)-1,2,3,4, 4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline hydrochloride and 2.8 g (19.37 mmoles) of phenylhydrazine hydrochloride were reacted and worked-up as described in Example 3. The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 86:10:0.6 respectively, to afford 3.0 g of the free base, which was taken up in methanol and brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 2.3 g of the title compound. M.P.=284-286°C.

$C_{23}H_{26}N_2O \cdot HCl$

Elemental analysis : Calcd. C,72.14; H,7.11; N,7.32; Cl,9.26;
Found C,72.18; H,7.10; N,7.30; Cl,9.21.

I.R. (KBr) : 3420; 3150; 1600; 1465; 1235; 1020 cm^{-1}

N.M.R. ($CDCl_3$) :δ7.7-6.6 (m,9H); 3.85 (s,3H); 3.2-2.5 (m,9H);
80MHz (free base) 2.35 (s,3H); 2.0-1.75 (m,2H).

Example 25

2-Methyl-4aα-(2-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline hydrochloride.

900 mg (2.60 mmoles) of 2-methyl-4aα-(2-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 1.5 ml (15.6 mmoles) of boron tribromide as described in Example 1. The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 79:15:1 respectively, to afford 640 mg of the free base, which was taken up in a 4:1 mixture of acetone/methanol and brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 545 mg of the title compound. M.P.=>300°C.

$C_{22}H_{24}N_2O \cdot HCl$

Elemental analysis: Calcd. C,71.63; H,6.83; N,7.59; Cl,9.61;
Found C,70.95; H,6.83; N,7.39; Cl,9.43.

I.R. (KBr) : 3220; 3140; 1600; 1465; 1440; 1240 cm^{-1}

Example 26

2-Methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,12,12aβ-octahydroquino [2,3-g]isoquinoline.

4.7 ml of methanesulfonic acid were added to a mixture of 1.0 g (3.1 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7, 8,8aβ-6-oxo-decahydroisoquinoline and 1.15 g (9.6 mmoles) of 2-aminobenzaldehyde in 32 ml of absolute ethanol. The solution was refluxed for 14 hours and the solvent was evaporated in vacuo. The residue was taken-up in saturated $NaHCO_3$ solution and AcOEt. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The solid residue was purified by silica gel flash column chromatography, eluting with CH_2Cl_2/MeOH/conc. NH_4OH 92:8:0.7 respectively, to afford 410 mg of the title compound. M.P.=159-162°C.

$C_{24}H_{26}N_2O$

I.R. (KBr) : 2940; 2920; 1600; 1580; 1250 cm^{-1}

Elemental analysis: Calcd. C,80.41; H,7.31; N,7.82;
Found C,79.50; H,7.30; N,7.49.

Example 27

2-Methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12aβ-octahydroquino [2,3-g]isoquinoline.

410 mg (1.14 mmoles) of 2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4, 4a,5,12,12aβ-octahydroquino[2,3-g]isoquinoline were reacted with 0.7 ml (6.84 mmoles) of boron tribromide as described in Example 1. The solid residue was purified by silica gel flash column chromatography eluting with CH_2Cl_2/MeOH/conc. NH_4OH 79:15:2 respectively, to yield 200 mg of the title compound. M.P.=275°C dec.

$C_{23}H_{24}N_2O$

I.R. (KBr) : 2920; 2795; 1615; 1580; 1490; 1240 cm^{-1}

Elemental analysis: Calcd. C,80.20; H,7.02; N,8.13;
Found C,80.06; H,7.10; N,8.06.

Example 28

2-(2-Phenylethyl)-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline.

670 mg (1.81 mmoles) of 2-(2-phenylethyl)-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline hydrochloride and 262 mg (1.81 mmoles) of phenylhydrazine hydrochloride were reacted and worked-up as described in Example 3.
The crude product was crystallized from a mixture of methanol/acetone to yield 680 mg of the title compound. M.P.=271-275°C.

$C_{30}H_{32}N_2O$

Example 29

2-(2-Phenylethyl)-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline.

680 mg (1.56 mmoles) of 2-(2-phenylethyl)-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with a 0.9 ml (9.36 mmoles) of boron tribromide as described in Example 1. The solid residue was purified by silica gel flash column chromatography, eluting with CH_2Cl_2/MeOH/conc. NH_4OH 94.5:5:0.5 respectively, to yield 180 mg of the title compound. M.P.=233-236°C.

$C_{29}H_{30}N_2O$

I.R. (KBr) : 3400; 3305; 2920; 1580; 1450 cm^{-1}

Elemental analysis: Calcd. C,82.43; H,7.16; N,6.63;
Found C,81.52; H,7.12; N,6.47.

Example 30

2-Ethyl-4aα-(3-methoxyphenyl)-6-benzyl-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline.

680 mg (1.89 mmoles) of 2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline, 85 mg (2.0 mmoles) of 60-65% NaH and 360 mg (2.0 mmoles) of benzylbromide were reacted as described in Example 8.
After the work-up, the crude product was crystallized from a mixture of methanol/acetone to yield 860 mg of the title compound.
M.P.=283-288°C.

$C_{31}H_{34}N_2O$

Example 31

2-Ethyl-4aα-(3-hydroxyphenyl)-6-benzyl-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline.

860 mg (1.0 mmoles) of 2-ethyl-4aα-(3-methoxyphenyl)-6-benzyl-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 1.1 ml (11.4 mmoles) of boron tribromide as described in Example 1. The crude product was triturated in hot methanol, filtered, washed and dried to yield 380 mg of the title compound.
M.P.=260-262°C.

$C_{30}H_{32}N_2O$

I.R. (KBr) : 3020; 2940; 1580; 1470; 1235 cm^{-1}

Elemental analysis: Calcd. C,82.53; H,7.30; N,6.42;
Found C,81.99; H,7.35; N,6.29.

Example 32

2,6-Diethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline.

545 mg (1.51 mmoles) of 2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a, 5,11,11aβ-octahydroindolo[2,3-g]isoquinoline, 60 mg (1.6 mmoles) of 60-65% NaH and 181 mg (1.6 mmoles) of ethyl bromide were reacted as described in Example 8.
After the work-up, the crude product was crystallized from a mixture of methanol/acetone to yield 620 mg of the title compound.
M.P.=277-281°C.

$C_{26}H_{32}N_2O$

Example 33

2,6-Diethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline.

620 mg (1.6 mmoles) of 2,6-diethyl-4aα-(3-methoxyphenyl)-1,2,3,4, 4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 0.9 ml (9.6 mmoles) of boron tribromide as described in Example 1. The crude product was triturated in hot methanol, filtered, washed and dried to yield 250 mg of the title compound.
M.P.=259-262°C.

$C_{25}H_{30}N_2O$

I.R. (KBr): 2980; 2920; 1610; 1580; 1455; 1350 cm^{-1}

Example 34

2-n-Propyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline hydrochloride.

900 mg (2.98 mmoles) of 2-n-propyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline and 431 mg (2.98 mmoles) of phenylhydrazine hydrochloride were reacted and worked-up as described in Example 3. The solid residue was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 93:7:0.5 respectively. The free base was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried to yield 420 mg of the title compound. M.P.=>300°C.

$C_{25}H_{30}N_2O \cdot HCl$

Elemental analysis: Calcd. C,73.06; H,7.60; N,6.82; Cl,8.63;
Found C,72.81; H,7.51; N,6.78; Cl,8.10.

Example 35

2-n-Propyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline hydrochloride.

420 mg (1.16 mmoles) of 2-n-propyl-4aα-(3-methoxyphenyl)-1,2,3,4, 4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 0.7 ml (6.84 mmoles) of boron tribromide as described in Example 1.
The solid residue was taken-up in methanol and the solution brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried to yield 190 mg of the title compound. M.P.=>300°C.

$C_{24}H_{28}N_2O \cdot HCl$

I.R. (KBr) : 3455; 3260; 3200; 1600; 1455 cm^{-1}

Elemental analysis: Calcd. C,72.61; H,7.36; N,7.06; Cl,8.93;
Found C,71.08; H,7.25; N,6,80; Cl,8.21.

Example 36

2-Cyclopropylmethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindole[2,3-g]isoquinoline hydrochloride.

800 mg (2.28 mmoles) of 2-cyclopropylmethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline and 340 mg (2.28 mmoles) od phenylhydrazine hydrochloride were reacted and worked-up as described in Example 3. The solid residue was purified by silica gel flash column chromatography eluting with a mixture of CH_2Cl_2/MeOH/conc. NH_4OH 93:7:0,5 respectively. The free base was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried to yield 360 mg of the title compound. M.P.=>300°C.

$C_{26}H_{30}N_2O \cdot HCl$

Elemental analysis: Calcd. C,73.82; H,7.39; N,6.62; Cl,8.38;
Found C,73.48; H,7.25; N,6.58; Cl,8.01.

Example 37

2-Cyclopropylmethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

360 mg (0.93 mmoles) of 2-cyclopropylmethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 0.57 ml (5.58 mmoles) of boron tribromide as described in Example 1.
The solid residue was taken-up in methanol and the solution brought to acidic pH with HCl/Et2O.
The precipitate was filtered, washed and dried to yield 180 mg of the title compound. M.P.=>300°C.

$C_{25}H_{28}N_2O \cdot HCl$

I.R. (KBr) : 3450; 3260; 3200; 1600; 1450 cm^{-1}

Elemental analysis: Calcd. C,73.42; H,7.15; N,6.85; Cl,8.67;
Found C,72.91; H,6.81; N,6.51; Cl,8.09.

Example 38

(+)-2-Ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

2.3 g (8.0 mmoles) of (-)-2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline and 1.17 g (8.1 mmoles) of phenylhydrazine hydrochloride were reacted and worked-up as described in Example 3. The solid residue was taken-up in 20 ml of acetone and the solution brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried to yield 1.36 g of the title compound. M.P.=274-277°C.

$C_{24}H_{28}N_2O \cdot HCl$

$[\alpha]_D^{20} = +147.0$ (C=1 in MeOH)

Elemental analysis: Calcd. C,72.61; H,7.36; N,7.06; Cl,8.93;
Found C,72.44; H,7.37; N,7.01; Cl,8.92.

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

Example 39

(+)-2-Ethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

1.41 g (3.93 mmoles) of (+)-2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline were reacted with 2.2 ml (23.58 mmoles) of boron tribromide as described in Example 1. The solid residue was taken-up in hot metanol and the solution was brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried to yield 0.95 of the title compound. M.P.=>300°C.

$C_{23}H_{26}N_2O \cdot HCl$

$[\alpha]_D^{20} = +141.1$ (C=1 in MeOH)

Elemental analysis: Calcd. C,72.14; H,7.11; N,7.32; Cl,9.26;
Found C,71.72; H,7.18; N,7.19; Cl,9.39.

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

Example 40

(-)-2-Ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline hydrochloride.

2.4 g (8.35 mmoles) of (+)-2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline and 1.2 g (8.40 mmoles) of phenylhydrazine hydrochloride were reacted and worked-up as described in Example 3.
The solid residue was taken-up in 20 ml of acetone and the solution was brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried to yield 1.55 g of the title compound. M.P.=273-276°C.

$[\alpha]_D^{20}$ = -143.1 (C=1 in MeOH)

Elemental analysis: Calcd. C,72.61; H,7.36; N,7.06; Cl,8.93;
Found C,72.38; H,7.41; N,7.00; Cl,9.00.

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

Example 41

(-)-2-Ethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydro-indolo[2,3-g]isoquinoline hydrochloride.

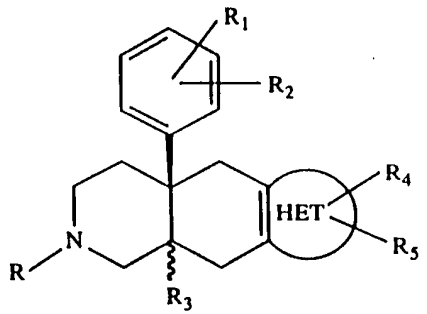
1.65 g (4.58 mmoles) of (-)-2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline and 2.6 ml (27.50 mmoles) of boron tribromide were reacted as described in Example 1.
The solid residue was taken-up in hot methanol and the solution was brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried to yield 1.1 g of the title compound. M.P.=>300°C.

$[\alpha]_D^{20}$ = -141.5 (C=1 in MeOH)

Elemental analysis: Calcd. C,72.14; H,7.11; N,7.32; Cl,9.26;
Found C,71.62; H,7.13; N,7,14; Cl,9.34.

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

Table I



	R	R_1	R_2	R_3	Het	R_4/R_5	Molecular Formula	Melting Point °C
Example 1	C_2H_5	m-OH	H	trans	2,3-indole	H	$C_{23}H_{26}N_2O$ .HCl	277-278
Example 2	CH_3	m-OH	H	cis	2,3-indole	H	$C_{22}H_{24}N_2O$	200-207
Example 3	C_2H_5	m-OCH_3	H	trans	2,3-indole	H	$C_{24}H_{28}N_2O$ .HCl	168-171
Example 4	CH_3	m-OCH_3	H	cis	2,3-indole	H	$C_{23}H_{26}N_2O$	202-206

TABLE I (continued)

	R	R_1	R_2	R_3	Het	R_4/R_5	Molecular Formula	Melting Point °C
Example 5	CH_3	m-OH	H	H-trans	2,3-indole	H	$C_{22}H_{24}N_2O \cdot HCl$	>300
Example 6	CH_3	m-OCH_3	H	H-trans	2,3-indole	H	$C_{23}H_{26}N_2O \cdot HCl \cdot \frac{1}{2}H_2O$	>300
Example 7	CH_3	m-OH	H	H-trans	2,3-indole	6-CH_3	$C_{23}H_{26}N_2O$	252-254
Example 8	CH_3	m-OCH_3	H	H-trans	2,3-indole	6-CH_3	$C_{24}H_{28}N_2O$	128-130
Example 9	CH_3	H	H	H-trans	2,3-indole	H	$C_{22}H_{24}N_2$	221-223
Example 10	CH_3	m-OH	H	H-trans	2,3-benzofuro	H	$C_{22}H_{23}NO_2$	258-261
Example 11	CH_3	m-OCH_3	H	H-trans	2,3-benzofuro	H	$C_{23}H_{25}NO_2 \cdot HCl$	246-248
Example 12	CH_3	m-OH	H	H-trans	2,3-indole	9-CH_3	$C_{23}H_{26}N_2O$	292-296
Example 13	CH_3	m-OCH_3	H	H-trans	2,3-indole	9-CH_3	$C_{24}H_{28}N_2O \cdot HCl$	245-250
Example 14	CH_3	m-OH	H	H-trans	2,3-indole	9-F	$C_{22}H_{23}FN_2O$	>300
Example 15	CH_3	m-OCH_3	H	H-trans	2,3-indole	9-F	$C_{23}H_{25}FN_2O \cdot HCl$	>300
Example 16	CH_3	m-OH	H	H-trans	2,3-indole	7-Cl	$C_{22}H_{23}ClN_2O$	>300
Example 17	CH_3	m-OCH_3	H	H-trans	2,3-indole	7-Cl	$C_{23}H_{25}ClN_2O \cdot HCl$	>300
Example 18	CH_3	m-OH	H	H-trans	2,3-indole	9-Cl	$C_{22}H_{23}ClN_2O \cdot HCl$	>300
Example 19	CH_3	m-OCH_3	H	H-trans	2,3-indole	9-Cl	$C_{23}H_{25}ClN_2O \cdot HCl$	>300

TABLE I (continued)

	R	R_1	R_2	R_3	Het	R_4/R_5	Molecular Formula	Melting Point °C
Example 20	C_2H_5	m-OCH_3	H	H-trans	2,3-indole	6-CH_3	$C_{25}H_{30}N_2O \cdot HCl$	234-240
Example 21	C_2H_5	m-OH	H	H-trans	2,3-indole	6-CH_3	$C_{24}H_{28}N_2O \cdot HCl$	>300
Example 22	CH_3	H	H	H-trans	2,3-indole	9-OCH_3	$C_{23}H_{26}N_2O$	201-203
Example 23	CH_3	H	H	H-trans	2,3-indole	9-OH	$C_{22}H_{24}N_2O \cdot HCl$	>300
Example 24	CH_3	o-OCH_3	H	H-trans	2,3-indole	H	$C_{23}H_{26}N_2O \cdot HCl$	284-286
Example 25	CH_3	o-OH	H	H-trans	2,3-indole	H	$C_{22}H_{24}N_2O \cdot HCl$	>300
Example 26	CH_3	m-OCH_3	H	H-trans	2,3-quinoline	H	$C_{24}H_{26}N_2O$	159-162
Example 27	CH_3	m-OH	H	H-trans	2,3-quinoline	H	$C_{23}H_{24}N_2O$	275 dec.
Example 28	$PhCH_2CH_2$	m-OCH_3	H	H-trans	2,3-indole	H	$C_{30}H_{32}N_2O$	271-275

TABLE I (continued)

	R	R_1	R_2	R_3	Het	R_4/R_5	Molecular Formula	Melting Point °C
Example 29	$PhCH_2CH_2$	m-OH	H	H-trans	2,3-indole	H	$C_{29}H_{30}N_2O$	233-236
Example 30	C_2H_5	m-OCH_3	H	H-trans	2,3-indole	6-CH_2Ph	$C_{31}H_{34}N_2O$	283-288
Example 31	C_2H_5	m-OH	H	H-trans	2,3-indole	6-CH_2Ph	$C_{30}H_{32}N_2O$	260-262
Example 32	C_2H_5	m-OCH_3	H	H-trans	2,3-indole	6-C_2H_5	$C_{26}H_{32}N_2O$	277-281
Example 33	C_2H_5	m-OH	H	H-trans	2,3-indole	6-C_2H_5	$C_{25}H_{30}N_2O$	259-262
Example 34	n-C_3H_7	m-OCH_3	H	H-trans	2,3-indole	H	$C_{25}H_{30}N_2O\cdot HCl$	>300
Example 35	n-C_3H_7	m-OH	H	H-trans	2,3-indole	H	$C_{24}H_{28}N_2O\cdot HCl$	>300
Example 36	c-$C_3H_5CH_2$	m-OCH_3	H	H-trans	2,3-indole	H	$C_{26}H_{30}N_2O\cdot HCl$	>300
Example 37	c-$C_3H_5CH_2$	m-OH	H	H-trans	2,3-indole	H	$C_{25}H_{28}N_2O\cdot HCl$	>300

TABLE I (continued)

	R	R_1	R_2	R_3	Het	R_4/R_5	Molecular Formula	Melting Point °C	$[\alpha]_D^{20}$ C=1, MeOH
Example 38	C_2H_5	m-OCH_3	H	H-trans	2,3-indole	H	$C_{24}H_{28}N_2O \cdot HCl$	274-277	+147.0
Example 39	C_2H_5	m-OH	H	H-trans	2,3-indole	H	$C_{23}H_{26}N_2O \cdot HCl$	>300	+141.1
Example 40	C_2H_5	m-OCH_3	H	H-trans	2,3-indole	H	$C_{24}H_{28}N_2O \cdot HCl$	273-276	-143.1
Example 41	C_2H_5	m-OH	H	H-trans	2,3-indole	H	$C_{23}H_{26}N_2O \cdot HCl$	>300	-141.5

Pharmacological Data

RECEPTOR AFFINITY STUDY

Tissue preparation

Radio receptor binding to delta, mu and kappa sites is performed on fresh guinea pig brain homogenates prepared according to Kosterlitz (1981). Whole brain, without cerebellum is homogenized in 50 mM Tris-buffer and centrifuged at 49,000 xg for 10 min.
The pellet is then resuspended in the same buffer, incubated at 37°C for 45 min. and centrifuged again.

1.9 ml of the final homogenate (1:100 in Tris-pH 7.4 0°C) is used for the binding assay.

Binding to delta sites

For binding experiments, ^{3}H-DADLE, which binds to mu and delta sites, is used in the presence of 30 nM of unlabelled DAGO to prevent mu binding. A concentration of radioligand near K_D is used in the binding assays evaluating compounds of the invention. Non-specific binding is determined by addition of Mr 2266, 2.5 µM. The tubes are incubated for 40 min at 25°C and bound ligand is separated from free by filtration through Whatman GF-G filters. The level of bound radioactivity on the filters is measured by liquid scintillation after solubilization in filtercount. The equilibrium dissociation constant (K_D) and the maximum binding capacity (B_{max}) are determined from the analysis of saturation curves, while the inhibition constant (K_i) is determined from the analysis of competition experiments (Hill 1910; Scatchard 1949; Cheng and Prusoff 1973; Gillan et al 1980).

Binding to mu sites (Magnan J., 1982)

^{3}H-[D-Ala^2,MePhe^4,Gly-Ol^5]Enkephalin (^{3}H-DAGO), an enkephalin analogue that binds selectively to mu receptor, is added to the biological substrate and incubated at 25°C for 40 min, filtered through Whatman

GF-C filters and washed with ice-cold Tris buffer. The filters are then dried, solubilized in Filtercount and the radioactivity monitored. Non-specific binding is determined in the presence of 10^{-6}M naloxone.

Binding to kappa sites

The binding to the kappa site was performed using the highly selective kappa opioid ligand ^{3}H-BRL 52537A (Sbacchi M, 1990). Final homogenate with solutions of the cold ligand and of the labelled ligand is incubated for 40 min. at 25°C, filtered through Whatman GF-C glass filter discs and washed. The radioactivity bound to the filters is counted by liquid scintillation spectrophotometry.

ANTINOCICEPTION

Tail-flick test in mice

The methodology employed is based on that described by D'Amour and Smith, J. Pharmacol. Exp. Ther. 72, 74 (1941).

Male Charles River mice (Swiss Strain) 29-35 g body weight are used.

Animals are allowed food and water ad libitum and are randomized into groups of 10 prior to experimentation. Before administration of the test compound, the reaction time of each animal is determined by focusing a beam of light onto the tail, eliciting a reflex withdrawal after a certain latency; only mice exhibiting a latency between 3-8 sec. are used subsequently in the evaluation of drug effects.

Test compounds are dissolved in either distilled water or distilled water plus 0.1M AMS and administered by the intrathecal route in a final volume of 5 µl/mouse, according to the method described by Hylden and Wilcox, Eur. J. Pharmacol. 67, 313 (1980).

Four hours prior the beginning of experiments, mice are anaesthetized with pentobarbital (80 mg/Kg i.p.) and a caudal cutaneous incision (1 cm) is performed on the back using a disposable 30 gauge 1/2 inch needles mated to a 50 µl luer siringe (Hamilton). The drug are delivered

intrathecally between L5 and L6 of spinous process.

Control animals receive 5 µl/mouse of the appropriate vehicle alone. Following a pretreatment period of 10 min., the mice are again placed under the heat source and the reaction time redetermined.

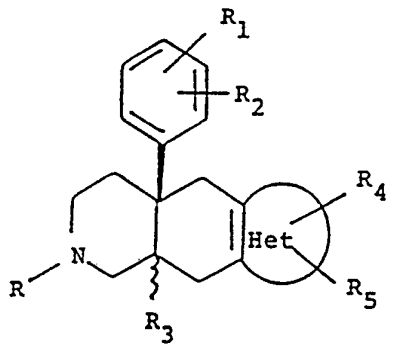
Percentage quantal protection is determined as the number of mice in which the reaction time is doubled compared to pretreatment values, expressed as a percentage of the total number of mice in the group.

PHARMACOLOGICAL TABLE

Example	Opioid Receptor Binding			Antinociception
	δ	μ	κ	Mouse Tail-Flick ED_{50} mg/mouse i.t.
	KinM			
1	16.4	2071	>1000	0.010
5	16.0	309	>1000	
7	33.6	306	>1000	
10	10.1	104	>1000	
12	61.9	678	>1000	
16	16.4	568	>1000	
39	6.24	2258	>1000	

Claims

1. A compound, or solvate or salt thereof, of formula (I):



(I)

in which,
R is linear or branched C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-5} alkenyl, aryl, aralkyl or furan-2-yl alkyl;
R_1 and R_2, which may be the same or different, are each hydrogen, hydroxy, C_{1-3} alkoxy, or halogen;
R_3 is hydrogen, hydroxy or C_{1-3} alkoxy;
"Het" is an optionally substituted single or fused heterocyclic ring, containing from 5 to 10 ring atoms and comprising up to four heteroatoms in the or each ring, selected from oxygen, nitrogen and sulphur;
R_4 and R_5, which may be the same or different, are each hydrogen, C_{1-3} alkyl, halogen, nitro, CF_3, cyano, C_{1-3} alkoxy carbonyl, NH_2, C_{1-3} alkylcarbonylamino, hydroxy, C_{1-3} alkoxy, or benzyl.

2. A compound according to claim 1, in which R is methyl, ethyl, cyclopropylmethyl, propyl, or 2-phenylethyl.

3. A compound according to claim 1 or 2, in which each of R_1 & R_2 is hydrogen, hydroxy or methoxy.

4. A compound according to any one of claims 1 to 3, in which Het is indolo, N-methylindolo, N-ethylindolo, N-benzylindolo, benzofuro, benzothieno, quino or quinoxalino.

5. A compound according to any one of claims 1 to 4 in which each of R_4 & R_5 is hydrogen, methyl, ethyl, fluorine, chlorine, hydroxy, methoxy or benzyl.

6. A compound selected from:

2-ethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ-octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aα-octahydro indolo[2,3-g]isoquinoline;

2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ -octahydroindolo[2,3-g]isoquinoline;

4aα-(3-methoxyphenyl)-2-methyl-1,2,3,4,4a,5,11,11aα octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ octahydroindolo [2,3-g]isoquinoline;

2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ octahydroindolo [2,3-g]isoquinoline;

2,6-dimethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ octahydroindolo[2,3-g]isoquinoline;

2,6-dimethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-phenyl-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g] isoquinoline;

2-methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydrobenzofuro [2,3-g]isoquinoline;

2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydrobenzofuro[2,3-g]isoquinoline;

2,9-dimethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline.

2,9-dimethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(3-hydroxyphenyl)-9-fluoro-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(3-methoxyphenyl)-9-fluoro-1,2,3,4,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(3-hydroxyphenyl)-7-chloro-1,2,3,4,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(3-methoxyphenyl)-7-chloro-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(3-hydroxyphenyl)-9-chloro-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(3-methoxyphenyl)-9-chloro-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-ethyl-6-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-ethyl-6-methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-phenyl-9-methoxy-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-phenyl-9-hydroxy-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(2-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(2-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-methyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,12,12aβ–octahydroquino[2,3-g]isoquinoline;

2-methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12aβ–octahydroquino[2,3-g]isoquinoline;

2-(2-phenylethyl)-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-(2-phenylethyl)-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-ethyl-4aα-(3-methoxyphenyl)-6-benzyl-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-ethyl-4aα-(3-hydroxyphenyl)-6-benzyl-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2,6-diethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2,6-diethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-n-propyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-n-propyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-cyclopropylmethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

2-cyclopropylmethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

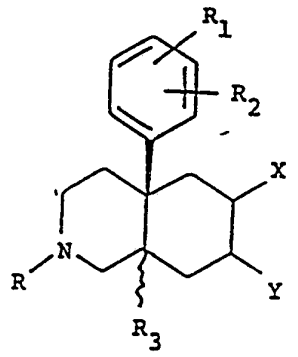
(+)-2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

(+)-2-ethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

(-)-2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline;

(-)-2-ethyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11aβ–octahydroindolo[2,3-g]isoquinoline.

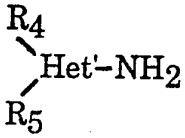
7. A process for the preparation of a compound of formula (I) according to any one of claims 1 to 6 which comprises reacting a compound of formula (II):



(II)

in which, simultaneously, one of X and Y is oxo and the other is hydrogen or oximino, and R, R_1, R_2 and R_3 are as defined for formula (I),

with a compound of formula (III):



(III)

in which Het' is a ring-opened precursor of Het, as defined for formula (I), and R_4 and R_5 are as defined for formula (I), and optionally thereafter performing one or both of the following steps:

a) converting the obtained compound of formula (I) to a further compound of formula (I),

b) forming a salt and/or solvate of the obtained compound of formula (I).

8.. A compound of formula (II) as defined in claim 7, which is (-)-2-ethyl-4aα(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline, or (+)-2-ethyl-4aα-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aβ-6-oxo-decahydroisoquinoline.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

10. A compound according to any one of claims 1 to 6 for use as an active therapeutic substance.

11. A compound according to any one of claims 1 to 6 for use in the treatment of pain.

12. The use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for the treatment of pain.

13. A method for the treatment and/or prophylaxis of pain in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound according to any one of claims 1 to 6.

INTERNATIONAL SEARCH REPORT

PCT/EP 92/01483

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D471/04; C07D491/048; A61K31/435; C07D495/04
A61K31/495; //(C07D471/04,221:00,209:00)(C07D491/048,

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	GB,A,1 436 376 (DU PONT) 19 May 1976 see claims 1,36	1,9
P,X	EP,A,0 485 636 (TORAY) 20 May 1992 see claim 1	1

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06 OCTOBER 1992	30.10.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 92/ 01483

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 13 is directed to a method of treatment of diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

Claims 20-30

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9201483 SA 61556

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/10/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-1436376	19-05-76	AT-B- 330179	25-06-76
		AU-A- 5820773	23-01-75
		BE-A- 802557	16-11-73
		CA-A- 1024149	10-01-78
		DE-A- 2336559	31-01-74
		DE-A- 2351599	31-01-74
		FR-A,B 2193600	22-02-74
		GB-A- 1436377	19-05-76
		JP-A- 49085075	15-08-74
		LU-A- 68066	26-09-73
		NL-A- 7310078	22-01-74
		SE-A- 7602150	23-02-76
		CH-A- 592628	31-10-77
		US-A- 4419517	06-12-83
EP-A-0485636	20-05-92	AU-A- 7952691	31-12-91
		WO-A- 9118901	12-12-91