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NEW 1,2,3,4,5,6-HEXAHYDROAZEPINO(4,5-B)INDOLES AND 1,2,3,4-TETRAHYDRO-BETA-CARBOLINES PROCESSES FOR PREPARING THESE AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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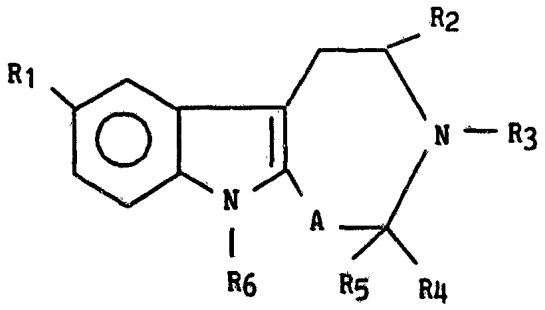
(56) Prior Art Documents
AU 58790/90 C07D 471/20
AU 613059 19152/88 C07D 471/16

(57) Claim

1. A compound selected from substituted indole of formula (I):



(I)

in which:

- A represents a σ bond or a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$,
- R_1 represents hydrogen, halogen, hydroxyl, linear or branched alkoxy having 1 to 4 carbon atoms, linear or branched alkyl having 1 to 6 carbon atoms optionally substituted with up to 3 halogen, oxo, hydroxyl or alkoxy having 1 to 4 carbon atoms,

.../2

- R_2 represents carboxyl, linear or branched alkoxycarbonyl having 1 to 6 carbon atoms and optionally substituted with optionally substituted phenyl; phenyloxycarbonyl, substituted phenyloxycarbonyl, carbamoyl, carbamoyl substituted on the nitrogen with up to 2 linear or branched alkyl having 1 to 6 carbon atoms or cycloalkyl having 4 to 7 carbon atoms; and in the case where A is a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$, R_2 can only represent hydrogen,

- R_3 represents hydrogen, linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 3 halogen, oxo, linear or branched alkoxy having 1 to 4 carbon atoms or optionally substituted phenyl,

- R_4 and R_5 together form a saturated or unsaturated 5- to 12-membered mono- or bicyclic ring-system which can comprise in the ring skeleton from 0 to 3 hetero atoms selected from oxygen, nitrogen and sulfur and which can optionally be substituted with up to 3 oxo, linear or branched alkyl having 1 to 6 carbon atoms, optionally substituted phenyl, phenylcarbonyl, substituted phenylcarbonyl, optionally substituted phenylalkyl having 7 to 9 carbon atoms, ~~optionally substituted fluorene, with, in the case where R_4 and R_5 form a bicyclic system, the possibility that one of the rings is an optionally substituted aromatic ring,~~ and in the case where A is a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$, R_4 and R_5 can also represent,

each independently of one another, hydrogen, optionally substituted phenyl, linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 2 oxo or optionally substituted phenyl, with the proviso that, when A is a σ bond with $R_1 = R_3 = R_6 = H$ and $R_2 =$ COOH then R_4 and R_5 together cannot form a cyclopentyl or a cyclohexyl, and when A is a radical of the formula

$-\underset{\underset{OR_7}{|}}{CH}-$ with R_7 = H or $CH_3\overset{\overset{O}{||}}{C}-$,then R_4 and R_5 must be other than H,

- R_6 represents hydrogen or a linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 2 oxo or optionally substituted phenyl,
- R_7 represents hydrogen or a linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 3 oxo, halogen, alkoxy having 1 to 4 carbon atoms, cycloalkyl having 3 to 6 carbon atoms or optionally substituted phenyl,
- its isomers, diastereoisomers, enantiomers,
- its addition salt with a pharmaceutically-acceptable acid, or, in the case where R_2 is a carboxyl, with a pharmaceutically-acceptable base,

the term substituted associated in the previous definitions with the expressions phenyl, phenylalkyl, phenyloxycarbonyl and phenylcarbonyl means that the aromatic rings may be substituted with up to 3 linear or branched alkyl having 1 to 6 carbon atoms, alkoxy having 1 to 4 carbon atoms, hydroxyl, nitro, trifluoromethyl or halogen.

25. A method of treating a mammal afflicted with a disorder selected from a disorder of the central nervous system, memory, pain, inflammation, stroke and convulsions comprising the step of administering to the said mammal an amount of a compound as claimed in claim 1 which is effective for alleviation of said disorder.

636232

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

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Lodged:

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Published:

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Related Art :

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Complete Specification for the invention entitled:

NEW 1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-b]INDOLES AND 1,2,3,4-TETRAHYDRO-β-CARBOLINES PROCESSES FOR PREPARING THESE AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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

The present invention relates to new 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles and 1,2,3,4-tetrahydro-β-carbolines, to processes for preparing these and to pharmaceutical compositions containing them.

The 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles mentioned in the prior art are all different from those claimed by the Applicant, none of them simultaneously possessing a hydroxyl, alkoxy or acetoxy at the 5- position with one or two substituents at the 6-position.

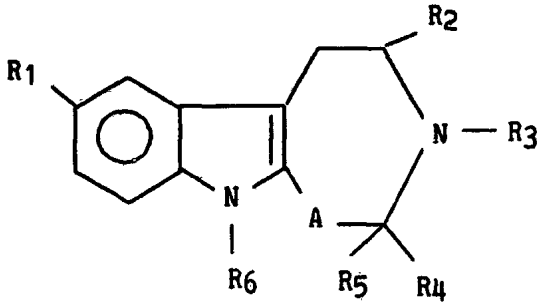
A few 5-hydroxy-1,2,3,4,5,6-hexahydroazepino-[4,5-b]indoles are described in the literature (FR 1,524,830) as possessing antitussive properties.

More generally, 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles are most often described as neuroleptics, antidepressants, sedatives and tranquillizers, and as a means of treating cerebrovascular disorders (Patents EP 203,902, EP 28,381, EP 64,317, FR 1,524,495).

As regards 1,2,3,4-tetrahydro-β-carbolines, while a large number of compounds have been prepared, only two products containing a carboxyl function at the 3-position and a spiran system at the 1-position are mentioned in the literature, without any pharmacological properties being claimed (Monatsch. Chem. (1985) 116 pp 851-5).

Apart from their good properties in relation to the central nervous system, more especially as anxiolytics, antidepressants and antipsychotics, and in some instances their good activity in the treatment of cerebrovascular disorders and disorders of memory, some of the compounds of the invention possess advantageous analgesic, anti-inflammatory, anticonvulsant and muscle- relaxant properties not possessed by the structurally most closely related compounds of the prior art.

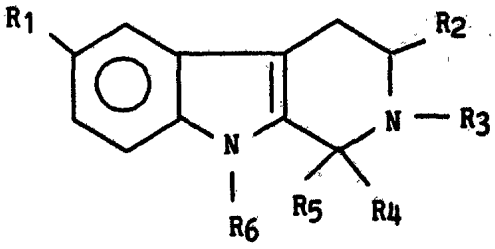
More specifically, the invention relates to the substituted indoles of formula (I):



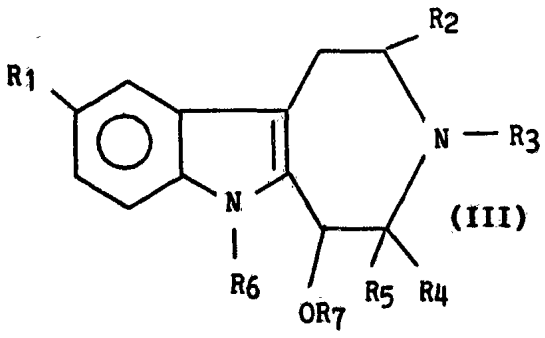
(I)

with A representing either a σ bond, the compounds of the invention then being the 1,2,3,4-tetrahydro-β-carbolines of formula (II), or a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$,

the compounds of the invention then being the 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles of formula (III):



(II)



(III)

in which:

- R_1 represents hydrogen, halogen, hydroxyl, linear or branched alkoxy having 1 to 4 carbon atoms, linear or branched alkyl having 1 to 6 carbon atoms optionally substituted with up to 3 halogen, oxo, hydroxyl or alkoxy having 1 to 4 carbon atoms,

- R_2 represents carboxyl, linear or branched alkoxycarbonyl having 1 to 6 carbon atoms and optionally substituted with optionally substituted phenyl, phenyloxycarbonyl, substituted phenyloxycarbonyl, carbamoyl, carbamoyl substituted on the nitrogen with up to 2 linear or branched alkyl having 1 to 6 carbon atoms or cycloalkyl having 4 to 7 carbon atoms, and in the case where A is a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$, R_2 can also be hydrogen,

- R_3 represents hydrogen, linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 3 halogen, oxo, linear or branched alkoxy having 1 to 4 carbon atoms or optionally substituted phenyl,

- R_4 and R_5 together form a saturated or unsaturated 5- to 12-membered mono- or bicyclic ring-system which can comprise in the ring skeleton from 0 to 3 hetero atoms selected from oxygen, nitrogen and sulfur and which can optionally be substituted with up to 3 oxo, linear or branched alkyl having 1 to 6 carbon atoms, optionally substituted phenyl, phenylcarbonyl, substituted phenylcarbonyl, optionally substituted phenylalkyl having 7 to 9 carbon atoms, optionally substituted fluorene, with, in the case where R_4 and R_5 form a bicyclic system, the possibility that one of the rings is an optionally substituted aromatic ring, and in the case where A is a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$, R_4 and R_5 can also represent, each independently of one another, hydrogen, optionally substituted phenyl, linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 2 oxo or optionally substituted phenyl, with the proviso that, when A is a σ bond with $R_1 = R_3 = R_6 = H$ and $R_2 = COOH$ then R_4 and R_5 together cannot form a cyclopentyl or a cyclohexyl, and when A is a radical of the formula

$-\underset{\underset{OR_7}{|}}{\overset{\overset{O}{\|}}{CH}}-$ with R_7 = H or CH_3C- , then R_4 and R_5 must be other than H,

- R_6 represents hydrogen or a linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 2 oxo or optionally substituted phenyl,

- R_7 represents hydrogen or a linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 3 oxo, halogen, alkoxy having 1 to 4 carbon atoms, cycloalkyl having 3 to 6 carbon atoms or optionally substituted phenyl,

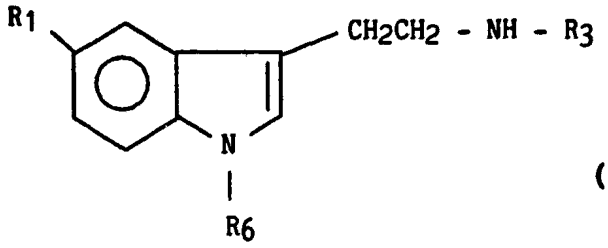
- their isomers, diastereoisomers, enantiomers,

- their addition salts with a pharmaceutically-acceptable acid, or, in the case where R_2 is a carboxyl, with a pharmaceutically-acceptable base,

the term substituted associated in the previous definitions with the expressions phenyl, phenylalkyl, phenyloxycarbonyl and phenylcarbonyl means that the aromatic rings may be substituted with up to 3 linear or branched alkyl having 1 to 6 carbon atoms, alkoxy having 1 to 4 carbon atoms, hydroxyl, nitro, trifluoromethyl or halogen.

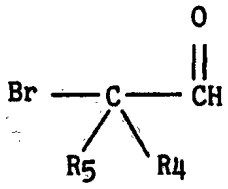
The invention also encompasses the processes for obtaining the compounds of the general formula (I). The processes for obtaining these compounds depend on the nature of the group A.

- Either a substituted tryptamine of general formula (IV):



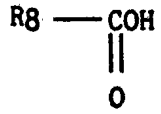
(IV)

in which R_1, R_3 and R_6 have the same meaning as in the compound of general formula (I), is reacted with an aldehyde of general formula (V):



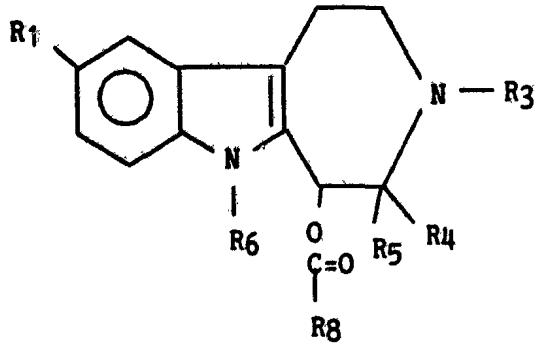
(V)

in which R_5 and R_4 have the same meaning as in the compound of general formula (I), by heating them in an organic acid of general formula (VI):



(VI)

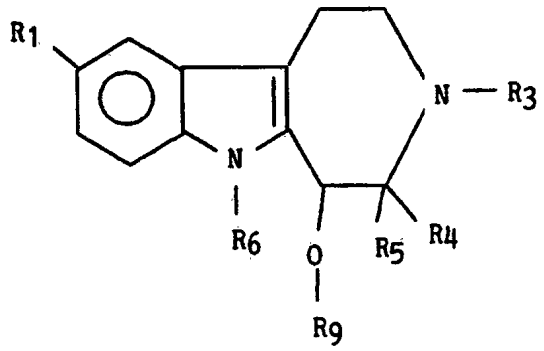
in which R_8 is a methyl, ethyl or trifluoromethyl group, so as to obtain the 1,2,3,4,5,6-hexahydroazepino[4,5-b]indole of general formula (VII):



(VII)

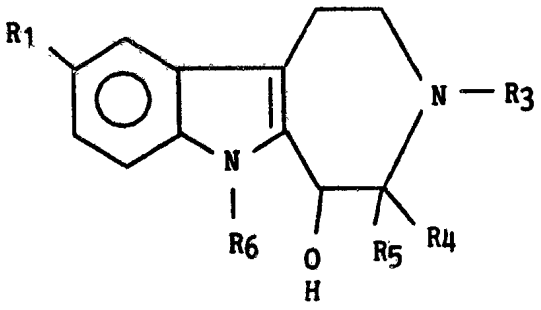
in which R_1, R_3, R_4, R_5 and R_6 have the same meaning as in the compound of general formula (I) and R_8 the same meaning as in the acid (VI), which can be either heated with an alcohol of general formula R_9OH, in which R_9 is a lower alkyl group,

branched or otherwise, having 1 to 6 carbon atoms or an aralkyl group, so as to obtain the 1,2,3,4,5,6-hexahydroazepino[4,5-b]indole of general formula (VIII):



(VIII)

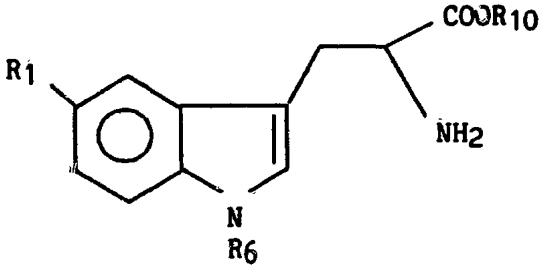
in which R_1, R_3, R_4, R_5 and R_6 have the same meaning as in the compound of general formula (I) and R_9 the same meaning as above, or heated in methanol in the presence of 10 equivalents of potassium carbonate so as to obtain the 1,2,3,4,5,6-hexahydroazepino[4,5- b]indole of general formula (IX):



(IX)

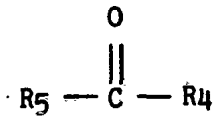
in which R_1, R_3, R_4, R_5 and R_6 have the same meaning as in the compound of general formula (I),

- or a substituted tryptophan of general formula (X):



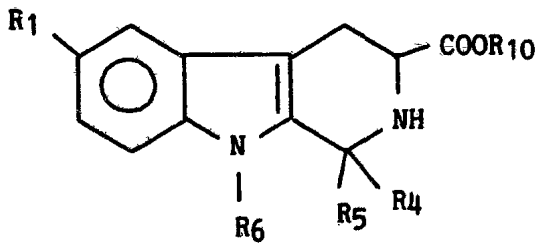
(X)

in which R_1 and R_6 have the same meaning as in the compound of general formula (I) and R_{10} is a lower alkyl, branched or otherwise, having 1 to 6 carbon atoms or an optionally substituted aryl or aralkyl group, is reacted with a ketone of general formula (XI):



(XI)

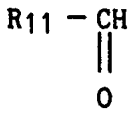
in which R_4 and R_5 have the same meaning as in the compound of general formula (I), under a nitrogen atmosphere, either in toluene or benzene under reflux in the presence of para-toluenesulfonic acid, the water formed during the condensation being removed by means of a water-extraction apparatus which can be, for example, a Dean Stark apparatus, or, in some cases, under reflux of methanol or of the ketone itself, so as to obtain, after purification, the β-carboline of general formula (XII):



(XII)

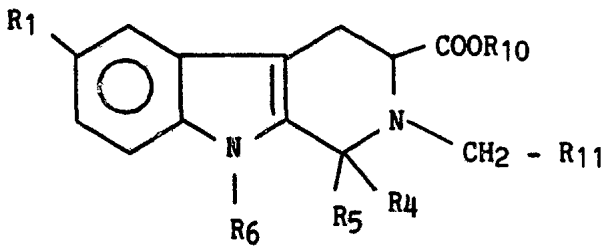
in which R_1, R_4, R_5, R_6 and R_{10} have the same meaning as in the compounds of general formulae (I) and (X), which can be:

- either reacted under reductive amination conditions with an aldehyde of general formula (XIII):



(XIII)

in which R_{11} is a hydrogen atom or a lower alkyl group, branched or otherwise, having 1 to 6 carbon atoms and optionally substituted with one or more halogen atoms, alkoxy groups or aryl groups, substituted or otherwise, so as to obtain the β-carboline of general formula (XIV):



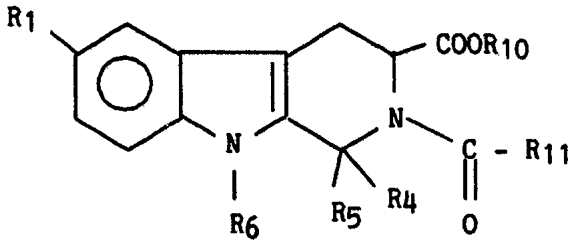
(XIV)

in which R_1, R_{10}, R_{11}, R_4, R_5 and R_6 have the same meaning as in the compounds of general formula (XII) and (XIII),

- or reacted with an acid chloride, or the corresponding acid anhydride, of general formula (XV):

(XV)

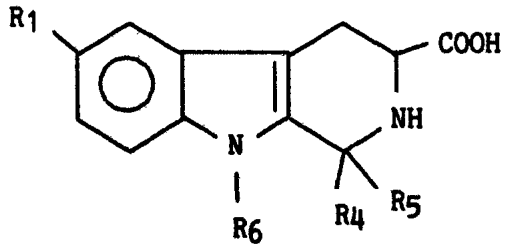
in which R_{11} has the same meaning as in the compound of general formula (XIII) so as to obtain the β-carboline of general formula (XVI):



(XVI)

in which R_1, R_{10}, R_{11}, R_6, R_5 and R_4 have the same meaning as in the compound of general formula (XIV),

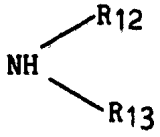
- or reacted, in the case where $R_{10} = CH_3$, with aqueous barium hydroxide solution so as to obtain the acids of general formula (XVII):



(XVII)

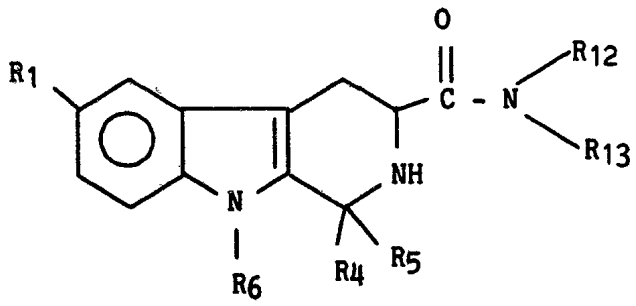
in which R_1, R_4, R_5 and R_6 have the same meaning as in the compounds of general formula (I),

- or reacted, in the case where $R_{10} = CH_3$, with an amine of general formula (XVIII):



(XVIII)

in which R_{12} and R_{13} represent, each independently of one another, a hydrogen atom or lower alkyl groups, branched or otherwise, having 1 to 6 carbon atoms or cycloalkyl groups having 4 to 7 carbon atoms, so as to obtain the amides of general formula (XIX):



(XIX)

in which R_1, R_4, R_5 and R_6 have the same meaning as in the compounds of general formula (I) and R_{12} and R_{13} the same meaning as in the amides of general formula (XVIII),

it being understood that the compounds of general formula (VII), (VIII), (IX), (XII), (XIV), (XVI), (XVII) and (XIX) form part of the invention and are special cases of the compounds of general formula (I).

The 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles and 1,2,3,4-tetrahydro-β-carbolines of general formula (I), as well as their addition salts with a pharmaceutically-acceptable inorganic or organic acid or, where it is possible, their

addition salts with a pharmaceutically-acceptable inorganic or organic base, are very advantageous active principles which may be used, for example, as anxiolytics, antidepressants, antipsychotics and analgesics. Some of these products are also anticonvulsant, muscle-relaxant, anti-inflammatory and effective in the treatment of cerebrovascular disorders and disorders of memory.

The compounds of general formula (I), as well as their addition salts with a pharmaceutically-acceptable inorganic or organic acid such as, for example, hydrochloric, methanesulfonic, citric or maleic acid, or, where it is possible, their addition salts with a pharmaceutically-acceptable inorganic or organic base such as, for example, sodium, potassium or calcium hydroxide, arginine, ethanolamine or diethanolamine, may be made into pharmaceutical preparations according to generally known processes, such as, for example, into tablets, hard gelatin capsules, dragées, solutions for oral administration, injections, suspensions for oral administration, emulsions and suppositories.

Apart from non-toxic and pharmaceutically-acceptable inert excipients such as, for example, distilled water, glucose, lactose, starch, talc, vegetable oils, ethylene glycol, and the like, these preparations can also contain preservatives: stabilizers, wetting agents, emulsifiers, and the like.

The compositions thereby obtained are generally presented in the form of measured doses, and can contain, depending on the conditions being treated and the patient's age and weight, from 0.1 to 500 mg of active principle.

They may, depending on the case, be administered orally, rectally or parenterally at a dose of 0.1 to 500 mg from one to several times a day.

The examples which follow illustrate the invention and in no way limit the latter.

EXAMPLE 1: [(3S)-3-METHOXYCARBONYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIRO-3'-[2-OXO- 2,3-DIHYDROINDOLE]

2.93 g (14.3 mmol) of L(-)-tryptophan methyl ester, 4.2 g (28.6 mmol) of isatin and 2.7 g of para-toluenesulfonic acid (monohydrate) are dissolved in the heated state in the minimum quantity of methanol enabling the reactants to be in solution in the heated state.

The reaction medium is brought to reflux under a nitrogen atmosphere for 48 hours, and the methanol is then removed by distillation under reduced pressure.

The residue obtained is purified by chromatography on a silica column (eluent: chloroform/methanol, 95/5). The product obtained is then recrystallized in methanol.

2.55 g (55%) of [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-3'-[2-oxo-2,3-dihydroindole] are thereby obtained.

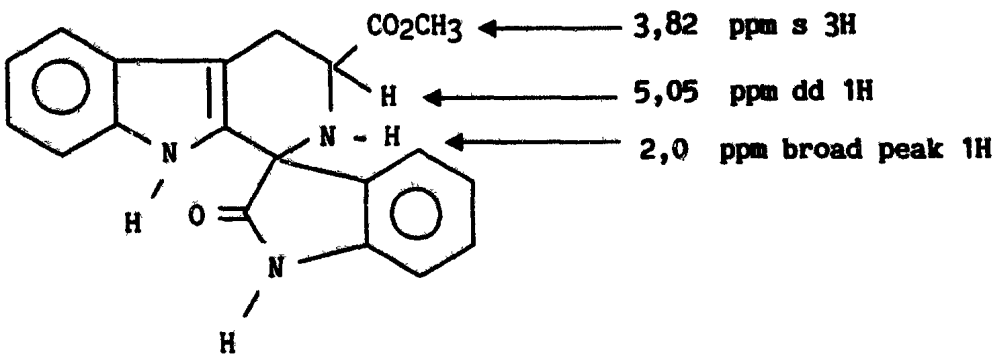
Melting point: 253° C

Optical rotation: $[\alpha]_D$ (MeOH): -151.6°

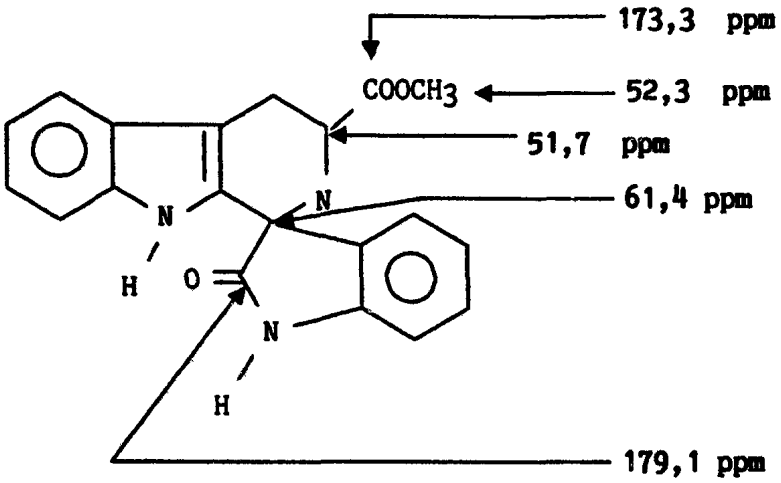
UV (MeOH): λmax at 215, 225, 245, 282 and 285 nm

IR (KBr): νC = O at 1715, 1730, 1620 cm-1, other bands 3290 and 3370 cm-1

^1H NMR 300 MHz ($CDCl_3$)



^{13}C NMR 75 MHz ($CDCl_3$)



EXAMPLE 2: [(3S)-3-METHOXYCARBONYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIROCYCLOHEXANE

3 g (14.6 mmol) of L(-)-tryptophan methyl ester, 2.86 g (29.2 mmol) of cyclohexanone and 0.28 g of para-toluenesulfonic acid (monohydrate) are dissolved in the heated state in sufficient toluene for the reactants to be in solution under reflux, under a nitrogen atmosphere, in a Dean and Stark apparatus enabling the water formed during the reaction to be removed.

The reaction medium is brought to reflux until the starting materials have disappeared (approximately 20 hours), and the toluene is then removed by distillation under reduced pressure.

The crude product obtained is recrystallized in methanol.

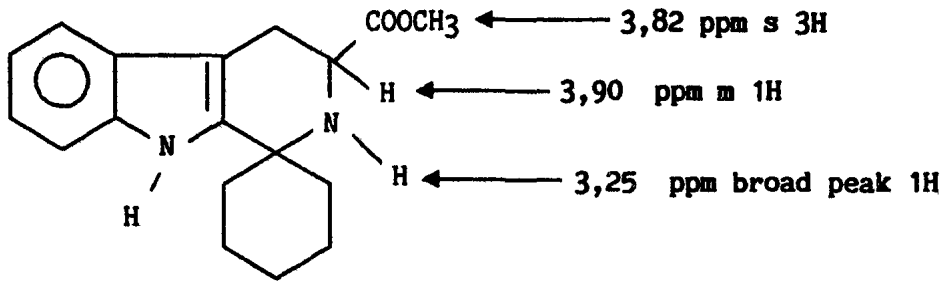
3.7 g (89%) of [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane are thereby obtained.

Melting point: 175° C

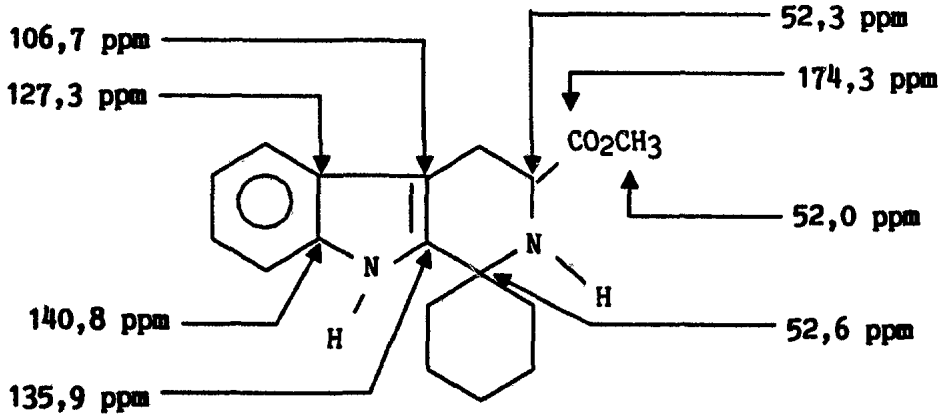
Optical rotation: α_D (MeOH): -70.9°

UV (MeOH): λmax at 225, 280 and 285 nm

^1H NMR 300 MHz ($CDCl_3$)



^{13}C NMR 75 MHz ($CDCl_3$)



EXAMPLE 3: [(3S)-3-CARBOXY-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIROCYCLOHEXANE

100 cm³ of saturated aqueous barium hydroxide solution are added to a solution of 1.5 g of [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane in 100 cm³ of dioxane. The mixture is brought to reflux for 2 h 30 min and then cooled, and gaseous CO_2 is bubbled through until the precipitation of barium carbonate is complete. The precipitate is removed by filtration and the filtrate is taken to dryness.

0.9 g (63%) of [(3S)-3-carboxy-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane is obtained.

Melting point: 198-201° C

Optical rotation: $[\alpha]_D$ = -69.9° (c = 4.81 gl⁻¹ MeOH)

UV (MeOH): λ max 290, 280 and 220 nm

^1H NMR ($CDCl_3$ + CD_3OD) δ : (ppm)

7.45 d(1H); 7.35 d(1H); 7.15 t(1H); 7.05 t(1H); 4.10 dd(1H); 3.35 dd(1H); 3.22 dd(1H); 2.4 to 1.8 unresolved complex (10H)

EXAMPLE 4: [(3S)-3-METHOXYCARBONYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIROCYCLOHEPTANE

Using the procedure described in Example 2, but replacing cyclohexanone by cycloheptanone, [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-cycloheptane is obtained.

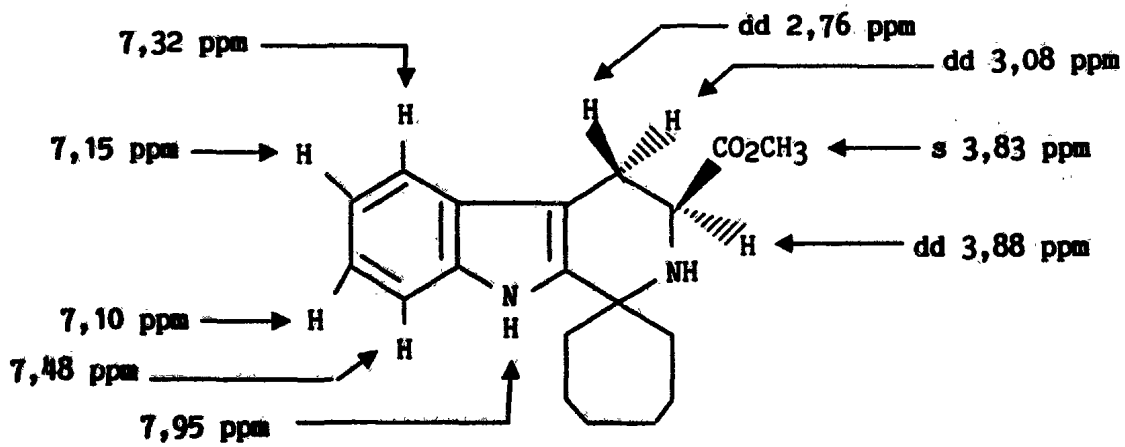
Melting point: 130-133° C

Optical rotation: α_D = -55° (c = 6.00 gl-1 MeOH)

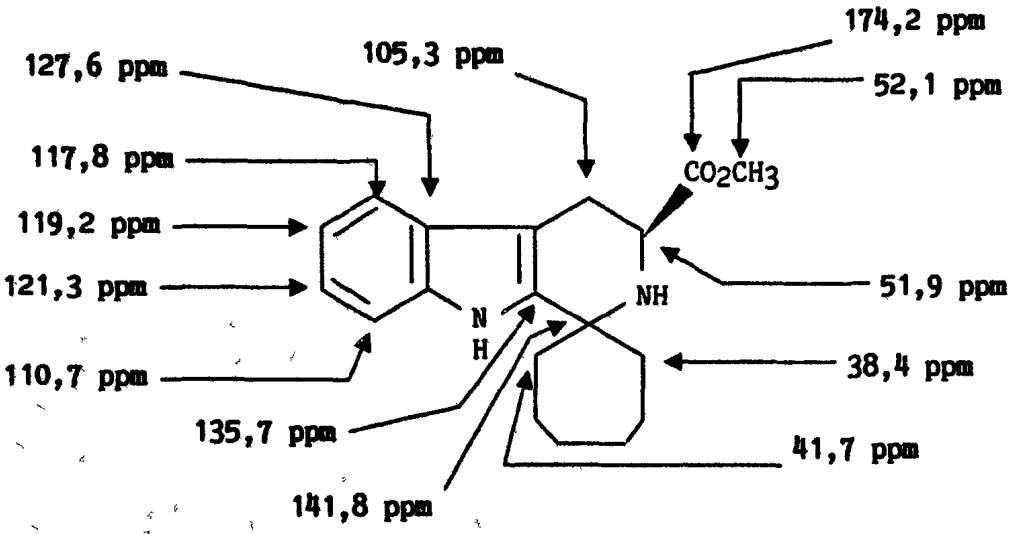
UV (MeOH): λmax 288, 280 and 225 nm

IR ($CHCl_3$ film) bands at 3400, 1730 cm-1

^1H NMR 300 MHz ($CDCl_3$)



^{13}C NMR 75 MHz ($CDCl_3$)



Other signals (CH_2) à 30,0; 29,6; 26,2; 23,1 and 22,4 ppm

EXAMPLE 5: [(3S)-3-(N-PROPYLCARBAMOYL)-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIROCYCLOHEXANE

2 g of [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane and 30 cm^3 of N-propylamine are introduced into a sealed tube, and the suspension is then heated at 60° C for 45 hours.

The N-propylamine is removed under reduced pressure and the residue is then purified by chromatography.

[(3S)-3-(N-Propylcarbamoyl)-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane is obtained in a 50% yield.

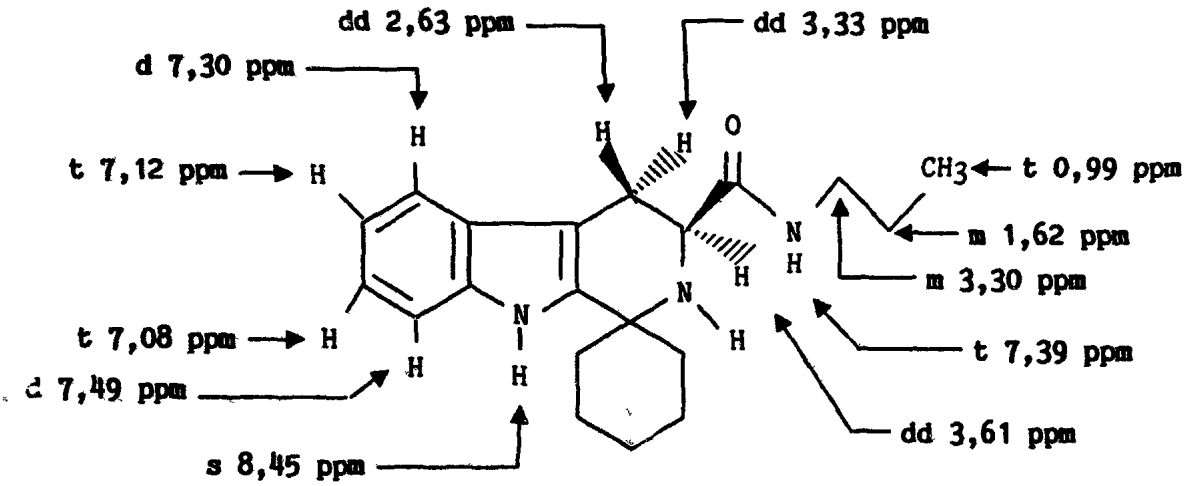
Melting point: 225-226° C

Optical rotation: α_D = -101.3° (c = 5.77 gl-1 MeOH)

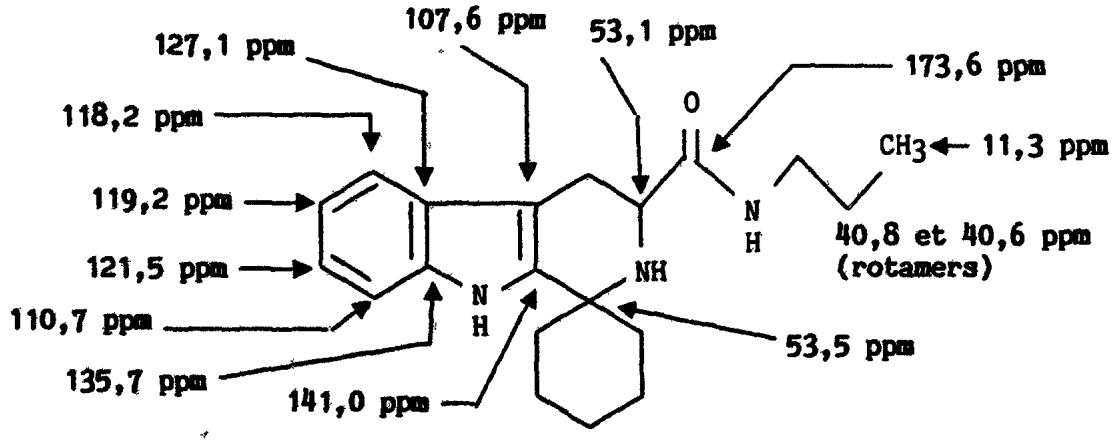
UV (MeOH): λmax 290, 283 and 225 nm

IR ($CHCl_3$ film): bands at 3200 (broad), 1650 cm-1

^1H NMR 300 MHz ($CDCl_3$)



^{13}C NMR 75 MHz ($CDCl_3$)



Other signals (CH_2) at 38.5, 34.3, 25.8, 25.4, 22.8, 21.6 and 21.2 ppm

EXAMPLE 6: [(3S)-3-(N-CYCLOHEXYLCARBAMOYL)-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIROCYCLOHEXANE

A suspension under an argon atmosphere of 2 g of [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane in 35 cm^3 of cyclohexylamine is heated to reflux for 20 hours.

The cyclohexylamine is removed by distillation and the residue is then purified by chromatography.

[(3S)-3-(N-Cyclohexylcarbamoyl)-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane is obtained in a 63% yield.

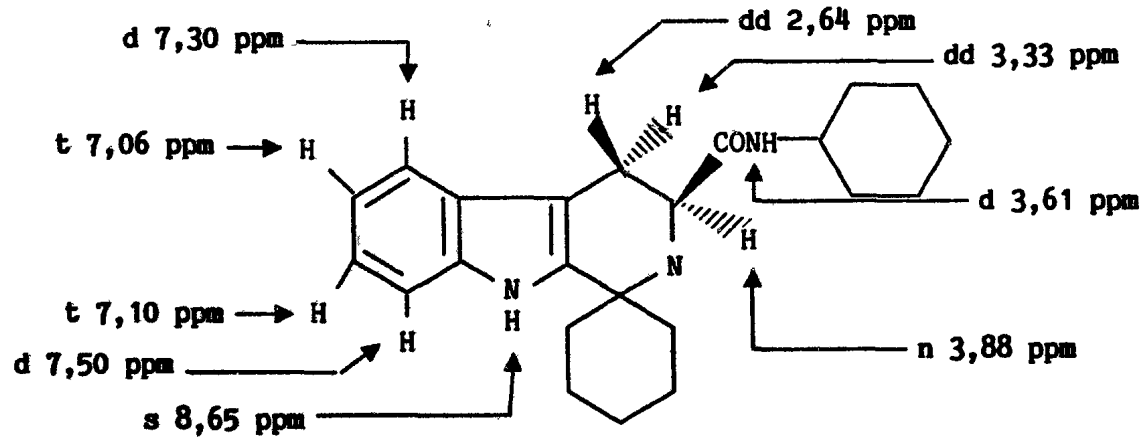
Melting point: 225-230° C

Optical rotation: α_D = -60.8° (c = 5.75 gl-1 MeOH)

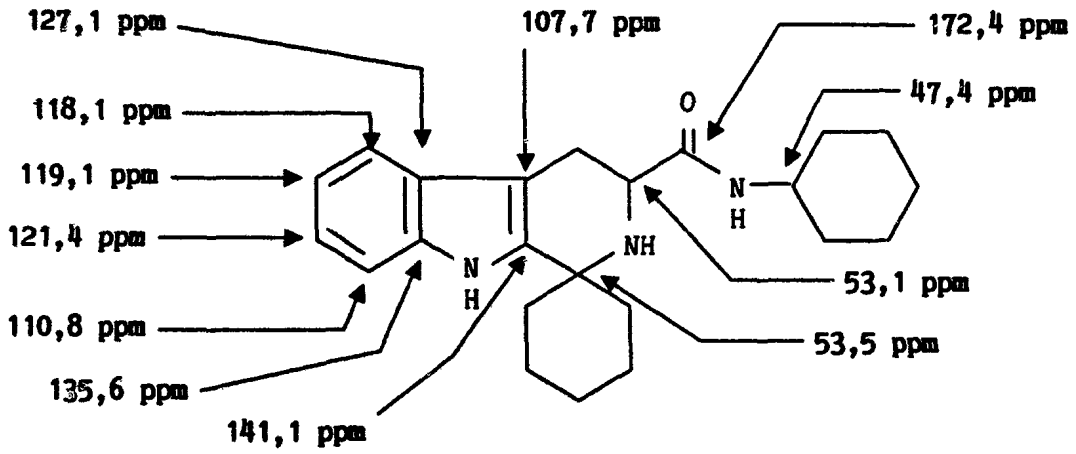
UV (MeOH): λmax 289, 280 and 225 nm

IR (KBr) 3290, 1660, 1580 cm-1

^{1}H NMR 300 MHz ($CDCl_3$)



^{13}C NMR 75 MHz ($CDCl_3$)



Other signals (CH_2) at 38.5, 34.1, 33.0, 32.9, 25.8, 25.5, 24.5, 21.7 and 21.2 ppm

EXAMPLE 7: [(3S)-3-CARBAMOYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIROCYCLOHEXANE

In a sealed tube, 1 g of [3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane is dissolved in 12 cm^3 of methanol, 3 cm^3 of liquid ammonia are then added and the mixture is maintained at room temperature for 36 hours.

The ammonia is allowed to outgas and the product formed, which crystallizes slowly, is isolated by filtration.

0.82 g (82%) of [3-carbamoyl-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane is thereby obtained.

Optical rotation: α_D = -117.6° (c = 4.02 gl-1 DMSO)

Melting point, base: 278-279° C; hydrochloride: 188-189° C

UV: λmax 295 and 220 nm

IR (KBr disk): bands at 3500, 3250, 1680, 1560 cm-1

^1H NMR (base) ($CDCl_3$ + DMSO-d_6) δ (ppm)

10.3 bs(1H); 7.4 d(1H); 7.3 d(1H), 7.05 t(1H); 6.95 t(1H); 6.8 bs(1H); 4.6 bs(2H); 3.6 m(1H); 3.15 dd(1H); 2.6 dd(1H); 2.15 dt(1H); 1.9-1.3 unresolved complexes (9H)

EXAMPLE 8: [(3S)-3-METHOXYCARBONYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIRO-4'-[1- METHYLPIPERIDINE]

3.7 g (17 mmol) of L(-)-tryptophan methyl ester, 3.85 g (34 mmol) of redistilled N-methyl-4-piperidone and 0.34 g of para-toluenesulfonic acid (monohydrate) are dissolved in the heated state in sufficient toluene for the reactants to be in solution under reflux, under a nitrogen atmosphere, in a Dean and Stark apparatus enabling the water formed during the reaction to be removed.

The reaction medium is brought to reflux until the starting materials have disappeared (approximately 20 hours), and the toluene is then removed by distillation under reduced pressure. The residue obtained is taken up with chloroform and washed copiously with 10% aqueous sodium bicarbonate solution so as to remove as much of the excess N-methyl-4-piperidone as possible.

After its solution in chloroform has been taken to dryness, the crude product is purified by chromatography on a silica column (eluent: $CHCl_3/CH_3OH$ with a concentration gradient).

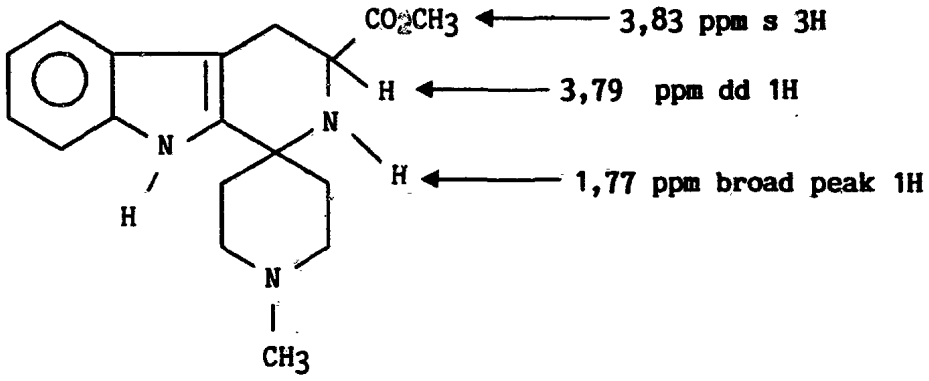
3.4 g (64%) of [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-[1-methylpiperidine] are thereby obtained in the form of a non-crystalline product.

Optical rotation: α_D (MeOH): -19.5°

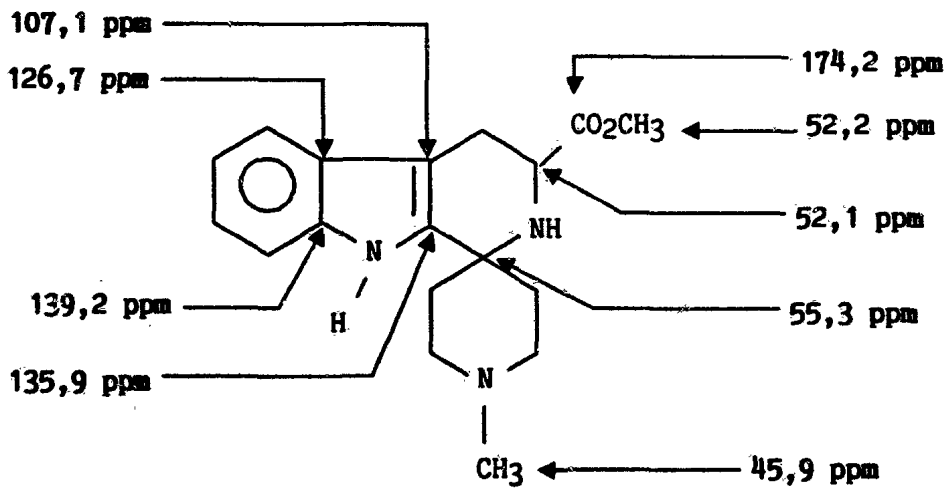
UV (MeOH): λmax at 220, 280 and 296 nm

IR ($CHCl_3$ film) νC = O at 1725 and 1740 cm-1

^1H NMR 300 MHz ($CDCl_3$)



^{13}C NMR 75 MHz ($CDCl_3$)



EXAMPLE 9: [(3S)-3-CARBOXY-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIRO-4'-[1-METHYLPIPERIDINE]

1 g (31.9 mmol) of [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-[1-methylpiperidine] is added to a mixture of 20 cm^3 of distilled water and 2 cm^3 of 38% potassium hydroxide solution.

The quantity of dioxane enabling dissolution to be obtained in the heated state is added, and the reaction medium is maintained for 10 hours under reflux under a nitrogen atmosphere. The reaction medium is then concentrated to 2/3 of its volume and 100 mg of Amberlist 77 cationic resin are added.

The resin is removed by filtration and the reaction medium concentrated under reduced pressure.

0.7 g (67%) of [(3S)-3-carboxy-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-[1-methylpiperidine] is thereby obtained.

UV (MeOH): λmax at 220, 280 and 290 nm

IR (film) broad band at about 1700 cm-1

EXAMPLE 10: [(3S)-3-METHOXYCARBONYL-2-METHYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIRO-4'-[1-METHYLPIPERIDINE]

98 mg (0.31 mmol) of [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-[1-methylpiperidine] and 39 mg of sodium cyanoborohydride are dissolved in a mixture of 4 cm^3 of 40% formaldehyde and 0.5 cm^3 of acetic acid. After one hour's stirring at room temperature, the reaction medium is poured into 10% aqueous sodium bicarbonate solution and extracted with chloroform. The chloroform phases are washed with water, dried over magnesium sulfate and then taken to dryness under reduced pressure.

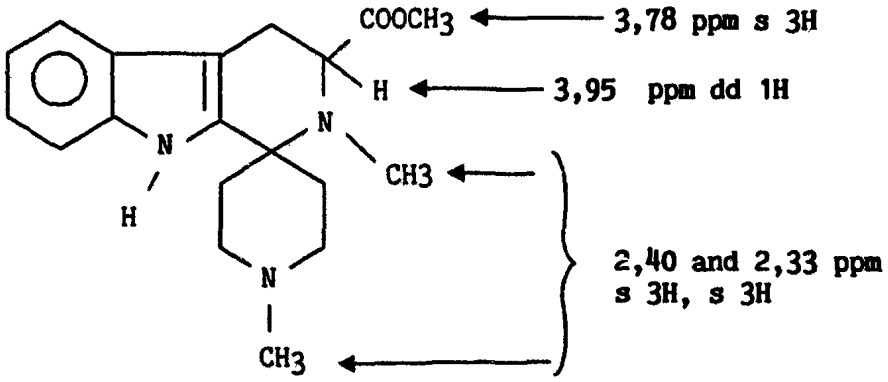
95 mg (93%) of [(3S)-3-methoxycarbonyl-2-methyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-[1-methylpiperidine] are thereby obtained in the form of a gum.

Optical rotation: α_D = (MeOH): -8°

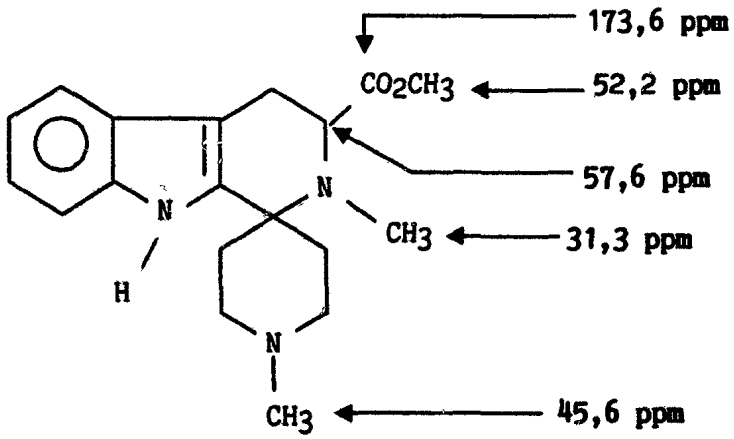
UV (MeOH): λmax at 225, 280 and 285 nm

IR ($CHCl_3$ film) νC = O at 1720 and 1735 cm-1

^1H NMR 300 MHz ($CDCl_3$)



^{13}C NMR 75 MHz ($CDCl_3$)



EXAMPLE 11: [(3S)-3-CARBOXY-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIRO-4'-PIPERIDINE

A mixture of 2.5 g of tryptophan and 1.8 g of 4-piperidone hydrochloride dissolved in a mixture of 70 cm^3 of dioxane, 40 cm^3 of water and 5 cm^3 of 97% sulfuric acid is heated to reflux for 48 hours under an argon atmosphere.

The reaction medium is cooled and the product formed, which precipitates slowly, is isolated by filtration.

2.3 g (62%) of [(3S)-3-carboxy-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-piperidine hydrochloride are thereby obtained.

UV (MeOH): λmax 295 and 222 nm

^1H NMR ($CDCl_3$ + CD_3OD) δ (ppm)
7.6 d(1H); 7.4 d(1H); 7.15 t(1H); 7.05 t(1H); 4.2 t(1H); 3.9 multiplet (2-3H); 3.5 multiplet (4H); 2.9 multiplet (3-4H)
^{13}C NMR (CD_3OD) δ(ppm) 171.6, 137.5, 130.0, 128.3, 123.5, 120.7, 119.2, 112.4, 105.7, 58.3, 54.5, 43.1, 42.0, 27.2, 25.9

EXAMPLE 12: [(3S)-3-METHOXYCARBONYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIRO-4'- PIPERIDINE

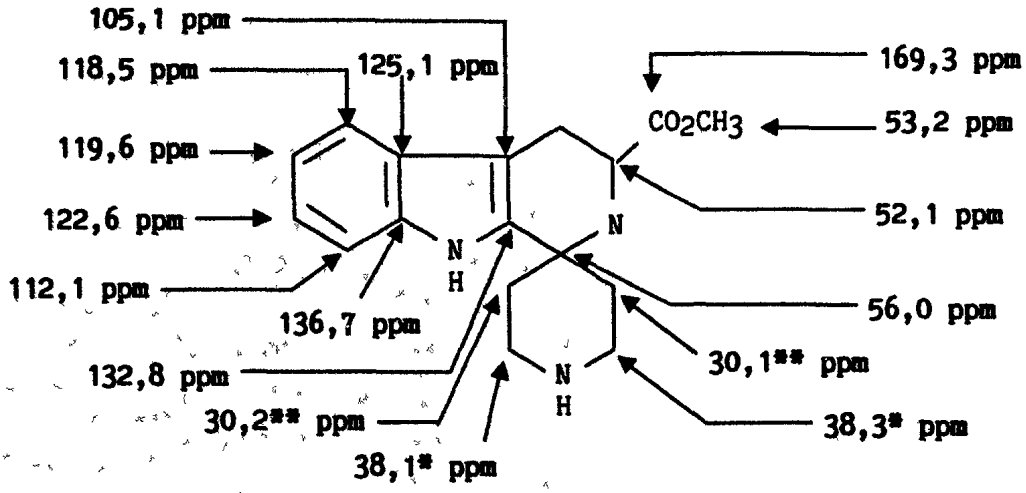
A suspension of 2.18 g of methyltryptophanate and 1.55 g of 4-piperidone hydrate hydrochloride in 160 cm^3 of benzene is heated to reflux for 29 hours in a Dean and Stark apparatus.

The benzene is removed by distillation, the residue is dissolved in sufficient methanol and gaseous HCl is bubbled through to saturation.

The product, which crystallizes slowly, is isolated by filtration.

2.15 g (58%) of [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-piperidine are thereby obtained.

Melting point: 182-185° C
Optical rotation: α_D = -46.8° (c = 2.71 gl^{-1} $CHCl_3/CH_3OH$, 3 : 1)
UV (MeOH): λmax 295 and 220 nm
^1H NMR (DMSO-d_6) δ(ppm) product in the form of a dihydrochloride 11.5 s(1H); 9.8 s(1H); 9.4 s(1H); 7.5 d, J = 7 Hz(1H); 7.45 d, J = 7 Hz(1H); 7.15 t J = 7 Hz(1H); 7.05 t J = 7 Hz(1H); 4.65 m(1H); 3.9 d(3H); 3.4 m(2H); 3.2-2.4 unresolved complexes (8H)
^{13}C NMR (DMSO-d_6) δ(ppm) product in the form of a dihydrochloride



EXAMPLE 13: [5-ACETOXY-1,2,3,4,5,6-HEXAHYDRO-AZEPINO[4,5-b]INDOLE]-4-SPIRO-1'-(3'-CYCLOHEXENE)

1.96 g (10.37 mmol) of 4-bromo-4-formylcyclohexene are added to a solution of 0.833 g (5.2 mmol) of tryptamine in 50 cm^3 of acetic acid, and the reaction medium is then heated to 70° C under a nitrogen atmosphere for 15 hours.

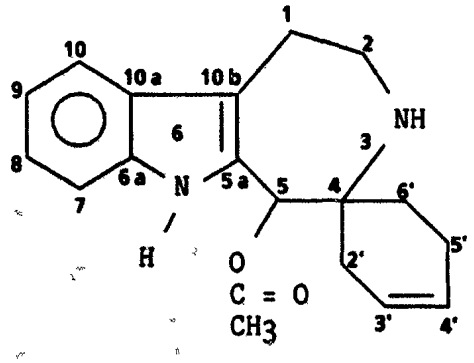
After removal of the acetic acid by distillation under reduced pressure, the residue is taken up with 100 cm^3 of methylene chloride. The organic solution is washed with 100 cm^3 of 10% aqueous sodium carbonate solution, dried over magnesium sulfate and then taken to dryness, yielding 2.52 g of crude product.

A purification by chromatography on a silica column (eluent: $CHCl_3$) enables 1.12 g (70%) of [5-acetoxy-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole]-4-spiro-1'- (3'-cyclohexene) to be isolated in the form of a mixture of two diastereoisomers, the proportion, 60:40, of which was determined by NMR.

UV (MeOH): λmax at 220, 280 and 290 nm

IR (KBr) νC = O: 1725 cm-1; νC - O - C: 1245, 1235 cm-1

^{1}H NMR 300 MHz (CD_3OD) δ(ppm)



7.55	1H	d J = 8Hz	C(10)H
7.35	1H	d J = 8Hz	C(7)H
7.18	1H	t J = 8Hz	C(8)H
7.1	1H	t J = 8Hz	C(9)H
5.85 and 5.71	1H	s (3:2)	C(5)-H
5.83-5.73	1H	m	C(3')H or C(4')H
5.66-5.5	1H	m	C(4')H or C(3')H
3.33-3.14	2H	m	C(2)-HH'
3.14-2.96	2H	m	C(1)-HH' 2.33-1.63 6H m
2.1 and 2.0	3H	s (3:2)	$OCOCH_3$

^{13}C NMR 75 MHz (CD_3OD) δ (ppm)

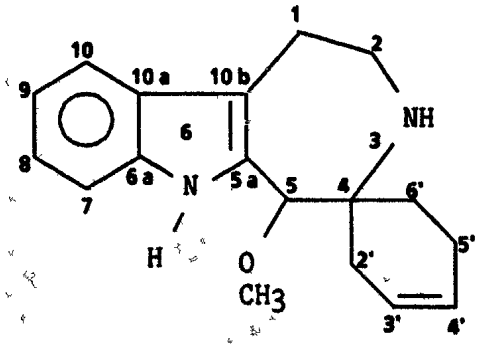
171.3 ($O\underline{C}OCH_3$); 135.0 (C 6a); 131.2 (C 5a); 127.6 (C 10a); 126.5 and 126.0 (C 3'); 123.3 (C 4'); 122.1 and 121.7 (C 8); 119.4 and 119.2 (C 9); 118.3 and 118.0 (C 10); 113.3 (C 10b); 111.3 (C 7); 75.1 and 71.9 (C 5); 55.0 (C 4); 41.9 and 41.8 (C 2); 36.0 and 33.6 (C 2'); 31.7 and 31.4; 26.1; 22.7; 20.7 ($OCO\underline{C}H_3$)

EXAMPLE 14: [5-METHOXY-1,2,3,4,5,6-HEXAHYDRO-AZEPINO[4,5-b]INDOLE]-4-SPIRO-1'-(3'-CYCLOHEXENE)

A simple heating in methanol under reflux for 1 hour permits the conversion of [5-acetoxy-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole]-4-spiro-1'-(3'-cyclohexene) to the 5-methoxy compound.

UV (MeOH): λmax at 220, 280 and 290 nm

IR (film) 3380, 3010, 2920, 1460, 1450, 1090 and 900 cm-1
^{1}H NMR 300 MHz (CD_3OD) δ (ppm)

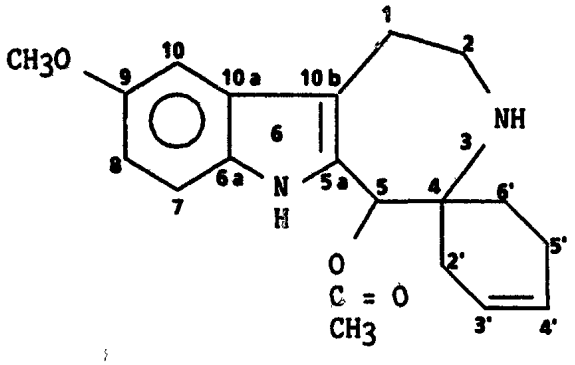


8.20 and 8.15	1H	bs (3:2)	N(6)H
7.52	1H	d J = 8Hz	C(10)-H
7.34	1H	d J = 8Hz	C(7)-H
7.22-7.06	2H	m	C(8)-H + C(9)-H
5.76-5.47	2H	m	C(3')H + C(4')-H
4.18 and 4.00	1H	s (3:2)	C(5)-H
3.34 and 3.27	3H	s (3:2)	$O\underline{CH_3}$
3.22-2.82	4H	m	C(1)-HH' + C(2)-HH'
2.75-2.48	1H	m	N(3)H
2.34-1.54	6H	m	

EXAMPLE 15: [9-METHOXY-5-ACETOXY-1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-b]INDOLE]-4-SPIRO-1'-(3'-CYCLOHEXENE)

Starting with 5-methoxytryptamine and using the procedure described in Example 6, [9-methoxy-5-acetoxy-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole]-4-spiro-1'- (3'-cyclohexene) is obtained in the form of a mixture of diastereoisomers.

UV (MeOH): λmax at 220, 280 and 290 nm
IR (film) νC = O: 1710 cm-1; νC - O - C: 1235, 1215 cm-1
^{1}H NMR 300 MHz ($CDCl_3$) δ (ppm)



8.46	1H	bs	N(6)H
7.16	1H	d	C(7)-H
6.94	1H	s	C(10)-H
6.84	1H	d	C(8)-H
5.72	1H	s	C(5)-H
5.82-5.66	1H	m	C(3')-H or C(4')H
5.60-5.49	1H	m	C(4')-H or C(3')-H
3.85	3H	s	OCH_3 3.29-3.16 2H m C(2)HH'
3.02-2.87	2H	m	C(1)HH'
2.67-2.52	1H	m	N(3)-H
2.33-1.64	6H	m	
2.07	3H	s	$CH_3C(=O)$

EXAMPLE 16: [5-ACETOXY-3-METHYL-1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-b]INDOLE]-4-SPIRO-1'-(3'-CYCLOHEXENE)

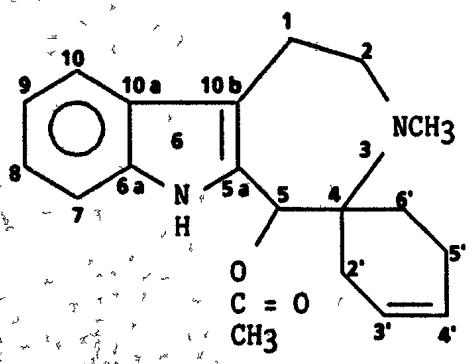
A solution of 0.2 g (1.15 mmol) of N-methyltryptamine and 0.240 mg (1.27 mmol) of 4-bromo-4-formylcyclohexene in 20 cm^3 with acetic acid is heated to 70° C for 4 days under a nitrogen atmosphere. After removal of the acetic acid by distillation under reduced pressure, the residue is taken up with 50 cm^3 of methylene chloride and washed with 10% aqueous sodium carbonate solution. The organic phase is dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product obtained is purified by chromatography on silica (eluent: CH_2Cl_2/CH_3OH, 97%/3%).

[5-Acetoxy-3-methyl-1,2,3,4,5,6-hexahydro-azepino[4,5-b]indole]-4 -spiro-1'-(3'-cyclohexene) is finally obtained in a 42% yield in the form of a mixture of diastereoisomers.

UV (MeOH): λmax at 223, 285 and 292 nm

IR (film) 3380, 3000, 2900, 1710, 1450, 1360, 1330, 1230, 1010, 950, 710 cm-1

^{1}H NMR 300 MHz ($CDCl_3$) δ(ppm)



8.38 and 8.35	1H	bs	N(6)-H
7.53	1H	d J = 8Hz	C(10)-H
7.27	1H	d J = 8Hz	C(7)-H
7.19	1H	t J = 8Hz	C(8)-H
7.10	1H	t J = 8Hz	C(9)-H
5.97 and 5.95	1H	s (2:3)	C(5)-H
5.79-5.66	1H	m	C(3')-H or C(4')-H
5.64-5.47	1H	m	C(4')-H or C(3')-H
3.68-3.54	1H	m	C(2)-H
3.46-3.07	3H	m	C(2)-H'+ C(1)-HH'
2.90-2.72	1H	m	
2.86 and 2.82	3H	s (3:2)	N-$\underline{CH_3}$
2.45-1.80	5H	m	
2.08 and 2.06	3H	s (3:2)	O$\underset{\underset{O}{\|}}{C}\underline{CH_3}$

EXAMPLE 17: 9-METHOXY-5-ACETOXY-4,4-DIMETHYL-1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-b]INDOLE

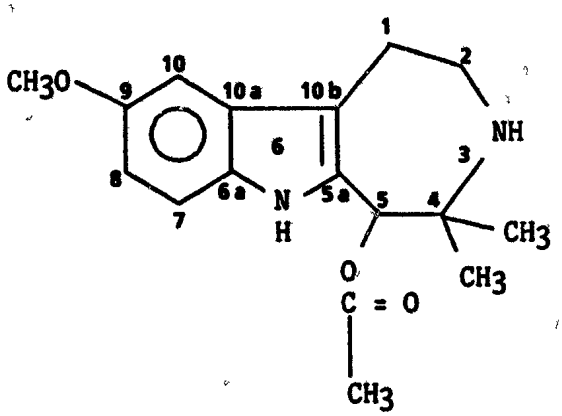
A solution of 5.34 g of 5-methoxytryptamine and 4.53 g of 2-bromo-2-formylpropane in 150 cm^3 of acetic acid is heated to 60° C under a nitrogen atmosphere for 2 hours. The acetic acid is removed by distillation under reduced pressure and the residue taken up with methylene chloride and washed with 10% aqueous sodium carbonate solution. The organic phase is dried over $MgSO_4$, filtered and concentrated under reduced pressure.

9-Methoxy-5-acetoxy-4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole is obtained in a 66% yield.

UV (MeOH): λmax at 215, 285 and 300 nm

IR (film) 3380, 2960, 2940, 2840, 1730 (νC = O), 1480, 1450, 1370, 1250 (νC - O - C), 1020, 960 cm^{-1}

^1H NMR 300 MHz ($CDCl_3$) δ(ppm)



8.55	1H	bs	N(6)-H
7.16	1H	d	C(7)-H
6.94	1H	d	C(10)-H
6.82	1H	dd	C(8)-H
3.85	3H	s	$\underline{CH_3}$-O
3.27-3.17	2H	m	C(1)-HH'
2.96-2.85	2H	m	C(2)-HH'
2.18	1H	bs	N(3)-H
2.08	3H	s	$\underline{CH_3}$-C(=O)-O
1.20 and 1.24	2x3H	2xs	$-CH_3$, $-CH_3$

^{13}C NMR 75 MHz ($CDCl_3$) δ(ppm)

171.1(C = O), 154.0(9), 132.6 (5a), 130.0 (6a), 128.3 (10a), 113.6 (10b), 112.5 (8), 111.9 (7), 100.2 (10), 77.6 (5), 55.8 (CH_3O), 53.9 (4), 42.6 (2), 28.8 (CH_3), 27.7 (1), 23.7 (CH_3), 21.0 ($\underline{CH_3}$ - C=O)

EXAMPLE 18: 5-HYDROXY-4,4-DIMETHYL-1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-b]INDOLE

STAGE 1: 5-Acetoxy-4,4-dimethyl-3-trifluoroacetyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole

A solution of 3.2 g of tryptamine and 3 g of 2-bromo-2-formylpropane in 150 cm^3 of acetic acid is heated to 60° C under a nitrogen atmosphere for 15 hours. The acetic acid is removed by distillation under reduced pressure and the residue is taken up with methylene chloride and washed with 10% aqueous sodium carbonate solution. After the organic solution has been taken to dryness, the residue is taken up in 10 cm^3 of pyridine and 5 cm^3 of trifluoroacetic anhydride. The reaction medium is poured into water and extracted with methylene chloride, then taken to dryness.

The crude product is recrystallized in acetone.

5-Acetoxy-4,4-dimethyl-3-trifluoroacetyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole is obtained in a 34% yield.

STAGE 2: 5-Hydroxy-4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole

2 g of 5-acetoxy-4,4-dimethyl-3-trifluoroacetyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole and 0.7 g of potassium carbonate in 50 cm^3 of methanol are stirred at room temperature under a nitrogen atmosphere for 4 hours. After filtration, the product is extracted with methylene chloride and isolated by

taking to dryness. 5-Hydroxy- 4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride is obtained by dissolving the base in acetone and adding an ethereal solution of hydrochloric acid.

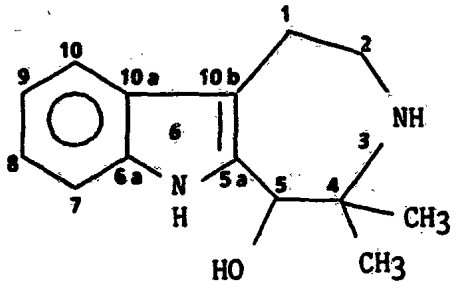
Yield: 95%

Analysis of the base:

UV (MeOH): λmax at 220, 283 and 290 nm

IR (film) 3380, 2960, 2900, 1450 cm-1

^{1}H NMR 300 MHz ($CDCl_3$) δ(ppm)



8.56	1H	bs	N(6)-H
7.45	1H	d	C(10)-H
7.20	1H	d	C(7)-H
7.15 and 7.05	2H	t,t	C(9)-H and C(8)-H
4.10	1H	s	C(5)-H
3.10-2.70	6H	m	C(1)-HH', C(2)-HH', N(3)-H, OH
1.09	3H	s	CH_3
1.01	3H	s	CH_3

EXAMPLE 19: TABLETS CONTAINING 50 MG OF [(3S)-3-METHOXYCARBONYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE]-1-SPIROCYCLOHEXANE

Preparation formula for 1,000 tablets.

[(3S)-3-Methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane..... 50 g

Wheat starch ..... 15 g

Corn starch ..... 15 g

Lactose	50 g
Magnesium stearate	1 g
Silica	1 g
Hydroxypropylcellulose	2 g

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

EXAMPLE A: TESTING FOR ANTI-INFLAMMATORY ACTIVITY

The anti-inflammatory potential of the compounds was investigated according to a model of acute inflammation induced by the subcutaneous injection of carrageenan into the rat hind foot, according to a technique based on that of WINTER et al. Proc. Soc., Exp. Biol Med, 111, 554 (1962) and WINEGAR et al. J. Pharmacol. Exp. Ther 166, 96 (1969).

Male Sprague-Dawley rats weighing 200 to 300 g are randomized in batches of 10 and receive the test substances by intraperitoneal administration 30 to 60 minutes before the local injection into the left hind foot of 0.1 ml of a 0.5% suspension of carrageenan in sterile physiological saline.

The right hind foot serving as a control receives an injection of physiological saline.

Three hours after the injection of carrageenan, the animals are anesthetized deeply with Narcorem R and the volume of both hind feet is measured by plethysmography.

The results are expressed as a percentage change in volume v%:

$$v\% = \frac{\text{volume left foot - volume right foot}}{\text{volume right foot}}$$

the anti-inflammatory activity AIA % is defined as :

$$AIA\% = 100 - \left(\frac{v\% \text{ (treated)}}{v\% \text{ (control)}} \times 100 \right)$$

Product	Dose	AIA%
[(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro cyclohexane	50 mg/Kg	14 %
[(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-[1-methyl piperidine]	25 mg/Kg	14 %

EXAMPLE B: TESTING FOR ANALGESIC ACTIVITY

The analgesic potential of these products was investigated according to the so-called "Acetic Acid Writhing" test, which is based on counting the abdominal cramps induced in mice by the intraperitoneal injection of acetic acid (GAIRIN et al. J. Pharmacol. Exp. Ther 245, 955 (1988)).

The mice, randomized in batches of 10, received the test products intraperitoneally 30 minutes before the intraperitoneal administration of 0.3 cm^3 of 1% acetic acid.

The number of cramps is counted between the 5th and 20th minute after the injection of acetic acid.

Products	Number of cramps per minute (between the 5th and the 20th minute)
- control	23 ± 14
- [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro cyclohexane, 50 mg/Kg	1 ± 1

The compounds of the literature structurally most closely related to the test products do not evince such analgesic activity.

EXAMPLE C: TESTING FOR ANXIOLYTIC ACTIVITY

The anxiolytic potential of these products was investigated according to the "elevated plus maze" test.

This test enables the behavior of the rat, treated or otherwise, to be studied in a situation of choice between a reassuring enclosed space ("enclosed branch") and an open space creating anxiety ("open branch").

The test consists in counting the number of entries into each branch of the maze during 5 minutes, and measuring the time spent in the "open branch".

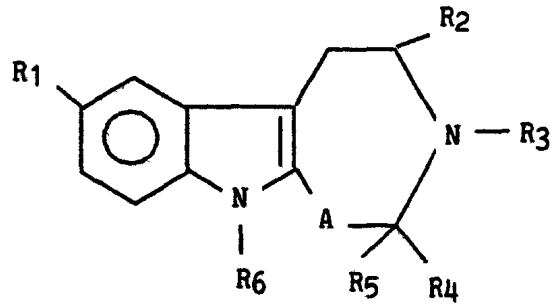
The rats are randomized in batches of 8 and receive the test products by intraperitoneal administration 60 minutes before the beginning of the test.

Product	Dose	total no. of entries	% of entries into the open branch	% of time spent in the open branch
- control		14 ± 2	28 % ± 5%	22 % ±5%
- [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (3S)]-1-spiro cyclohexane	50 mg/Kg IP	18 ± 2	42 % ± 4%	40 % ±6%
- [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-[1-methyl piperidine]	100 mg/Kg IP	18 ± 1	44 % ± 3%	41 % ±4%

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

~~CLAIMS~~

1. A compound selected from substituted indole of formula (I):



(I)

in which:

- A represents a σ bond or a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$,
- R_1 represents hydrogen, halogen, hydroxyl, linear or branched alkoxy having 1 to 4 carbon atoms, linear or branched alkyl having 1 to 6 carbon atoms optionally substituted with up to 3 halogen, oxo, hydroxyl or alkoxy having 1 to 4 carbon atoms,
- R_2 represents carboxyl, linear or branched alkoxycarbonyl having 1 to 6 carbon atoms and optionally substituted with optionally substituted phenyl; phenyloxycarbonyl, substituted phenyloxycarbonyl, carbamoyl, carbamoyl substituted on the nitrogen with up to 2 linear or branched alkyl having 1 to 6 carbon atoms or cycloalkyl having 4 to 7 carbon atoms; and in the case where A is a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$, R_2 can only represent hydrogen,
- R_3 represents hydrogen, linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 3 halogen, oxo, linear or branched alkoxy

having 1 to 4 carbon atoms or optionally substituted phenyl,

- R_4 and R_5 together form a saturated or unsaturated 5- to 12-membered mono- or bicyclic ring-system which can comprise in the ring skeleton from 0 to 3 hetero atoms selected from oxygen, nitrogen and sulfur and which can optionally be substituted with up to 3 oxo, linear or branched alkyl having 1 to 6 carbon atoms, optionally substituted phenyl, phenylcarbonyl, substituted phenylcarbonyl, optionally substituted phenylalkyl having 7 to 9 carbon atoms, ~~optionally substituted fluorene, with, in the case where R_4 and R_5 form a bicyclic system, the possibility that one of the rings is an optionally substituted aromatic ring,~~ and in the case where A is a radical of the formula $-\underset{\displaystyle OR_7}{\overset{\displaystyle |}{CH}}-$, R_4 and R_5 can also represent,

each independently of one another, hydrogen, optionally substituted phenyl, linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 2 oxo or optionally substituted phenyl, with the proviso that, when A is a σ bond with $R_1 = R_3 = R_6 = H$ and $R_2 = COOH$ then R_4 and R_5 together cannot form a cyclopentyl or a cyclohexyl, and when A is a radical of the formula

$-\underset{\displaystyle OR_7}{\overset{\displaystyle |}{CH}}-$ with $R_7 = H$ or $CH_3\overset{\displaystyle O}{\overset{\displaystyle ||}{C}}-$,then R_4 and R_5 must be

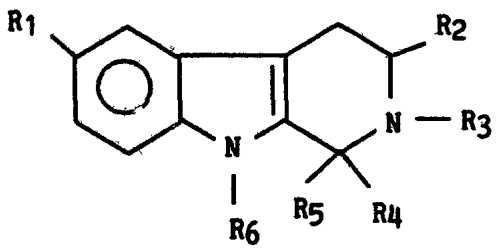
other than H,

- R_6 represents hydrogen or a linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 2 oxo or optionally substituted phenyl,

- R_7 represents hydrogen or a linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 3 oxo, halogen, alkoxy having 1 to 4 carbon atoms, cycloalkyl having 3 to 6 carbon atoms or optionally substituted phenyl,
- its isomers, diastereoisomers, enantiomers,
- its addition salt with a pharmaceutically-acceptable acid, or, in the case where R_2 is a carboxyl, with a pharmaceutically-acceptable base,

the term substituted associated in the previous definitions with the expressions phenyl, phenylalkyl, phenyloxycarbonyl and phenylcarbonyl means that the aromatic rings may be substituted with up to 3 linear or branched alkyl having 1 to 6 carbon atoms, alkoxy having 1 to 4 carbon atoms, hydroxyl, nitro, trifluoromethyl or halogen.

2. A compound as claimed in claim 1 selected from substituted indole of formula (I) for which A represents a σ bond, which corresponds to the 1,2,3,4- tetrahydro-β-carbolines of formula (II):

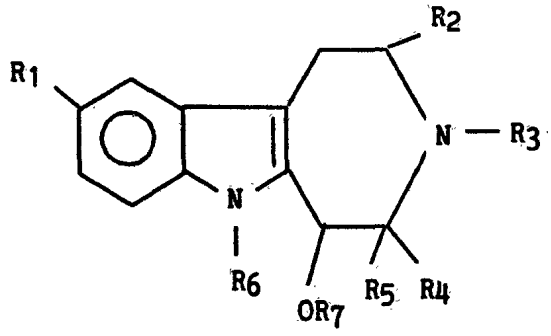


(II)

with R_1, R_2, R_3, R_4, R_5 and R_6 having the same meaning as in claim 1,

- its isomers, diastereoisomers, enantiomers,
- its addition salt with a pharmaceutically-acceptable acid or, in the case where R_2 is a carboxyl, with a pharmaceutically-acceptable base.

3. A compound as claimed in claim 1 selected from substituted indole of formula (I) for which A represents a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$, which corresponds to the 1,2,3,4,5,6-hexahydroazepino [4,5-b] indoles of formula (III):



(III)

with R_1, R_2, R_3, R_4, R_5, R_6 and R_7 having the same meaning as in claim 1,

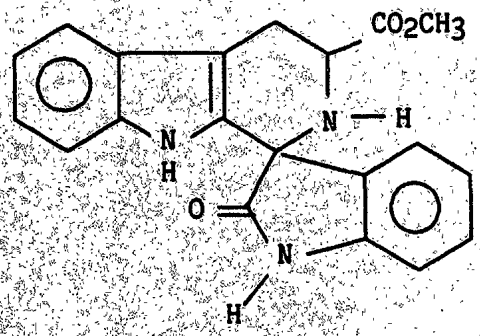
- its isomers, diastereoisomers, enantiomers,
- its addition salt with a pharmaceutically-acceptable acid or, in the case where R_2 is a carboxyl, with a pharmaceutically-acceptable base.

4. A compound as claimed in claim 1 selected from substituted indole of formula (I) with R_6 being hydrogen and R_3 being either hydrogen or linear or branched alkyl having 1 to 6 carbon atoms,

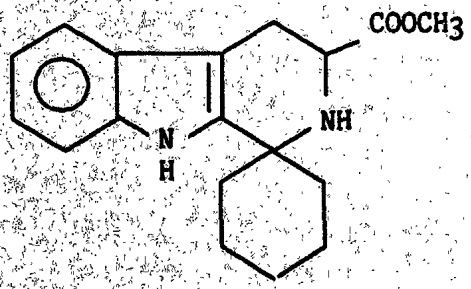
- its isomers, diastereoisomers and enantiomers,
- its addition salt with a pharmaceutically-acceptable acid or, in the case where R_2 is a carboxyl, with a pharmaceutically-acceptable base.

5. A compound as claimed in claim 1, which is [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-3'-[2-oxo-2,3-dihydroindole] having the below

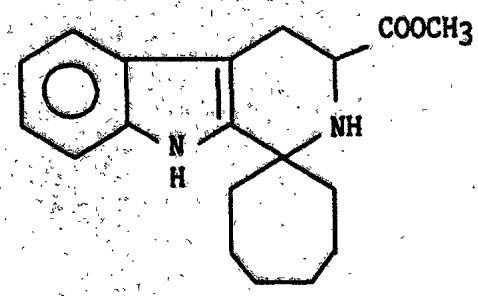
formula, or its isomers or an addition salt with a pharmaceutically-acceptable acid.



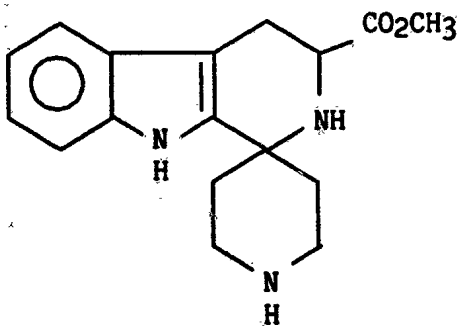
6. A compound as claimed in claim 1, which is [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane, having the below formula, or its isomers or an addition salt with a pharmaceutically-acceptable acid.



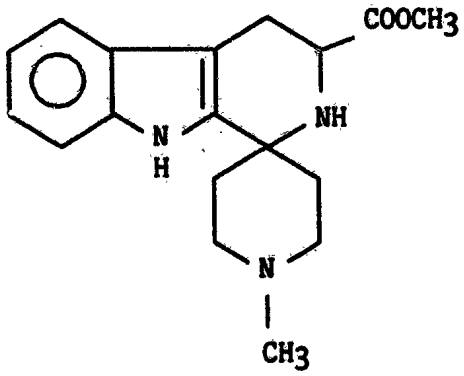
7. A compound as claimed in claim 1, which is [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β- carboline]-1-spirocycloheptane having the below formula, or its isomers or an addition salt with a pharmaceutically-acceptable acid



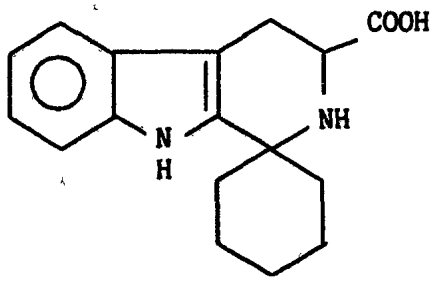
8. A compound as claimed in claim 1 which is [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β- carboline]-1-spiro-4'-piperidine having the below formula, or its isomers or an addition salt with a pharmaceutically-acceptable acid.



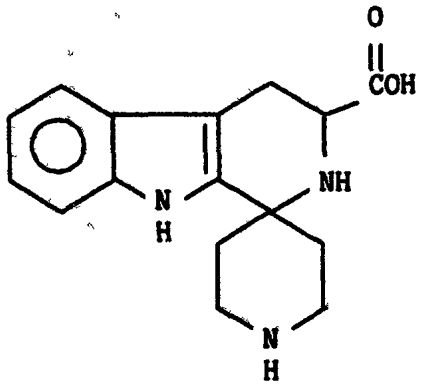
9. A compound as claimed in claim 1 which is [(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydro-β- carboline]-1-spiro-4'-[1'-methylpiperidine] having the below formula, or its isomers or an addition salt with a pharmaceutically-aceptable acid.



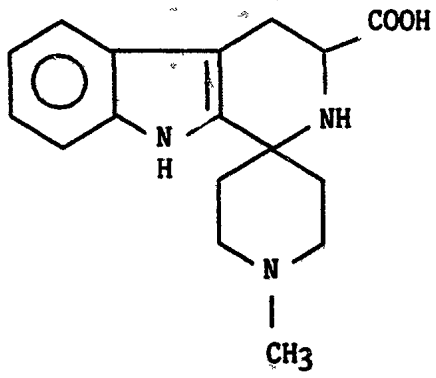
10. A compound as claimed in claim 1 which is [(3S)-3-carboxy-1,2,3,4-tetrahydro-β-carboline]- 1-spiro-4'-cyclohexane having the below formula, or its isomers or an addition salt with a pharmaceutically-acceptable acid or a pharmaceutically-acceptable base.



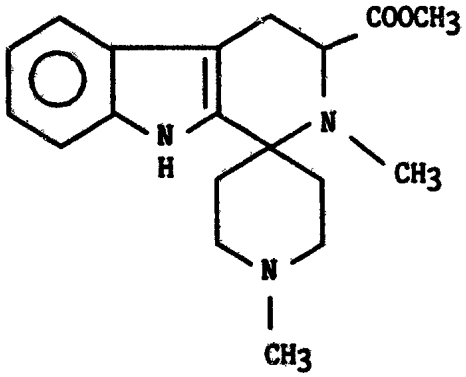
11. A compound as claimed in claim 1 which is [(3S)-3-carboxy-1,2,3,4-tetrahydro-β-carboline]- 1-spiro-4'-piperidine having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid or a pharmaceutically-acceptable base.



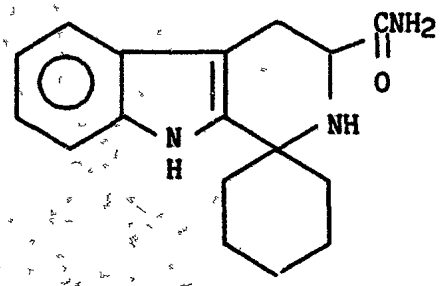
12. A compound as claimed in claim 1 which is [(3S)-3-carboxy-1,2,3,4-tetrahydro-β-carboline]- 1-spiro-4'-[1'-methylpiperidine] having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid or a pharmaceutically-acceptable base.



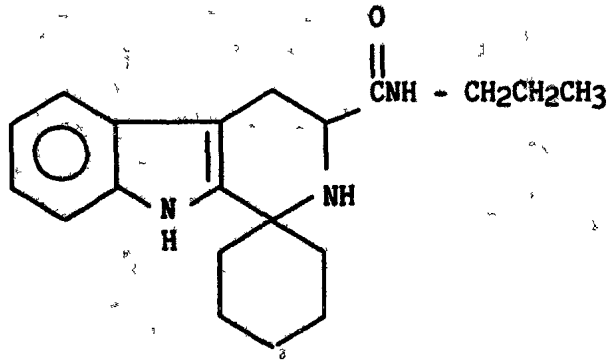
13. A compound as claimed in claim 1 which is [(3S)-3-methoxycarbonyl-2-methyl-1,2,3,4-tetrahydro-β-carboline]-1-spiro-4'-[1'-methylpiperidine] having the below formula or its isomers or an addition salt with a pharmaceutically-acceptable acid.



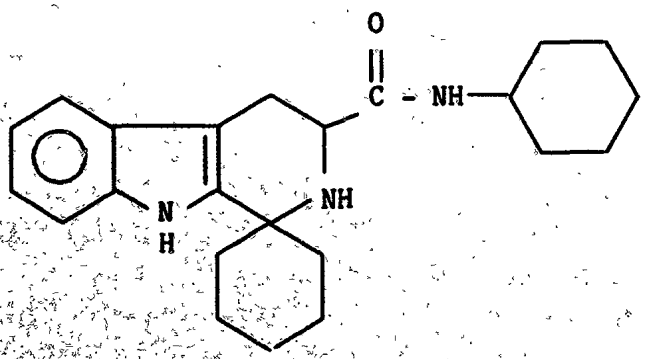
14. A compound as claimed in claim 1 which is [(3S)-3-carbamoyl-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid.



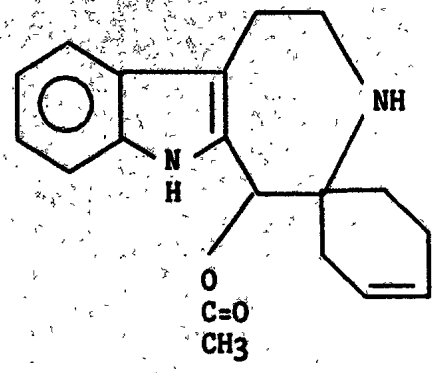
15. A compound as claimed in claim 1 which is [(3S)-3-(N-propylcarbamoyl)-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid.



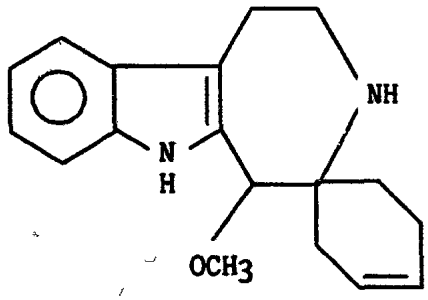
16. A compound as claimed in claim 1 which is [(3S)-3-(N-cyclohexylcarbamoyl)-1,2,3,4-tetrahydro-β-carboline]-1-spirocyclohexane having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid.



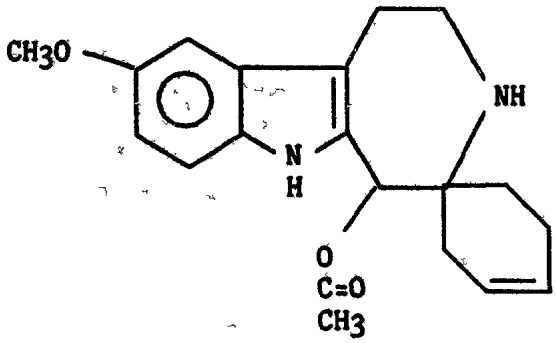
17. A compound as claimed in claim 1 which is [5-acetoxy-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole]-4-spiro-1'-(3'-cyclohexene) having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid.



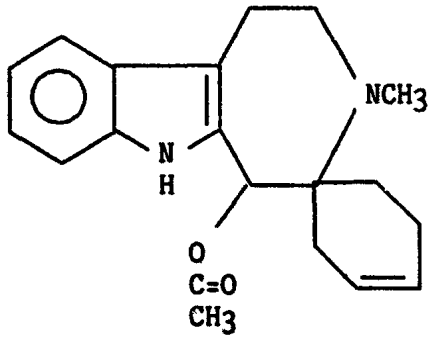
18. A compound as claimed in claim 1 which is [5-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole]-4-spiro-1'-(3'-cyclohexene) having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid.



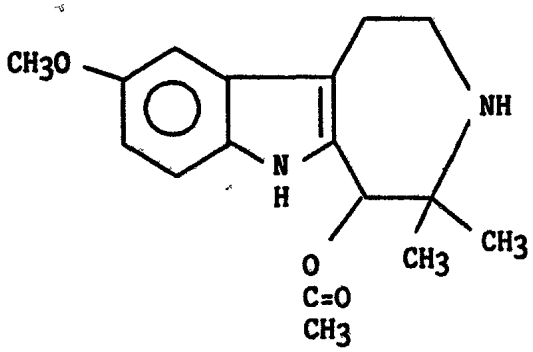
19. A compound as claimed in claim 1 which is [5-acetoxy-9-methoxy-1,2,3,4,5,6-hexahydroazepino [4,5-b] indole]-4-spiro-1'-(3'-cyclohexene) having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid.



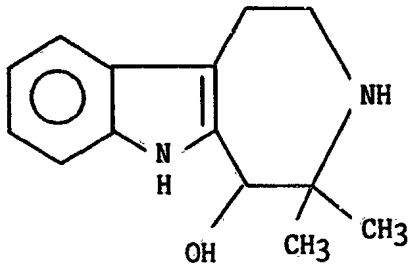
20. A compound as claimed in claim 1 which is [5-acetoxy-3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b] indole] -4- spiro-1'-(3'-cyclohexene) having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid.



21. A compound as claimed in claim 1 which is 5-acetoxy-9-methoxy-4,4-dimethyl-1,2,3,4,5,6- hexahydro-azepino [4,5-b] indole having the below formula, or its isomers, or an addition salt with a pharmaceutically-acceptable acid

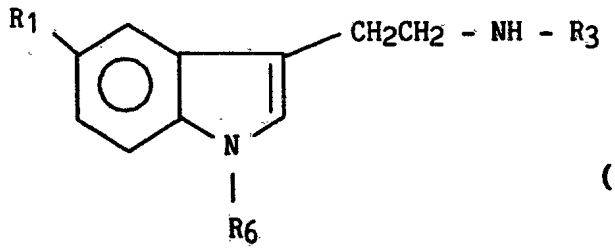


22. A compound as claimed in claim 1 which is 5-hydroxy-4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b] indole having the below formula, or its isomers, or an addition salt with a pharmaceutically-accepable acid.



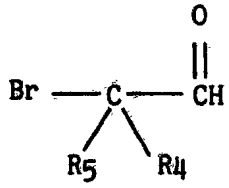
23. A process for preparing a compound of claim 1, which varies according to the nature of the group A,

- either a substituted tryptamine of general formula (IV):



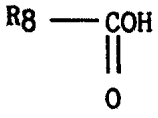
(IV)

in which R_1, R_3 and R_6 have the same meaning as in the compound of general formula (I), is reacted with an aldehyde of general formula (V):



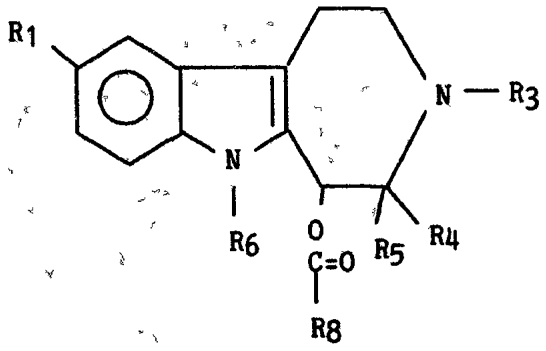
(V)

in which R_5 and R_4 have the same meaning as in the compound of general formula (I), by heating them in an organic acid of general formula (VI):



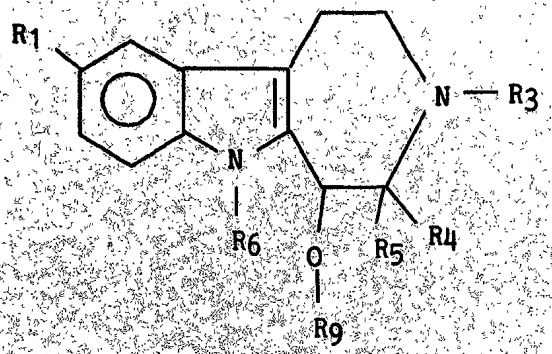
(VI)

in which R_8 is a methyl, ethyl or trifluoromethyl group, so as to obtain the 1,2,3,4,5,6-hexahydroazepino[4,5-b]indole of general formula (VII):



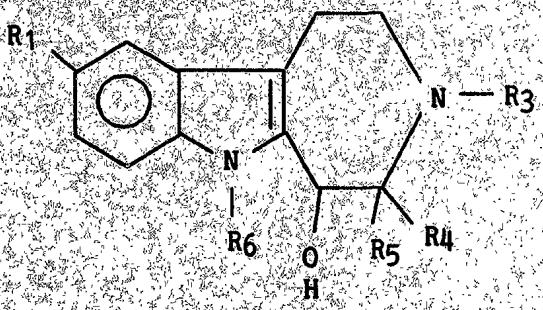
(VII)

in which R_1, R_3, R_4, R_5 and R_6 have the same meaning as in the compound of general formula (I) and R_8 the same meaning as in the acid (VI), which can be either heated with an alcohol of general formula R_9OH, in which R_9 is a lower alkyl group, branched or otherwise, having 1 to 6 carbon atoms or an aralkyl group, so as to obtain the 1,2,3,4,5,6-hexahydroazepino[4,5-b]indole of general formula (VIII):



(VIII)

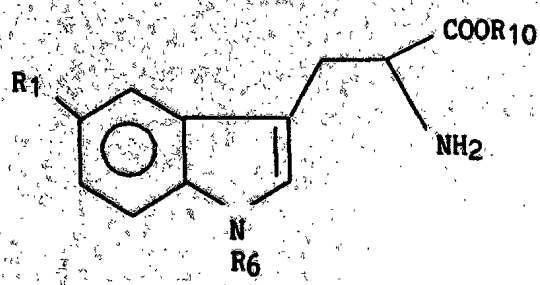
in which R_1, R_3, R_4, R_5 and R_6 have the same meaning as in the compound of general formula (I) and R_9 the same meaning as above, or heated in methanol in the presence of 10 equivalents of potassium carbonate so as to obtain the 1,2,3,4,5,6-hexahydroazepino[4,5- b]indole of general formula (IX):



(IX)

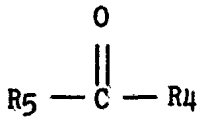
in which R_1, R_3, R_4, R_5 and R_6 have the same meaning as in the compound of general formula (I),

- or a substituted tryptophan of general formula (X):



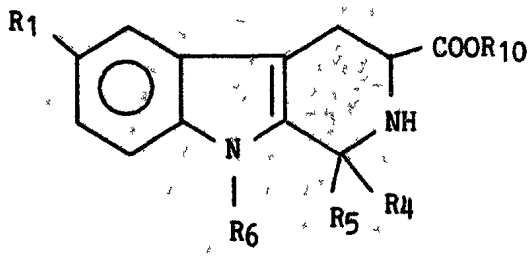
(X)

in which R_1 and R_6 have the same meaning as in the compound of general formula (I) and R_{10} is a lower alkyl, branched or otherwise, having 1 to 6 carbon atoms or an optionally substituted aryl or aralkyl group, is reacted with a ketone of general formula (XI):



(XI)

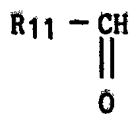
in which R_4 and R_5 have the same meaning as in the compound of general formula (I), under a nitrogen atmosphere, either in toluene or benzene under reflux in the presence of para-toluenesulfonic acid, the water formed during the condensation being removed by means of a water-extraction apparatus which can be, for example, a Dean and Stark apparatus, or, in some cases, under reflux of methanol or of the ketone itself, so as to obtain, after purification, the β-carboline of general formula (XII):



(XII)

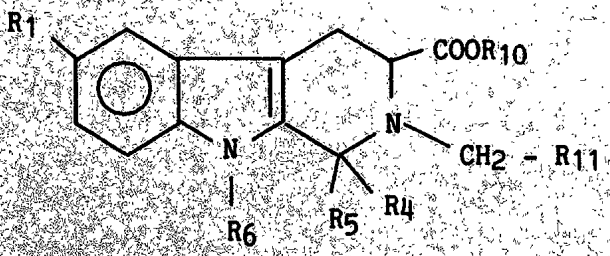
in which R_1, R_4, R_5, R_6 and R_{10} have the same meaning as in the compounds of general formulae (I) and (X), which can be:

- either reacted under reductive amination conditions with an aldehyde of general formula (XIII):



(XIII)

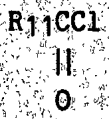
in which R_{11} is a hydrogen atom or a lower alkyl group, branched or otherwise, having 1 to 6 carbon atoms and optionally substituted with one or more halogen atoms, lower alkoxy groups having 1 to 4 carbon atoms or aryl groups, substituted or otherwise, so as to obtain the β-carboline of general formula (XIV):



(XIV)

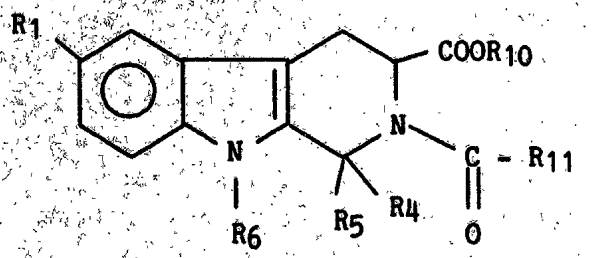
in which R_1, R_{10}, R_{11}, R_4, R_5 and R_6 have the same meaning as in the compounds of general formula (XII) and (XIII),

- or reacted with an acid chloride, or the corresponding acid anhydride, of general formula (XV):



(XV)

in which R_{11} has the same meaning as in the compound of general formula (XIII) so as to obtain the β-carboline of general formula (XVI):

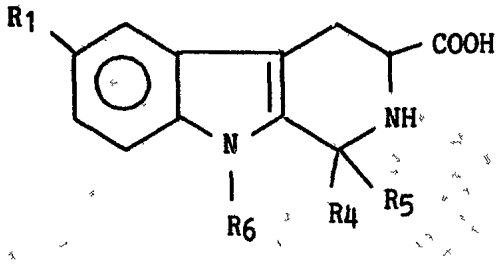


(XVI)

in which R_1, R_{10}, R_{11}, R_6, R_5 and R_4 have the same meaning as in the compound of general formula (XIV),

- or reacted, in the case where $R_{10} = CH_3$, with

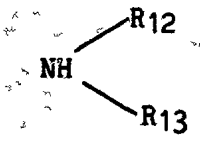
aqueous barium hydroxide solution so as to obtain the acids of general formula (XVII):



(XVII)

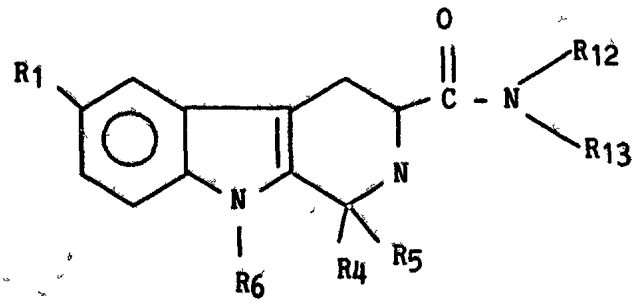
in which R_1, R_4, R_5 and R_6 have the same meaning as in the compounds of general formula (I),

- or reacted, in the case where $R_{10} = CH_3$, with an amine of general formula (XVIII):



(XVIII)

in which R_{12} and R_{13} represent, each independently of one another, a hydrogen atom or lower alkyl groups, branched or otherwise, having 1 to 6 carbon atoms or cycloalkyl groups having 4 to 7 carbon atoms, so as to obtain the amides of general formula (XIX):



(XIX)

in which R_1, R_4, R_5 and R_6 have the same meaning as in the compounds of general formula (I) and R_{12} and R_{13} the same meaning as in the amides of general formula (XVIII).

24. A pharmaceutical composition containing as active principle a compound as claimed in claim 1, alone or in combination with one or more pharmaceutically acceptable, non-toxic, inert excipients or vehicles.

25. A method of treating a mammal afflicted with a disorder selected from a disorder of the central nervous system, memory, pain, inflammation, stroke and convulsions comprising the step of administering to the said mammal an amount of a compound as claimed in claim 1 which is effective for alleviation of said disorder.

DATED THIS 9TH DAY OF FEBRUARY, 1993

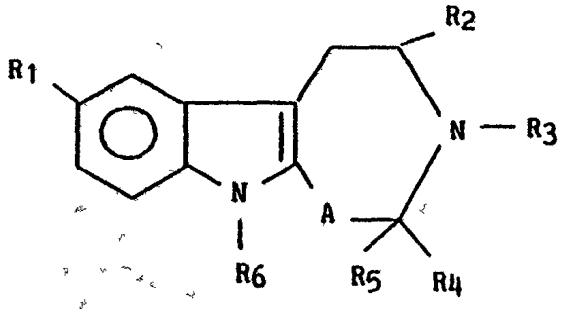
ADIR ET COMPAGNIE

WATERMARK PATENT & TRADEMARK ATTORNEYS
THE ATRIUM
290 BURWOOD ROAD
HAWTHORN VICTORIA 3122
AUSTRALIA

LCG:CJH:JC
DOC 30: AU7929391.WPC

ABSTRACT

A compound selected from substituted indole of formula (I):



(I)

in which:

- A represents a σ bond or a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$,
- R_1 represents hydrogen, halogen, hydroxyl, linear or branched alkoxy having 1 to 4 carbon atoms, linear or branched alkyl having 1 to 6 carbon atoms optionally substituted with up to 3 halogen, oxo, hydroxyl or alkoxy having 1 to 4 carbon atoms,
- R_2 represents carboxyl, linear or branched alkoxycarbonyl having 1 to 6 carbon atoms and optionally substituted with optionally substituted phenyl; phenyloxycarbonyl, substituted phenyloxycarbonyl, carbamoyl, carbamoyl substituted on the nitrogen with up to 2 linear or branched alkyl having 1 to 6 carbon atoms or cycloalkyl having 4 to 7 carbon atoms; and in the case where A is a radical of the formula $-\underset{\underset{OR_7}{|}}{CH}-$, R_2 can also be hydrogen,
- R_3 represents hydrogen, linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 3 halogen, oxo, linear or branched alkoxy

having 1 to 4 carbon atoms or optionally substituted phenyl,

- R_4 and R_5 together form a saturated or unsaturated 5- to 12-membered mono- or bicyclic ring-system which can comprise in the ring skeleton from 0 to 3 hetero atoms selected from oxygen, nitrogen and sulfur and which can optionally be substituted with up to 3 oxo, linear or branched alkyl having 1 to 6 carbon atoms, optionally substituted phenyl, phenylcarbonyl, substituted phenylcarbonyl, optionally substituted phenylalkyl having 7 to 9 carbon atoms, optionally substituted fluorene, with, in the case where R_4 and R_5 form a bicyclic system, the possibility that one of the rings is an optionally substituted aromatic ring, and in the case where A is a radical of the formula $-\underset{\displaystyle OR_7}{\overset{\displaystyle |}{CH}}-$, R_4 and R_5 can also represent,

each independently of one another, hydrogen, optionally substituted phenyl, linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 2 oxo or optionally substituted phenyl, with the proviso that, when A is a σ bond with $R_1 = R_3 = R_6 = H$ and $R_2 = COOH$ then R_4 and R_5 together cannot form a cyclopentyl or a cyclohexyl, and when A is a radical of the formula

$-\underset{\displaystyle OR_7}{\overset{\displaystyle |}{CH}}-$ with $R_7 = H$ or $CH_3\overset{\displaystyle O}{\overset{\displaystyle ||}{C}}-$, then R_4 and R_5 must be

other than H,

- R_6 represents hydrogen or a linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 2 oxo or optionally substituted phenyl,

- R_7 represents hydrogen or a linear or branched alkyl having 1 to 6 carbon atoms and optionally substituted with up to 3 oxo, halogen, alkoxy having 1 to 4 carbon atoms, cycloalkyl having 3 to 6 carbon atoms or optionally substituted phenyl,

- its isomers, diastereoisomers, enantiomers,

- its addition salt with a pharmaceutically-acceptable acid, or, in the case where R_2 is a carboxyl, with a pharmaceutically-acceptable base,

the term substituted associated in the previous definitions with the expressions phenyl, phenylalkyl, phenyloxycarbonyl and phenylcarbonyl means that the aromatic rings may be substituted with up to 3 linear or branched alkyl having 1 to 6 carbon atoms, alkoxy having 1 to 4 carbon atoms, hydroxyl, nitro, trifluoromethyl or halogen.