

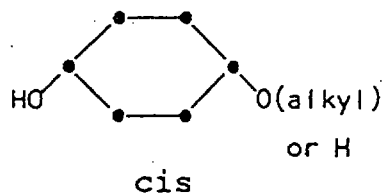
Compounds of Formula (III), wherein R¹ is other than H, are central or peripheral serotonin 5HT₂ receptor antagonists. Compounds wherein R¹ is H are primarily useful as intermediates.

Groups which R represents include methyl, ethyl, allyl, n-propyl, isopropyl, crotyl, methallyl, n-hexyl, sec-amyl, sec-octyl, n-heptyl, 2,4-dimethyl-pentyl, 2-ethylpentyl, cyclopropyl, cyclopropylmethyl, cyclopentyl methyl, 2-cyclobutyl ethyl, cyclohexyl, isobutyl, sec.-butyl, 3-methyl-2-butyl, isoamyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl(isohexyl), 2-hexyl, 3-hexyl, n-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, n-octyl, 2-octyl, 3-octyl, 4-octyl, isooctyl, 2-methylheptyl, 3-methyl-2-heptyl, and the like. Illustrative of the groups which R² represents include 4-methoxycyclohexyl, 3-ethoxycyclohexyl, 3-methoxycyclopentyl, 3-methoxycycloheptyl, 3-n-propoxycycloheptyl, 3-ethoxycyclopentyl, 4-isopropoxycyclohexyl, 2-methoxycycloheptyl 2-oxopropyl, 1-methyl-2-oxopropyl, 1-ethyl-2-oxopropyl, 1-methyl-2-oxobutyl, 1-ethyl-2-oxobutyl, 1-methyl-3-oxobutyl, 1-ethyl-3-oxobutyl, cyclohexyl, 3-ketocyclohexyl, cyclopentyl, 3-ketocycloheptyl, cycloheptyl, 3-ketocyclopentyl, 4-ketocyclohexyl, 2-ketocycloheptyl.

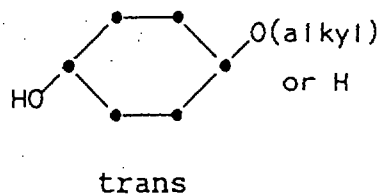
Compounds according to the above formula are named as ergoline derivatives in which the trans(-) or 5R,10R configuration of the bridgehead hydrogens is specified (The same configuration as in the naturally-occurring 9,10-dihydro ergot alkaloids). In United States Patent 3,580,916, a different naming system is used; the basic ring system is named as a 6aR,10aR-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-f,g]-quinoline. Illustratively, by the alternate naming system 9,10-dihydrolysergic acid becomes 6aR,10aR-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-f,g]quinoline-9β-carboxylic acid. Another equally valid name for dihydrolysergic acid is 6-methyl-8β-carboxyergoline. The trivial name "ergoline" is used herein with the numbering system specified in (III) above for compounds in which R¹ is other than methyl and the 9,10-dihydrolysergic acid nomenclature for 6-methyl derivatives.

In addition, in 9,10-dihydrolysergic acid, the C-8 carboxyl is beta or R. Thus, again using the ergoline naming system, derivatives of 9,10-dihydrolysergic acid become derivatives of 5R,3R,10P(or 5β,8β,10α) 6-methylethylergoline-8β-carboxylic acid.

While the configuration at asymmetric carbons 5,8 and 10 in Formula (III) is set (5β,8β and 10α), generally speaking, the alkoxyalkyl ester group (or hydroxycycloalkyl group) contains two additional asymmetric carbons. For example, 3-methoxycyclohexanol exists as two racemates, each racemate containing two enantiomers or stereoisomers. However, where the alkoxyalkyl ester group (or hydroxycycloalkyl group) possesses a plane of symmetry, as in a 4-alkoxycyclohexanol, mirror images turn out to be superimposable, and the compound actually exists in only two forms. These forms are designated as the cis form and the trans form, drawn for convenience in two dimensions as (IVa) and (IVb).



(IVa)



(IVb)

When a monoester of a 1-substituted-9,10-dihydrolysergic acid is formed with a cis or trans 4-alkoxycycloalkanol, the product will be a single geometrical isomer. In general, the two esters in this instance will also be named, for the sake of simplicity, as cis and trans 4-alkoxycyclohexyl (or 4-hydroxycycloalkyl) esters.

This invention contemplates all such forms useful as peripheral serotonin antagonists; that is, the individual diastereoisomers and geometrical isomers as well as racemates.

Preferred compounds of the invention include those having one or more of the following features:

- (A) R² is C₁-C₃ alkoxy-C₅-C₇ cycloalkyl;
- (B) R² is C₅-C₇ cycloalkyl or keto-substituted C₅-C₇ cycloalkyl;
- (C) R² is C₃-C₇ ketoalkyl;
- (D) R¹ is methyl;
- (E) R² is trans 4-methoxycyclohexyl;
- (G) R is isopropyl;

Pharmaceutically-acceptable acid addition salts of the compounds of Formula (III) include salts derived

from non-toxic inorganic acids such as: hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydriodic acid, phosphorous acid and the like, as well as salts derived from non-toxic organic acids such as aliphatic mono and dicarboxylic acids, phenyl-substituted alkanolic acids, alkanolic and alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such pharmaceutically-acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, fluoride, acetate, propionate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methoxybenzoate, phthalate, terephthalate, benzenesulfonate, toluenesulfonate, chlorobenzenesulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycollate, malate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate and the like salts.

Illustrative compounds of this invention include:

- 1-methyl-6-ethyl-8 β -(2-methoxy)cyclopentylloxycarbonylsergoline hydrochloride
- 1-n-propyl-6-allyl-8 β -(3-ethoxy)cycloheptyloxycarbonylsergoline sulfate
- 4-methoxycyclohexyl 1-methyl-9,10-dihydrolysergic acid phosphate
- 3-methoxycyclohexyl 1-n-octyl-9,10-dihydrolysergic acid maleate
- 1-isopropyl-6-n-propyl-8 β -(2-n-propoxy)cyclohexylloxycarbonylsergoline hydrobromide
- 1-allyl-6-ethyl-8 β -(4-ethoxy)cycloheptyloxycarbonylsergoline succinate
- 1,6-diethyl-8 β -(2-keto)propylloxycarbonylsergoline succinate
- 1-methyl-6-ethyl-8 β -(1-methyl-2-keto)butylloxycarbonylsergoline hydrochloride
- 1,6-diethyl-8 β -cyclohexylloxycarbonylsergoline succinate
- 1-methyl-6-ethyl-8 β -cyclopentylloxycarbonylsergoline hydrochloride
- 1-n-propyl-6-allyl-8 β -cycloheptyloxycarbonylsergoline sulfate
- 1-isopropyl-6-n-propyl-8 β -(2-oxo)cyclohexylloxycarbonylsergoline hydrobromide
- 1-allyl-6-ethyl-8 β -(4-oxo)cycloheptyloxycarbonylsergoline tartrate
- 1-n-propyl-6-allyl-8 β -(1-ethyl-3-keto)butylloxycarbonylsergoline sulfate
- 1-isopropyl-6-n-propyl-8 β -(1-methyl-2-keto)-propylloxycarbonylsergoline hydrobromide
- 3-oxobutyl 1-methyl-9,10-dihydrolysergic acid
- 4-oxopentyl 1-ethyl-9,10-dihydrolysergic acid
- 1-methyl-4-oxopentyl 1-allyl-9,10-dihydrolysergic acid
- 1-allyl-6-ethyl-8 β -(3-keto)butylloxycarbonylsergoline tartrate and the like.

The preparation of compounds represented by Formula (III) above can be accomplished by the general method of United States Patent 3,580,916. According to this procedure, dihydrolysergic acid is first alkylated on the indole nitrogen using standard procedures, e.g., base plus an alkyl halide. Liquid ammonia is a convenient solvent with sodamide as the base and primary or secondary C₁-C₈ alkyl, C₃-C₈ cycloalkyl or C₃-C₆ substituted C₁-C₅ primary or secondary alkyl iodide or a C₂-C₄ alkenyl chloride or bromide as the alkylating agent. (See also United States Patent 3,183,234, which contains general directions and a specific example of the above alkylation procedure).

An alternate indole-N-alkylation procedure whereby an arylsulfonate is used in the presence of an alkali metal hydroxide is more fully described in United States Patent 4,734,501. According to this procedure, for example, an arylsulfonate of the structure R-O-SO₂-phenyl-Y, wherein arylsulfonate of the structure R-O-SO₂-phenyl-Y, wherein Y is H, 4-CH₃, 4-Br, or 4-NO₂, can be reacted with 9,10-dihydrolysergic acid in an aprotic solvent, conveniently DMSO, in the presence of sodium or potassium hydroxide, to yield the desired 1-N-alkylated product.

With the indole nitrogen substituent in place, the next step in the synthetic procedure is esterification. This procedure requires relatively mild reaction conditions as noted in United States patent 3,580,916. The reaction is an otherwise standard acid-catalyzed esterification. The free acid prepared above and compounds of formula R²OH are the reactants and a convenient work-up of the esterification mixture involves partitioning between water and a water-immiscible solvent; [(ethylene dichloride)/H₂O], for example.

A preferred procedure, utilizing a further aspect of this invention, is to use a novel synthetic step whereby the free 9,10-dihydrolysergic acid is reacted with a sulfonate of the formula R²-O-SO₂-Z, wherein Z is C₁-C₃ alkyl, phenyl or substituted phenyl wherein said substituents can be lower alkyl (CH₃, C₂H₅), nitro, halo(Br, Cl), alkoxy (CH₃O) and the like, in the presence of excess potassium carbonate or similar base in an aprotic solvent. The tosylate ester is preferred. The quantity of base must be sufficient to form a salt with the lysergic acid carboxyl group plus sufficient excess to scavenge any sulfonic acid by-product. This process is applicable to the preparation of alkoxyalkyl esters, cycloalkyl and ketocycloalkyl esters, and in fact is generally applicable to the preparation of carbocyclic acid esters of C₅-C₇ cycloalkanols.

Procedures hitherto available for the preparation of such esters have given low yields, and in some instances, esterification was not observed--see Shaw et al., *J. Org. Chem.*, **43**, 1017 (1978) **39**, 1968 (1974), Sowinski et al, *ibid*, **44**, 2369 (1979), Pfeffer et al *Tetrahedron Letters*, 4063 (1972) or Liotta et al, *ibid*, 2417 (1974).

- 5 An alternative procedure for the preparation of compounds of Formula (III) wherein R² is C₃-C₆ keto-alkyl involves the acid-catalyzed esterification of the N-alkylated dihydrolysergic acid with an alcohol of formula R⁵OH, wherein R⁵ is a C₃-C₆ hydroxyalkyl group



- 15 wherein R⁹ is as defined above and R¹² is a C₂-C₅ alkyl group containing a secondary hydroxy group). As noted above, a convenient workup of the esterification product involves partitioning between water and a water-immiscible solvent.

- Next, the secondary alcohol group of the ester can be oxidized to the ketone, yielding the ketoalkyl esters of this invention where R¹ is methyl (esters of 9,10-dihydrolysergic acid). It should be noted that, if the alkanediol (R⁵OH) is not symmetrical, the resulting ester may be a mixture; ie., if the diol is 1-ethyl-2-hydroxypropanol, a mixture of the 1-ethyl-2-hydroxypropyl and 1-methyl-2-hydroxybutyl esters will result. These esters can be separated mechanically, or the mixture can be oxidized and the keto esters separated. However, since differences in pharmacologic activity between any two such isomeric esters would not be expected to be large (less than an order of magnitude), the mixture could be employed as such. However, it will be apparent that use of a symmetrical diol such as butane-2,3-diol would be preferred since its use
- 20
- 25 would avoid the aforesaid isomer problem. However, if the diol contains a primary alcohol, reaction conditions can be employed which favor reaction on the primary alcohol group; for example secondary alcohols typically react more slowly than primary alcohols in a standard acid-catalyzed esterification.

- Suitable oxidizing agents for the final step include acetic anhydride/DMSO, dicyclohexylcarbodiimide, chromate salts, positive halogen agents such as Ca(OCl)₂, NaOCl and the like.

- 30 If the desired final product is not a 9,10-dihydrolysergic acid ester (ie; not a 1-R-6-methylergoline-8β-carboxylic acid ester), but is a 6-ethyl, 6-n-propyl, 6-n-butyl, 6-allyl or the like derivative, the replacement of the 6-methyl group may take place prior to the final esterification. In this procedure, a lower alkyl (methyl or ethyl) ester of a 1-R-9,10-dihydrolysergic acid can be conveniently utilized. Replacement of the 6-methyl group with ethyl, n-propyl, allyl, n-amyl, n-butyl, n-hexyl, or the like, can then be carried out by the procedure of Kornfeld and Bach, United States Patent 4,166,182, whereby the N-methyl group is reacted
- 35
- 40 with cyanogen bromide to form an N-cyano derivative. The cyano group can be removed by hydrogenation using zinc dust and hydrochloric acid. Alternatively, basic hydrolysis can be used. Either procedure provides a secondary amine group at 6, but also a free 8β-carboxylic acid, because the hydrolysis also saponifies the 8β-lower alkyl ester group. Next, re-esterification with the desired R²OH alkanol can be carried out followed by alkylation or allylation at N-6 using an allyl chloride or alkyl iodide in the presence of base, conveniently in DMF (dimethylformamide).

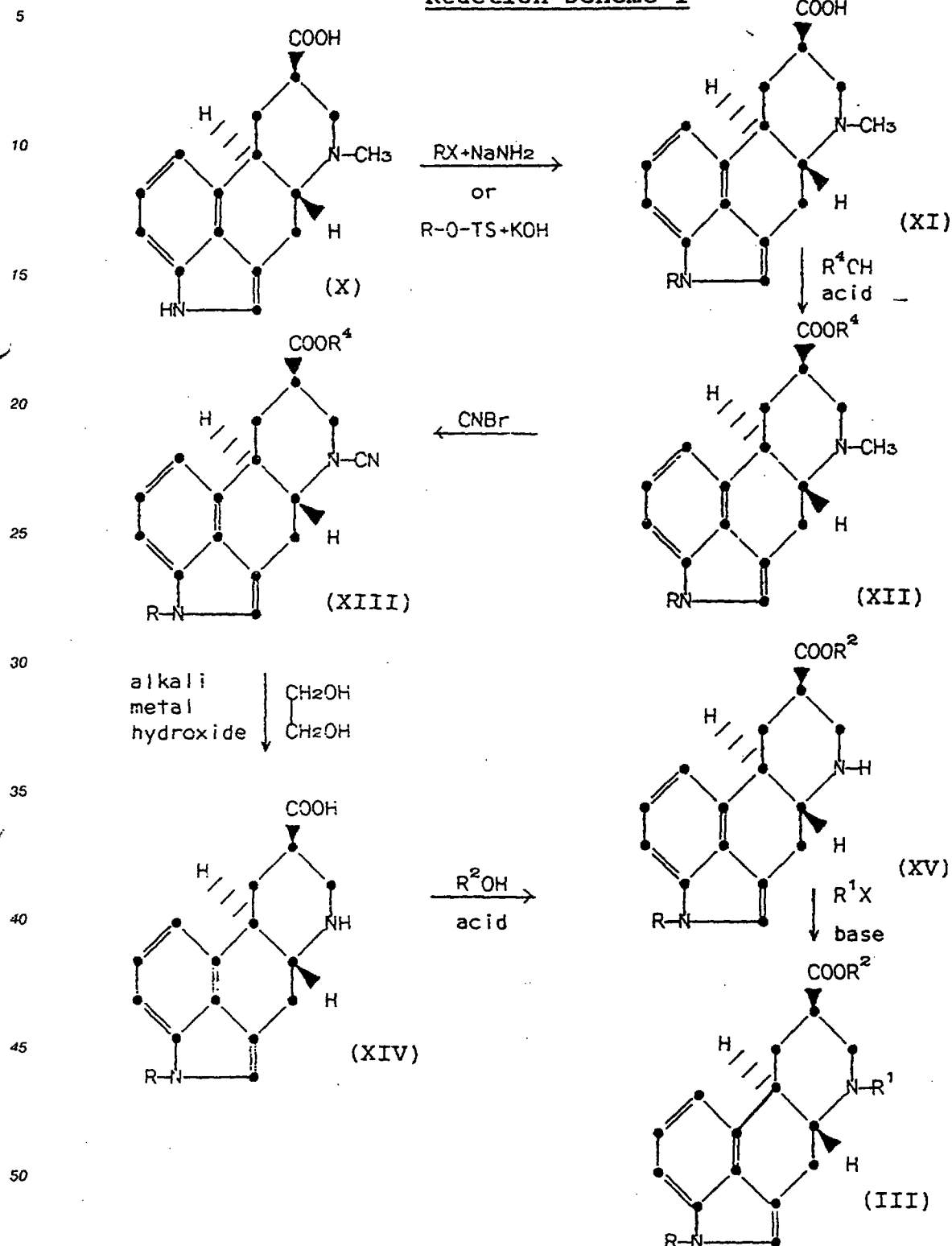
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This procedure is graphically illustrated in Reaction Scheme 1 below.

Reaction Scheme 1



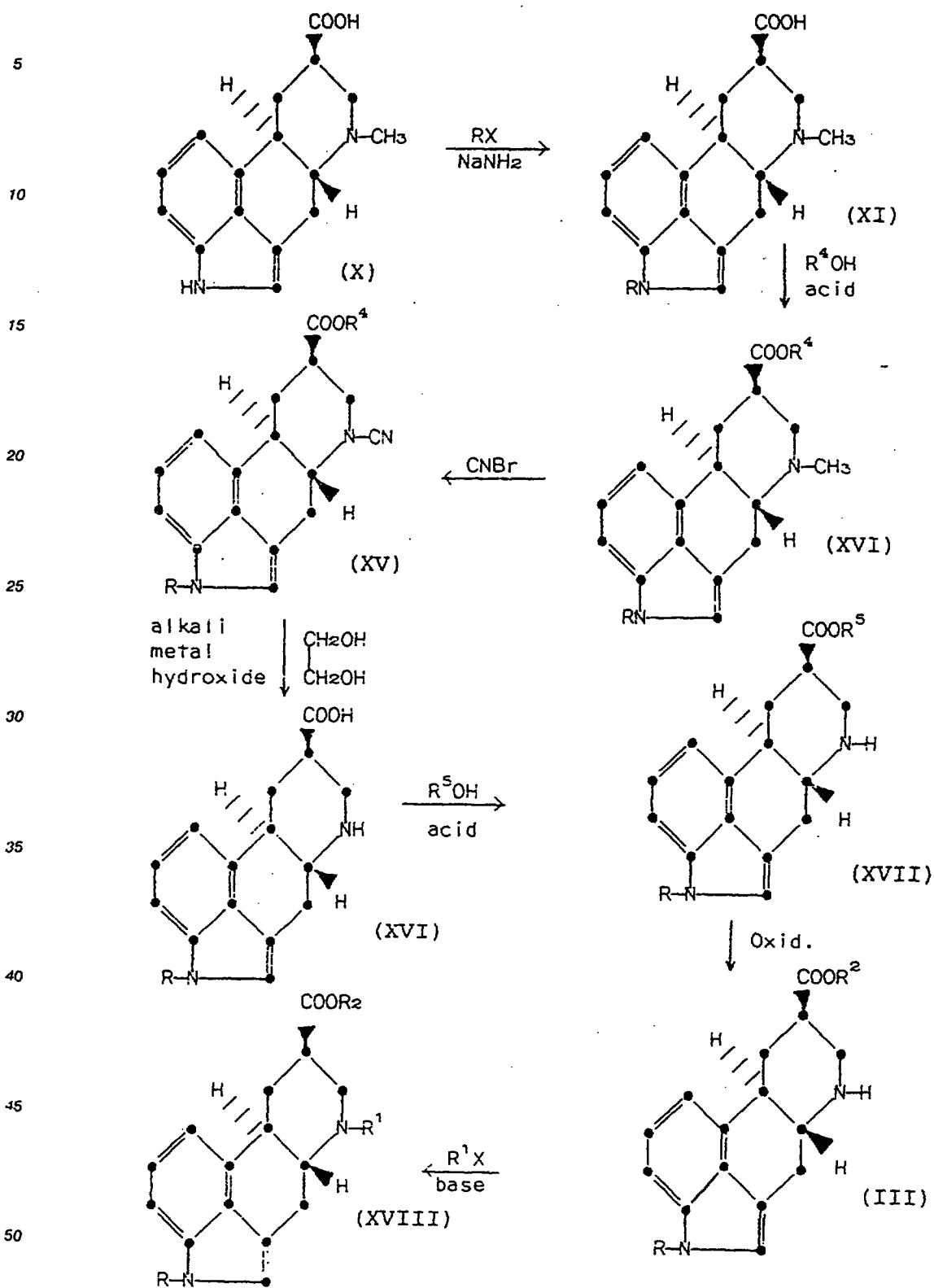
More specifically, in the above Reaction Scheme 1, 9,10-dihydrolysergic acid (X) is alkylated on the indole nitrogen with an alkyl (C_1 - C_8 alkyl) halide, a C_2 - C_4 alkenyl- CH_2 halide, a C_3 - C_6 cycloalkyl halide or a C_3 - C_6 cycloalkyl- C_1 - C_5 alkyl halide, using a strong base such as sodamide to create the reactive anion or

preferably using an aryl sulfonate such as a p-tosylate in the presence of potassium hydroxide in DMSO. The N¹ product (XI) is then esterified with a lower alkanol R⁴OH (a C₁-C₂ alkanol preferably) to yield the 1-R ester (XII). This intermediate is then reacted with CNBr by standard procedures to replace the methyl group and form an 6-cyano derivative (XIII). Removal of the cyano group under the preferred basic conditions yields a 1-substituted-9,10-dihydro-6-desmethylysergic acid (XIV), because the basic conditions also saponifies the C-8 ester group. Next, the 1-R-6-desmethyldihydrolysergic acid is re-esterified with a compound of formula R²OH or a tosyl ester thereof to yield the N⁶-desmethyl ester (XV). The piperidine ring nitrogen (N⁶) is then realkylated with a C₁-C₄ alkyl or allyl halide in the presence of base under standard conditions to yield the compounds of this invention (III).

It might seem redundant to realkylate at N⁶ with a methyl group since that group is present in the 9,10-dihydrolysergic acid starting material. However, this process would enable one to insert a radiolabeled (C¹⁴ or H³) methyl group suitable for metabolic studies.

The alternative procedure for preparation of the compounds of Formula (III) wherein R² is C₃-C₆ ketoalkyl, is more specifically outlined below in Reaction Scheme 2:

Reaction Scheme 2



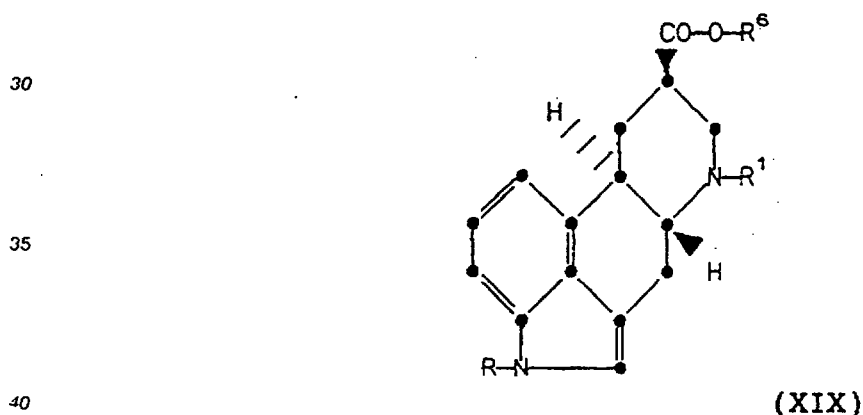
wherein R^4 is C_1 - C_2 alkyl, R^1 and R are as previously defined and R^5 is hydroxy C_3 - C_6 alkyl in which the hydroxyl group is a secondary hydroxyl group.

In Reaction Scheme 2, 9,10-dihydrolysergic acid (X) is alkylated on the indole nitrogen with an R -hal where "hal" is a halide such as I, Cl, or Br, using a strong base such as sodamide to create the reactive anion. Alternatively, an aryl sulfonate, $R-O-SO_2$ -phenyl-Y, can be reacted with the indole nitrogen in the

presence of an alkali metal halide in an aprotic solvent. The N-1 alkyl or allyl product (XI) is then esterified with a lower alkanol R^4OH (a C_1-C_2 alkanol preferably) to yield the N-1 alkylated ester (XIV). This compound is then reacted with $CNBr$ by standard procedures to replace the N-6 methyl group and form an N-cyano derivative (XV). Removal of the cyano group under the preferred basic conditions yields a 1-R-9,10-dihydro-6-desmethylysergic acid (XVI), because the basic conditions also saponifies the C-8 ester group. Next, the 1-R-6-desmethyldihydrolysergic acid (or 1-R-8 β -carboxyergoline) is re-esterified with a desired alkanediol (R^5OH) to yield the N-6-desmethyl ester (XVII). The secondary hydroxyl in the side chain is now oxidized to a ketone group to yield an ergoline ketoalkyl ester (XVIII). The piperidine ring nitrogen (N-6) is then realkylated with a C_1-C_4 alkyl or allyl halide and base under standard conditions to yield the compounds of Formula (III) wherein R^2 is C_3-C_6 ketoalkyl.

The above procedure is particularly useful where the esterifying alcohol R^5OH is symmetrical. Alternate procedures are available for the preparation of ketoalkyl esters of 1-alkyl or allyl-9,10-dihydrolysergic acid and related N-6 homologues whereby a keto alcohol is used directly to yield a compound according to III. Alternatively, a "protected" C_3-6 keto alcohol can be used to form the ester; i.e., a ketal of 2-keto propanol can be formed with ethylene glycol. The primary hydroxyl can then be replaced by chloro (using $SOCl_2$) and the ketal chloride reacted with the sodium salt of the 1-R-9,10-dihydrolysergic acid. The ketal protecting group is removed by treatment with acid. Obviously, the usual acid catalyzed esterification could not be used with an ketalalkanol because the ketal group would come off during such esterification and alternate procedures available in the art should be used. Also, if it is desirable to avoid an acid catalyzed reaction with a ketoalkanol, a carboxy activating group can be employed to form the ester under non-acidic conditions; i.e., acid chloride or bromide with base. Also carboxy activating agents such as carbodiimide and azolide N,N'-carbonylimidazole can be employed.

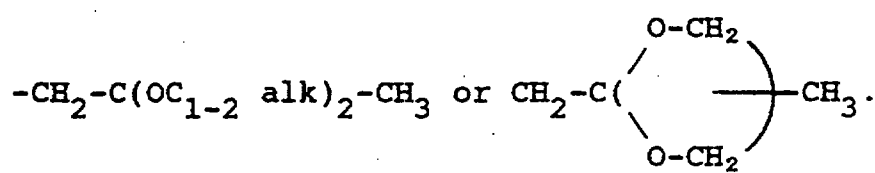
Alternatively, a keto alcohol in which the ketone group is protected, as by ketal formation, can be employed in the esterification procedure in Reaction Scheme 2, to yield an ergoline ester lacking an N-6 substituent, analogous to Formula (XVII). Alkylation or allylation at N-6 then yields a further intermediate containing an ester with a protected keto group: (XIX)



wherein R^5 is a C_3-C_6 protected keto alkyl



wherein R^9 has its previous meaning and R^{11} is C_2-C_5 alkyl containing a protected keto function; for example



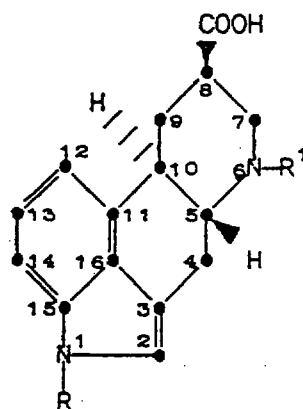
Treatment of (XIX) with acid then removes the protecting group to yield a ketoalkyl ester of a 1-substituted-9,10-dihydrolysergic acid or a 1-substituted-6-alkyl (or allyl) ergoline-8 β -carboxylic acid.

The C₃-C₆ alkanediols (R⁵OH) used to esterify the 1-substituted-9,10-dihydrolysergic acid (or N-6 homologues or congeners thereof) as the last intermediate prior to oxidation of the secondary alcohol to a ketone, will have at least one center of asymmetry, the carbon carrying the secondary alcohol. The diol will also have a second asymmetric carbon if the other hydroxyl is secondary. Where the esterifying hydroxyl is primary, the final keto alkyl ester will not have an asymmetric center since the asymmetric center in the starting alcohol will be removed by the oxidative process. If the esterifying hydroxyl is secondary, however, the final product will have four asymmetric carbons C-6, C-8, C-10 and the side chain asymmetric carbon attached to the carboxyl oxygen. The 9,10-dihydrolysergic acid or ergoline-8 β -carboxylic acid asymmetric carbons are all R and the side chain carbon in the ketoalkyl group can be S or R. The parent alcohol will then have four stereoisomers, RR, RS, SR and SS. Where the diol is symmetrical, as in butane-2,3-diol, a plane of symmetry exists and there are only three stereoisomers, RR, SS and RS (same as SR). However, esterification removes the plane of symmetry and there are two more diastereoisomers (as with a non-symmetrical diol) designated as RRR-RR, RRR-SR, RRR-RS, and RRR-SS yielding only two keto esters after oxidation (RRR-S and RRR-R).

Finally, one skilled in the art will appreciate that the above processes can also be carried out on the corresponding 9-10 unsaturated lysergic acid derivatives. In this regard, a final step of standard Pd/C catalyzed hydrogenation would yield the compounds of the present invention.

According to one aspect of the invention there is provided a process of preparing a compound of Formula (III) which comprises:

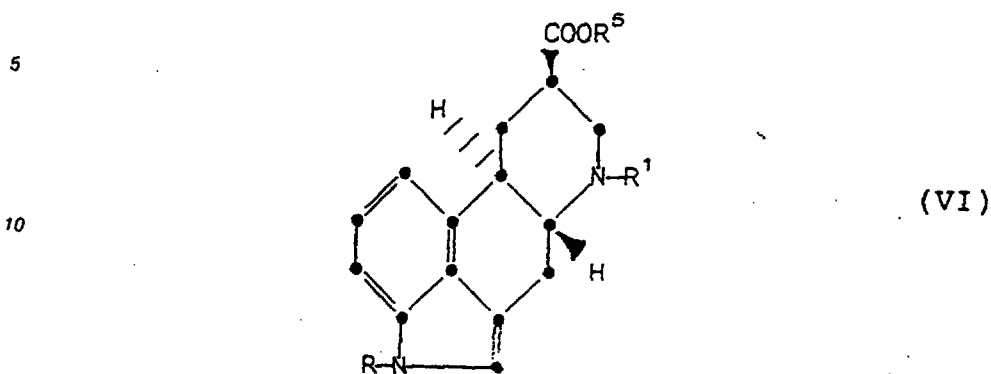
A) esterifying the 8-carboxylic acid function of a compound of Formula (V):



(V)

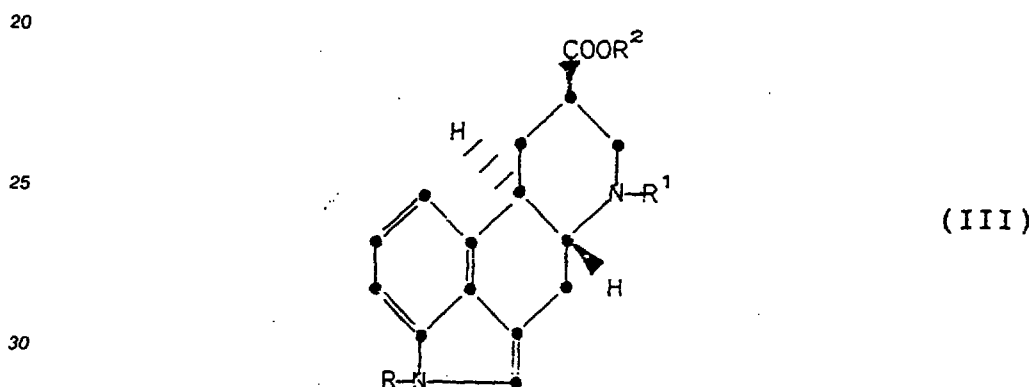
wherein R and R¹, are as defined in above; or

B) oxidizing a compound of Formula (VI):



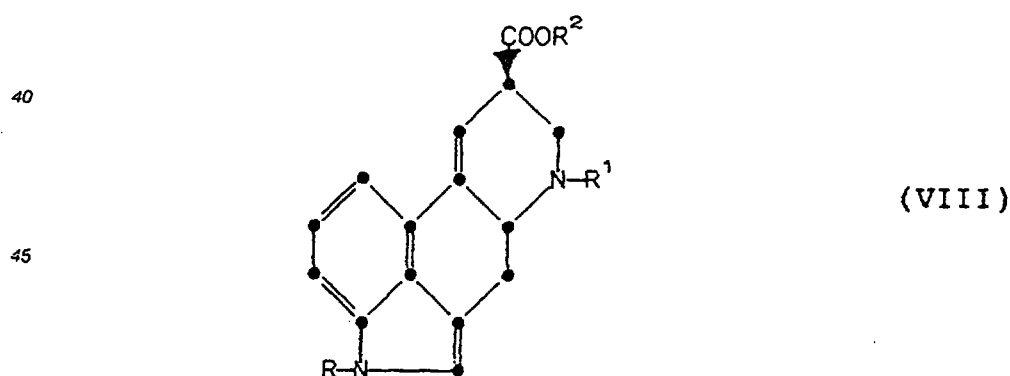
wherein R^5 is as defined in above

C) alkylating a compound of Formula (III):



wherein one only of R and R^1 is hydrogen and R^2 is as defined above; or,

35 D) hydrogenating a compound of Formula (VIII):



The following examples illustrate the process and compounds of the present invention.

Example 1

55 Preparation of Trans-4-methoxycyclohexyl 1-Isopropyl-9,10-dihydrolysergate.

A reaction mixture, prepared from 1 g of 1-isopropyl-9,10-dihydrolysergic acid, 1.77 g of potassium carbonate and 15 ml of DMF, was heated to about 70°C. 3.28 g of cis-4-methoxycyclohexyl tosylate were

added. After about 18 hours, at 70 °C, HPLC (reverse phase, 3:1 acetonitrile/0.1M aqueous ammonium acetate) indicated that the reaction was about 87% complete. The reaction mixture was then partitioned between 100 ml of distilled water and 100 ml of ethyl acetate. TLC (Chloroform/methanol/acetic acid, 18:6:1) indicated no desired product in the aqueous layer. The organic layer was extracted twice with 50 ml portions of distilled water and was then dried. Evaporation of the solvent gave 1.37 g of a 16:84 mixture of the cis and trans-4-methoxycyclohexyl 1-isopropyl-9,10-dihydrolysergate. The residue was dissolved in 15 ml of anhydrous ethanol containing .37 g of maleic acid. 250 ml of diethyl ether were added, whereupon a crystalline maleate began to form. The mixture was chilled overnight at about 0 °C and was then filtered. The filter cake was washed with ether and then dried. Assay indicated 91.4% trans and 8.6% cis esters; wt = .86 g. This residue was dissolved in 35 ml of anhydrous ethanol and 400 ml of ether added. This time, the crystalline product was 8.4% cis and 93.6% trans; wt = .74 g. Recrystallization of this residue from ethyl acetate/toluene gave a residue which contained 5.6% cis and 94.4% trans esters. This residue was dissolved in 27 ml of anhydrous ethanol and 300 ml of ether added. Crystals thus produced weighed .48 g and contained 3.6% cis and 96.4% trans ester. The process was repeated using 21 ml of anhydrous ethanol and 250 ml of ether. 0.38 g of 4-methoxycyclohexyl 1-isopropyl-9,10-dihydrolysergate maleate were obtained which contained 2% cis and 98% trans ester; mp = 172-173 °C; molecular ion⁻ (free base) at 424.

Analysis:	Calc.:	C, 66.65;	H, 7.46;	N, 5.18;
	Found:	C, 66.50;	H, 7.56;	N, 5.08.

Example 2

Preparation of Cis-4-methoxycyclohexyl-1-Isopropyl-9,10-dihydrolysergate.

4-Methoxycyclohexanol (27.9 g) was reacted with 1-isopropyl-9,10-di-hydrolysergic acid (6.24 g) and p-toluenesulfonic acid (3.8 g) at room temperature for 3 days. It was then heated at about 90 °C for 3 hours. At this time, HPLC analysis showed 19% unreacted lysergic acid, 70% 4-methoxycyclohexyl ester and 4% desmethyl compound (4-hydroxycyclohexyl ester). The reaction mixture was dissolved in (CH₂Cl)₂ and the organic solution washed with dilute ammonium hydroxide (pH ≈ 10). The crude product was isolated by evaporation of the organic solvent. It was treated with an excess of maleic acid and the maleate salt thus formed was crystallized from methanol/ether. The crystals were dissolved in boiling methanol, the hot solution treated with decolorizing charcoal and filtered. Addition of ether to the filtrate yielded 1.2 g of crystalline cis-4-methoxycyclohexyl 1-isopropyl-9,10-dihydrolysergate maleate (90% pure). A second crop, weight 2.26 g, was shown by HPLC to be 86% pure. The combined fractions were purified by preparative HPLC [C-18, 50:50 CH₃CN/NH₄OAc (1)]. The maleate salt was reformed. Recrystallization from methanol/ether gave 1.27 g of 99% pure cis isomer; molecular ion at 424.

Analysis:	Calc.:	C, 66.65;	H, 7.46;	N, 5.18;
	Found:	C, 66.38;	H, 7.74;	N, 5.37.

The preparation of starting materials is illustrated below.

Preparation 1

Cis-4-methoxycyclohexyl Tosylate.

A solution was prepared by dissolving 65.45 g of 4-methoxycyclohexanol in 81 ml of pyridine. The solution was cooled to about 10 °C. 105.4 g of p-toluene sulfonyl chloride were added in batchwise fashion over 15 minute period. The reaction mixture was stirred for 1 hour in the range 10-20 °C. and 4 hours at 25-30 °C. at which time it was added to 500 ml of an ice/water mixture containing 100 ml of 12N hydrochloric acid. A precipitate which resulted was separated by filtration, and the filter cake washed with water. The wet filter cake was slurried with 300 ml of anhydrous ethanol. The slurry was warmed on the steam bath and then cooled at about 0 °C. The chilled slurry was filtered and the filter cake washed with cold anhydrous ethanol; yield = 106.9 g; 82.4% cis ester by HPLC (C-18; 60:40 methanol/H₂O). Recrystallizations from pet.

ether gave 81.62 g of 93.6% cis ester. A second recrystallization from anhydrous ethanol yielded 72.04 g of 98% cis 4-methoxycyclohexyltosylate melting at 85-7 °C.

Analysis:	Calc.:	C, 59.13;	H, 7.09;	N, 11.28;
	Found:	C, 59.32;	H, 7.20;	N, 11.49.

Preparation 2

Preparation of Cis-4-methoxycyclohexanol.

Following the procedure of J. Org. Chem., 28 1923 (1963), 13.35 g of AlCl_3 and 125 ml of ether were stirred under N_2 . 25 ml of 1M LiAlH_4 in ether were added by syringe to the solution. Next, 13 g of 4-methoxycyclohexanol in 50 ml of ether were added to the stirred mixture over a 30 minute period. The mixture was then allowed to settle. The supernate was removed. The solid remaining was washed three times with 25, 50 and 50 ml portions of ether. The solid precipitate was filtered and the filter cake thoroughly washed with ether. (The filtrate, and washings contained trans-4-methoxycyclohexanol). The dried precipitate (19.17 g) was slurried in 100 ml of ether. 100 ml of 10% sulfuric acid were slowly added thereto (30 minutes). The cis isomer obtained from the decompositions of the AlCl_3 complex was in the ether layer which was separated. The separated layer was washed successively with 100 ml water, 50 ml saturated aqueous sodium bicarbonate and 50 ml of brine. The ethereal solution was dried and the ether evaporated to yield 1.7 g of cis-4-methoxycyclohexanol. An additional 4 g were obtained from the water layer.

Example 3

Preparation of R-1-Methyl-2-oxopropyl-1-isopropyl-9,10-dihydrolysergate

Two-thirds of a gram of R,R-1-methyl-2-hydroxypropyl-1-isopropyl-9,10-dihydrolysergate maleate was partitioned between 50 ml of ethylene dichloride and 50 ml of saturated aqueous sodium bicarbonate. The organic layer, shown by TLC (chloroform/methanol/acetic acid, 18:6:1) to be one-spot material, was dried and the solvent evaporated in vacuo. The crystalline residue (.38 g) was mixed with 1 ml DMSO (dimethylsulfoxide) and 7 ml of acetic anhydride. The reaction mixture was stirred overnight at room temperature. HPLC indicated absence of starting material. 10 ml of ethanol were added and the mixture stirred for one additional hour. The oxidation mixture was partitioned between 75 ml of ethylene dichloride and 75 ml of saturated aqueous sodium bicarbonate. The ethylene dichloride layer was separated and dried. The residue was purified using preparative HPLC over C-18 reverse phase silica: (acetonitrile/water/triethylamine 65:35:0.02;) 100 ml/min; 200 ml fractions. Fractions 9-20, containing R-1-methyl-2-oxopropyl 1-isopropyl-9,10-dihydrolysergate formed in the above oxidation, were combined, partially evaporated and extracted twice with 200 ml portions of ethylene dichloride, and dried. Evaporation of the solvent from the combined extracts gave 0.38 g of ester. The ester was converted to the corresponding maleate salt by dissolving 0.38 g of the free base in 10 ml of ethyl acetate. 0.13 g of maleic acid were added to the solution. A crystalline salt started to precipitate. 100 ml of ether were added and the crystallization mixture chilled (about 0 °C) overnight. Crystals were separated by filtration, and the filter cake washed with ether and dried. Recrystallization from ethyl acetate gave 150 mg of R-1-methyl-2-oxopropyl 1-isopropyl-9,10-dihydrolysergate maleate.

Analysis:	Calc.:	C, 65.04;	H, 6.87;	N, 5.62
	Found:	C, 64.83;	H, 7.10;	N, 5.43.

The above procedure was carried out on S,S-1-methyl-2-hydroxypropyl 1-isopropyl-9,10-dihydrolysergate. .54 g of the maleate salt of this alcohol were converted to the free base and the free base oxidized with acetic anhydride-DMSO reagent to yield .36 g of S-1-methyl-2-oxopropyl 1-isopropyl-9,10-dihydrolysergate which free base was converted to the maleate salt by the procedure of the above example; yield of maleate salt = 170 mg; mass spectrum - molecular ion (of free base) at 382.

Analysis:	Calc.:	C, 65.04;	H, 6.87;	N, 5.62;
	Found:	C, 64.80;	H, 7.11;	N, 5.32.

5 HPLC indicated the product contained 88.1% of the S isomer and 6.7% of the R isomer.

Starting materials useful in preparing the compound of this invention, as set forth in the above examples, are synthesized as follows.

Preparation 3

2R,3R 1-Methyl-2-hydroxypropyl 1-isopropyl-9,10-dihydrolysergate

A reaction mixture, prepared from 4 g of 1-isopropyl-9,10-dihydrolysergic acid, 4.05 g of p-toluenesulfonic acid monohydrate and 40 g of 2R,3R-(-)-butanediol (commercially available) was heated to about 60 °C for about 18 hours. At this time, all solids had dissolved and TLC (CHCl₃/MeOH/acetic acid 9:3:0.5) showed absence of starting material. The reaction mixture was cooled and was then added to 160 ml of purified water. The pH of the solution was adjusted to about 8.0 with 28% aqueous ammonium hydroxide. The alkaline mixture was stirred and then filtered. The filter cake was rinsed with water. The filter cake, containing 2R,3R 1-methyl-2-hydroxypropyl 1-isopropyl-9,10-dihydrolysergate formed in the above reaction, weighed 3.96 g (80.5% crude yield); MP = 193-200 °C; molecular ion at 384.

Analysis:	Calc.:	C, 71.84;	H, 8.39;	N, 7.29;
	Found:	C, 71.58;	H, 8.50;	N, 7.02.

25

The maleate salt was prepared in 92 ml methanol using a slight molar excess of maleic acid. Ether (540 ml) was added to the cooled solution to the point of incipient precipitation. Crystals of the maleate salt which precipitated were collected by filtration. The filter cake was dried; weight = 3.54 g; MP = 182-183.5 °C;

30 $[\alpha]_D^{25} = -58.5^\circ$

Analysis:	Calc.:	C, 64.78;	H, 7.25;	N, 5.60;
	Found:	C, 64.68;	H, 7.33;	N, 5.76.

35

An additional 1.03 g of maleate salt were recovered from the filtrate.

Preparation 4

40 Preparation of 2S,3S 1-Methyl-2-hydroxypropyl 1-isopropyl-9,10-dihydrolysergate

A reaction mixture was prepared from 1.00 g of 1-isopropyl-9,10-dihydrolysergic acid, 1.0 g of p-toluenesulfonic acid, 0.5 g of 2S,3S-O-isopropylidene L-butanediol [prepared by the method of Platner and Rapaport J.A.C.S., 93 1756 (1971)], 0.16 g of water and 15 ml of acetonitrile. The reaction mixture was heated to reflux temperature for about 48 hours. The reaction mixture was cooled and the solids which precipitated were separated by filtration. The filter cake was discarded. The filtrate was evaporated to dryness and the residue partitioned between 50 ml of (CH₂Cl)₂ and 50 ml of water. The pH of the aqueous layer was adjusted to about 9.0 with 28% aqueous ammonium hydroxide. The two layers were thoroughly mixed. The layers were separated. The organic layer was emulsified and was therefore washed with 50 ml of brine. The organic layer was dried and the solvent evaporated therefrom. The residue (0.9 g) was purified by HPLC over a C-18 column (eluate = CH₃CN/H₂O 65:35 plus a trace of Et₃N).

2S,3S 1-Methyl-2-hydroxypropyl 1-isopropyl-9,10-dihydrolysergate thus purified was converted to the maleate salt as in the previous preparation. 1.3 g of base plus 0.43 g of maleic acid gave 1.2 g of salt; MP = 194-195.5 °C (with decomposition); molecular ion of base = 384;

55 $[\alpha]_D^{25} = -43.37^\circ$

Analysis:	Calc.:	C, 64.78;	H, 7.25;	N, 5.60;
	Found:	C, 64.67;	H, 7.16;	N, 5.42.

5

Example 4

Preparation of Cyclohexyl 1-Isopropyl-9,10-dihydrolysergate (1-Isopropyl-6-methyl-8 β -cyclohexyloxycarbonylsergoline)

10

A reaction mixture, prepared from 12.5 g of 1-isopropyl-9,10-dihydrolysergic acid (from Garbrecht, and Lin, United States Patent 3,183,234), 50 ml of cyclohexanol, and 7.6 g of p-toluenesulfonic acid, was heated at about 90°C for 24 hours. The reaction mixture was cooled and the cooled mixture partitioned between (CH₂Cl)₂ and dilute aqueous ammonium hydroxide (pH=10). The organic layer was separated and the separated layer washed with water and then dried. Evaporation of the solvent in vacuo yielded a residue comprising cyclohexyl 1-isopropyl-9,10-dihydrolysergate formed in the above reaction. The free base was dissolved in methanol and a molar equivalent of maleic acid added. Ether was added and a crystalline maleate salt was obtained, which salt was separated by filtration. Two recrystallizations from a methanol/ether solvent mixture gave cyclohexyl 1-isopropyl-9,10-dihydrolysergate maleate melting at 203-5°C; [α]_D²⁵ = -51.7° (1% methanol); yield = 7.1 g (2 crops); Mass spectrum; m/e at 394 (free base).

20

Analysis:	Calc.:	C, 68.21;	H, 7.50;	N, 5.49;
	Found:	C, 67.96;	H, 7.71;	N, 5.29.

25

Example 5

Preparation of 1-Isopropyl-6-ethyl-8 β -cyclohexyloxycarbonylsergoline

30

Following the procedure of Example 10, 1.5 g of 1-isopropylsergoline-8 β -carboxylic acid were esterified with 15 g of cyclohexanol in the presence of 1.5 g of p-toluenesulfonic acid to yield 1-isopropyl-8 β -(cyclohexyloxycarbonyl)sergoline. The product, 1.91 g of an oil, was converted to the maleate salt in a 6:1 ether/ethyl acetate solvent mixture. The salt was isolated by evaporation and then recrystallized from ether/methanol; yield = .93 g of cyclohexyl 1-isopropyl-8 β -(cyclohexyloxycarbonyl)sergoline maleate (96.77% pure by HPLC); molecular ion at 380; [α]_D²⁵ = -40.64°.

35

Analysis:	Calc.:	C, 67.72;	H, 7.31;	N, 5.64;
	Found:	C, 67.95;	H, 7.54;	N, 5.36.

40

Two grams of 1-isopropyl-8 β -cyclohexyloxycarbonylsergoline maleate were converted to the free base by partitioning between 100 ml of (CH₂Cl)₂ and 100 ml. of saturated aqueous sodium bicarbonate. The free base passed into the organic layer. The organic layer was separated and the solvent evaporated therefrom. The resulting residue was dissolved in 15 ml of DMF, and .67 g of potassium carbonate and .75 g of ethyl iodide added to the solution. This reaction mixture was stirred at ambient temperature for about 3 days at which time HPLC indicated that starting material was no longer present. The reaction mixture was partitioned between 50 ml ethyl acetate and 50 ml of water. The organic layer was separated and the separated layer twice extracted with 50 ml portions of water. The organic layer was dried and the solvent removed by evaporation. The resulting residue (weight = 1.67 g) comprising cyclohexyl 1-isopropyl-6-ethyl-8 β -cyclohexyloxycarbonylsergoline formed in the above reaction, was converted to the corresponding hydrochloride salt in ethyl acetate solution with gaseous HCl. Two crops of the crystalline salt were recovered by filtration; yield = 1.42 g; purity by HPLC >99.2%. The crystalline fraction was slurried in a THF/ether solvent mixture and the slurry filtered. 1-Isopropyl-6-ethyl-8 β -cyclohexyloxycarbonylsergoline hydrochloride thus prepared melted above 220°C; yield = 1.33 g; molecular ion at 408.

55

Analysis (block dried);	Calc.:	C, 70.17;	H, 8.38;	N, 6.29;
	Found:	C, 70.02;	H, 8.50;	N, 6.47.

5 Other 6-alkyl derivatives of cyclohexyl 1-isopropyl-8 β -cyclohexyloxycarbonyl ergoline prepared by the above reaction sequence include

1-Isopropyl-6-n-propyl-8 β -cyclohexyloxyergoline hydrochloride: yield = 1.14 g (from 2.0 g starting material); mp > 220 °C.; purity > 98.6%; molecular ion at 422;

Analysis (block dried);	Calc.:	C, 70.64;	H, 8.56;	N, 6.10;
	Found:	C, 70.41;	H, 8.51;	N, 6.36.

1-Isopropyl-6-n-butyl-8 β -cyclohexyloxycarbonyl ergoline hydrochloride: yield = 1.45 g (purity > 99.1%); mp > 220 °C.; molecular ion at 436;

Analysis (block dried);	Calc.:	C, 71.09;	H, 8.74;	N, 5.92;
	Found:	C, 70.85;	H, 8.62;	N, 5.66.

Example 6

Preparation of 4-Oxocyclohexyl 1-isopropyl-9,10-dihydrolysergate

25 Following the procedure of Example 10, 3.12 g of 1-isopropyl-9,10-dihydrolysergic acid were esterified with 1.2 g of 4-oxocyclohexanol in the presence of 4 ml of triethylamine and 3.83 g of methyl 2-chloropyridinium chloride in 10 ml of CH₂Cl₂. The reaction mixture was refluxed for 3 hours and stirred overnight at room temperature. Water and (CH₂Cl)₂ were added. The organic layer was separated and the solvent evaporated therefrom to leave a brown oil comprising 4-oxocyclohexyl 1-isopropyl-9,10-dihydrolysergate free base formed in the above reaction. The free base was converted to the maleate salt as in Example 11. Recrystallization of the salt from acetone/ether and then methanol/ether gave .05 g of crystalline material salt; .03 g of free base of 95.5% purity were also recovered; molecular ion at 408.

Useful starting material for the above reactions are prepared as follows.

Preparation 5

Preparation of 4-Hydroxycyclohexanone.

40 Four grams of 4-methoxycyclohex-3-en-1-ol were dissolved in 50 ml of CHCl₃. About .01 g of p-toluene-sulfonic acid were added and the reaction mixture stirred at room temperature for about 1 hour. The reaction mixture was washed with 50 ml of water. The CHCl₃ layer was separated and dried and the volatile constituents removed therefrom in vacuo. The product of the reaction, 4-oxocyclohexanol, was used without further purification.

Preparation 6

Preparation of 1-Isopropylergoline-8 β -carboxylic acid

50 A reaction mixture was prepared by adding 11.6 ml of 18M sulfuric acid to a mixture of 50 g of 1-isopropyl-9,10-dihydrolysergic acid (prepared according to the procedure of column 3, United States Patent 3,103,234) and 500 ml of methanol. The esterification mixture was stirred overnight at room temperature. TLC (18:6:1 CHCl₃/MeOH/acetic acid) indicated the esterification was complete. About 1/3 of the MeOH was removed by evaporation. 600 ml of saturated aqueous sodium bicarbonate were added (pH = 8-9). The alkaline mixture was filtered and the filter cake dried; yield of methyl 1-isopropyl-9,10-dihydrolysergate was 40.1 g (98% pure by LC.).

A reaction mixture was prepared from 39.9 g of methyl 1-isopropyl-9,10-dihydrolysergate, 14.8 g of CNBr and 400 ml of CH₂Cl₂. The reaction mixture was stirred at room temperature overnight, by which time

TLC (same solvent system as above) indicated absence of starting material. Evaporation of the volatile constituents gave a solid residue (wt = 46.7 g) comprising methyl 1-isopropyl-6-cyanoergoline-8 β -carboxylate formed in the above reaction. The residue was dissolved in 460 ml of refluxing MeOH and the hot solution filtered. Crystals formed in the filtrate, which was then chilled overnight. The crystals were filtered and the filter cake washed with MeOH. Methyl 1-isopropyl-6-cyanoergoline thus prepared was one spot material; yield = 35.3 g. NMR confirmed the structure.

A reaction mixture was prepared by combining 25g of methyl 1-isopropyl-6-cyanoergoline-8 β -carboxylate, 8.89 NaOH pellets and 250 ml of ethylene glycol. The reaction mixture was heated in the range 130-40° C for about 3 hours. 750 ml of water were added. The pH of the resulting solution was adjusted to about 5 with glacial acetic acid (30 mls.). Crystals began to form and the solution was chilled overnight. The crystals were separated by filtration and the filter cake washed with water; yield (after drying) = 19.6 g of 1-isopropylergoline-8 β -carboxylic acid, (97.3% pure by HPLC).

This invention also provides novel methods whereby 5HT₂ receptors are blocked. Such methods are potentially useful in treating disease states in which an excess of circulating serotonin is a major contributing cause. These disease states include hypertension, anorexia nervosa, depression, mania, carcinoid syndrome, migraine and vasospasm. The compounds according to Formula (III) show relatively slight affinity for other receptors, α_1 , α_2 , β , histamine, carbachol etc. and thus are highly selective in their action. Formulations in which a compound of this invention is an active ingredient also form another aspect of this invention.

In order to demonstrate that compounds according to Formula (III) have an extremely high affinity for 5HT₂ receptors, apparent dissociation constants (K_B) as a measure of affinity for 5HT₂ receptors, expressed as the negative logarithm, have been determined according to the following protocol.

Male Wistar rats (150-300 gram weight) were killed and their external jugular veins and thoracic aortas dissected free of connective tissue, cannulated in situ and placed in a modified Krebs' bicarbonate buffer in a suitable tissue bath. Two L-shaped 30-gauge stainless-steel hypodermic needles were inserted in each cannula and the dissected vessels gently pushed onto the needles. One needle was attached with thread to a stationary glass rod and the other to the transducer. [The procedure employed was that described by Hooker, Calkins and Fleisch, Blood Vessels, 14, 1, (1977) for use with circular smooth muscle preparations.]

The modified Krebs' bicarbonate buffer had the following makeup: (concentrations in millimoles): sodium chloride, 118.2; potassium chloride, 4.6; calcium chloride dihydrate, 1.8; potassium dihydrogen-phosphate, 1.2; magnesium sulfate, 1.2; dextrose, 10.0; sodium bicarbonate, 24.8; and water q.s. to 1000 g. The tissue baths were maintained at 37° C. and were aerated with 95% oxygen-5% CO₂. An initial optimum resting force of 1 and 4 g was applied to the jugular vein and aorta, respectively. Isometric contractions were recorded as changes in grams of force on a Beckman Dynograph with Statham UC-3 transducers and microscale accessory attachment. Tissues were allowed to equilibrate 1 to 2 hours before exposure to drugs. Control responses to serotonin in the jugular vein and to norepinephrine in the aorta were obtained. The vessels were then incubated with appropriate concentrations of antagonist for one hour. Responses to serotonin or to norepinephrine were then repeated in the presence of the antagonist. Contraction to serotonin was evaluated in the jugular vein since this tissue produces marked responses to serotonin in the absence of alpha receptors -- see Cohen and Wiley, J. Pharm. Exp. Ther., 205, 400 (1978). Alpha receptor antagonist activity was evaluated in the aorta(α_1) or guinea pig ileum (α_2).

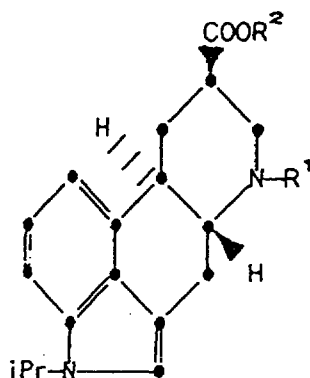
Apparent antagonist dissociation constants were determined for each concentration of antagonist according to the following equation:

$$K_B = \frac{[B]}{[\text{dose ratio}-1]}$$

wherein [B] is the concentration of the antagonist and the dose ratio is the ED₅₀ of the agonist in the presence of the antagonist divided by the control ED₅₀. These results are then expressed as the negative logarithm of K_B . The -log K_B values obtained for compounds of this invention are given below in Table 1.

TABLE 1

Apparent Dissociation Constants for 5HT₂ receptors determined in the rat jugular vein.



Compound		salt	5HT ₂
R ¹	R ²		-Log K _b ± S.E.
CH ₃	cis-4-methoxy cyclohexyl	maleate	9.54 ± 0.11(13)
CH ₃	trans-4-methoxy cyclohexyl	maleate	8.96 ± 0.07(18)
CH ₃	R-CH(CH ₃)COCH ₃	maleate	9.45 ± .05
CH ₃	S-CH(CH ₃)COCH ₃	maleate	9.57 ± .10
CH ₃	cyclohexyl	maleate	8.67 ± S.E.

Table 1 (Continued)

Compound		salt	5HT ₂
R ¹	R ²		-Log K _b ± S.E.
CH ₃	4-oxocyclohexyl	maleate	10.01 ± 0.08
C ₂ H ₅	cyclohexyl	HCl	7.81 ± 0.17
n-C ₃ H ₇	cyclohexyl	HCl	7.07 ± 0.05
n-C ₄ H ₉	cyclohexyl	HCl	7.4 ± 0.19

In mammals, hypertension may be mediated through 5HT₂ receptors. Thus, compounds of Formula (III) would be expected to lower blood pressure in humans as does ketanserin, another 5HT₂ blocker, but without the side effects attributable to alpha adrenergic receptor blockade of ketanserin.

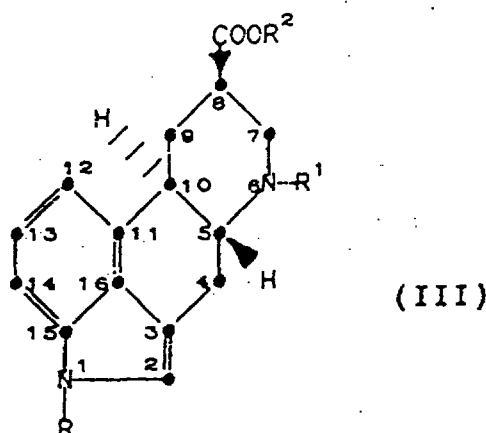
In carrying out our novel therapeutic process, a pharmaceutically-acceptable salt of a drug according to Formula (III) above formed with a non-toxic acid is administered orally or parenterally to a mammal with an excess of circulatory serotonin in which mammal is desirable to block 5HT₂ receptors in order to alleviate symptoms attributable to excessive serotonin levels such as high blood pressure and migraine. For parenteral administration, a water soluble salt of the drug is dissolved in an isotonic salt solution and administered by the i.v. route. For oral administration, a pharmaceutically-acceptable salt of the drug is mixed with standard pharmaceutical excipients such as starch and loaded into capsules or made into tablets, each containing 0.1 to 100 mg of active drug. Dosage levels of from 0.1-10 mg/kg have been found to be effective in blocking 5HT₂ receptors. Thus, the oral dosage would be administered 2-4 times per day, giving a daily dosage range of about .003 to about 10.0 mg/kg. per day.

Other oral dosage forms, suspensions, elixirs and tablets, can also be utilized and are preparable by standard procedures.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of Formula (III):



wherein R is primary or secondary C₁-C₃ alkyl, C₂-C₄ alkenyl-CH₂, C₃-C₃ cycloalkyl or C₃-C₆ cycloalkyl-substituted C₁-C₅ primary or secondary alkyl, the total number of carbon atoms in R not to exceed 8; R¹ is allyl, H, or C₁-C₂ straight chain alkyl, and R² is C₁-C₃ alkoxy-C₅-C₇ cycloalkyl; C₃-C₇ ketoalkyl; or C₅-C₇ cycloalkyl or keto-substituted C₅-C₇ cycloalkyl; or a pharmaceutically-acceptable salt thereof.

2. A compound as claimed in claim 1, wherein R² is C₁-C₃ alkoxy-C₅-C₇ cycloalkyl.
3. A compound as claimed in claim 1, wherein R² is C₃-C₇ ketoalkyl.
4. A compound as claimed in claim 1, wherein R² is C₅-C₇ cycloalkyl or keto substituted C₅-C₇ cycloalkyl.
5. A compound as claimed in any one of claims 1 to 4, wherein R is isopropyl.
6. A compound as claimed in any one of claims 1 to 5, wherein R¹ is methyl.
7. A compound as claimed in any one of claims 1, 2, 5, and 6, wherein R² is trans 4-methoxycyclohexyl.
8. Trans-4-methoxycyclohexyl 1-isopropyl-9,10-dihydrolysergate, or a pharmaceutically acceptable salt thereof.

In mammals, hypertension may be mediated through 5HT₂ receptors. Thus, compounds of Formula (III) would be expected to lower blood pressure in humans as does ketanserin, another 5HT₂ blocker, but without the side effects attributable to alpha adrenergic receptor blockade of ketanserin.

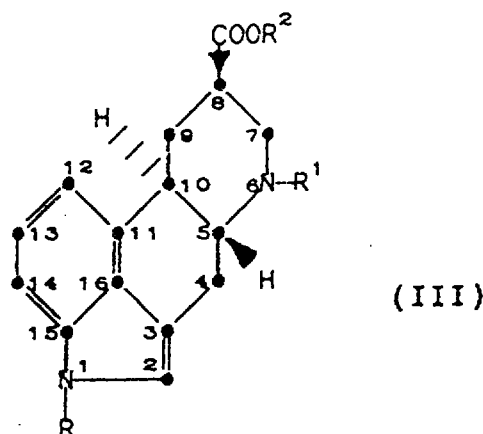
In carrying out our novel therapeutic process, a pharmaceutically-acceptable salt of a drug according to Formula (III) above formed with a non-toxic acid is administered orally or parenterally to a mammal with an excess of circulatory serotonin in which mammal is desirable to block 5HT₂ receptors in order to alleviate symptoms attributable to excessive serotonin levels such as high blood pressure and migraine. For parenteral administration, a water soluble salt of the drug is dissolved in an isotonic salt solution and administered by the i.v. route. For oral administration, a pharmaceutically-acceptable salt of the drug is mixed with standard pharmaceutical excipients such as starch and loaded into capsules or made into tablets, each containing 0.1 to 100 mg of active drug. Dosage levels of from 0.1-10 mg/kg have been found to be effective in blocking 5HT₂ receptors. Thus, the oral dosage would be administered 2-4 times per day, giving a daily dosage range of about .003 to about 10.0 mg/kg. per day.

Other oral dosage forms, suspensions, elixirs and tablets, can also be utilized and are preparable by standard procedures.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of Formula (III):



wherein R is primary or secondary C₁-C₈ alkyl, C₂-C₄ alkenyl-CH₂, C₃-C₈ cycloalkyl or C₃-C₆ cycloalkyl-substituted C₁-C₅ primary or secondary alkyl, the total number of carbon atoms in R not to exceed 8; R¹ is allyl, H, or C₁-C₄ straight chain alkyl, and R² is C₁-C₃ alkoxy-C₅-C₇ cycloalkyl; C₃-C₇ ketoalkyl; or C₅-C₇ cycloalkyl or keto-substituted C₅-C₇ cycloalkyl; or a pharmaceutically-acceptable salt thereof.

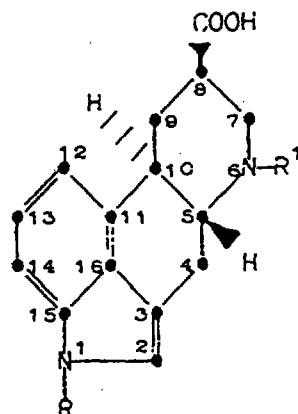
2. A compound as claimed in claim 1, wherein R² is C₁-C₃ alkoxy-C₅-C₇ cycloalkyl.
3. A compound as claimed in claim 1, wherein R² is C₃-C₇ ketoalkyl.
4. A compound as claimed in claim 1, wherein R² is C₅-C₇ cycloalkyl or keto substituted C₅-C₇ cycloalkyl.
5. A compound as claimed in any one of claims 1 to 4, wherein R is isopropyl.
6. A compound as claimed in any one of claims 1 to 5, wherein R¹ is methyl.
7. A compound as claimed in any one of claims 1, 2, 5, and 6, wherein R² is trans 4-methoxycyclohexyl.
8. Trans-4-methoxycyclohexyl 1-isopropyl-9,10-dihydrolysergate, or a pharmaceutically acceptable salt thereof.



9. Trans-4-methoxycyclohexyl 1-isopropyl-9,10-dihydrolysergate maleate.

10. A process for preparing a compound of Formula (III) as defined in any one of claims 1 to 9, which comprises:

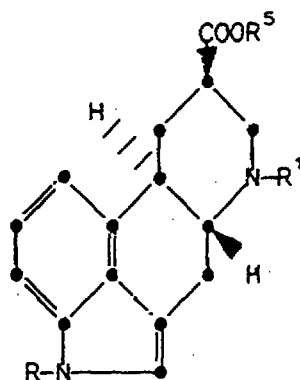
A) esterifying the 8-carboxylic acid function of a compound of Formula (V):



(V)

wherein R and R¹, are as defined in claim 1; or

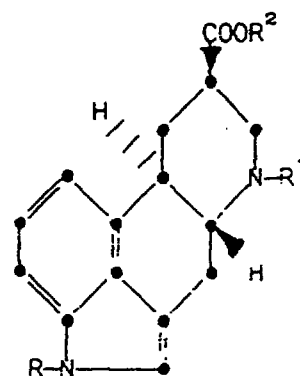
B) oxidizing a compound of Formula (VI):



(VI)

wherein R⁵ is a C₃-C₆ hydroxyalkyl group;

C) alkylating a compound of Formula (III):

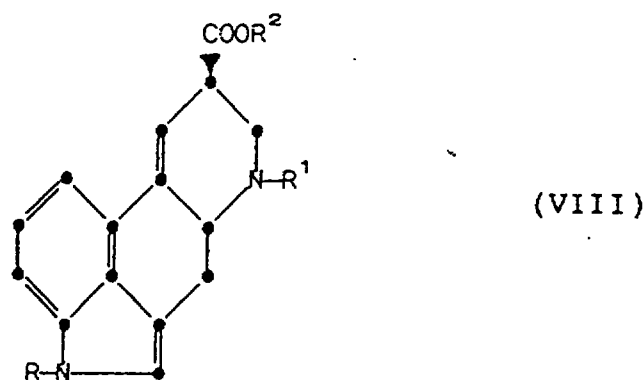


(III)

wherein only one of R and R¹ is hydrogen, or,



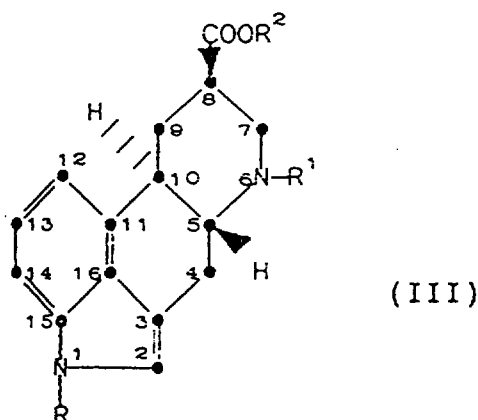
D) hydrogenating a compound of Formula (VIII):



11. A process according to claim 10 for preparing a compound of Formula (III), which comprises: reacting a compound of Formula (V) with a compound of the formula R^2-O-SO_2-Z , wherein Z is C_1-C_3 alkyl, phenyl or phenyl substituted by C_1-C_3 alkyl, nitro, halo, or C_1-C_3 alkoxy, in the presence of a base, wherein R^2 is as defined in claim 1.
12. A compound of Formula (III), or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 9, for use as a $5HT_2$ antagonist.
13. Trans-4-methoxycyclohexyl 1-isopropyl-9,10-dihydrolysergate maleate for use in treating migraine.
14. A pharmaceutical formulation comprising as an active ingredient a compound of Formula (III), or a pharmaceutically-acceptable acid-addition salt thereof, as claimed in any one of claims 1 to 9, associated with one or more pharmaceutically-acceptable carriers therefor.

Claims for the following Contracting State : AT

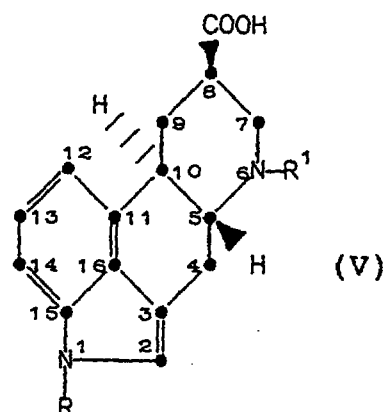
1. A process for preparing a compound of Formula (III):



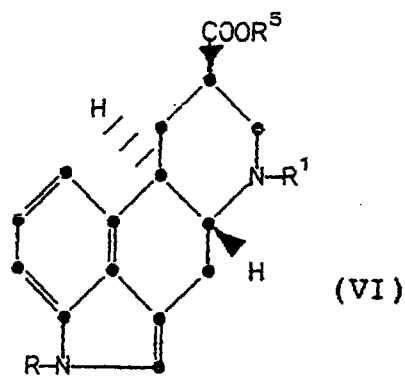
wherein R is primary or secondary C_1-C_8 alkyl, C_2-C_4 alkenyl- CH_2 , C_3-C_8 cycloalkyl or C_3-C_6 cycloalkyl-substituted C_1-C_5 primary or secondary alkyl, the total number of carbon atoms in R not to exceed 8; R^1 is allyl, H, or C_1-C_4 straight chain alkyl, and R^2 is C_1-C_3 alkoxy- C_5-C_7 cycloalkyl; C_3-C_7 ketoalkyl; or C_5-C_7 cycloalkyl or keto-substituted C_3-C_7 cycloalkyl; or a pharmaceutically-acceptable salt thereof, which comprises:



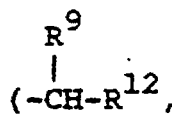
A) esterifying the 8-carboxylic acid function of a compound of Formula (V):



wherein R and R¹, are as defined in claim 1; or
B) oxidizing a compound of Formula (VI):



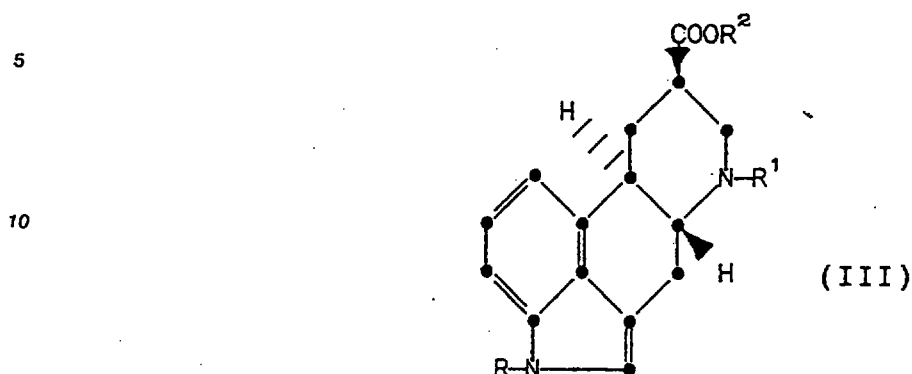
wherein R⁵ is a C₃-C₆ hydroxyalkyl group



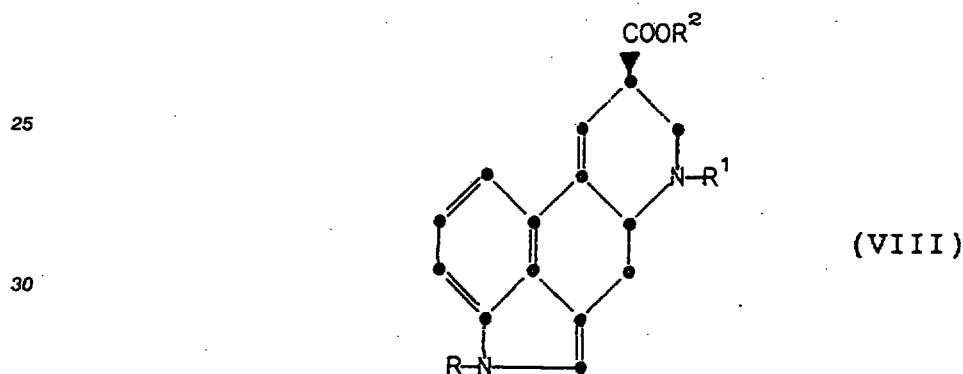
wherein R⁹ is H, methyl, or ethyl, and R¹² is a C₂-C₅ alkyl group containing a secondary hydroxy group).



C) alkylating a compound of Formula (III):



wherein only one of R and R¹ is hydrogen, or,
D) hydrogenating a compound of Formula (VIII):



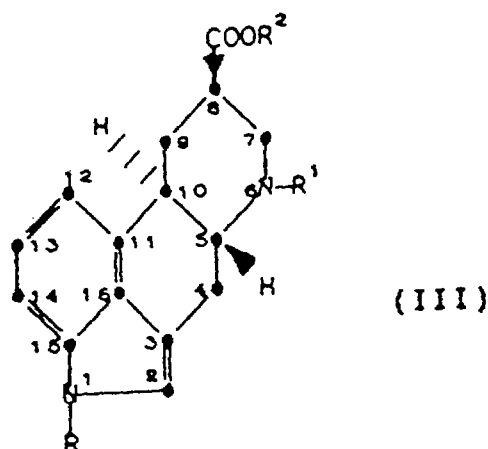
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2. A process according to claim 1 for preparing a compound of Formula (III), which comprises: reacting a compound of Formula (V) with a compound of the formula R^2-O-SO_2-Z , wherein Z is C_1-C_3 alkyl, phenyl or phenyl substituted by C_1-C_3 alkyl, nitro, halo, or C_1-C_3 alkoxy, in the presence of a base, wherein R^2 is as defined in claim 1.
 3. A process according to claim 1 or 2, wherein R^2 is C_1-C_3 alkoxy- C_5-C_7 cycloalkyl.
 4. A process according to claim 1 or 2, wherein R^2 is C_3-C_7 ketoalkyl.
 5. A process according to claim 1 or 2, wherein R^2 is C_5-C_7 cycloalkyl or keto substituted C_5-C_7 cycloalkyl.
 6. A process according to any one of claims 1 to 4, wherein R is isopropyl.
 7. A process according to any one of claims 1 to 5, wherein R^1 is methyl.
 8. A process according to any one of claims 1, 2, 5, and 6, wherein R^2 is trans 4-methoxycyclohexyl.
 9. A process according to claim 1 or 2, for preparing trans-4-methoxycyclohexyl 1-isopropyl-9,10-dihydrolysergate, or a pharmaceutically acceptable salt thereof.



Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel (III):



worin R ein primärer oder sekundärer C₁-C₈-Alkyl-, C₂-C₄-Alkenyl-CH₂-, C₃-C₈-Cycloalkyl- oder C₃-C₆-cycloalkylsubstituierter primärer oder sekundärer C₁-C₅-Alkylrest ist, wobei die Gesamtzahl von Kohlenstoffatomen in dem Rest R nicht höher als 8 ist; R¹ ein Allylrest, H oder ein geradkettiger C₁-C₄-Alkylrest ist; und R² ein C₁-C₃-Alkoxy-C₅-C₇-cycloalkylrest; C₃-C₇-Ketoalkylrest oder C₅-C₇-Cycloalkylrest oder ein ketosubstituierter C₅-C₇-Cycloalkylrest ist; und pharmazeutisch annehmbare Salze davon.

2. Verbindung nach Anspruch 1, worin R² ein C₁-C₃-Alkoxy-C₅-C₇-cycloalkylrest ist.

3. Verbindung nach Anspruch 1, worin R² ein C₃-C₇-Ketoalkylrest ist.

4. Verbindung nach Anspruch 1, worin R² ein C₅-C₇-Cycloalkylrest oder ein mit Keto substituierter C₅-C₇-Cycloalkylrest ist.

5. Verbindung nach einem der Ansprüche 1 bis 4, worin R ein Isopropylrest ist.

6. Verbindung nach einem der Ansprüche 1 bis 5, worin R¹ ein Methylrest ist.

7. Verbindung nach einem der Ansprüche 1, 2, 5 und 6, worin R² ein trans-4-Methoxycyclohexylrest ist.

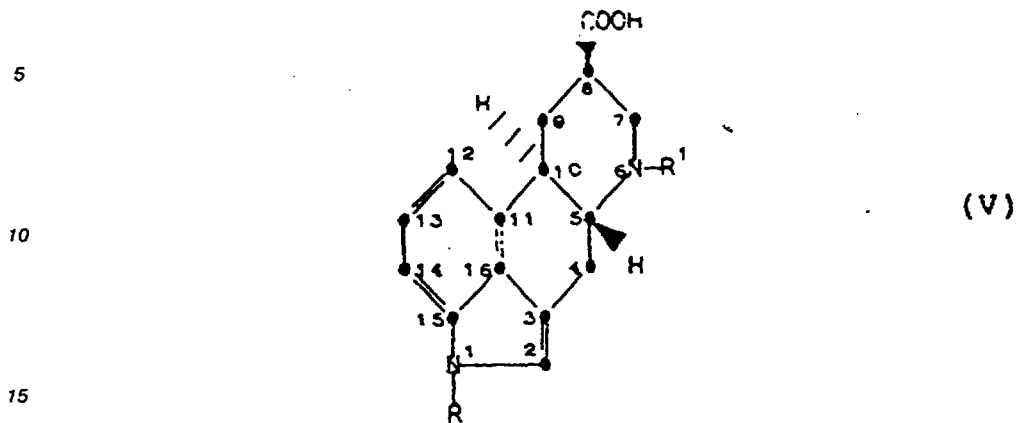
8. trans-4-Methoxycyclohexyl-1-isopropyl-9,10-dihydrolysergat oder ein pharmazeutisch annehmbares Salz davon.

9. trans-4-Methoxycyclohexyl-1-isopropyl-9,10-dihydrolysergatsmaleat.

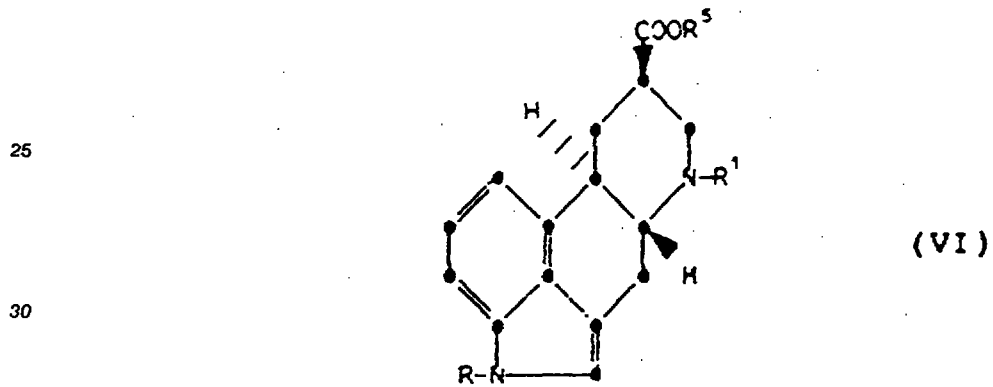
10. Verfahren zur Herstellung einer Verbindung der Formel (III), wie in einem der Ansprüche 1 bis 9 definiert, umfassend, daß man:



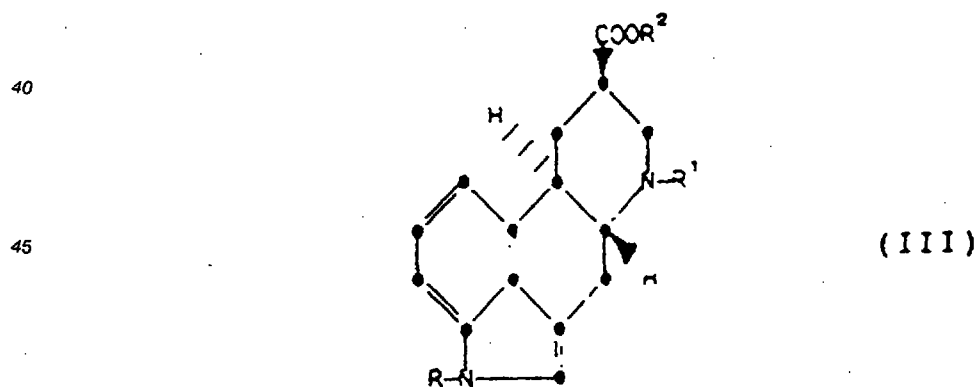
(A) die Carbonsäurefunktion an Position 8 einer Verbindung der Formel (V):



worin R und R¹ wie in Anspruch 1 definiert sind, verestert; oder
(B) eine Verbindung der Formel (VI):



35 worin R⁵ eine C₃-C₆-Hydroxyalkylgruppe ist, oxidiert;
(C) eine Verbindung der Formel (III):

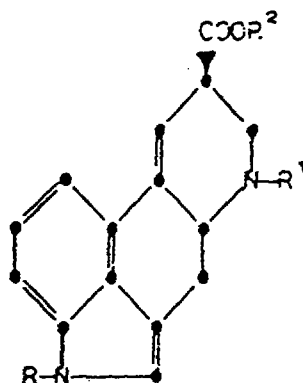


worin nur einer der Reste R und R¹ Wasserstoff ist, alkyliert; oder

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(D) eine Verbindung der Formel (VIII):



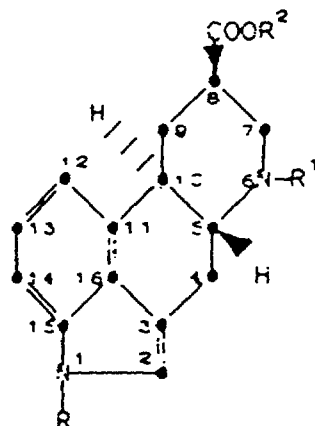
(VIII)

hydriert.

11. Verfahren nach Anspruch 10 zur Herstellung einer Verbindung der Formel (III), umfassend, daß man eine Verbindung der Formel (V) mit einer Verbindung der Formel R^2-O-SO_2-Z , worin Z ein C_1-C_3 -Alkyl-, Phenyli- oder mit C_1-C_3 -Alkyl-, Nitro-, Halogen- oder C_1-C_3 -Alkoxyresten substituierter Phenylrest ist, in Gegenwart einer Base umsetzt, wobei R^2 wie in Anspruch 1 definiert ist.
12. Verbindung der Formel (III) oder ein pharmazeutisch annehmbares Salz davon, wie in einem der Ansprüche 1 bis 9 beansprucht, zur Verwendung als 5HT₂-Antagonist.
13. trans-4-Methoxycyclohexyl-1-isopropyl-9,10-dihydrolysergatmaleat zur Verwendung zur Behandlung von Migräne.
14. Pharmazeutische Formulierung umfassend als aktiven Inhaltsstoff eine Verbindung der Formel (III) oder ein pharmazeutisch annehmbares Säureadditionssalz davon nach einem der Ansprüche 1 bis 9 zusammen mit einem oder mehreren pharmazeutisch annehmbaren Trägern.

Patentansprüche für folgenden Vertragsstaat : AT

1. Verfahren zur Herstellung einer Verbindung der Formel (III):



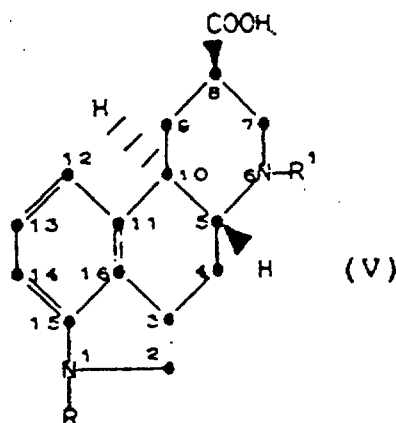
(III)

worin R ein primärer oder sekundärer C_1-C_8 -Alkyl-, C_2-C_4 -Alkenyl- CH_2 -, C_3-C_8 -Cycloalkyl- oder C_3-C_6 -cycloalkylsubstituierter primärer oder sekundärer C_1-C_5 -Alkylrest ist, wobei die Gesamtzahl von Kohlenstoffatomen in dem Rest R nicht höher als 8 ist; R^1 ein Allylrest, H oder ein geradkettiger C_1-C_4 -

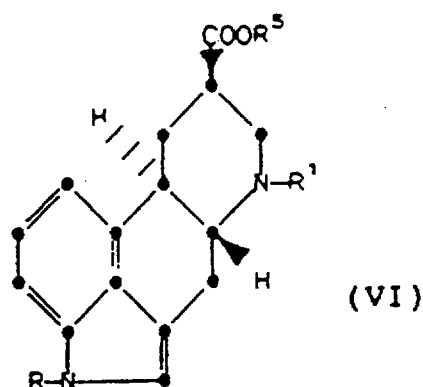


Alkylrest ist; und R^2 ein C_1 - C_3 -Alkoxy- C_5 - C_7 -cycloalkylrest; C_3 - C_7 -Ketoalkylrest oder C_5 - C_7 -Cycloalkylrest oder ketosubstituierter C_5 - C_7 -Cycloalkylrest ist; oder pharmazeutisch annehmbarer Salze davon, umfassend, daß man

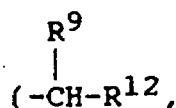
(A) die Carbonsäurefunktion an Position 8 einer Verbindung der Formel (V):



worin R und R¹ wie in Anspruch 1 definiert sind, verestert; oder
(B) eine Verbindung der Formel (VI):



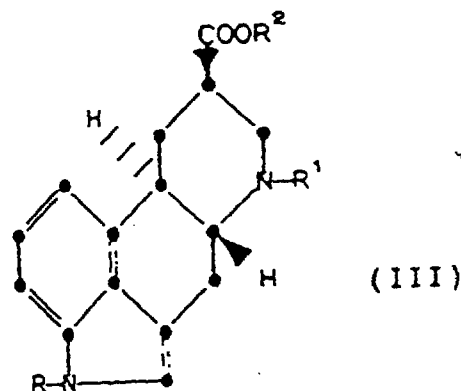
worin R⁵ eine C_3 - C_5 -Hydroxyalkylgruppe



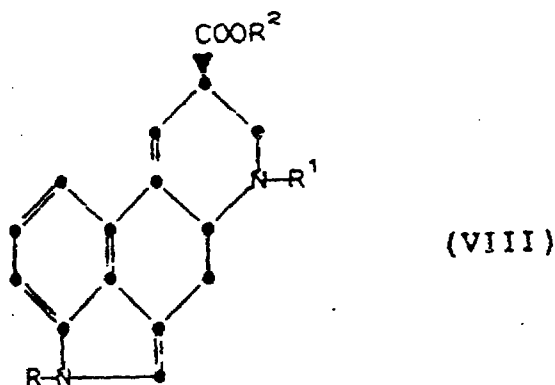
worin R^9 H, Methyl oder Ethyl ist und R^{12} eine C_2 - C_5 -Alkylgruppe ist, die eine sekundäre Hydroxygruppe enthält) ist, oxidiert;



(C) eine Verbindung der Formel (III):



worin nur einer der Reste R und R¹ Wasserstoff ist, alkyliert; oder
(D) eine Verbindung der Formel (VIII):



hydriert.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (III), umfassend, daß man eine Verbindung der Formel (V) mit einer Verbindung der Formel R^2-O-SO_2-Z , worin Z ein C_1-C_3 -Alkyl-, Phenyl- oder mit C_1-C_3 -Alkyl-, Nitro-, Halogen- oder C_1-C_3 -Alkoxyresten substituierter Phenylrest ist, in Gegenwart einer Base umsetzt, wobei R^2 wie in Anspruch 1 definiert ist.
3. Verfahren nach Anspruch 1 oder 2, worin R^2 ein C_1-C_3 -Alkoxy- C_5-C_7 -cycloalkylrest ist.
4. Verfahren nach Anspruch 1 oder 2, worin R^2 ein C_3-C_7 -Ketoalkylrest ist.
5. Verfahren nach Anspruch 1 oder 2, worin R^2 ein C_5-C_7 -Cycloalkylrest oder ein mit Keto substituierter C_5-C_7 -Cycloalkylrest ist.
6. Verfahren nach einem der Ansprüche 1 bis 4, worin R ein Isopropylrest ist.
7. Verfahren nach einem der Ansprüche 1 bis 5, worin R^1 ein Methylrest ist.
8. Verfahren nach einem der Ansprüche 1, 2, 5 und 6, worin R^2 ein trans-4-Methoxycyclohexylrest ist.
9. Verfahren nach Anspruch 1 oder 2 zur Herstellung von trans-4-Methoxycyclohexyl-1-isopropyl-9,10-dihydrolysergat oder einem pharmazeutisch annehmbaren Salz davon.



Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

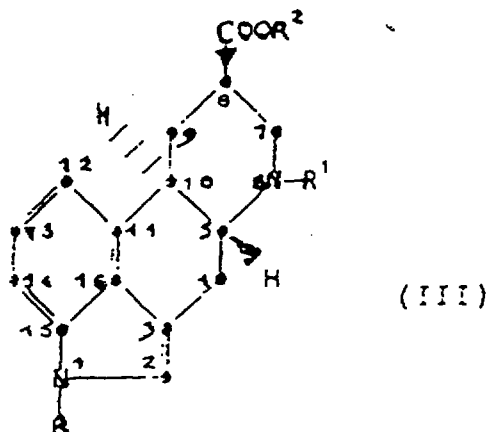
1. Composé de formule (III)

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dans laquelle R représente un groupe alkyle primaire ou secondaire en C₁-C₈, un groupe alcényl(en C₂-C₄)-CH₂, un groupe cycloalkyle en C₃-C₈ ou un groupe alkyle primaire ou secondaire en C₁-C₅ substitué par un groupe cycloalkyle en C₃-C₆, le nombre total des atomes de carbone dans R ne devant pas dépasser 8; R' représente un groupe allyle, H ou un groupe alkyle en C₁-C₄ à chaîne droite; et R² représente un groupe alcoxy(en C₁-C₃)cycloalkyle en C₅-C₇; un groupe cétoalkyle en C₃-C₇; ou encore un groupe cycloalkyle en C₅-C₇ ou un groupe cycloalkyle en C₅-C₇ substitué par un groupe céto; ou bien un de ses sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel R² représente un groupe alcoxy(en C₁-C₃)cycloalkyle en C₅-C₇.

3. Composé selon la revendication 1, dans lequel R² représente un groupe cétoalkyle en C₃-C₇.

4. Composé selon la revendication 1, dans lequel R² représente un groupe cycloalkyle en C₅-C₇ ou un groupe cycloalkyle en C₅-C₇ substitué par un groupe céto.

5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel R représente un groupe isopropyle.

6. Composé selon l'une quelconque des revendications 1 à 5, dans lequel R' représente un groupe méthyle.

7. Composé selon l'une quelconque des revendications 1, 2, 5 et 6, dans lequel R² représente un groupe trans-4-méthoxycyclohexyle.

8. 1-isopropyl-9,10-dihydrolysergate de trans-4-méthoxycyclohexyle ou un de ses sels pharmaceutiquement acceptables.

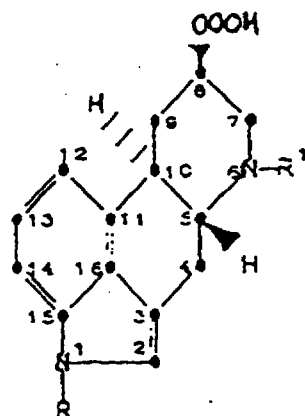
9. 1-isopropyl-9,10-dihydrolysergate maléate de trans-4-méthoxycyclohexyle.

10. Procédé pour préparer un composé de formule (III) tel que défini dans l'une quelconque des revendications 1 à 9, qui comprend le fait de :

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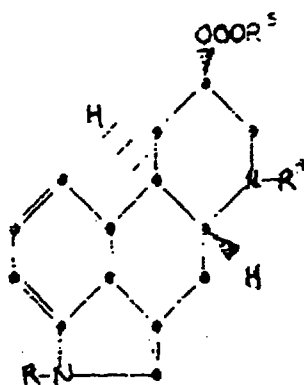


A) estérifier la fonction acide 8-carboxylique d'un composé de formule (V)



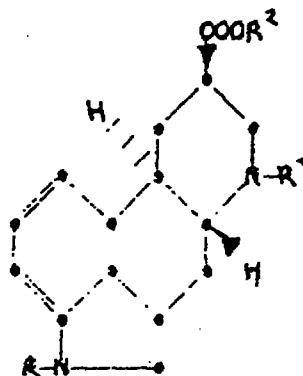
(V)

dans laquelle R et R^1 sont tels que définis à la revendication 1; ou
B) oxyder un composé de formule (VI)



(VI)

dans laquelle R^5 représente un groupe hydroxyalkyle en $\text{C}_3\text{-C}_6$;
C) alkyler un composé de formule (III)

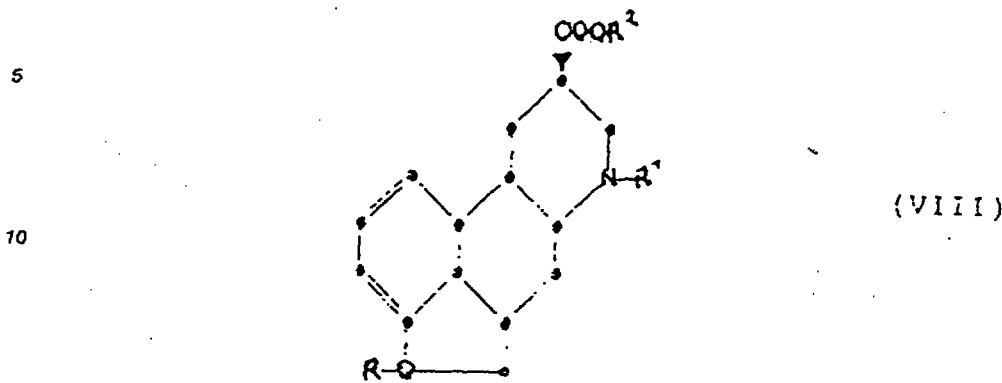


(III)

dans laquelle seulement un des radicaux R et R^1 représente un atome d'hydrogène; ou



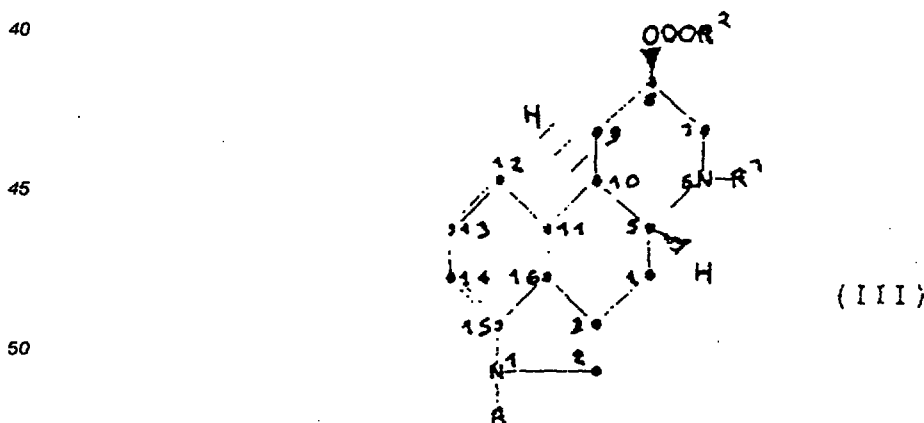
D) hydrogéner un composé de formule (VIII)



11. Procédé selon la revendication 10, pour préparer un composé de formule (III), qui comprend le fait de : faire réagir un composé de formule (V) avec un composé de formule R^2-O-SO_2-Z où Z représente un groupe alkyle en C_1-C_3 , un groupe phényle ou un groupe phényle substitué par un groupe alkyle en C_1-C_3 , par un groupe nitro, par un atome d'halogène ou par un groupe alcoxy en C_1-C_3 , en présence d'une base, dans laquelle R^2 est tel que défini à la revendication 1.
12. Composé de formule (III) ou un de ses sels pharmaceutiquement acceptables, tel que revendiqué dans l'une quelconque des revendications 1 à 9, pour être utilisé comme antagoniste des $5HT_2$.
13. 1-isopropyl-9,10-dihydrolysergate maléate de trans-4-méthoxycyclohexyle pour être utilisé dans le traitement de la migraine.
14. Formulation pharmaceutique comprenant, comme ingrédient actif, un composé de formule (III) ou un de ses sels d'addition d'acides pharmaceutiquement acceptables, tel que revendiqué dans l'une quelconque des revendications 1 à 9, en association avec un ou plusieurs supports pharmaceutiquement acceptables pour l'ingrédient.

Revendications pour l'Etat contractant suivant : AT

1. Procédé pour préparer un composé de formule (III)

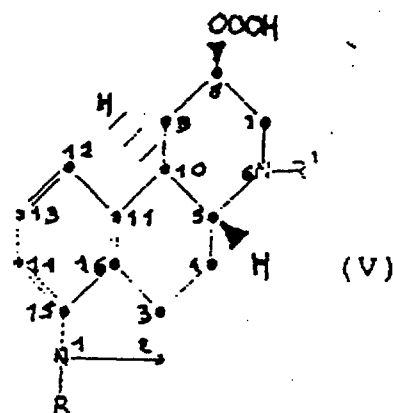


dans laquelle R représente un groupe alkyle primaire ou secondaire en C_1-C_3 , un groupe alcényle(en C_2-C_4)- CH_2 , un groupe cycloalkyle en C_3-C_6 ou un groupe alkyle primaire ou secondaire en C_1-C_5 substitué par un groupe cycloalkyle en C_3-C_6 , le nombre total des atomes de carbone dans R ne devant pas dépasser 8; R^1 représente un groupe allyle, H ou un groupe alkyle en C_1-C_4 à chaîne



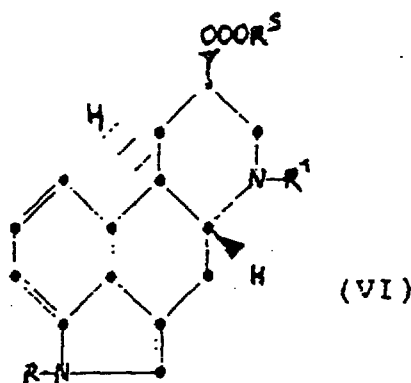
droite; et R^2 représente un groupe alcoxy(en C_1-C_3)cycloalkyle en C_5-C_7 ; un groupe cétoalkyle en C_3-C_7 ; ou encore un groupe cycloalkyle en C_5-C_7 ou un groupe cycloalkyle en C_5-C_7 substitué par un groupe céto; ou bien un de ses sels pharmaceutiquement acceptables, qui comprend le fait de

A) estérifier la fonction acide 8-carboxylique d'un composé de formule (V)

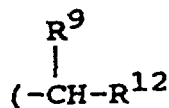


dans laquelle R et R^1 sont tels que définis à la revendication 1; ou

B) oxyder un composé de formule (VI)



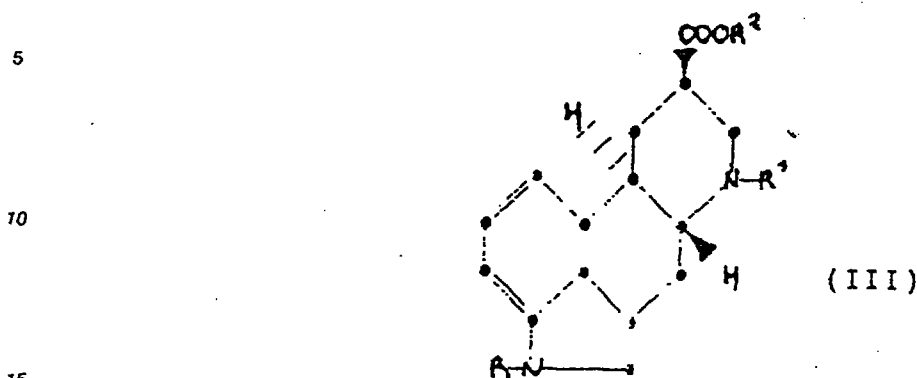
dans laquelle R^5 représente un groupe hydroxyalkyle en C_3-C_6



où R^9 représente H, un groupe méthyle ou un groupe éthyle, et R^{12} représente un groupe alkyle en C_2-C_5 contenant un groupe hydroxyle secondaire);

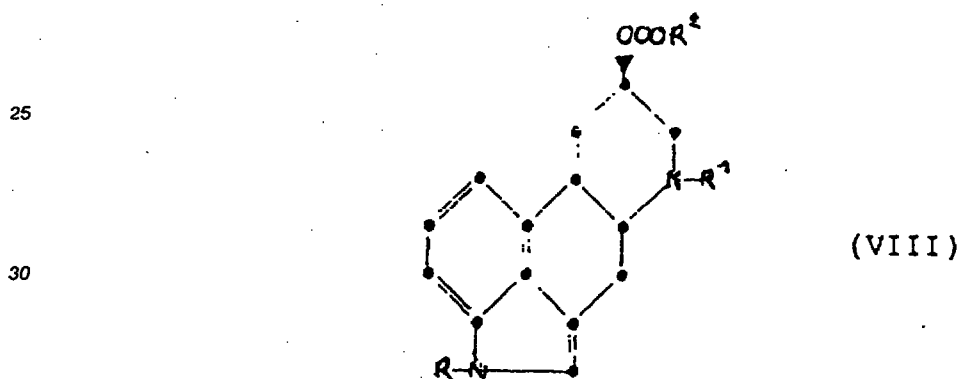


C) alkyler un composé de formule (III)



dans laquelle seulement un des radicaux R et R' représente un atome d'hydrogène; ou

20 D) hydrogéner un composé de formule (VIII)



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2. Procédé selon la revendication 1, pour préparer un composé de formule (III), qui comprend le fait de : faire réagir un composé de formule (V) avec un composé de formule R^2-O-SO_2-Z où Z représente un groupe alkyle en C_1-C_3 , un groupe phényle ou un groupe phényle substitué par un groupe alkyle en C_1-C_3 , par un groupe nitro, par un atome d'halogène ou par un groupe alcoxy en C_1-C_3 , en présence d'une base, dans laquelle R^2 est tel que défini à la revendication 1.
 3. Procédé selon la revendication 1 ou 2, dans lequel R^2 représente un groupe alcoxy(en C_1-C_3)-cycloalkyle en C_5-C_7 .
 4. Procédé selon la revendication 1 ou 2, dans lequel R^2 représente un groupe cétoalkyle en C_3-C_7 .
 5. Procédé selon la revendication 1 ou 2, dans lequel R^2 représente un groupe cycloalkyle en C_5-C_7 ou un groupe cycloalkyle en C_5-C_7 substitué par un groupe céto.
 6. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel R représente un groupe isopropyle.
 7. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel R^1 représente un groupe méthyle.
 8. Procédé selon l'une quelconque des revendications 1, 2, 5 et 6, dans lequel R^2 représente un groupe trans-4-méthoxycyclohexyle.



9. Procédé selon la revendication 1 ou 2, pour préparer le 1-isopropyl-9,10-dihydrolysergate de trans-4-méthoxycyclohexyle ou un de ses sels pharmaceutiquement acceptables.

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