100-6387

NAPHTHOXAZINES

The invention relates to naphthoxazines.

The invention provides 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazines in free base or acid addition salt form, for use as a psychostimulant and/or anti-depressant.

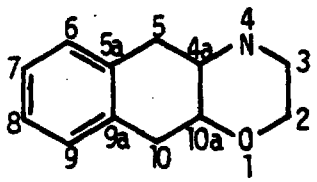
The basic compound 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine (also known in the literature as 2,4,4a,5,10,10a-hexahydro-4H-naphth[2,3-b]-1,4-oxazine or "naphthalane morpholine") and some N-substituted derivatives of this compound have been disclosed for the first time by L.Knorr in Liebigs Ann. Chem. 307, 171 (1899). Further N-substituted derivatives with analgesic and CNS depressant activity have been reported in the meantime. However, no 3,4,4a,5,10,10a-hexahydro-naphth[2,3-b]-1,4-oxazine substituted in the aromatic ring and having pharmaceutical activity has been disclosed so far.

Although some 6,9-disubstituted naphthoxazine-2-ones are known from K. Drandarov et al., Journal of Chromatography, 285 (1984), p. 374, only procedures resulting in reactions selective for some of the functional groups of these and related compounds are reported there.

Thus the invention also provides 3,4,4a,5,10,10a-hexahydro-2H-naphth-[2,3-b]-1,4-oxazines substituted in the aromatic ring by pharmacologically acceptable groups, in free base or acid addition salt form, for use as a pharmaceutical.

According to the present invention it has now surprisingly been found that the 3,4,4a,5,10,10a-hexahydro-naphth[2,3-b]-1,4-oxazines, hereinafter referred to as compounds of the invention, exhibit a totally unexpected psychostimulating and/or anti-depressive activity.

The compounds of the invention have the following structure:



A

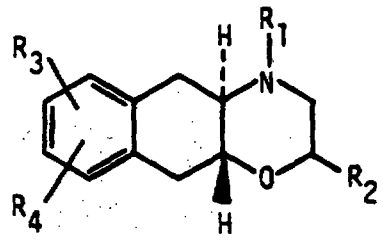
This basic structure may be substituted by pharmacologically acceptable groups. Examples of such groups are well known to the skilled man. In particular the 2, 4, 6, 7, 8 and 9 positions may be substituted. The compounds bearing on the aromatic ring of structure A (positions 6 to 9) at least one substituant chosen from the group alkoxy, alkylthio, alkylsulfoxide, alkylsulfone, alkyl, hydroxy, halogen and trifluoromethyl are preferred.

The compounds of the invention possess at least two asymmetrical carbon at in positions 4a and 10a. They may therefore appear in racemic or optically active forms. The invention relates to both the racemates and the optically active forms.

In positions 4a and 10a the compounds of the invention may have the cis configuration or the trans configuration. The compounds with the trans configuration are preferred.

The compounds of the invention may be present in free base form or as acid addition salts. The invention relates to both the free bases and the addition salt forms. Examples of suitable pharmaceutically acceptable acid addition salt forms are the hydrochlorides, hydrobromides, hydrogen maleates and hydrogen fumarates.

The invention relates in particular to compounds of formula I

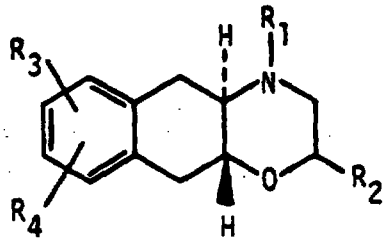


I

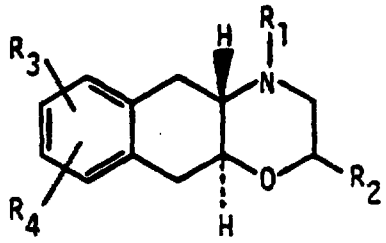
wherein R_1 and R_2 independently are hydrogen or (C_{1-4})alkyl,
R_3 is hydroxy or (C_{1-4})alkoxy and
R_4 is (C_{1-4})alkylthio, (C_{1-4})alkylsulfoxide, (C_{1-4})alkylsulfone, chlorine, bromine, iodine or trifluoromethyl,

in free base or acid addition salt form.

The compounds of formula I have the trans configuration in positions 4a and 10a. Following accepted nomenclature conventions, the above representation of formula I embraces the trans isomers with the configuration IA as well as those with the configuration IB.



IA



IB

As indicated above, the formula I also covers the corresponding racemates.

In the case where R_2 is not hydrogen, again both possible isomers as well as the corresponding racemates are covered by the invention.

Any alkyl, alkoxy, alkylthio, alkyl-SO- or alkyl-SO_2- preferably has one or two carbon atoms and especially one carbon atom.

R_3 and R_4 preferably are in para position for each other, i.e. in positions 6 and 9.

In a group of compounds of formula I,

R_1 and R_2 independently are hydrogen or (C_{1-4})alkyl,
R_3 and R_4 are in para position,
R_3 is (C_{1-4})alkoxy and
R_4 is chlorine, bromine, iodine or (C_{1-4})alkylthio.

The following significances are preferred:

R_1 is (C_{1-4})alkyl, particularly methyl;
R_2 is hydrogen;
R_3 is (C_{1-4})alkoxy, particularly methoxy;
R_4 is chlorine, bromine, iodine or (C_{1-4})alkylthio, particularly iodine or methylthio.

The compounds of the invention in free base or acid addition salt form may be prepared by a process which includes the step of

a) introducing in 2,3 position of a correspondingly substituted 1,4-dihydro-naphthaline an optionally substituted amino-ethyleneoxy bridge, or

b) reducing in 3 position a correspondingly substituted 2,4,4a,5,10,10a-hexahydro-3H-naphth[2,3-b]-1,4-oxazin-3-one, or

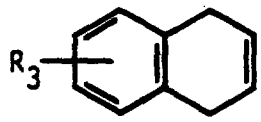
c) substituting in 4 position a correspondingly substituted 4-unsubstituted 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine, or

d) converting a thus obtained naphthoxazine into a further 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine substituted in the aromatic ring

and recovering the resultant naphthoxazine in free base or acid addition salt form.

In particular a compound of formula I in free base form or in acid addition salt form, may be prepared by a process which includes the step of

a) introducing in 2,3 position of a 1,4-dihydro-naphthaline of formula IX



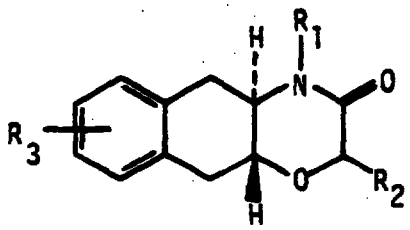
IX

wherein R_3 is hydroxy or (C_{1-4})alkoxy, an aminoethyleneoxy bridge of formula

$$-NR_1-CH_2-CHR_2-O-$$

wherein R_1 and R_2 are as defined above, or

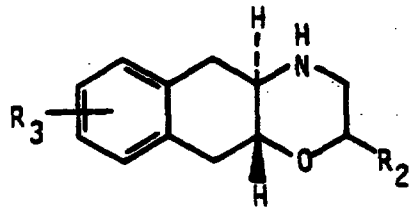
b) reducing in 3 position a 2,4,4a,5,10,10a-hexahydro-3H-naphth[2,3-b]-1,4-oxazine-3-one of formula IV



IV

wherein R_1, R_2 and R_3 are as defined above, or

c) alkylating in 4 position a 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine of formula III



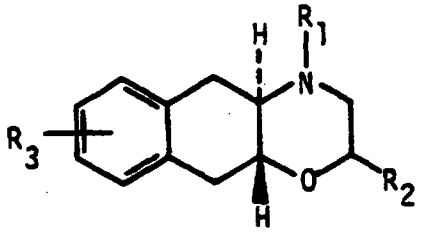
III

wherein R_2 and R_3 are as defined above, or

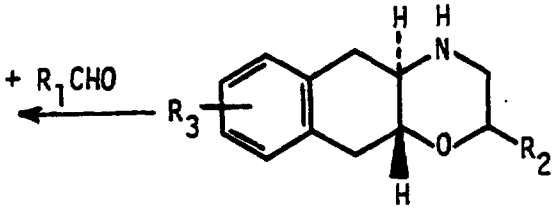
d) converting a 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine into a compound of formula I,

and recovering the resultant compound of formula I in free base or acid addition salt form.

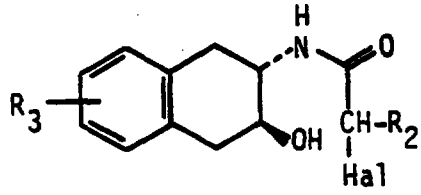
The steps a) to c) can be effected according to conventional methods, e.g. according to the following scheme which is illustrated in example 1 under a) to g). In this scheme R_1, R_2 and R_3 are as defined above and Hal is halogen, e.g. chlorine.



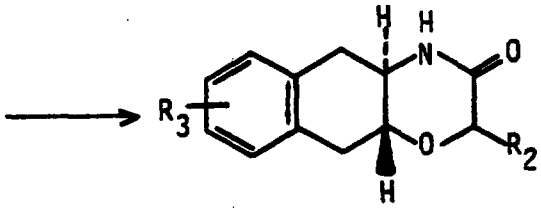
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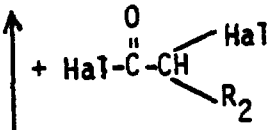
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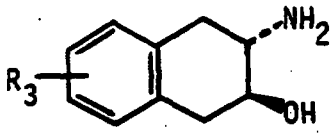


V

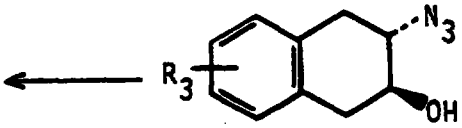


IVa

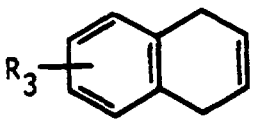




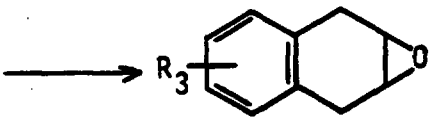
VI



VII



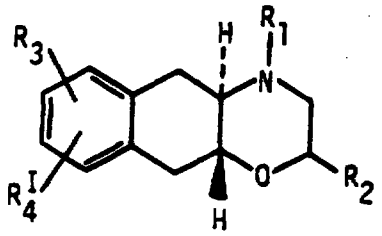
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VIII

According to the invention, step d) can be effected as follows:

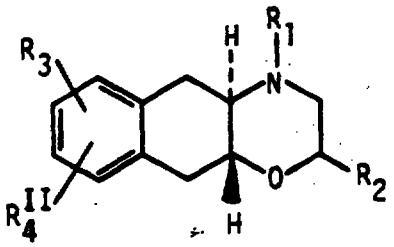
a') for the production of a compound of formula Ia



Ia

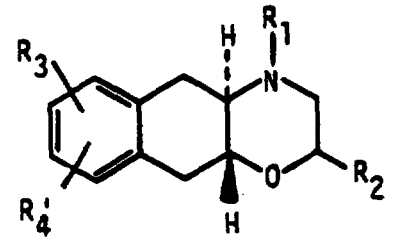
wherein R_1, R_2 and R_3 are as defined above and R_4^I is chlorine, bromine or iodine, introducing an halogen in a compound of formula II defined above, or

b') for the production of a compound of formula Ib



Ib

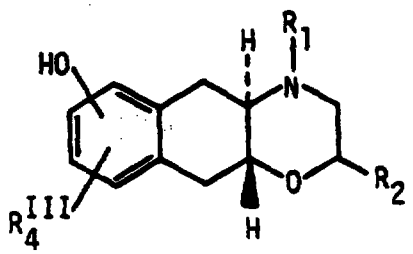
wherein R_1, R_2 and R_3 are as defined above and R_4^{II} is (C_{1-4})alkylthio or trifluoromethyl, replacing in a compound of formula Ia'



Ia'

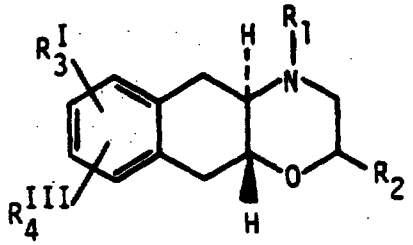
wherein R_1, R_2 and R_3 are as defined above and R_4' is a leaving group, the leaving group R_4' with a group R_4^{II}, or

c') for the production of a compound of formula Ic



Ic

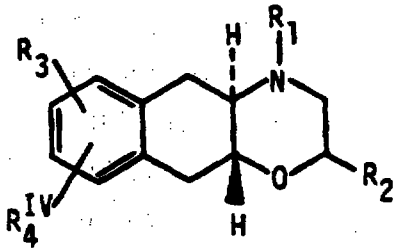
wherein R_1 and R_2 are as defined above and R_4^{III} is chlorine, bromine, iodine, (C_{1-4})alkylthio or trifluoromethyl, converting the alkoxy group of a compound of formula Id



Id

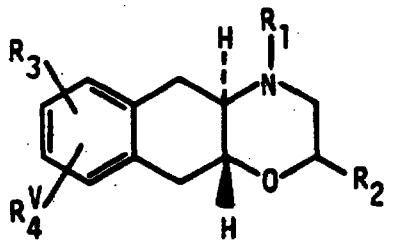
wherein R_1, R_2 and R_4^{III} are as defined above and R_3^{I} is (C_{1-4})alkoxy, into an hydroxy group, or

d') for the production of a compound of formula Ie



Ie

wherein R_1, R_2 and R_3 are as defined above and R_4^{IV} is (C_{1-4})alkylsulfoxide or (C_{1-4})alkylsulfone, oxidizing a compound of formula If



If

wherein R_1, R_2 and R_3 are as defined above and R_4^{V} is (C_{1-4})alkylthio, to the corresponding sulfoxide or sulfone,

and recovering the resultant compound of formula I in free base or acid addition salt form.

Introduction of halogen into compounds of formula II as in process a') may take place in known manner, for example adding silver trifluoroacetate, in an aprotic solvent, e.g. methylene chloride.

Substitution of the leaving group R_4' in the compounds of formula Ia' as in process b') may take place in accordance with known methods, R_4' being preferably halogen. Substitution of halogen by an alkylthio group occurs for example using the lithium salt of the corresponding thioalcohol with copper-I-oxide as the catalyst, in a dipolar-aprotic solvent, e.g. dimethylformamide, or also by means of a halogen-metal exchange using n-butyllithium, followed by reaction with the corresponding dialkyl disulphite or alkylthiosulphinic ester, in an aprotic solvent, e.g. tetrahydrofuran. Substitution of halogen by trifluoromethyl may take place for example using sodium trifluoroacetate.

The conversion of the alkoxy group into an hydroxy group as in process c') may take place in accordance with usual methods, for example reacting the compound of formula Id with boron tribromide in an inert organic solvant, or by treatment with strong mineral acids, e.g. hydrobromic acid.

The oxidation as in process d') may take place in accordance with known methods, e.g. using hydrogen peroxide.

Working up of the reaction mixtures obtained according to the above processes, and purification of the compounds of formula I thus obtained, may be effected in accordance with known methods.

The compounds of formula I may exist in free form or in the form of their addition salts with acids. Acid addition salts can be produced from the free base forms in known manner, and vice versa.

The starting compounds which are used for the processes described above consist in various 4a,10a-trans stereoisomers. Each of these processes may take place using starting compounds in form of the individual optically active isomers or their isomer mixtures, particularly their racemates, and leads to the corresponding end products.

The racemates may be separated into the individual optically active components, using known methods, e.g. formation of acid addition salts with optically active acids, e.g. (+)-[respect. (-)]-di-O,O'-p-toluolyl-D-(-)[respect. L-(+)]-tartaric acid, and fractionated cristallisation of the diastereoisomeric acid addition salts.

Insofar as the production of the starting products is not described, these are known, or they may be produced by known processes or in analogous manner to known processes. For example, the compound of formula IX, in which R_3 is methoxy, is described in German Published Specification No. 2 618 276.

The invention also comprises the starting compounds of formulae II, III and IV as defined above per se and the use of the compounds of formulae II, III and IV as pharmaceuticals.

The compounds according to the invention exhibit pharmacological activity and may therefore be used as pharmaceuticals.

They possess central, noradrenergic activity, which was demonstrated in the model of the rat with a bilaterally injured hypothalamus. In this test, male animals having a weight of ca. 250 g are anaesthetised with Pentobarbital (40 mg/kg i.p.), and treated with 19.5 to 26 µg of 6-OH-dopamine in the anterior hypothalamus (duration of injection: 15 minutes). After three days, the behaviour in the observation cage and the motor response in the light closet are determined, and the material values compared statistically with control values.

In this test, doses of ca. 0.1 to 20 mg/kg p.o. of the compounds produce an antagonistic effect on the induced behaviour hypokinesia.

Furthermore, in the sleep/wake cycle of the long-term implanted rat, the compounds effect an increase in vigilance at 1 to 100 mg/kg p.o., by bringing about a lengthening of the wake phases.

The compounds according to the invention may therefore be indicated for use as psychostimulants and antidepressants.

An indicated daily dose is from about 1 to 50 mg. Suitable forms of dosage generally contain about 0.3 to 50 mg of active substance, together with solid or liquid carrier substances or diluents.

In accordance with the foregoing, the present invention also provides

a) a pharmaceutical composition comprising a compound according to the invention in association with a pharmaceutical carrier or diluent, for use as a psychostimulant and/or anti-depressant,

b) a pharmaceutical composition comprising a 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine substituted in the aromatic ring by pharmacologically acceptable groups, in pharmaceutically acceptable form, in association with a pharmaceutical carrier or diluent.

Pharmaceutical compositions may be prepared by employing conventional techniques known in the galenic art. Suitable galenic forms for administration include e.g. tablets and liquid preparations.

In the following examples, all temperatures are uncorrected and are in degrees Centigrade.

EXAMPLE 1: trans-3,4,4a,5,10,10a-hexahydro-9-iodo-6-methoxy-4-methyl-2H-naphth[2,3-b]-1,4-oxazine

3.27 g (0.014 M) of trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-2H-naphth[2,3-b]-1,4-oxazine and 3.09 g (0.014 M) of silver trifluoroacetate are suspended in 100 ml of absolute methylene chloride. 3.43 g (0.027 M) of iodine dissolved in 200 ml of absolute methylene chloride are subsequently added in drops over the course of 10 minutes. The reaction mixture is stirred for 3 hours at 20 °, and is then filtered through a Hyflo filter. The residue of filtration is washed with 50 ml of methylene chloride. The methylene chloride solution is extracted with 50 ml of water, the organic phase dried and concentrated by evaporation. Trans-3,4,4a,5,10,10a-hexahydro-9-iodo-6-methoxy-4-methyl-2H-naphth[2,3-b]-1,4-oxazine is obtained as an oil. 1-H-NMR 90 MHz ($CDCl_3$): δ = 2.40 (S; 3H, N-CH3), 3.81 (s; 3H, O-CH3), 6.45 and 7.64 (AB, J = 9 Hz; 2H, aromatic-H).

The starting material may be produced as follows:

a) 1a,2,7,7a-tetrahydro-3-methoxy-naphth[2,3-b]oxirane

3.00 g (0.019 M) of 1,4-dihydro-5-methoxynaphthalene are dissolved in 52 ml of methylene chloride, and cooled with an ice bath to 0 °. 3.07 g (0.018 M) of m-chloro-perbenzoic acid are subsequently added to this solution over the course of one minute. The ice bath is removed, and the reaction mixture is stirred for 15 hours at room temperature. The suspension is then added to a mixture of 20 ml of 10 % sodium hydroxide and 40 g of ice. The organic phase is separated, and the aqueous phase is extracted twice, each time with 20 ml of methylene chloride. The combined organic phases are washed

with water and sodium chloride solution, dried and concentrated by evaporation. 1a,2,7,7a-tetrahydro-3-methoxy-naphth[2,3-b]oxirane is obtained (melting point 49.5 - 50.5 °, after purification by column chromatography, silica gel 0.063 - 0.200 mm, methylene chloride and recrystallisation from hexane).

b) trans-3-azido-1,2,3,4-tetrahydro-5-methoxy-2-naphthalinol

30.0 g (0.170 M) of 1a,2,7,7a-tetrahydro-3-methoxy-naphth[2,3-b]oxirane are dissolved in dimethyl sulphoxide. Furthermore, 90.0 g (1.384 M) of sodium azide are suspended in DMSO and 19.5 g (0.200 M) of concentrated sulphuric acid are dissolved in DMSO. The total quantity of DMSO is 1000 ml. The solutions and supensions are combined. Stirring subsequently takes place for 15 hours at 60 °. 1500 ml of methylene chloride are then added to the reaction mixture. A suspension is obtained, which is filtered over Hyflo. The rose solution is concentrated by evaporation at 60 ° (10 torr), then at 80 ° (high vacuum 1/100 torr). Trans-3-azido-1,2,3,4-tetrahydro-5-methoxy-2-naphthalinol (m.p. 83 - 84 °) and its structural isomer trans-3-azido-1,2,3,4-tetrahydro-8-methoxy-2-naphthalinol (m.p. 145 - 147 °) are obtained in a ratio of 1 : 1. The structural isomers are separated by fractional crystallisation (methylene chloride/hexane).

c) trans-3-amino-1,2,3,4-tetrahydro-5-methoxy-2-naphthalinol

4.0 g of palladium on charcoal (10 %) are coated with 100 ml of ethanol. 8.76 g (0.040 M) of trans-3-azido-1,2,3,4-tetrahydro-5-methoxy-2-naphthalinol are dissolved in 100 ml of ethanol, and the solution is added to the catalyst suspension. The mixture is subsequently hydrogenated at 20 ° at 1.2 bar hydrogen pressure. Every 10 minutes for 50 minutes, the reaction vessel is emptied and rinsed with hydrogen. The reaction mixture is then filtered through a G 4 Hyflo suction filter. The catalyst is washed with methylene chloride and the filtrate concentrated by evaporation. Trans-3-amino-1,2,3,4-tetrahydro-5-methoxy-2-naphthalinol is obtained (m.p. 130 - 132 ° after purification by column chromatography, silica gel, methylene chloride and 10 % methanol).

d) trans-2-chloro-N-(1,2,3,4-tetrahydro-2-hydroxy-5-methoxy-3-naphthalinyl)acetamide

1.01 g (0.005 M) of trans-3-amino-1,2,3,4-tetrahydro-5-methoxy-2-naphthalinol are dissolved in 50 ml of absolute methylene chloride. 0.81 g (0.008 M) of triethylamine are added, and the mixture left to cool to 0 °. At this temperature, 0.68 g (0.006 M) of chloroacetyl chloride (dissolved in 5 ml of absolute methylene chloride) are then added in drops over the course of 5 minutes. Stirring is effected for 2 hours at room temperature. The reaction mixture is subsequently washed once with 1 N hydrochloric acid and once with ice water. It is extracted three times,

each with 20 ml of methylene chloride, the combined organic phases are dried, and the solvent is concentrated by evaporation. Trans-2-chloro-N-(1,2,3,4-tetrahydro-2-hydroxy-5-methoxy-3-naphthalinyl)-acetamide is obtained (m.p. 176 - 178 °, recrystallisation from methylene chloride/ether).

e) trans-2,4,4a,5,10,10a-hexahydro-6-methoxy-3H-naphth[2,3-b]-1,4-oxazine-3-one

0.86 g (0.036 M) of sodium hydride and 0.24 g (0.652 mM) of tetrabutylammonium iodide are suspended in 100 ml of absolute tetrahydrofuran. A solution of 8.8 g (0.033 M) of trans-2-chloro-N-(1,2,3,4-tetrahydro-2-hydroxy-5-methoxy-3-naphthalinyl)acetamide in 300 ml of absolute THF is subsequently added in drops at room temperature over the course of 15 minutes. Stirring is effected for 18 hours at room temperature, under an argon atmosphere. The solvent is subsequently concentrated by evaporation, and the residue taken up in methylene chloride/ice water (1 : 1, 100 ml). The aqueous phase is separated, and the organic phase is extracted with 20 ml each of 1 N hydrochloric acid and water. The entire aqueous phases are again extracted with methylene chloride (twice, each time with 20 ml). The combined organic phases are dried and concentrated by evaporation. Trans-2,4,4a,5,10,10a-hexahydro-6-methoxy-3-naphth[2,3-b]-1,4-oxazin-3-one is obtained (m.p. 237 - 240 °, methylene chloride, acetone, ether).

f) trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-2H-naphth[2,3-b]-1,4-oxazine

3.87 g (0.102 M) of lithium aluminium hydride are suspended in 100 ml of absolute tetrahydrofuran. A solution of 5.93 g (0.025 M) of trans-2,4,4a,5,10,10a-hexahydro-6-methoxy-3H-naphth[2,3-b]-1,4-oxazin-3-one in 300 ml of absolute THF is subsequently added in drops. The reaction mixture is refluxed for 2 hours and then cooled to - 20 °. 100 ml of ice water and 200 ml of methylene chloride are added, and stirring is effected for 15 minutes. The suspension is then filtered over Hyflo, the methylene chloride phase separated and the residue of filtration washed with 50 ml of methylene chloride. The combined organic phases are dried and concentrated by evaporation. Trans-3,3,4a,5,10,10a-hexahydro-6-methoxy-2H-naphth[2,3-b]-1,4-oxazine is obtained as an oil. 1-H-NMR 360 MHz (CDCl3): δ = 2.34 (dd, J = 12 and 17 Hz; 1 H, c-5 H axial), 3.81 (s; 3 H, O-CH3).

g) trans-3,3,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-2H-naphth[2,3-b]-1,4-oxazine

2 g of palladium on charcoal (10 %) are suspended in 100 ml of methanol. To this are added 4.82 g (0.022 M) of trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-2H-naphth[2,3-b]-1,4-oxazine and 23.65 ml of formalin (37 %), both dissolved in a total of 200 ml of methanol. The mixture is subsequently hydrogenated at 20 °, at 1.2 bar hydrogen pressure. After 6 hours, the reaction mixture is filtered through a Hyflo suction filter, washed with 100 ml of methylene chloride, and

the filtrate is concentrated by evaporation. The residue is taken up again in 100 ml of methylene chloride, and washed once each time with 20 ml of saturated potassium carbonate solution and water. The methylene chloride phase is dried and concentrated by evaporation. Trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-2H-naphth[2,3-b]-1,4-oxazine is obtained (m.p. 268 - 270 °, recrystallisation from methylene chloride, methanol, acetone).

The following compounds of formula Ia are produced in analogous manner to example 1:

Example	R_1	R_2	R_3 (in 6)	R_4 (in 9)	Racemate Antipode	m.p. (Hydrochloride)
1b	$-CH_2CH_3$	H	$-OCH_3$	Br	racemate	300°
1c	$-(CH_2)_2-CH_3$	"	"	"	"	256-258°
1d	$-CH_3$	$-CH_3$	"	"	"	283-284°
1e	"	H	"	Cl	"	286-287°
1f	"	H	"	Br	"	286-287°
1g	"	$-CH_2CH_3$	"	"	"	285-286°
1h	"	"	"	Cl	"	230° (decomp.)
1i	"	"	"	I	"	268-270°
1j	$-CH_2CH_3$	$-CH_3$	"	"	"	271-272°
1k	$-CH_3$	H	Br	$-OCH_3$	"	263-265° (decomp.)
1l	"	"	I	$-OCH_3$	"	284-286° (decomp.)
1m	"	"	$-OCH_3$	I	(+)	284-286°
1n	"	"	"	"	(-)	284-286°

EXAMPLE 2: trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine (racemate) and (-)-(4aR,10aR)-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine

0.44 g (1.2 mM) of trans-3,4,4a,5,10,10a-hexahydro-9-iodo-6-methoxy-4-methyl-2H-naphth[2,3-b]-1,4-oxazine (for production see example 1), dissolved in 5 ml of DMF, as well as 2.34 g (16.3 mM) of copper-I-oxide, are added to a suspension of 0.53 g (9.8 mM) of methylthiolithium in 10 ml of dimethylformamide. The reaction mixture is subsequently stirred for 5 hours at 80 ° under an argon atmosphere. The preparation is then filtered through Hyflo, washed with 20 ml of methylene chloride, and the filtrate is concentrated by evaporation. The residue is taken up in 30 ml of methylene chloride/30 ml of ice water, the organic phase is separated, and the aqueous phase is extracted three times, each with 10 ml of methylene chloride. The combined organic phases are dried and concentrated by evaporation. Trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine is obtained as an oil. The oil is purified by chromatography (silica gel, methylene chloride, 5 % methanol). 1-H-NMR 90 MHz (CDCl3): δ= 2.36 (s; 3H, N-CH3), 2.42 (s; 3H, S-CH3), 3.81 (s; 3H, O-CH3).

1.40 g (5.0 mM) of the compound thus obtained are dissolved in 50 ml of acetone and cooled to 0 °. 2.75 ml (5.5 mM) of 2 N ethereal hydrochloric acid are subsequently added whilst stirring. The precipitated salt is filtered off and washed with ether. Trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine hydrochloride is obtained (m.p. 238 - 240 ° [decomposition], recrystallisation from acetone/ether).

Splitting of the racemic form:

4.96 g (17.8 mM) of trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine are dissolved in 150 ml of acetone. To this is added a solution of 7.19 g (17.8 mM) of (+)-di-O,O'-p-toluoyl-D-(-)-tartaric acid in 100 ml of acetone. The precipitating salt is stirred for one hour at room temperature and filtered off. The salt is recrystallised three times from methylene chloride/methanol (1 : 1). The salt is subsequently taken up in a mixture of 100 ml of ice water/10 ml of conc. ammonia/30 ml of methylene chloride. The organic phase is separated and the aqueous phase is extracted twice, each time with 20 ml of methylene chloride. The combined organic phases are dried and concentrated by evaporation. (-)-(4aR,10aR)-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine is obtained as an oil and has a rotation value $[\alpha]_D^{20}$ = - 121.3 ° [c = 0.52; methylene chloride/methanol (1 : 1)].

1.40 g (5.0 mM) of (-)-(4aR,10aR)-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine are dissolved in 50 ml of acetone and cooled to 0 °. 2.75 ml (5.5 mM) of 2 N ethereal hydrochloric acid are subsequently added whilst stirring. The precipitated salt is filtered off and washed with ether. (-)-(4aR,10aR)-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine hydrochloride is obtained (m.p. 237 - 239 °). Recrystallisation from acetone/ether, with the rotation value $[\alpha]_D^{20}$ = - 117.4 ° [c = 0.52; methylene chloride/methanol (1 : 1)].

The following compounds of formula Ib are produced in analogous manner to example 2:

Example	R_1	R_2	R_3 (in 6)	R_4 II (in 9)	Racemate Antipode	m.p.
2b	H	H	$-OCH_3$	$-SCH_3$	racemate	192-194(1)
2c	$-CH_3$	"	"	"	(+)	245-247°(2)
2d	"	$-CH_3$	"	"	racemate	211-213°(2)
2e	$-(CH_2)_2CH_3$	H	"	"	"	242-244°(2)
2f	$-CH_2CH_3$	"	"	"	"	238-239°(2)
2g	$-CH_3$	"	"	$-SCH_2CH_3$	"	209-210°(2)
2h	"	$-CH_2CH_3$	"	$-SCH_3$	"	210-212°(2)
2i	"	$-(CH_2)_2CH_3$	"	"	"	269-270°(2)
2j	$-CH_2CH_3$	$-CH_3$	"	"	"	231-232°(2)
2k	$-CH_3$	H	$-SCH_3$	$-OCH_3$	"	255-256°(2)
2l	"	"	$-OCH_3$	$-SCH(CH_3)_2$	"	214°(2)

(1) Hydrogen maleate

(2) Hydrochloride

EXAMPLE 3: trans-3,4,4a,5,10,10a-hexahydro-6-hydroxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine

1.63 g (5.84 mM) of trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine (for production see example 2) are dissolved in 65 ml of methylene chloride and the solution is cooled to - 40 ° under an argon atmosphere. 29 ml (29 mM) of a 1 M boron tribromide solution in methylene chloride are then added over the course of 10 minutes. The reaction mixture is left to reach room temperature and stirred 15 hours. The reaction product is then poored on ice and extracted once with 15 ml of 10 % sodium carbonate solution and once with 15 ml of water. The organic phase is dried and concentrated by evaporation. The crude product is taken up in 30 ml of acetone and 10 ml of ethereal hydrochloric acid (2 N) are added. The precipitated salt is filtered off. The hydrochloride of the title compound is obtained. M.p. 250 ° (decomposition), recrystallisation from methanol/acetone.

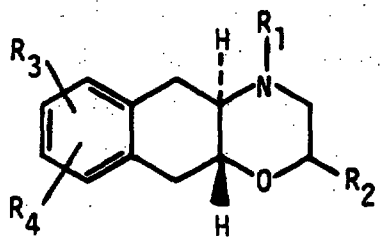
Trans-3,4,4a,5,10,10a-hexahydro-6-hydroxy-4-methyl-2H-naphth[2,3-b]-1,4-oxazine is produced in analogous manner to example 3. M.p. of the hydrochloride: 310 - 312 ° (decomposition).

EXAMPLE 4: trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylsulfoxide-2H-naphth[2,3-b]-1,4-oxazine

2.79 g (10 mM) of trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine (for production see example 2) are dissolved in 10 ml methylene chloride and 1.90 g (10 mM) p-toluenesulfonic acid hydrate are added. After cooling to 0 ° a solution of 1.7 g (10 mM) m-chloro-

CLAIMS

1. A process for the production of a compound of formula I



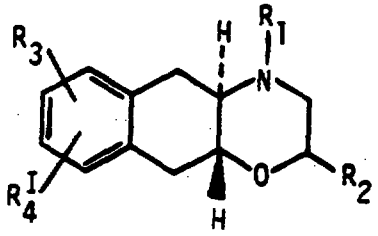
I

wherein R_1 and R_2 independently are hydrogen or (C_{1-4})alkyl,
R_3 is hydroxy or (C_{1-4})alkoxy and
R_4 is (C_{1-4})alkylthio, (C_{1-4})alkylsulfoxide, (C_{1-4})alkylsulfone, chlorine, bromine, iodine or trifluoromethyl,

in free base or acid addition salt form, which comprises

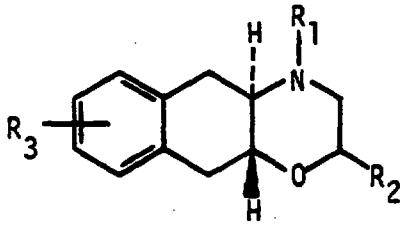
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a') for the production of a compound of formula Ia



Ia

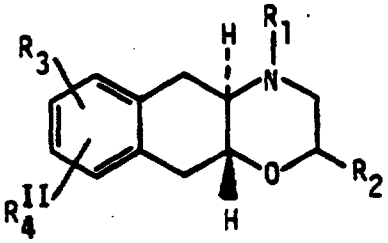
wherein R_1, R_2 and R_3 are as defined above and R_4^I is chlorine, bromine or iodine, introducing an halogen in a compound of formula II



II

wherein R_1, R_2 and R_3 are as defined above, or

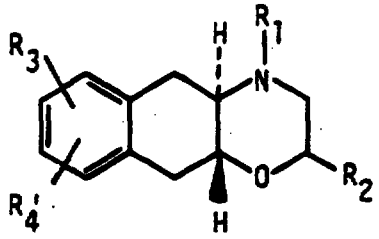
b') for the production of a compound of formula Ib



Ib

wherein R_1, R_2 and R_3 are as defined above and R_4^{II} is (C_{1-4})alkylthio or trifluoromethyl, replacing in a compound of formula Ia'

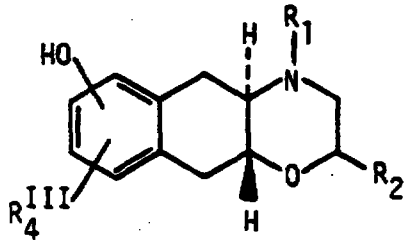
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Ia'

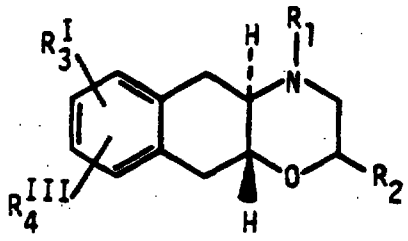
wherein R_1, R_2 and R_3 are as defined above and R_4' is a leaving group, the leaving group R_4' with a group R_4^{II}, or

c') for the production of a compound of formula Ic



Ic

wherein R_1 and R_2 are as defined above and R_4^{III} is chlorine, bromine, iodine, (C_{1-4})alkylthio or trifluoromethyl, converting the alkoxy group of a compound of formula Id

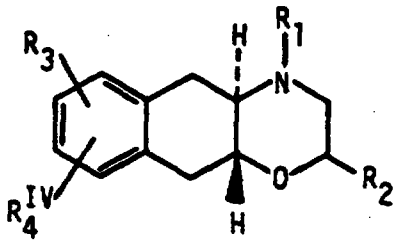


Id

wherein R_1, R_2 and R_4^{III} are as defined above and R_3^I is (C_{1-4})alkoxy, into an hydroxy group, or

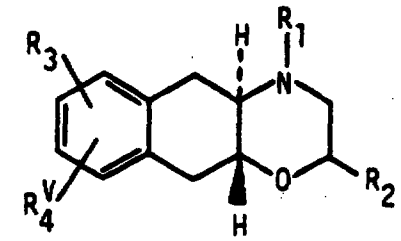
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d') for the production of a compound of formula Ie



Ie

wherein R_1, R_2 and R_3 are as defined above and R_4^{IV} is (C_{1-4})alkylsulfoxide or (C_{1-4})alkylsulfone, oxidizing a compound of formula If



If

wherein R_1, R_2 and R_3 are as defined above and R_4^{V} is (C_{1-4})alkylthio, to the corresponding sulfoxide or sulfone,

and recovering the resultant compound of formula I in free base or acid addition salt form.

2. A process for the production of a compound of formula I as defined in claim 1 in free base or in acid addition salt form substantially as hereinbefore described with reference to any one of the examples.

3. A compound of formula I as defined in claim 1 in free base or in acid addition salt form whenever produced by a process claimed in claim 1 or 2.

* C L M S *

4. A 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine in free base or acid addition salt form, for use as a psychostimulant.

5. A 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine in free base or acid addition salt form, for use as an anti-depressant.

6. A 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine substituted in the aromatic ring by pharmacologically acceptable groups, in free base or acid addition salt form, for use as a pharmaceutical.

7. A compound according to any one of claims 4 to 6 having the trans configuration in positions 4a and 10a.

8. A compound of formula I as defined in claim 1, in free base or acid addition salt form.

9. A compound of claim 8, wherein

R_1 and R_2 independently are hydrogen or (C_{1-4})alkyl,
R_3 and R_4 are in para position,
R_3 is (C_{1-4})alkoxy, and
R_4 is chlorine, bromine, iodine or (C_{1-4})alkylthio.

10. A compound of claim 8, wherein

R_1 is (C_{1-4})alkyl,
R_2 is hydrogen,
R_3 is (C_{1-4})alkoxy, and
R_4 is chlorine, bromine, iodine or (C_{1-4})alkylthio.

11. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methoxy and R_4 is iodine or methylthio.

12. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is iodine in 9 position.

* C L M S *

13. A compound of claim 8, wherein R_1 is ethyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is bromine in 9 position.

14. A compound of claim 8, wherein R_1 is n-propyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is bromine in 9 position.

15. A compound of claim 8, wherein R_1 and R_2 are methyl, R_3 is methoxy in 6 position and R_4 is bromine in 9 position.

16. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is chlorine in 9 position.

17. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is bromine in 9 position.

18. A compound of claim 8, wherein R_1 is methyl, R_2 is ethyl, R_3 is methoxy in 6 position and R_4 is bromine in 9 position.

19. A compound of claim 8, wherein R_1 is methyl, R_2 is ethyl, R_3 is methoxy in 6 position and R_4 is chlorine in 9 position.

20. A compound of claim 8, wherein R_1 is methyl, R_2 is ethyl, R_3 is methoxy in 6 position and R_4 is iodine in 9 position.

21. A compound of claim 8, wherein R_1 is ethyl, R_2 is methyl, R_3 is methoxy in 6 position and R_4 is iodine in 9 position.

22. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is bromine in 6 position and R_4 is methoxy in 9 position.

* C L M S *

23. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is iodine in 6 position and R_4 is methoxy in 9 position.

24. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is iodine in 9 position, in form of the (+)-isomer.

25. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is iodine in 9 position, in form of the (-)-isomer.

26. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is methylthio in 9 position.

27. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is methylthio in 9 position, in form of the (+)-isomer.

28. A compound of claim 8, wherein R_1 and R_2 are hydrogen, R_3 is methoxy in 6 position and R_4 is methylthio in 9 position.

29. A compound of claim 8, wherein R_1 and R_2 are methyl, R_3 is methoxy in 6 position and R_4 is methylthio in 9 position.

30. A compound of claim 8, wherein R_1 is n-propyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is methylthio in 9 position.

* C L M S *

31. A compound of claim 8, wherein R_1 is ethyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is methylthio in 9 position.

32. A compound of claim 8, wherein R_1 and R_2 are methyl. R_3 is methoxy in 6 position and R_4 is ethylthio in 9 position.

33. A compound of claim 8, wherein R_1 is methyl, R_2 is ethyl, R_3 is methoxy in 6 position and R_4 is methylthio in 9 position.

34. A compound of claim 8, wherein R_1 is methyl, R_2 is n-propyl, R_3 is methoxy in 6 position and R_4 is methylthio in 9 position.

35. A compound of claim 8, wherein R_1 is ethyl, R_2 is methyl, R_3 is methoxy in 6 position and R_4 is methylthio in 9 position.

36. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methylthio in 6 position and R_4 is methoxy in 9 position.

37. A compound of claim 8, wherein R_1 is methyl, R_2 is hydrogen, R_3 is methoxy in 6 position and R_4 is isopropylthio in 9 position.

38. A compound of any one of claims 3 and 8 to 37 in pharmaceutically acceptable form for use as a pharmaceutical.

39. A compound of any one of claims 3 and 8 to 37 in pharmaceutically acceptable form for use as a psychostimulant.

* C L M S *

40. A compound of any one of claims 3 and 8 to 37 in pharmaceutically acceptable form for use as an anti-depressant.

41. A pharmaceutical composition comprising a 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine in pharmaceutically acceptable form, in association with a pharmaceutical carrier or diluent, for use as a psychostimulant and/or antidepressant

42. A pharmaceutical composition comprising a 3,4,4a,5,10,10a-hexahydro-2H-naphth[2,3-b]-1,4-oxazine substituted in the aromatic ring by pharmaceutically acceptable groups, in pharmaceutically acceptable form, in association with a pharmaceutical carrier or diluent.

43. A pharmaceutical composition comprising a compound of any one of claims 3 and 8 to 37 in pharmaceutically acceptable form, in association with a pharmaceutical carrier or diluent.

* C L M S *

44. trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-napth[2,3-b]-1,4-oxazine in (-)(4aR,10aR) form or in the form of a racemate in free base form or in acid addition salt form.

45. trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-napth[2,3-b]-1,4-oxazine in (-)(4aR,10aR) form in free base form or in acid addition salt form.

46. trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-napth[2,3-b]-1,4-oxazine in (-)(4aR,10aR) form in acid addition salt form.

47. trans-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-napth[2,3-b]-1,4-oxazine in the form of a racemate in free base form or in acid addition salt form.

48. A compound according to any one of claims 44 to 47 in pharmaceutical acceptable form for use as a pharmaceutical.

49. A compound according to any one of claims 44 to 47 in pharmaceutical acceptable form for use as a psychostimulant.

50. A compound according to any one of claims 44 to 47 in pharmaceutical acceptable form for use as an antidepressant.

51. A compound according to claim 46 in pharmaceutically acceptable form for use as a pharmaceutical.

52. A compound according to claim 46 in pharmaceutically acceptable form for use as a psychostimulant.

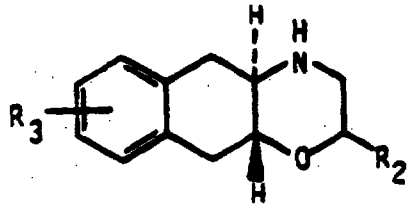
* C L M S *

53. A compound according to claim 46 in pharmaceutically acceptable form for use as an anti-depressant.

54. A pharmaceutical composition comprising a compound of any one of claims 44 to 47 in pharmaceutically acceptable form, in association with a pharmaceutical carrier or diluent.

55. A compound of formula II as defined in claim 1.

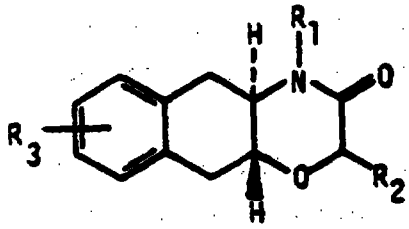
56. A compound of formula III



III

wherein R_2 and R_3 are as defined in claim 1.

57. A compound of formula IV



IV

wherein R_1, R_2 and R_3 are as defined in claim 1.

58. A compound of any one of claims 55 to 57 for use as a pharmaceutical.

* C L M S *