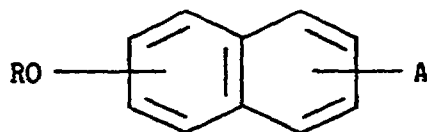


The present invention relates to new 1-alkoxy-(2-acylaminoethyl)naphthalene compounds, a process for their preparation and pharmaceutical compositions containing them.

A certain number of (2-aminoethyl)naphthalenes have already been described. Patent Application JP 50089352 describes naphthalene derivatives having analgesic anti-inflammatory antipyretic activity. Patent Application JP 61282348 describes (arylalkylaminoalkyl)naphthalenes as fungicidal agents. US Patent 4327022 describes aminoalkyldialkoxynaphthalenes as cardiotoxic agents. Patent Application EP 149588 describes (hydroxyaminoalkyl)methoxynaphthalenes as lipoxygenase inhibitors and thus useful in the treatment of asthma, inflammation and psoriasis. Patent Application FR 70.44709 describes 1-phenyl-2-[2-(naphth-1-yl)ethylamino]ethanols as anti-spasmodic and vasodilatory agents.

The Applicant has now discovered that the new 1-alkoxy-(2-acylaminoethyl)naphthalene compounds possess valuable pharmacological properties with respect to the central nervous system, especially anxiolytic, anti-psychotic and analgesic properties, and with respect to ovulation, cerebral circulation and immunomodulation, and are clearly distinguished from the aminoalkylnaphthalene compounds already described.

More especially, the invention relates to compounds of the general formula (I) :



(I)

wherein :

A represents a group $(\text{CH}_2)_2-\text{N}-\text{C}-\text{R}_2$,
 $\begin{array}{c} | \\ \text{R}_1 \end{array} \quad \begin{array}{c} || \\ \text{O} \end{array}$

R represents a straight-chain or branched lower alkyl group,

R₁ represents a hydrogen atom or a straight-chain or branched lower alkyl group,

R₂ represents . a hydrogen atom,
 . a straight-chain or branched lower alkyl group or a cycloalkyl group, each of which is optionally substituted by a halogen atom,
 . an aryl or heteroaryl or aryl-lower alkyl group or substituted aryl or substituted heteroaryl or substituted arylalkyl group, there being understood by heteroaryl group an unsaturated mono- or bi-cyclic group comprising from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur, each ring comprising 4 or 5 apices, and there being understood by aryl group phenyl or naphthyl,
 . an imidazolyl group that is optionally reduced and/or substituted by an oxo group,
 . a group of formula :

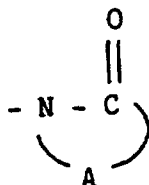
G representing a straight-chain or branched lower alkyl group, and

R₃ and R₄, which are the same or different, each representing a lower alkyl group or a hydrogen atom or a phenyl or phenyl-lower alkyl group, or R₃ and R₄,

together with the nitrogen atom to which they are attached, forming an aromatic or non-aromatic, mono- or bi-cyclic, heterocyclic system, each ring having five or six apices optionally comprising an additional hetero atom and optionally being substituted by one or more lower alkyl or oxo, aryl or aryl-lower alkyl, or substituted aryl or substituted aryl-lower alkyl groups,

the term "substituted" used in relation to aryl and arylalkyl or heteroaryl groups in the definition of R_2 , R_3 , R_4 indicating that those groups are substituted by one or more radicals selected from lower alkyl, lower alkoxy, trifluoromethyl and halogen,

or R₁ forms, with R₂ and the group N-CO, a heterocyclic system of the formula :



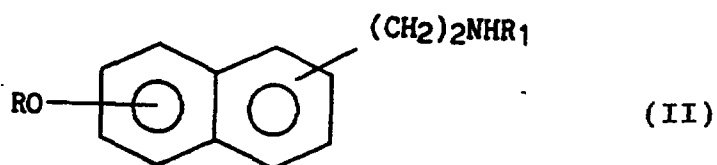
A representing a straight-chain or branched alkyl radical having from 2 to 8 carbon atoms,

their isomers, epimers and diastereoisomers and also, where appropriate, their addition salts with a pharmaceutically acceptable acid, the terms "lower alkyl" and "lower alkoxy" indicating groups comprising from 1 to 6 carbon atoms and "cycloalkyl" indicating groups comprising from 3 to 8 carbon atoms.

Of the pharmaceutically acceptable acids which may, where appropriate, be added to compounds of formula (I) to obtain a salt, there may be mentioned, by way of non-limiting example, hydrochloric acid, sulphuric acid, tartaric acid, maleic acid, fumaric acid, oxalic acid,

methanesulphonic acid and camphoric acid etc..

The presents invention relates also to a process for the preparation of compounds of formula (I) which is characterised in that there is used as starting material a compound of formula (II) :



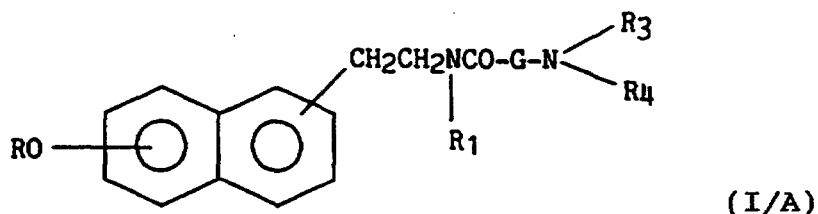
wherein R and R₁ are as defined for formula (I), which is treated :

- either with a compound of formula (III) :

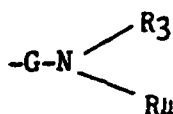


wherein E denotes a leaving group selected from hydroxy, lower alkoxy and halogen, and G, R₃ and R₄ are as defined for formula (I),

optionally in the presence of an alkaline agent, to yield a compound of formula (I/A), a particular case of compounds of formula (I) :



wherein R, R₁, R₃, R₄ and G are as defined hereinbefore, R₂ in this case indicating a group :



which is purified, if desired, by conventional methods such as chromatography and crystallisation, and which if desired is converted into a salt with a pharmaceutically acceptable acid,

- or with an acid chloride of formula (IV) :

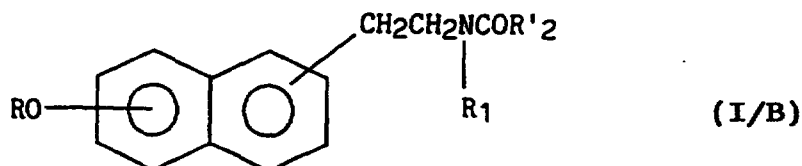


or with the corresponding acid anhydride,

R'_2 representing :

- a straight-chain or branched lower alkyl group or a cycloalkyl group, each of which is optionally substituted by a halogen atom,
- an aryl or heteroaryl or aryl-lower alkyl group, each of which is optionally substituted by one or more halogen atoms or groups selected from lower alkyl, lower alkoxy and trifluoromethyl,
- an imidazolyl group that is optionally reduced and/or substituted by an oxo group,

to yield a compound of formula (I/B) :



a particular case of compounds of formula (I) wherein R, R_1 and R'_2 are as defined hereinbefore,

which, if necessary, is purified by conventional methods, such as chromatography and/or crystallisation,

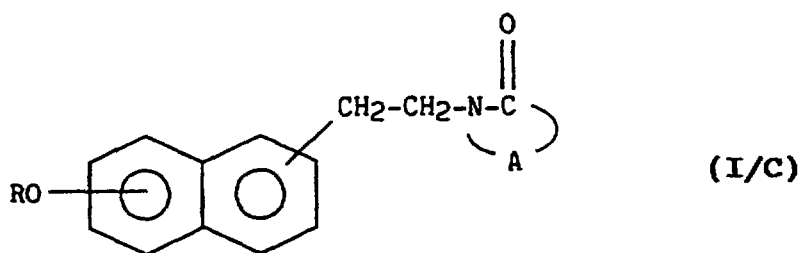
which compound of formula (I/B), when R'_2 represents a straight-chain or branched lower alkyl group that is substituted by a halogen atom, may, if desired, be subjected to the action of an amine of formula (V) :



wherein R_3 and R_4 are as defined hereinbefore,

in excess or in the presence of a tertiary amine or an alkali metal salt, to yield a compound of formula (I/A) as defined hereinbefore, which, if desired, is purified by a conventional method, such as chromatography and/or crystallisation, and/or converted into a salt with a pharmaceutically acceptable acid,

which compound of formula (I/B), when R'_2 represents a straight-chain or branched alkyl substituent that comprises at least two carbon atoms and is substituted by a halogen atom and when, simultaneously, R_1 represents a hydrogen atom, may, if desired, be subjected to the action of a strong base and preferably an alkali metal alcoholate to yield a compound of formula (I/C) :



wherein R is as defined hereinbefore and A represents a straight-chain or branched alkyl group comprising from 2 to 8 carbon atoms, a particular case of compounds of formula (I) in which R_1 and R_2 form with NCO a monocyclic system that is substituted by an oxo group and is optionally substituted by one or more lower alkyl groups, which, if desired, is purified by a method selected from crystallisation and chromatography.

The compounds of formula (I) have valuable pharmacological properties.

The pharmacological study of the compounds of the invention demonstrated that they were of low toxicity, had a very high selective affinity for melatonin receptors and significant effects on the central nervous system and, in particular, sedative, anxiolytic, anti-psychotic and analgesic properties, as well as effects on the microcirculation, were revealed, enabling it to be ascertained that the compounds of the invention are useful in the treatment of stress, sleep disorders, anxiety, seasonal depression, insomnia and fatigue due to shift work, schizophrenias, panic attack, melancholia, regulation of the appetite, insomnia, psychotic disorders, epilepsy, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, loss of memory, Alzheimer's disease, and also cerebral circulation disorders.

In another field of activity, the compounds of the invention appear to possess ovulation-inhibiting properties and immunomodulating properties and their use thus appears possible in the treatment of certain cancers and, when administered externally, they appear useful in the treatment of psoriasis, acne and seborrhoea, and they protect the skin and promote hair growth. They may also be of veterinary use for their property regarding animal fur.

The present invention relates also to pharmaceutical compositions comprising the compounds of formula (I) or, where appropriate, one of their addition salts with a pharmaceutically acceptable acid, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

Of the pharmaceutical compositions according to the invention there may be mentioned more especially those suitable for oral, parenteral, nasal, per- or trans-cutaneous, rectal, perlingual, ocular or respiratory administration and, in particular, tablets or dragées, sublingual tablets, sachets, paquets, gelatin capsules, glossettes, pills, suppositories, creams, ointments, dermal gels, injectable or drinkable ampoules etc...

The dosage varies according to the age and weight of the patient, the route of administration, the nature of the therapeutic indication or possible associated treatments and ranges from 0.1 mg to 1 g per 24 hours.

The following Examples illustrate the invention without in any way limiting it.

The compounds described in the "preparations" do not form part of the invention, but the description thereof facilitates the production of the compounds of the invention.

PREPARATION 1 : 2-(7-METHOXYNAPHTH-1-YL)ETHYLAMINE

STEP A : ETHYL (7-METHOXY-1,2,3,4-TETRAHYDRO-1-NAPHTHYLIDENE)ACETATE

Mix 50 g of 7-methoxy-1-tetralone, 40 g of ethyl bromoacetate and 150 cm³ of benzene using a dropping funnel. Add the mixture to zinc wire (18.6 g) activated according to Reformatsky and an iodine crystal. Heat to 60°C and then reflux for 45 minutes.

Hydrolyse on ice in the presence of hydrochloric acid. Extract with benzene, dry and bring to the boil in the

presence of P_2O_5 . Filter and bring to dryness.
The residue is used as it is in the following Step.

Yield : 80 %.

STEP B : ETHYL (7-METHOXYNAPHTH-1-YL)ACETATE

Mix 50 g of ethyl 7-methoxy-1,2,3,4-tetrahydro-1-naphthylidene acetate with 7.35 g of sulphur and heat at $215^{\circ}C$ for 10 hours. Cool, add 300 cm^3 of ethyl acetate, stir for 30 minutes and filter. Bring to dryness. The residue obtained is used as it is for the hydrolysis Step.

Yield : 70 %.

STEP C : (7-METHOXYNAPHTH-1-YL)ACETIC ACID

Heat at reflux for 3 hours in 250 cm^3 of 20 % sodium hydroxide in ethanol a mixture of the ethyl 7-methoxynaphth-1-yl acetate obtained in the preceding Step. Bring to dryness and wash the residue with ether. Precipitate with a stream of gaseous hydrogen chloride.

Melting point : $155-156^{\circ}C$.

Yield : 68 %.

STEP D : (7-METHOXYNAPHTH-1-YL)ACETIC ACID CHLORIDE

With the application of heat dissolve in 300 ml of chloroform the 7-methoxynaphth-1-ylacetic acid obtained in the preceding Step. Heat to reflux and then add thionyl chloride dropwise. Reflux for two hours and evaporate to dryness. An oil is obtained which crystallises on cooling. The residue obtained is used as it is in the following Step.

STEP E : (7-METHOXYNAPHTH-1-YL)ACETAMIDE

The (7-methoxynaphth-1-yl)acetic acid chloride obtained in the preceding step is dissolved in 200 ml of anhydrous ether. After cooling the solution using an ice-salt bath, add 200 ml of a concentrated aqueous ammonium hydroxide solution with stirring. Stir for 30 minutes and suction off the resulting precipitate. Recrystallise from ethanol.

Yield : 95 %

Melting point : 201-202°C.

STEP F : (7-METHOXYNAPHTH-1-YL)ACETONITRILE

Suspend the (7-methoxynaphth-1-yl)acetamide obtained in Step E in 80 ml of anhydrous THF. Add triethylamine. Cool the solution in an ice-bath and then add trifluoroacetic anhydride dropwise with magnetic stirring. Stir for one hour at room temperature. Bring to dryness. The residue is taken up in water. Suction off the resulting precipitate, dry and recrystallise from diisopropyl ether.

Yield : 83 %

Melting point : 82-84°C

Spectral characteristics :

Infrared : 2240 cm^{-1} CN

STEP G : 2-(7-METHOXYNAPHTH-1-YL)ETHYLAMINE

Place in an autoclave a solution of (7-methoxynaphth-1-yl)acetonitrile in ethanol saturated with ammonium hydroxide. Add Raney nickel and hydrogen under 300 atmospheres.

Stir at 60°C for one night. Filter and evaporate the filtrate in vacuo. The oil obtained is used as it is as starting material.

PREPARATION 2 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-N-METHYLAMINE

The title compound is obtained by proceeding as in Preparation 1, but replacing the ammonium hydroxide solution in Step E with methylamine and directly reducing the amide obtained.

PREPARATION 3 : 2-(6-METHOXYNAPHTH-1-YL)ETHYLAMINE

The title compound is obtained by proceeding as in Preparation 1, but replacing the 7-methoxy-1-tetralone in Step A with 6-methoxy-1-tetralone.

PREPARATION 4 : 2-(5-METHOXYNAPHTH-1-YL)ETHYLAMINE

The title compound is obtained by proceeding as in Preparation 1, but replacing the 7-methoxy-1-tetralone in Step A with 5-methoxy-1-tetralone.

PREPARATION 5 : 2-(7-METHOXYNAPHTH-2-YL)ETHYLAMINE

The title compound is obtained by proceeding as in Preparation 1, but replacing the 7-methoxy-1-tetralone in Step A with 7-methoxy-2-tetralone.

PREPARATION 6 : 2-(6-METHOXYNAPHTH-2-YL)ETHYLAMINE

The title compound is obtained by proceeding as in Preparation 1, but replacing the 7-methoxy-1-tetralone in Step A with 6-methoxy-2-tetralone.

EXAMPLE 1 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]ACETAMIDE

Dissolve 0.01 ml of 2-(7-methoxynaphth-1-yl)ethylamine in 6 ml of pyridine. Cool in an ice-bath and then, with stirring, add dropwise 0.012 mol of acetyl chloride. Continue stirring for 30 minutes and then pour the reaction mixture onto ice. Suction off the resulting precipitate, wash, dry and recrystallise from diisopropyl ether.

Yield : 92 %

Melting point : 109-110°C

Spectral characteristics :

Infrared : 3240 cm^{-1} ν NH

1640 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 1.93 ppm, singlet, 3H, COCH_3

δ : 3.96 ppm, singlet, 3H, OCH_3

**EXAMPLE 2 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
PHENYLACETAMIDE**

Dissolve 0.01 mol of 2-(7-methoxynaphth-1-yl)ethylamine hydrochloride (obtained by dissolving 2-(7-methoxynaphth-1-ylethylamine in ether and bubbling a stream of gaseous hydrogen chloride through, then suctioning off the resulting precipitate) in 60 ml of a water/chloroform mixture. Add, with magnetic stirring, 0.01 mol of potassium carbonate.

Cool and add dropwise 0.012 mol of phenylacetyl chloride. Continue stirring for 30 minutes at room temperature and bring the chloroform phase to dryness. Recrystallise from diisopropyl ether.

Yield : 92 %

Melting point : 101-102°C

Spectral characteristics :

Infrared : 3220 cm^{-1} ν NH

1640 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.50 ppm, unresolved peaks, 2H, $\text{CH}_2\text{-N}$

δ : 3.93 ppm, singlet, 1H, OCH_3

EXAMPLE 3 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]ISO-BUTYRAMIDE

The title compound is obtained by proceeding as in Example 1, but replacing the acetyl chloride with isobutyryl chloride.

Yield : 91 %

Melting point : $77\text{-}78^\circ\text{C}$

Spectral characteristics :

Infrared : 3240 cm^{-1} ν NH

1640 cm^{-1} ν CO

1620 cm^{-1} ν CC

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 1.11 ppm, doublet, 6H, 2CH_3 (isopropyl)

δ : 2.29 ppm, multiplet, 1H, CH (COCH)

δ : 3.98 ppm, singlet, 3H, OCH_3

EXAMPLE 4 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-PROPIONAMIDE

The title compound is obtained by proceeding as in Example 1, but replacing the acetyl chloride with propionyl chloride.

Melting point : $104\text{-}104.5^\circ\text{C}$.

**EXAMPLE 5 : N-[2-(7-METHOXY-NAPHTH-1-YL)ETHYL]-
PENTANAMIDE**

The title compound is obtained by proceeding as in Example 1, but replacing the acetyl chloride with pentanoyl chloride.

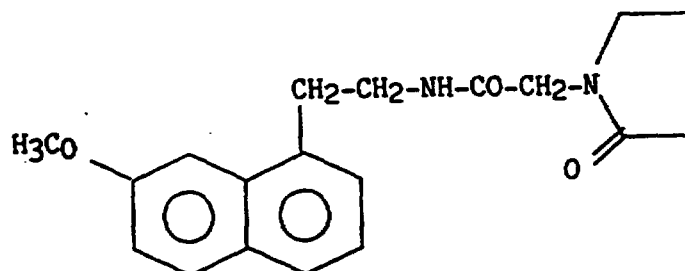
Crystallisation solvent : cyclohexane

Melting point : 90°C.

**EXAMPLE 6 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-(2-
OXOPYRROLIDIN-1-YL)ACETAMIDE**

OR

**1-{2[(2-OXOPYRROLIDIN-1-YL)ACETAMIDO]-
ETHYL}-7-METHOXYNAPHTHALENE**



Heat at a temperature of 80°C for 3 hours, with magnetic stirring, a mixture of 0.02 mol of 2-(7-methoxynaphth-1-yl)ethylamine and 0.022 mol of methyl (2-oxopyrrolidin-1-yl)acetate.

Take up the reaction mixture in slightly acidic water, and suction off the resulting precipitate.

Recrystallise from di-n-butyl ether.

Yield : 55 %

Melting point : 125-126°C

Spectral characteristics :

Infrared : 3310 cm⁻¹ √ NH
3060-2820 cm⁻¹ √ CH(CH₂CH₂)
1690 cm⁻¹ √ CO (CON)
1630-1600 cm⁻¹ √ CC (aromatic)

1030 cm^{-1} ν OCH₃

¹H Nuclear Magnetic Resonance, solvent CDCl₃ :

δ : 3.88 ppm, singlet, 2H, NHCOCH₂

δ : 4.00 ppm, singlet, 3H, OCH₃

**EXAMPLE 7 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-4-
CHLOROBUTYRAMIDE**

Dissolve 0.02 mol of 2-(7-methoxynaphth-1-yl)ethyl-amine hydrochloride in a mixture of water/chloroform. Add potassium carbonate and stir for 15 minutes in an ice-bath. Subsequently, add 0.022 mol of 4-chlorobutyryl chloride dropwise.

Continue stirring at room temperature for 1/2 hour.

Bring the chloroform phase to dryness.

Recrystallise the residue from a toluene/cyclohexane mixture (1:1).

Yield : 93 %

Melting point : 97-98°C

Spectral characteristics :

Infrared : 3320 cm^{-1} ν NH

 1635 cm^{-1} ν CO

**EXAMPLE 8 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
PYRROLIDIN-2-ONE**

Dissolve 0.01 mol of sodium in 50 cm³ of ethanol. Add, with magnetic stirring, the N-[2-(7-methoxynaphth-1-yl)ethyl]4-chlorobutyramide obtained in Example 7.

Continue stirring for 20 minutes.

Bring to dryness. Dissolve in 40 cm³ of anhydrous dimethylformamide.

Heat at the boil for 7 hours.

Evaporate in vacuo and take up in ether.

Filter and bring to dryness. Recrystallise from petroleum

ether.

Yield : 35 %

Melting point : 60-61°C

Spectral characteristics :

Infrared : 3060-2820 cm^{-1} $\downarrow$ CH
1670 cm^{-1} $\downarrow$ CO

EXAMPLE 9 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-BROMOACETAMIDE

The method of operation is the same as in Example 7, replacing the 4-chlorobutyryl chloride with bromoacetic acid chloride.

Melting point : 100-101°C

Yield : 93 %

Spectral characteristics :

Infrared : 3260 cm^{-1} $\downarrow$ NH
1635 cm^{-1} $\downarrow$ CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 2.83 ppm, singlet, 2H, (CH_2Br)

δ : 3.98 ppm, singlet, 3H, (OCH_3)

EXAMPLE 10 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-MORPHOLINOACETAMIDE

Dissolve, with magnetic stirring, 0.01 mol of morpholine in 50 cm^3 of acetone. Add 0.012 mol of triethylamine and 0.01 mol of N-[2-(7-methoxynaphth-1-yl)ethyl]-2-bromoacetamide. Reflux for 1 hour with magnetic stirring. Suction off the resulting precipitate and evaporate the filtrate.

Take up the residue in alkaline water. Suction off the precipitate, wash, dry and recrystallise from a toluene/-cyclohexane mixture.

Spectral characteristics :

Infrared : 1645 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.98 ppm, singlet, 3H, OCH_3

δ : 2.92 ppm, singlet, 2H, $(\text{CO}-\text{CH}_2)$

Melting point : 114-115°C

Yield : 93 %.

EXAMPLE 11 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-(4-
[(2,3,4-TRIMETHOXYPHENYL)METHYL]-
PIPERAZIN-1-YL)ACETAMIDE HYDROCHLORIDE

The title compound is obtained by proceeding as in the preceding Example, but replacing the morpholine with 1-[(2,3,4-trimethoxyphenyl)methyl]piperazine. The hydrochloride is obtained by dissolving the product in acetone, bubbling a stream of HCl through, evaporating, and recrystallising from absolute alcohol.

Spectral characteristics :

Infrared : 1670 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.99 ppm, singlet, 3H, OCH_3

Melting point : 207-208°C

Yield : 90 %

EXAMPLE 12 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-N-METHYLACETAMIDE

The title compound is obtained by replacing the 2-(7-methoxynaphth-1-yl)ethylamine in Example 1 with N-[2-(7-methoxynaphth-1-yl)ethyl]-N-methylamine.

Spectral characteristics :

Infrared : 1640 cm^{-1} ν CO

¹H Nuclear Magnetic Resonance, solvent CDCl₃ :

δ : 3.98 ppm, singlet, 3H, OCH₃

**EXAMPLE 13 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
BENZAMIDE**

The title compound is obtained by replacing the phenylacetyl chloride in Example 2 with benzoyl chloride.

Spectral characteristics :

Infrared : 1640 cm⁻¹ νCO

¹H Nuclear Magnetic Resonance, solvent CDCl₃ :

δ : 3.98 ppm, singlet, 3H, OCH₃

Melting point : 128-130°C

Yield : 94 %.

**EXAMPLE 14 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]PARA-
TOLUOYL CARBOXAMIDE**

The title compound is obtained by replacing the phenylacetyl chloride in Example 2 with paratoluoyl chloride.

Spectral characteristics :

Infrared : 1635 cm⁻¹ νCO

¹H Nuclear Magnetic Resonance, solvent CDCl₃ :

δ : 3.95 ppm, singlet, 3H, OCH₃

**EXAMPLE 15 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-4-
FLUOROBENZAMIDE**

The title compound is obtained by replacing the phenylacetyl chloride in Example 2 with parafluorobenzoyl chloride.

Spectral characteristics :

Infrared : 1635 cm^{-1} $\downarrow$ CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.95 ppm, singlet, 3H, OCH_3

EXAMPLE 16 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-3-TRIFLUOROMETHYL BENZAMIDE

The title compound is obtained by replacing the phenylacetyl chloride in Example 2 with 3-trifluoromethylbenzoyl chloride.

Spectral characteristics :

Infrared : 1635 cm^{-1} $\downarrow$ CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.95 ppm, singlet, 3H, OCH_3

EXAMPLE 17 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-3,5-DICHLOROBENZAMIDE

The title compound is obtained by replacing the phenylacetyl chloride in Example 2 with 3,5-dichlorobenzoyl chloride.

Yield : 93 %

Melting point : 138°C

EXAMPLE 18 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-ISONICOTINAMIDE

The title compound is obtained by replacing the phenylacetyl chloride in Example 2 with isonicotinoyl chloride.

Spectral characteristics :

Infrared : 1635 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.95 ppm, singlet, 3H, OCH_3

EXAMPLE 19 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-THIOPHENECARBOXAMIDE

The title compound is obtained by replacing the phenylacetyl chloride in Example 2 with 2-thiophene-carbonyl chloride.

Spectral characteristics :

Infrared : 1635 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.95 ppm, singlet, 3H, OCH_3

EXAMPLE 20 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-QUINOXALINECARBOXAMIDE

The title compound is obtained by replacing the phenylacetyl chloride in Example 2 with 2-quinoxaloyl chloride.

Spectral characteristics :

Infrared : 1635 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.95 ppm, singlet, 3H, OCH_3

EXAMPLE 21 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]INDOL-2-YLCARBOXAMIDE

The title compound is obtained by replacing the phenylacetyl chloride in Example 2 with 2-indolyl

chloride.

Melting point : 198-199°C

Spectral characteristics :

Infrared : 3400 cm^{-1} ν NH (indole)
3300 cm^{-1} ν NH
1640 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.98 ppm, singlet, 3H, OCH_3

EXAMPLE 22 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-BENZYLAMINOACETAMIDE

The title compound is obtained by proceeding as in Example 10 but replacing the morpholine with benzylamine.

Spectral characteristics :

Infrared : 1635 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.95 ppm, singlet, 3H, OCH_3

EXAMPLE 23 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-(N',N'-DIETHYL)AMINOACETAMIDE

The title compound is obtained by proceeding as in Example 10 but replacing the morpholine with N,N-diethylamine.

Spectral characteristics :

Infrared : 1635 cm^{-1} ν CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.95 ppm, singlet, 3H, OCH_3

EXAMPLE 24 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-AMINOACETAMIDE, HYDROCHLORIDE

Dissolve 0.012 mol of hexamethylene tetramine in 15 cm³ of chloroform with magnetic stirring, and introduce 0.01 mol of N-[2-(7-methoxynaphth-1-yl)ethyl]-2-bromoacetamide obtained in Example 9 dissolved in 20 cm³ of chloroform. Bring to reflux for 100 hours. Suction off, dry. Introduce the precipitate into a flask with a ground neck. Add 150 cm³ of alcohol and 30 cm³ of concentrated hydrochloric acid. Reflux for 2 hours. Evaporate the solvent. Recrystallise from alcohol at 90°C.

Spectral characteristics :

Infrared : 1635 cm⁻¹ ν CO

¹H Nuclear Magnetic Resonance, solvent CDCl₃ :

δ : 3.95 ppm, singlet, 3H, OCH₃

EXAMPLE 25 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-[4-(4-FLUOROPHENYL)PIPERAZIN-1-YL]-ACETAMIDE

The title compound is obtained by proceeding as in Example 10 but replacing the morpholine with 1-(4-fluorophenyl)piperazine.

EXAMPLE 26 : N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-2-[4-(3-TRIFLUOROMETHYLPHENYL)PIPERAZIN-1-YL]ACETAMIDE

The title compound is obtained by proceeding as in Example 10 but replacing the morpholine with 1-(3-trifluoromethyl)piperazine.

**EXAMPLE 27 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
BUTYRAMIDE**

The title compound is obtained by proceeding as in Example 1 but replacing the acetyl chloride with butyryl chloride.

Melting point : 99°C

**EXAMPLE 28 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-4-
IMIDAZOLYLACETAMIDE**

Dissolve 0.01 mol of 2-(7-methoxynaphth-1-yl)ethyl-amine hydrochloride in 60 ml of a mixture of water and chloroform. Add, with magnetic stirring, 0.025 mol of potassium carbonate. Cool and add dropwise 0.012 mol of 4-imidazoleacetic acid chloride hydrochloride. Continue stirring for 30 minutes at room temperature and evaporate the chloroform phase to dryness. Recrystallise.

Yield : 67 %

Spectral characteristics :

Infrared : 1640 cm^{-1} $\downarrow$ CO

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.91 ppm, singlet, 1H, OCH_3

**EXAMPLE 29 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-2-
IMIDAZOLINONE-4-CARBOXAMIDE**

The title compound is obtained by proceeding as in Example 1 but replacing the acetyl chloride with 2-imidazolinone-4-carboxylic acid chloride.

Yield : 55 %

Spectral characteristics :

^1H Nuclear Magnetic Resonance, solvent CDCl_3 :

δ : 3.89 ppm, singlet, 1H, OCH_3

EXAMPLE 30 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
CYCLOHEXANECARBOXAMIDE (R₂ = cyclo-
hexyl)

The title compound is obtained by proceeding as in
Example 1 but replacing the acetyl chloride with cyclo-
hexanecarboxylic acid chloride.

Recrystallisation solvent : cyclohexane

Melting point : 105-106°C

EXAMPLE 31 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
CYCLOPROPANECARBOXAMIDE (R₂ = cyclo-
propyl)

The title compound is obtained by proceeding as in
Example 1 but replacing the acetyl chloride with cyclo-
propylcarboxylic acid chloride.

Crystallisation solvent : cyclohexane

Melting point : 91-92°C

EXAMPLE 32 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
IODOACETAMIDE

The title compound is obtained by treating the N-[2-
(7-methoxynaphth-1-yl)ethyl]-2-bromoacetamide obtained in
Example 9 with potassium iodide.

Recrystallisation solvent : ethanol

Melting point : 110-112°C

**EXAMPLE 33 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
FORMAMIDE**

Place 0.01 mol of 2-(7-methoxynaphth-1-yl)ethylamine and 0.02 mol of formic acid in a porcelain crucible. Heat at 120° until a dry residue is obtained. Recrystallise.

Melting point : 93°C

Spectral characteristics :

Nuclear Magnetic Resonance :

δ : 4.05 ppm, singlet, 3H, OCH₃

**EXAMPLE 34 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
CYCLOBUTANECARBOXAMIDE**

The title compound is obtained by proceeding as in Example 1 but replacing the acetyl chloride with cyclobutanecarboxylic acid chloride.

**EXAMPLE 35 : N-[2-(7-METHOXYNAPHTH-1-YL)ETHYL]-
CYCLOPENTANECARBOXAMIDE**

The title compound is obtained by proceeding as in Example 1 but replacing the acetyl chloride with cyclopentanecarboxylic acid chloride.

By proceeding as in the preceding Examples, the following are obtained in the same way :

N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-4-BROMOBUTYRAMIDE

N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-5-BROMOPENTANAMIDE

N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-3-BROMOPROPIONAMIDE

**N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-3-MORPHOLINOPROPION-
AMIDE**

N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-4-MORPHOLINOBTYRAMIDE

N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-4-{4-[(2,3,4-TRI-METHOXYPHENYL)METHYL]-1-PIPERAZINYL}BUTYRAMIDE
N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-3-{4-[(2,3,4-TRI-METHOXYPHENYL)METHYL]-1-PIPERAZINYL}PROPIONAMIDE
N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]PIPERIDIN-2-ONE
N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-2-BROMOPROPIONAMIDE
N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]-2-{4-[(2,3,4-TRI-METHOXYPHENYL)METHYL]-1-PIPERAZINYL}PROPIONAMIDE

By replacing the 2-(7-methoxynaphth-1-yl)ethylamine in the preceding Examples with 2-(6-methoxynaphth-1-yl)-ethylamine or with 2-(5-methoxynaphth-1-yl)ethylamine, the compounds of the preceding Examples methoxylated respectively in the 6 or 5 position of the naphthalene are obtained instead of compounds methoxylated in the 7 position.

The following are obtained by replacing the 2-(7-methoxynaphth-1-yl)ethylamine in the preceding Examples with 2-(7-methoxynaphth-2-yl)ethylamine :

N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]ACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]PHENYLACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]ISOBUTYRAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]PROPIONAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]PENTANAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-(2-oxopyrrolidin-1-yl)acetamide
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-4-CHLOROBUTYRAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]PYRROLIDIN-2-ONE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-BROMOACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-MORPHOLINOACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-{4-[2,3,4-TRIMETHOXY-PHENYL)METHYL]PIPERAZIN-1-YL}ACETAMIDE HYDROCHLORIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-N-METHYLACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]BENZAMIDE

N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]PARATOLUOYLCARBOXAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-4-FLUOROBENZAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-3-TRIFLUOROMETHYL-
BENZAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-3,5-DICHLOROBENZAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]ISONICOTINAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-THIOPHENECARBOXAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-QUINOXALINE-
CARBOXAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-INDOL-2-YLCARBOXAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-BENZYLAMINOACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-(N',N'-DIETHYL-
AMINO)ACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-AMINOACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-[4-(4-FLUOROPHENYL)-
PIPERAZIN-1-YL]ACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-[4-(3-TRIFLUORO-
METHYLPHENYL)PIPERAZIN-1-YL]ACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]BUTYRAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-4-IMIDAZOLYLACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]-2-IMIDAZOLINONE-4-
CARBOXAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]CYCLOHEXANECARBOXAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]CYCLOPROPANECARBOXAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]IODOACETAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]FORMAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]CYCLOBUTANECARBOXAMIDE
N-[2-(7-METHOXYNAPHTH-2-YL)ETHYL]CYCLOPENTANECARBOXAMIDE

If, in those syntheses, the 2-(7-methoxynaphth-2-yl)ethylamine is replaced with 2-(6-methoxynaphth-2-yl)ethylamine, the isomers of the preceding compounds in which the methoxy group is in the 6 position are obtained.

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

EXAMPLE A : ACUTE TOXICITY STUDY

The acute toxicity was determined after oral administration to groups each comprising 8 mice (26 ± 2 grams). The animals were observed at regular intervals during the course of the first day and daily for the two weeks following treatment. The LD_{50} causing the death of 50 % of the animals was determined.

The LD_{50} of the tested compounds is greater than 1000 mg/kg^{-1} for most of the compounds studied, which indicates the weak toxicity of the compounds of the invention.

EXAMPLE B : MEASUREMENT OF ACTIVITY

The animals are placed in plexiglass boxes fitted with photoelectric cells and the boxes are placed in a darkened atmosphere. Six animals are tested simultaneously and the number of interruptions of the photoelectric beams by each animal is recorded informatively for one hour.

The compounds to be tested are administered by the intraperitoneal route immediately before the animals are placed in the apparatus.

The compounds of the invention reduce the activity of the animals.

EXAMPLE C : FOUR PLATES TEST

The compounds of the invention are administered by the oesophageal route to groups each comprising ten mice. One group is given acacia syrup.

30 minutes after the administration of the compounds to be studied, the animals are placed in cages in which the

floor comprises four metallic plates. Each time the animal moves from one plate to another it receives a slight electrical discharge (0.35 mA). The number of moves from one plate to another is recorded for one minute. After administration, the compounds of the invention significantly increase the number of moves from one plate to another, demonstrating the anxiolytic activity of the compounds of the invention.

**EXAMPLE D : ACTIVITY OF THE COMPOUNDS OF THE
INVENTION ON ISCHAEMIC MICROCIRCULATION**

The experimental study was carried out on the cremaster muscles of male rats (Sprague-Dawley) after ligation of the common iliac artery.

The muscles were placed in a transparent chamber, perfused with a solution of bicarbonate buffer equilibrated with a gas mixture of CO₂/N₂ 5/95 %. The speed of the red corpuscles and the diameter of the first or second order arterioles irrigating the cremaster were measured, and the arteriolar blood flow was calculated. Identical information was obtained for four types of veinules.

The same type of measurement was carried out simultaneously :

- on the normally perfused cremaster,
- on the cremaster with ligation, that is to say the ischaemic cremaster, 2, 7, 14 and 21 days after ligation.

Two groups of animals were studied :

- a control group without treatment,

- a group treated per os with a compound of the invention at a dose of 0.1 mg/kg^{-1} per day.

Compared with the controls, there was no difference observed either in the speed of the corpuscles or in the diameter of the vessels in the normally irrigated cremaster muscles of the treated animals.

On the other hand, in the case of the ischaemic cremaster muscle, the mean diameter of the arterioles was improved in the treated animals by comparison with the controls. The speed of the red corpuscles was normalised by a 21-day treatment.

Indeed, in the treated animals, the speed of the red corpuscles and the blood flow measured 7 days after ligature are not significantly different from the values obtained for the non-ischaemic cremaster. Those results are obtained without modification of the arterial pressure.

These results indicate that chronic treatment by a compound of the invention improves the microcirculation and the blood supply of ischaemic areas.

EXAMPLE E : STIMULATION OF IMMUNE RESPONSES

Red corpuscles from sheep were administered to groups each comprising six mice. Those groups of mice were then treated by the subcutaneous route with compounds of the invention for six days, and a control group was treated with a placebo. The mice were then left to rest for four weeks and subsequently were given a reminder injection of sheep red blood corpuscles without being given any further administrations of a compound of the invention. The immune response was evaluated 3 days after the

reminder injection. It was statistically higher in the group treated with the compounds of the invention.

EXAMPLE F : INHIBITION OF OVULATION

Adult female rats with regular four-day cycles are used.

Vaginal smears were taken daily and rats were selected after they had shown at least two consecutive cycles of four days.

Each cycle is made up of two days of dioestrus, one day of proestrus and one day of oestrus.

In the afternoon of the day of proestrus, the luteinizing hormone is released in the blood by the hypophysis. That hormone induces ovulation, which is demonstrated by the presence of eggs in the oviduct on the day of oestrus.

The compounds of the invention are administered by the oral route at midday on the day of oestrus. The treated rats and control rats are sacrificed on the day of oestrus. The oviducts are examined. A significant percentage decrease in the number of eggs is observed in the oviducts of treated rats.

EXAMPLE G : DEMONSTRATION OF ANALGESIC ACTIVITY

The activity on pain was researched in mice (23-25 g) in accordance with a protocol derived from the technique described by SIEGMUND (SIEGMUND E.A., R.A. CADMUS & GOLU, J. Pharm. Exp. Ther. 119, 1874, 1954). The mice, divided randomly into groups each comprising 12 animals, received treatment by the oral route (excipient for the controls)

1 hour before intraperitoneal injection of a 0.02 % aqueous alcoholic solution of phenyl-p-benzoquinone (Sigma). The writhes were counted between the 5th and 10th minute after the injection.

It was apparent that some of the compounds of the invention possess an analgesic activity.

EXAMPLE H : POTENTIALISATION OF SLEEP INDUCED BY BARBITURATES

Mice (22-25 mg) are injected with 50 mg/kg⁻¹ of pentobarbital by the intraperitoneal route. The time when sleep commences and the duration of sleep are measured. Sleep is recognised as when the animals cease the reflex of turning. The compounds to be tested are administered by the intraperitoneal route 30 minutes before the injection of the barbiturate. Some compounds of the invention increase the duration of sleep induced by pentobarbital.

EXAMPLE I : MELATONIN RECEPTOR BINDING TEST

The binding to melatonin receptors of the compounds of the invention was carried out according to conventional methods. It appears that the compounds of the invention bind very specifically to melatonin receptors with an affinity greater than that of melatonin itself. The most interesting have a K.d of 5.5×10^{-13} whilst melatonin itself has a K.d of 6.3×10^{-11} , which indicates that some compounds of the invention have a selective affinity for melatonin receptors which is 100 times greater than that of melatonin itself.

EXAMPLE J : HYPOGLYCAEMIC ACTIVITY STUDY

KK male mice were placed in cages at the age of eight weeks. They are used for the experiment when their weight is greater than 40 grams at the age of 4-5 months.

The compound of the invention is suspended in acacia syrup. Each compound tested is administered orally 18 hours before the blood sample is taken.

The blood is taken by drawing off at the level of the caudal vein in a hematocrit tube, and is then centrifuged. The plasma is collected and the extent of glycaemia is ascertained.

It appears that some of the compounds of the invention decrease glycaemia significantly.

EXAMPLE K : PHARMACEUTICAL COMPOSITION : TABLETS

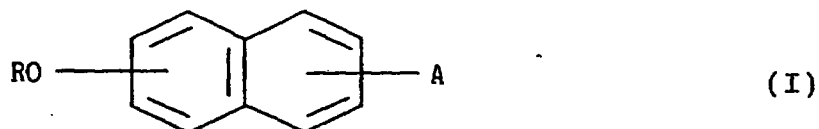
Tablets each comprising 50 mg of N-[2-(7-methoxy-1-naphthyl)ethyl]butyramide

N-[2-(7-methoxy-1-naphthyl)ethyl]butyramide	50 g
wheat starch	15 g
corn starch	15 g
lactose	15 g
magnesium stearate	2 g
silica	1 g
hydroxypropylcellulose	2 g

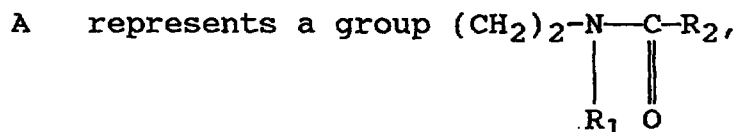


CLAIMS for the Contracting States: AT BE CH DE DK FR GB
IT LI LU NL SE

1 - Compounds of the general formula (I) :



wherein :



R represents a straight-chain or branched lower alkyl group,

R₁ represents a hydrogen atom or a straight-chain or branched lower alkyl group,

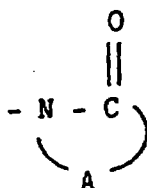
R₂ represents . a hydrogen atom,
 . a straight-chain or branched lower alkyl group or a cycloalkyl group, each of which is optionally substituted by a halogen atom,
 . an aryl or heteroaryl or aryl-lower alkyl group or substituted aryl or substituted heteroaryl or substituted arylalkyl group, there being understood by heteroaryl group an unsaturated mono- or bi-cyclic group comprising from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur, each ring comprising 4 or 5 apices, and there being understood by aryl group phenyl or naphthyl,

- $$\text{-G-N} \begin{array}{l} \diagup \text{R}_3 \\ \diagdown \text{R}_4 \end{array}$$

R₃ and R₄, which are the same or different, each representing a lower alkyl group or a hydrogen atom or a phenyl or phenyl-lower alkyl group, or R₃ and R₄, together with the nitrogen atom to which they are attached, forming an aromatic or non-aromatic, mono- or bi-cyclic, heterocyclic system, each ring having five or six apices optionally comprising an additional hetero atom and optionally being substituted by one or more lower alkyl or oxo, aryl or aryl-lower alkyl, or substituted aryl or substituted aryl-lower alkyl groups,

the term "substituted" used in relation to aryl and arylalkyl or heteroaryl groups in the definition of R_2 , R_3 , R_4 indicating that those groups are substituted by one or more radicals selected from lower alkyl, lower alkoxy, trifluoromethyl and halogen,

or R_1 forms, with R_2 and the group N-CO, a heterocyclic system of the formula :



A representing a straight-chain or branched alkyl radical having from 2 to 8 carbon atoms,



and also, where appropriate, their isomers, epimers and diastereoisomers and their addition salts with a pharmaceutically acceptable acid,

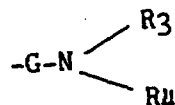
the terms "lower alkyl" and "lower alkoxy" indicating groups comprising from 1 to 6 carbon atoms and "cycloalkyl" indicating groups comprising from 3 to 8 carbon atoms.

2 - Compounds according to claim 1 wherein the OR group is in the 7-position, and also, where appropriate, their isomers, epimers and diastereoisomers and their addition salts with a pharmaceutically acceptable acid.

3 - Compounds according to claim 1 wherein R_1 represents a hydrogen atom or forms, with R_2 and the group N-CO, the 2-pyrrolidinone system, and also, where appropriate, their isomers, epimers and diastereoisomers and their addition salts with a pharmaceutically acceptable acid.

4 - Compounds according to claim 1 wherein R_2 represents:

- . a straight-chain or branched lower alkyl group or a cycloalkyl group, each of which is optionally substituted by a halogen atom,
- . a mono- or bi-cyclic aryl or heteroaryl group or an aryl-lower alkyl group, each of which is optionally substituted by one or more halogen atoms or groups selected from lower alkyl, lower alkoxy and trifluoromethyl,
- . a group of formula :



G representing a straight-chain or branched lower alkyl group, and

R_3 and R_4 , together with the nitrogen atom to which they



are attached, forming a mono- or bi-cyclic, heterocyclic system, each ring having five or six apices optionally comprising an additional hetero atom and optionally being substituted by a lower alkyl or oxo, aryl or aryl-lower alkyl, or substituted aryl or substituted aryl-lower alkyl group, the term "substituted" used in relation to aryl and arylalkyl groups indicating that those groups may be substituted by one or more radicals selected from lower alkyl, lower alkoxy, trifluoromethyl and halogen, and also, where appropriate, their isomers, epimers and diastereoisomers and their addition salts with a pharmaceutically acceptable acid.

5 - Compounds according to either claim 1 or 2 wherein the group OR is in the 7-position, R_1 represents a hydrogen atom and R_2 represents a straight-chain or branched lower alkyl group or a cycloalkyl group, each of which is optionally substituted by a halogen atom, and also, where appropriate, their isomers, epimers and diastereoisomers.

6 - Compounds according to claim 1 wherein the group OR is in the 7-position, R_1 represents a hydrogen atom and R_2 represents a mono- or bi-cyclic aryl or heteroaryl group optionally substituted by one or more halogen atoms, and also, where appropriate, their isomers, epimers and diastereoisomers.

7 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]cyclopropylcarboxamide.

8 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl](2-oxopyrrolidin-1-yl)acetamide.

9 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]pyrrolidin-2-one.



10 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]acetamide.

11 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]isobutyramide.

12 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]butyramide.

13 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]propionamide.

14 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]-4-chlorobutyramide.

15 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]-2-morpholinoacetamide.

16 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]-2-{4-[(2,3,4-trimethoxyphenyl)-methyl]piperazin-1-yl}acetamide, and also the addition salts thereof with a pharmaceutically acceptable acid.

17 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]benzamide.

18 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]-3,5-dichlorobenzamide.

19 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]-(indol-2-yl)carboxamide.

20 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]pentanamide.



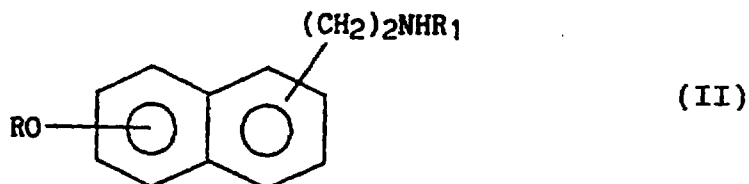
21 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]cyclobutanecarboxamide.

22 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]-2-iodoacetamide.

23 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]-2-bromoacetamide.

24 - Compound according to claim 1, which is N-[2-(7-methoxynaphth-1-yl)ethyl]-2-chloroacetamide.

25 - Process for the preparation of compounds of formula (I) according to claim 1, characterised in that there is used as starting material a compound of formula (II) :

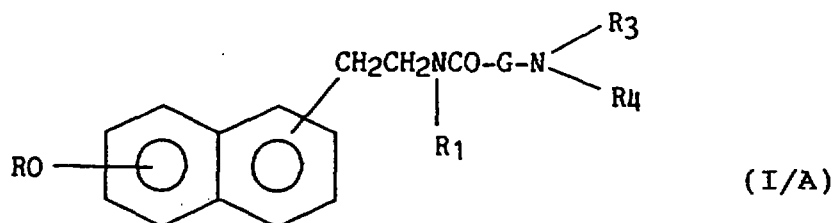


wherein R and R₁ are as defined for formula (I), which is treated :

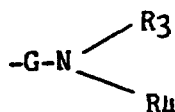
- either with a compound of formula (III) :



wherein E denotes a leaving group selected from hydroxy, lower alkoxy and halogen, and G, R₃ and R₄ are as defined for formula (I), optionally in the presence of an alkaline agent, to yield a compound of formula (I/A), a particular case of compounds of formula (I) :



wherein R, R₁, R₃, R₄ and G are as defined hereinbefore, R₂ in this case indicating a group :



which is purified, if desired, by conventional methods such as chromatography and crystallisation, and which if desired is converted into a salt with a pharmaceutically acceptable acid,

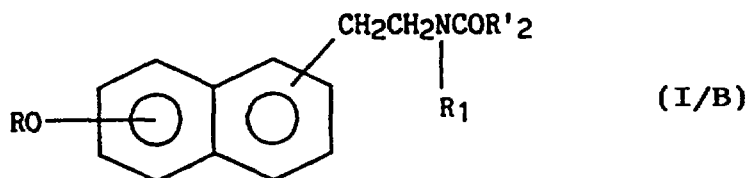
- or with an acid chloride of formula (IV) :



or with the corresponding acid anhydride, R'₂ representing :

- a straight-chain or branched lower alkyl group or a cycloalkyl group, each of which is optionally substituted by a halogen atom,
- an aryl or heteroaryl or aryl-lower alkyl group, each of which is optionally substituted by one or more halogen atoms or groups selected from lower alkyl, lower alkoxy and trifluoromethyl,
- an imidazolyl group that is optionally reduced and/or substituted by an oxo group,

to yield a compound of formula (I/B) :





wherein R, R₁ and R'₂ are as defined hereinbefore, which, if necessary, is purified by conventional methods, such as chromatography and/or crystallisation,

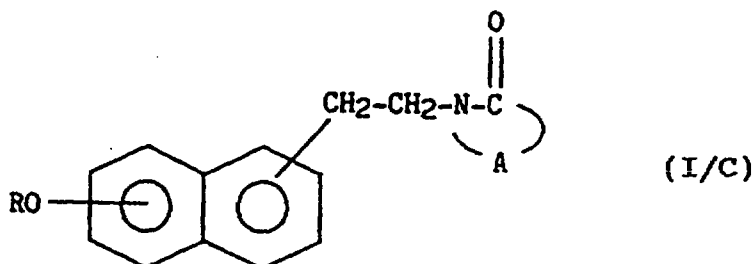
which compound of formula (I/B), when R'₂ represents a straight-chain or branched lower alkyl group that is substituted by a halogen atom, may, if desired, be subjected to the action of an amine of formula (V) :



wherein R₃ and R₄ are as defined hereinbefore,

in excess or in the presence of a tertiary amine or an alkali metal salt, to yield a compound of formula (I/A) as defined hereinbefore, which, if desired, is purified by a conventional method, such as chromatography and/or crystallisation, and/or converted into a salt with a pharmaceutically acceptable acid,

which compound of formula (I/B), when R'₂ represents a straight-chain or branched alkyl substituent that comprises at least two carbon atoms and is substituted by a halogen atom and when, simultaneously, R₁ represents a hydrogen atom, may, if desired, be subjected to the action of a strong base and preferably an alkali metal alcoholate to yield a compound of formula (I/C) :

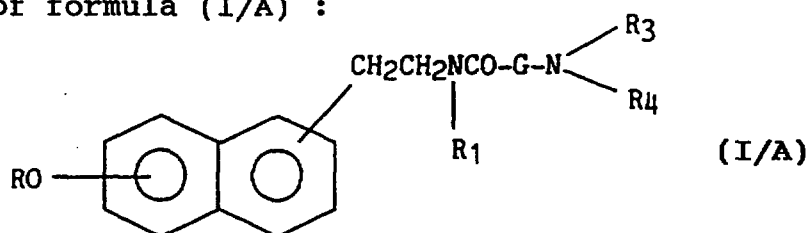


wherein R is as defined hereinbefore and A represents a straight-chain or branched alkyl group comprising from 2

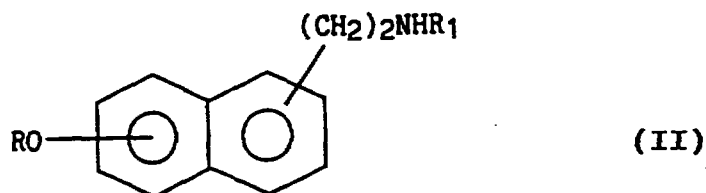


to 8 carbon atoms, a particular case of compounds of formula (I) in which R_1 and R_2 form with NCO a monocyclic system that is substituted by an oxo group and is optionally substituted by one or more lower alkyl groups, which, if desired, is purified by a method selected from crystallisation and chromatography.

26 - Process according to claim 25 for the preparation of compounds of formula (I/A) :



wherein R, R_1 , R_3 , R_4 and G are as defined for formula (I), characterised in that a compound of formula (II) :



wherein R and R_1 are as defined for formula (I) is treated with a compound of formula (III) :

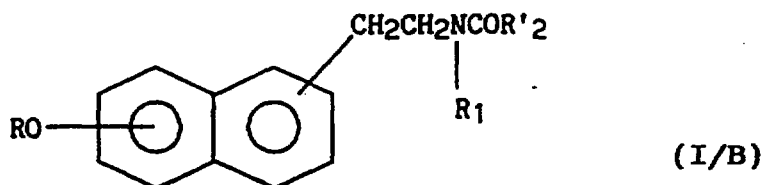


wherein E represents a leaving group selected from hydroxy, lower alkoxy and halogen, and G, R_3 and R_4 are as defined for formula (I), optionally in the presence of an alkaline agent, to yield a compound of formula (I/A) which, if desired, is purified by conventional methods, such as chromatography and crystallisation, of which, where appropriate, the isomers are separated, and which, if desired, is



converted into a salt with a pharmaceutically acceptable acid.

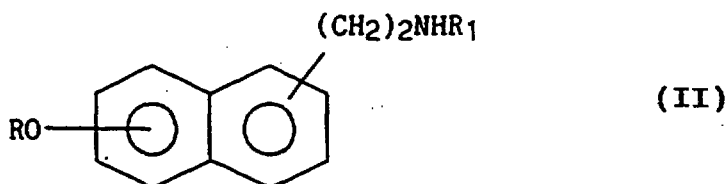
27 - Process according to claim 25 for the preparation of compounds of formula (I/B) :



wherein R and R₁ are as defined for formula (I), and R₂ represents :

- a straight-chain or branched lower alkyl group or a cycloalkyl group, each of which is optionally substituted by a halogen atom,
- an aryl or heteroaryl or aryl-lower alkyl group, each of which is optionally substituted by one or more halogen atoms or groups selected from lower alkyl, lower alkoxy and trifluoromethyl,

characterised in that a compound of formula (II) :



wherein R and R₁ are as defined for formula (I) is treated

- with an acid chloride of formula (IV) :



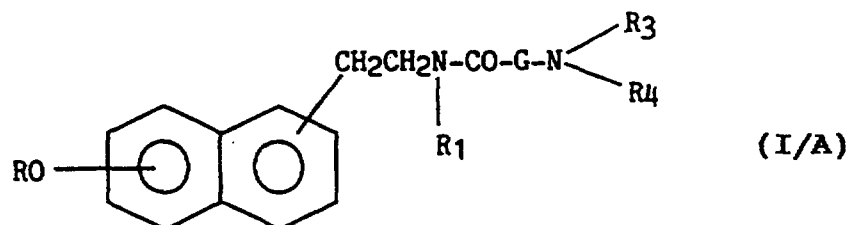
wherein R'₂ is as defined above,

- or with the corresponding acid anhydride to yield a compound of formula (I/B) which, if necessary, is purified by conventional methods, such as

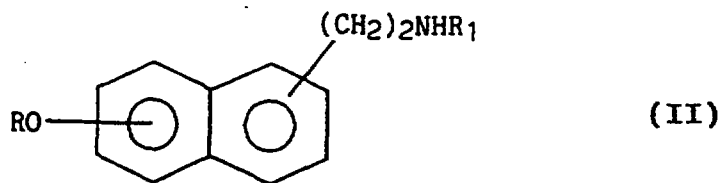


chromatography and/or crystallisation, and of which, where appropriate, the isomers are separated.

28 - Process according to claim 25 for the preparation of compounds of formula (I/A) :



wherein R, R₁, R₃ and R₄ are as defined for formula (I), characterised in that a compound of formula (II) :



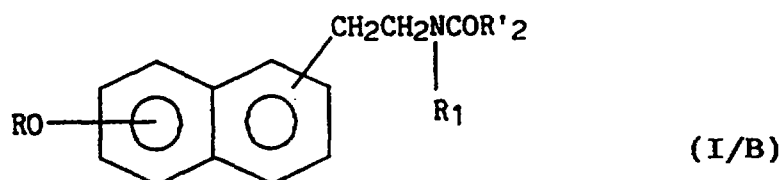
wherein R and R₁ are as defined for formula (I) is treated

- with an acid chloride of formula (IV) :



- or with the corresponding acid anhydride, wherein R'₂ represents a straight-chain or branched lower alkyl group that is substituted by a halogen atom,

to yield a compound of formula (I/B) :





wherein R, R₁ and R'₂ are as defined hereinbefore, which, if necessary, is purified by conventional methods, such as chromatography and/or crystallisation,

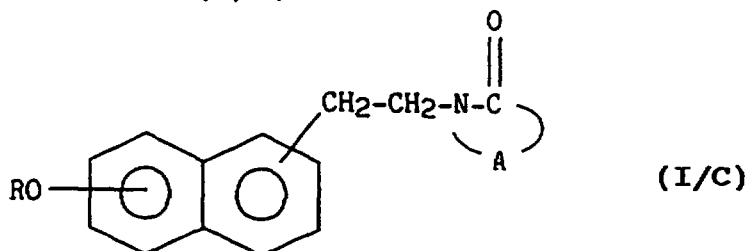
which is subjected to the action of an amine of formula (V) :



wherein R₃ and R₄ are as defined hereinbefore,

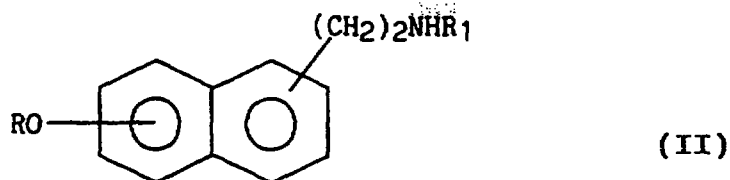
in excess or in the presence of a tertiary amine or an alkali metal salt to yield a compound of formula (I/A) as defined hereinbefore, which, if desired, is purified by a conventional method, such as chromatography and/or crystallisation, and/or converted into a salt with a pharmaceutically acceptable acid.

29 - Process according to claim 25 for the preparation of compounds of formula (I/C) :



wherein R is as defined for formula (I) and A represents a straight-chain or branched alkyl group comprising from 2 to 8 carbon atoms,

characterised in that a compound of formula (II) :



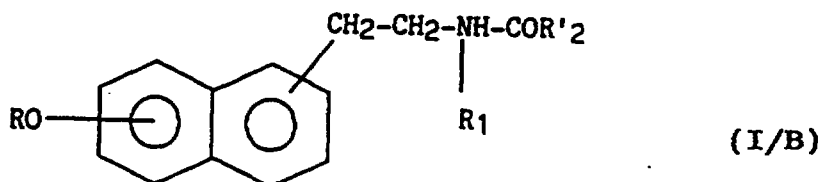
wherein R is as defined for formula (I), is treated

- with an acid chloride of formula (IV) :



- or with the corresponding acid anhydride, wherein R'₂ represents a straight-chain or branched lower alkyl group that is substituted by a halogen atom,

to yield a compound of formula (I/B) :



wherein R and R'₂ are as defined hereinbefore,

which, if necessary, is purified by conventional methods, such as chromatography and/or crystallisation, which is subjected to the action of a strong base and preferably an alkali metal alcoholate to yield a compound of formula (I/C), which, if desired, is purified by a method selected from crystallisation and chromatography.

30 - Pharmaceutical composition comprising as active ingredient at least one compound according to any one of claims 1 to 24, in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or



carriers.

31 - Pharmaceutical composition according to claim 30 useful in the treatment of disorders of the melatonin-ergic system and especially stress, anxiety, seasonal depression, insomnia and fatigue due to shiftwork, schizophrenias, panic attack, melancholia, regulation of the appetite, insomnia, psychotic disorders, epilepsy, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, loss of memory, Alzheimer's disease, and also cerebral circulation disorders, certain cancers, psoriasis, acne, seborrhoea, and also as an ovulation inhibitor or in veterinary medicine in fur disorders.