P/00/001
Section 29

AUSTRALIA 636041

Patents Act 1990

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

I/We, being the person(s) identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

[71] Applicant: ADIR ET COMPAGNIE

Address: 1 rue Carle Hebert, F-92415 Courbevoie Cedex, France

[70] Nominated Person: ADIR ET COMPAGNIE

Address: 1 rue Carle Hebert, F-92415 Courbevoie Cedex, France

[54] Invention Title: NEW OXAZOLOPYRIDINE COMPOUNDS, PROCESS FOR PREPARING THESE AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

[72] Name(s) of actual inventor(s): GERALD GUILLAUMET, CHRISTINE FLOUZAT, DANIEL HENRI CAIGNARD, PIERRE RENARD, MICHELLE DEVISSAGUET and BEATRICE GUARDIOLA

[74] Address for service in Australia: c/o WATERMARK PATENT & TRADEMARK ATTORNEYS, of The Atrium, 290 Burwood Road, Hawthorn, Victoria 3122, Australia Attorney Code: WM

BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
90 08202	France	Fr	29th June 1990

TICK IF APPLICABLE

☐ For the purposes of Section 40, the specification relies on Section 6 of the Act (Microoganisms).

Drawing number recommended to accompany the abstract .....

FO26236 28/06/91

By our/my Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

.....
Louis C. Gebhardt

Registered Patent Attorney

27th June 1991
(Date)

(CONVENTION. Company.) Form 8.

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

In support of the Convention Application made by(1) ADIR ET COMPAGNIE 1 rue Carle Hébert, F-92415 COURBEVOIE CEDEX

(hereinafter referred to as the applicant) for a patent for an invention entitled:(2) New oxazolopyridine compounds, process for preparing these and pharmaceutical compositions containing them

I,(3) Gérard ADAM

of ADIR ET COMPAGNIE 1 rue Carle Hébert, F-92415 COURBEVIOE CEDEX

do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was

made in(4) France

on the 29 day of June 1990, by ADIR ET COMPAGNIE under N° 90.08202

on the day of 19, by

3.(5) Gérald GUILLAUMET : 2 rue Auguste Renoir, F-45100 ORLEANS
Christine FLOUZAT : 9 rue barrière de Jaude, F-63000 CLERMONT FERRAND
Daniel Henri CAIGNARD : 69 bis rue Brancion, F-75015 PARIS

is/are the actual inventor of the invention and the facts upon which the applicant is entitled to make the application are as follows:

The applicant is the assignee of Gérald GUILLAUMET, Christine FLOUZAT, Daniel Henri CAIGNARD, Pierre RENARD, Michelle DEVISSAGUET, Béatrice GUARDIOLA

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at COURBEVOIE

this 28 day of May 1991

(6) Gérard ADAM Proxy for ADIR ET COMPAGNIE

To: THE COMMISSIONER OF PATENTS.

(1) Here insert (in full) Name of Company.

(2) Here insert title of Invention.

(3) Here insert full Name and Address, of Company official authorized to make declaration.

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors.

(6) Signature.

Pierre RENARD : 50 avenue de Villeneuve l'Etang, F-78000 VERSAILLES
Michelle DEVISSAGUET : 14 Boulevard d'Inkermann, F-92200 NEUILLY SUR SEINE
Béatrice GUARDIOLA : 6 rue Edouard Nortier, F-92200 NEUILLY SUR SEINE

AU9179420

(12) PATENT ABRIDGMENT (11) Document No. AU-B-79420/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 636041

(54) Title
NEW OXAZOLOPYRIDINE COMPOUNDS, PROCESS FOR PREPARING THESE AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

International Patent Classification(s)
(51)[5] C07D 498/04 A61K 031/44 C07D 213/74 A61K 031/445

(21) Application No. : 79420/91 (22) Application Date : 28.06.91

(30) Priority Data

(31) Number (32) Date (33) Country
90 08202 29.06.90 FR FRANCE

(43) Publication Date : 12.03.92

(44) Publication Date of Accepted Application : 08.04.93

(71) Applicant(s)
ADIR ET COMPAGNIE

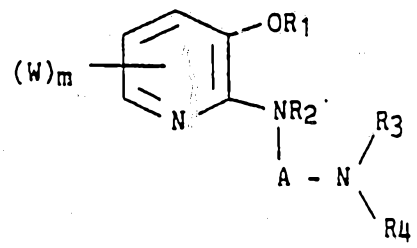
(72) Inventor(s)
GERALD GUILLAUMET; CHRISTINE FLOUZAT; DANIEL HENRI CAIGNARD; PIERRE RENARD; MICHELLE DEVISSAGUET; BEATRICE GUARDIOLA

(74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

(56) Prior Art Documents
AU 87942/91 C07D 498/04 213/74 A61K 31/495
AU 74146/91 C07D 498/04 491/56 A61K 31/495
AU 625886 60165/90 C07D 498/04 213/74 A61K 31/495

(57) Claim

1. A compound of formula (I)



(I)

in which:

R_1 and R_2 each represent a hydrogen atom or, with the nitrogen and oxygen which bear them, form an - O - CO - N link,

W represents a halogen atom or a lower alkyl or alkoxy group optionally substituted with one or more halogen atoms, such as trifluoromethyl, and m being between 0 and 3,

A is a linear or branched alkyl radical comprising from 1 to 6 carbon atoms,

R_3 and R_4, which may be identical or different, represent:

.../2

- a hydrogen atom,
- a linear or branched lower alkyl group,
- a linear or branched lower alkenyl group,
- a cycloalkyl group having 6 to 10 carbon atoms,
- an aryl or (lower alkyl)aryl group,

each of these groups being optionally substituted with one or more halogen atoms or trifluoromethyl, hydroxyl or lower alkoxy groups,

or alternatively:

R_3 and R_4, with the nitrogen atom to which they are linked, constitute a saturated or unsaturated, mono- or bicyclic nitrogenous heterocyclic system comprising at most 12 atoms - not counting the hydrogen atoms - among which may be included one to three hetero atoms selected from nitrogen, oxygen and sulfur, unsubstituted or substituted with a lower alkyl or phenyl or phenyl(lower alkyl) or diphenyl-(lower alkyl) group, it being possible for the phenyl, phenyl(lower alkyl) or diphenyl(lower alkyl) groups to be substituted with one or more halogen atoms or a hydroxyl, lower alkyl, lower alkoxy or trifluoromethyl groups, on condition that R_3 and R_4, with the nitrogen atom to which they are linked, do not constitute a 1-arylpiperazine or 1-heteroaryl-piperazine system,

on the understanding that lower alkyl, lower alkenyl or lower alkyloxy radical is understood to mean a linear or branched group comprising from 1 to 6 carbon atoms, and that aryl or heteroaryl groups are understood to mean unsaturated mono- or bicyclic groups comprising from 5 to 12 carbon atoms - not counting the hydrogen atoms - incorporating or otherwise in their carbon skeleton 1, 2 or 3 hetero atoms selected from nitrogen, oxygen and sulfur,

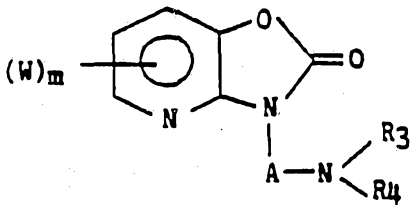
its isomers, epimers and diastereoisomers,

as well as its addition salts with a pharmaceutically acceptable acid and, when R_1 and R_2 each represent a hydrogen atom, its addition salts with a pharmaceutically

.../3

acceptable base.

2. A compound as claimed in claim 1 for which R_1 and R_2 together form a CO group, of formula (I/A):



(I/A)

its isomers as well as its addition salts with a pharmaceutically acceptable acid.

16. A method of treating a mammal afflicted with a disorder selected from pain and disorders of cerebral circulatory insufficiency, comprising the step of administering to the said mammal an amount of a compound as claimed in Claim 1 which is effective for alleviation of said disorder.

[redacted]

630041

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

Name of Applicant : ADIR ET COMPAGNIE

Address of Applicant : 1 rue Carle Hebert, F-92415 Courbevoie Cedex, France

Actual Inventor : GERALD GUILLAUMET, CHRISTINE FLOUZAT, DANIEL HENRI CAIGNARD, PIERRE RENARD, MICHELLE DEVISSAGUET and BEATRICE GUARDIOLA

Address for Service : WATERMARK PATENT & TRADEMARK ATTORNEYS.
LOCKED BAG NO. 5, HAWTHORN, VICTORIA 3122, AUSTRALIA

Complete Specification for the invention entitled:

NEW OXAZOLOPYRIDINE COMPOUNDS, PROCESS FOR PREPARING THESE AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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

The present invention relates to new oxazolo-[4,5-b]pyridine compounds, to a process for preparing these and to pharmaceutical compositions containing them.

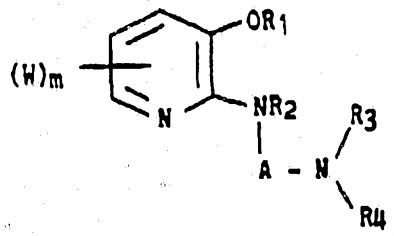
The properties, both analgesic and anti-inflammatory, of 2-phenyl-3H-oxazolo[5,4]- and -[4,5]pyridines are already known (Patents US 4,038,396, FR 2,328,471, FR 2,319,354, GB 1,421,619).

However, these products possess an essentially anti-inflammatory profile, as confirmed by the therapeutic indications mentioned in the patents cited above, or else have the drawback of not dissociating the two types of activity: analgesic on the one hand, antipyretic and anti-inflammatory on the other hand.

The Applicant has now discovered new compounds exhibiting a good level of analgesic activity but possessing the especially advantageous feature of being completely devoid of anti-inflammatory activity: the compounds of the present invention are, in effect, endowed with a high level of pure analgesic activity. It is the case that most non-morphinic analgesic substances known to date also possess anti-inflammatory activity (for example salicyl derivatives, pyrazole derivatives, etc.), and they consequently intervene in the processes occurring in inflammation. These processes involve a very large number of chemical mediators (prostaglandins, thromboxane A2, etc.); multifarious side-effects accordingly ensue, the best known of these being attack of the gastric mucosa with a possibility of ulcers, and inhibition of platelet aggregation with disorders of coagulation. Apart from the disturbances they cause, these concomitant effects prohibit the use of these products in many subjects who are especially sensitive to them. Being devoid of all anti-inflammatory activity, the compounds of the present invention hence do not interfere with the mediators of inflammation, and are hence devoid of the side-effects mentioned above. This feature, combined with their complete absence of toxicity and their high level of activity, renders the compounds of the present invention usable as an analgesic much more safely and without

the restrictions in their use customarily known for the large majority of these products. In addition, some products of the invention have evinced an affinity for muscarine receptors, which distinguishes them completely from the prior art.

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



(I)

in which:

R_1 and R_2 each represent a hydrogen atom or, with the nitrogen and oxygen which bear them, form an - O - CO - N link,

W represents a halogen atom or a lower alkyl or alkoxy group optionally substituted with one or more halogen atoms, such as trifluoromethyl, and m being between 0 and 3,

A is a linear or branched alkyl radical comprising from 1 to 6 carbon atoms,

R_3 and R_4, which may be identical or different, represent:

- a hydrogen atom,
- a linear or branched lower alkyl group,
- a linear or branched lower alkenyl group,
- a cycloalkyl group having 6 to 10 carbon atoms,
- an aryl or (lower alkyl)aryl or aryl(lower alkyl) group,

each of these groups being unsubstituted or substituted with one or more halogen atoms or trifluoromethyl, hydroxyl or lower alkoxy groups,

or alternatively:

R_3 and R_4, with the nitrogen atom to which they are linked, constitute a saturated or unsaturated, mono- or bicyclic nitrogenous heterocyclic system comprising at most 12 atoms - not counting the hydrogen

atoms - among which may be included one to three hetero atoms selected from nitrogen, oxygen and sulfur, unsubstituted or substituted with a lower alkyl or phenyl or phenyl(lower alkyl) or diphenyl-(lower alkyl) group, it being possible for the phenyl, phenyl(lower alkyl) or diphenyl(lower alkyl) groups to be substituted with one or more halogen atoms or hydroxyl, lower alkyl, lower alkoxy or trifluoromethyl groups, on condition that R_3 and R_4, with the nitrogen atom to which they are linked, do not constitute a 1-arylpiperazine or 1-heteroaryl-piperazine system,

on the understanding that lower alkyl, lower alkenyl or lower alkyloxy radical is understood to mean a linear or branched group comprising from 1 to 6 carbon atoms, and that aryl or heteroaryl groups are understood to mean unsaturated mono- or bicyclic groups comprising from 5 to 12 carbon atoms - not counting the hydrogen atoms - incorporating or otherwise in their carbon skeleton one, two or three hetero atoms selected from nitrogen, oxygen and sulfur,

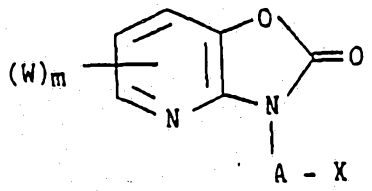
their isomers, epimers and diastereoisomers,

as well as their addition salts with a pharmaceutically acceptable acid and, when R_1 and R_2 each represent a hydrogen atom, their addition salts with a pharmaceutically acceptable base.

Among acids which may be added to the compounds of formula (I) to form an addition salt, hydrochloric, sulfuric, phosphoric, tartaric, malic, maleic, fumaric, oxalic, methanesulfonic, ethanesulfonic, camphoric, citric, etc., acids may be mentioned by way of example.

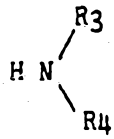
Among bases which may be added to the compounds of formula (I) for which R_1 and R_2 each represent a hydrogen atom, alkali metal hydroxides, alkali metal salts, etc., may be mentioned by way of example.

The invention also encompasses the process for obtaining compounds of formula (I), wherein a compound of formula (II):



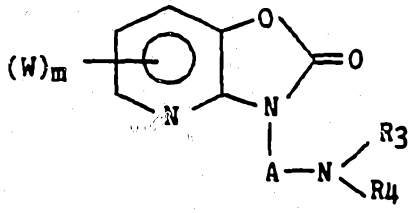
(II)

in which W, m and A have the same meaning as in the formula (I) and X represents a halogen atom,
is reacted, preferably under an inert atmosphere, with a compound of formula (III), preferably in excess:



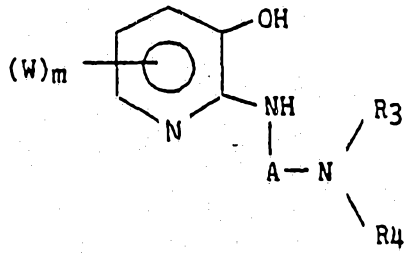
(III)

in which R_3 and R_4 have the same meaning as in the formula (I),
in an organic medium in the presence of a basic agent and at a temperature between room temperature and the refluxing temperature of the chosen solvent, to lead, after cooling, extraction and, where appropriate, purification, to a compound of formula (I/A):



(I/A)

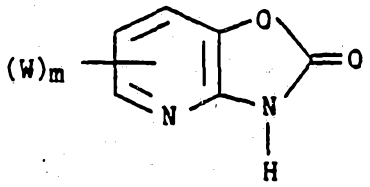
a special case of the compounds of formula (I) for which R_1 with R_2 forms a C = O group,
which may, if so desired, be separated, where applicable, into its isomers and then salified with a pharmaceutically acceptable acid,
which compound of formula (I/A) may be treated, if so desired, with an alkaline agent in aqueous solution, at a temperature between room temperature and the boiling point of the reaction medium, to lead, where appropriate after acidification and/or neutralization of the reaction medium, to a compound of formula (I/B):



(I/B)

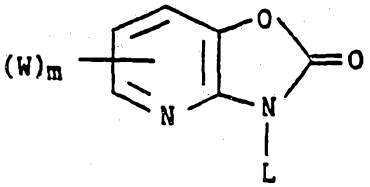
a special case of the compounds of formula (I) in which R_1 and R_2 each represent a hydrogen atom and W, m, A, R_3 and R_4 have the same meaning as above, which is purified, if necessary, by a technique selected from crystallization and chromatography and which is salified, if so desired, with a pharmaceutically acceptable acid or base.

The compounds of formula (II) may be obtained by reacting a compound of formula (IV):



(IV)

in which W and m have the same meaning as in the formula (I),
with an alkali metal hydroxide in an aqueous medium or an alkali metal alcoholate in an organic medium, to lead to a derivative of formula (V):



(V)

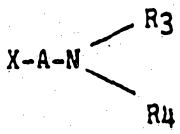
in which W and m have the same meaning as above and L represents an alkali metal,
which is condensed with a compound of formula (VI):

X-A-X' (VI)

in which A has the same meaning as above and X and X', which may be identical or different, each represent a halogen atom,

preferably under an inert atmosphere, in an organic medium at a temperature between room temperature and the refluxing temperature of the chosen solvent, to lead, after, where appropriate, extraction and purification by chromatography and/or crystallization, to the compound of formula (II).

The compounds of formula (I/A) may also be obtained by condensation of a compound of formula (V) as shown above with a compound of formula (VII):



(VII)

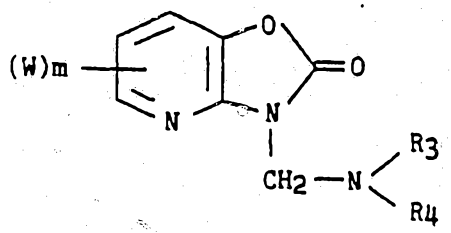
in which X, A, R_3 and R_4 have the same meaning as above, in an organic medium at a temperature between room temperature and the refluxing temperature of the chosen solvent, to lead, after, where appropriate, cooling, extraction and purification, to a compound of formula (I/A) as defined above, the isomers of which, where applicable, are separated and which is salified, if so desired, with a pharmaceutically acceptable acid.

The compounds of formula (VII) will advantageously be obtained by condensation of a compound of formula (VI) as defined above with an amine of formula (III) as defined above, preferably under an inert atmosphere, in an organic medium at a temperature between room temperature and the refluxing temperature of the chosen solvent, to lead, after, where appropriate, extraction and purification, to a compound of formula (VII).

A special case of the compounds of the present invention consists of the compounds of formula (I) in which A is a methylene link $-CH_2-$.

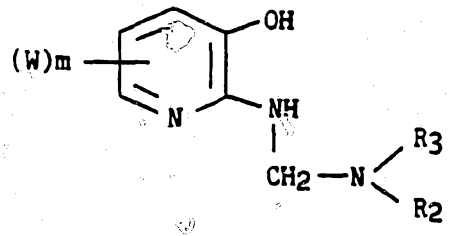
These compounds will advantageously be obtained in a single step by dissolving a compound of formula (IV), a slight excess of an amine of formula (III) and an excess of formaldehyde in a lower aliphatic alcohol medium, and heating the solution thereby obtained to a temperature between room temperature and the boiling point of the solution,

to lead, after, where appropriate, cooling, allowing the mixture to stand for one to two hours, filtration and, where appropriate, chromatography on a silica column, to a compound of formula (I/A1):



(I/A1)

a special case of the compounds of formula (I/A) in which A is a methylene link $-CH_2-$ and in which W and m have the same meaning as in the formula (I), which may be salified, if so desired, with a pharmaceutically acceptable acid and converted, if so desired, to a compound (I/B1):



(I/B1)

a special case of the compound of formula (I/B) in which A is a methylene link CH_2 and W and m have the same meaning as in the formula (I),

by treatment of a compound of formula (I/A1) with an alkaline agent in aqueous solution as described for the conversion of the compounds of formula (I/A) to a compound of formula (I/B).

The compounds of formula (I) possess advantageous pharmacological properties.

In particular, these compounds have evinced advantageous analgesic activity.

A pharmacological study of the compounds of the invention showed that they were of low toxicity, endowed with a high level of pure analgesic activity, devoid of an anti-inflammatory component and hence devoid of drawbacks inherent in most compounds exhibiting this activity (ulcerogenic action on the mucosi, interference with coagulation, etc.). This spectrum of activity hence

renders the compounds of the present invention especially advantageous in a number of indications such as rheumatic pain such as that associated with sprains, fractures and dislocations, post-traumatic pain, postoperative pain, dental pain, neurological pain such as facial neuralgia, visceral pain such as nephritic colic, dysmenorrhea, proctological surgery, pancreatitis, diverse pains, headache, cancer pain, etc.

In addition, the compounds of the invention have evinced a good affinity for MI receptors. This means that they may be used profitably in disorders of cerebral circulatory insufficiency, the multifarious disorders resulting from normal or pathological aging, memory loss and Alzheimer's disease.

The subject of the present invention is also pharmaceutical compositions containing the products of formula (I) or one of their addition salts with a pharmaceutically acceptable acid, alone or in combination with one or more pharmaceutically acceptable, non-toxic, inert excipients or vehicles.

Among the pharmaceutical compositions according to the invention, there may be mentioned, more especially, those which are suitable for oral, parenteral, nasal, rectal, perlingual, ocular or respiratory administration, and in particular injections, aerosols, eye or nasal drops, simple or sugar-coated tablets, sublingual tablets, sachets, packets, hard gelatin capsules, sublingual preparations, troches, suppositories, creams, ointments, skin gels, and the like.

The appropriate dosage varies according to the patient's age and weight, the administration route and the nature of the therapeutic indication and of any associated treatments, and ranges between 1 centigram and 4 grams per 24 hours.

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

The ^1H nuclear magnetic resonance spectra were recorded using TMS as an internal reference. The infrared spectra were recorded using a KBr disk containing

approximately 1% of the test product.

The products obtained according to the procedures described under the heading "Preparations" do not form part of the invention; they nevertheless constitute synthesis intermediates useful for the preparation of the compounds of the invention.

PREPARATIONS:

PREPARATION 1: 3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE*

5.5 g (0.05 mol) of 2-amino-3-hydroxypyridine are introduced into a three-necked flask and the system is placed under argon. 100 ml of anhydrous tetrahydrofuran (THF) are added. 12.15 g (0.075 mol) of 1,1-carbonyldiimidazole are then introduced. The mixture is heated to reflux for 5 hours (under argon). The THF is then evaporated off. The residue is taken up with dichloromethane. Washes of the organic phase are performed with NaOH solution (5%) (6 x 150 ml); the cyclized product passes into the aqueous phase and is precipitated at a pH in the region of 5 (by adding 2 N hydrochloric acid solution). The product is filtered off and stored in a desiccator.

Yield: 77%

Melting point: 212-214°C

PREPARATION 2: 5-METHYL-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE*

STAGE A: 2-NITRO-3-HYDROXY-6-METHYLPYRIDINE

5.45 g (50 mmol) of 5-hydroxy-2-methylpyridine are added to 20 ml of concentrated sulfuric acid while cooling in an ice bath. The temperature is maintained at +6°C and 2.35 ml of fuming nitric acid are added with stirring. The mixture is left overnight at room temperature. 100 g of ice are added with stirring. The product is filtered off, rinsed with water and dried.

STAGE B: 2-AMINO-3-HYDROXY-6-METHYLPYRIDINE

3.5 g of 2-nitro-3-hydroxy-6-methylpyridine are placed under a hydrogen pressure in 50 ml of methanol in the presence of 1 gram of palladinized charcoal. The mixture is stirred and filtered. The methanol is

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* See nomenclature appended on page 22

evaporated off.

STAGE C: 5-METHYL-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

1.24 g (10 mmol) of 2-amino-3-hydroxy-6-methylpyridine are introduced into a three-necked round-bottomed flask. The contents are placed under argon. 20 ml of anhydrous tetrahydrofuran and then 2.43 g (15 mmol) of 1,1-carbonyldiimidazole are added. The mixture is heated to reflux for 6 hours. The reaction medium is evaporated. The crystals obtained are washed with water, filtered off and redissolved in hot methanol. The solution is filtered and re-evaporated.

Yield: 75%

Melting point: 243°C

Spectral characteristics:

^{1}H NMR Solvent $CDCl_3$: δ ppm

δ: 12.3 1H, unresolved complex, NH

δ: 7.5 1H; doublet; H_7; J = 8 Hz

δ: 6.9 1H; doublet; H_6; J = 8 Hz

δ: 2.4 3H; singlet; CH_3

Infrared: 1750 cm^{-1}, ν (C=O)

1610 cm^{-1}, ν (C=C)

PREPARATION 3: 3-(2-BROMOETHYL)-3H-OXAZOLO[4,5-b]-PYRIDIN-3-ONE

STAGE A: OXAZOLO[4,5-b]PYRIDIN-2-ONE SODIUM DERIVATIVE

6 g (44.11 mmol) of 3H-oxazolo[4,5-b]pyridin-2-one are dissolved in a sufficient quantity of tetrahydrofuran, and this solution is then added to an ethanolic solution of sodium ethylate obtained from 1 gram (43.50 mmol) of sodium in approximately 150 ml of ethanol. The mixture is evaporated under vacuum and the residue is taken up with a sufficient quantity of dimethylformamide to dissolve it.

STAGE B: 3-(2-BROMOETHYL)-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

7.6 ml (88.22 mmol) of 1,2-dibromoethane, dissolved in approximately 50 ml of dimethylformamide, are placed in a round-bottomed flask under argon, surmounted by a condenser, and the solution obtained in the

preceding step is then added slowly with stirring. The mixture is brought to 100°C for 2 hours.

After cooling, the dimethylformamide is evaporated under vacuum and the residue is then taken up with water and extracted with methylene chloride. After drying over $MgSO_4$, the methylene chloride is evaporated off and the residue is purified on a flash silica column (230-240 mesh) in methylene chloride. After evaporation, 5.2 g of a white powder are obtained.

Yield: 50%

PREPARATION 4: 3-(3-BROMOPROPYL)-3H-OXAZOLO[4,5-b]-PYRIDIN-2-ONE

Using the procedure described in Preparation 3, but replacing 1,2-dibromoethane in stage B by 1,3-dibromopropane, the product of the title is obtained.

PREPARATION 5: 3-(4-BROMO-n-BUTYL)-3H-OXAZOLO-[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Preparation 3, but replacing 1,2-dibromoethane in stage B by 1,4-dibromo-n-butane, the product of the title is obtained.

Yield: 50%

Melting point: 46°C

Spectral characteristics:

^1H NMR Solvent $CDCl_3$: δ ppm

δ: 1.92-2.09 ppm, multiplet; 4H; $-CH_2-\underline{CH_2}-\underline{CH_2}-CH_2-Br$

δ: 3.47 ppm; triplet; 2H; $\underline{CH_2}-Br$

δ: 3.99 ppm; triplet; 2H

δ: 7.06 ppm; doublet of doublet; 1H; H_6;
JH_6H_7 = 8.3 Hz
JH_6H_5 = 5.3 Hz

δ: 7.40 ppm; doublet of doublet; 1H; H_7;
JH_7H_6 = 8.3 Hz
JH_7H_5 = 1 Hz

δ: 8.11 ppm; doublet of doublet; 1H; H_5;
JH_5H_6 = 5.3 Hz
JH_5H_7 = 1 Hz

PREPARATION 6: 5-METHYL-3-(2-BROMOETHYL)-3H-OXAZOLO-[4,5-b]PYRIDIN-2-one

Using the procedure described in Preparation 3,

but replacing 3H-oxazolo[4,5-b]pyridin-2-one by 5-methyl-3H-oxazolo[4,5-b]pyridin-2-one, the product of the title is obtained.

EXAMPLE 1: 3-(2-PIPERIDINOETHYL)-3H-OXAZOLO-[4,5-b]PYRIDIN-2-ONE

0.01 mol of 3-(2-bromoethyl)-3H-oxazolo[4,5-b]-pyridin-2-one, dissolved in acetonitrile, 0.15 mol of piperidine and 0.015 mol of diisopropylethylamine are introduced into a round-bottomed flask placed under argon and surmounted by a condenser. The mixture is brought to 80°C for 12 hours. It is cooled, the acetonitrile is evaporated off under vacuum and the residue is taken up with water. The alkalinity of the medium is checked and the medium is extracted with dichloromethane. The organic phase is dried over magnesium sulfate and evaporated and the residue is recrystallized.

Yield: 97%

Melting point: 84°C

Spectral characteristics:

Infrared: 3100-2700 cm^{-1}, ν (CH)
1760 cm^{-1}, ν (C=O)
1590 cm^{-1}, ν (C=C) conjugated

Nuclear magnetic resonance:

^1H NMR Solvent $CDCl_3$: δ ppm

δ: 1.34-1.56, 6H; multiplet; piperidine (β and γ to the nitrogen)

δ: 2.42-2.55, 4H; multiplet; piperidine (α to the nitrogen)

δ: 2.76, 2H; triplet; piperidine CH_2-$\underline{CH_2}$; J = 4.1 Hz

δ: 4.07, 2H; triplet; $\underline{CH_2}$-CH_2; piperidine; J = 6.1 Hz

δ: 7.03 ppm: 1H; doublet of doublet; aromatic; H_6

δ: 7.38 ppm: 1H; doublet of doublet; aromatic; H_7

δ: 8.09 ppm: 1H; doublet of doublet; aromatic; H_5

EXAMPLE 2: 3-[2-(4-METHYL-1-PIPERAZINYL)ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by 1-methylpiperazine, the product of the title is obtained.

Yield: 90%

Melting point: 85°C

Spectral characteristics:

Infrared: 3100-2700 cm^{-1}, ν (CH)
1760 cm^{-1}, ν (C=O)
1590 cm^{-1}, ν (C=C) conjugated

Nuclear magnetic resonance:

^1H NMR Solvent $CDCl_3$: δ ppm

δ: 2.23, singlet; 3H; $\underline{CH_3}$

δ: 2.25-2.70, multiplet; 8H; piperazine

δ: 2.79, 2H; triplet; piperazine CH_2-$\underline{CH_2}$

δ: 4.05, 2H; triplet; piperazine $\underline{CH_2}$-CH_2

δ: 7.04: 1H; doublet of doublet; aromatic; H_6

δ: 7.39: 1H; doublet of doublet; aromatic; H_7

δ: 8.09 1H; doublet of doublet; aromatic; H_5

EXAMPLE 3: 3-[2-(1-PYRROLIDINYL)ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE (OXALATE)

Using the procedure described in Example 1, but replacing piperidine by pyrrolidine, the product of the title is obtained in the form of a base. The product is dissolved in ethanol and 0.01 mol of oxalic acid is added. The product is drained.

Melting point: 180°C

Spectral characteristics:

Infrared: 3100-2700 cm^{-1}, ν (CH)
1760 cm^{-1}, ν (C=O)
1590 cm^{-1}, ν (C=C)

Nuclear magnetic resonance:

^1H NMR Solvent $CDCl_3$: δ ppm

δ: 7.04: 1H; doublet of doublet; aromatic; H_6

δ: 7.39: 1H; doublet of doublet; aromatic; H_7

δ: 8.09 1H; doublet of doublet; aromatic; H_5

EXAMPLE 4: 3-(2-MORPHOLINOETHYL]-3H-OXAZOLO-[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by morpholine, the product of the title is obtained.

Yield: 98%

Melting point: 83°C

Spectral characteristics:

Infrared: 3100-2700 cm^{-1}, ν (CH)
1760 cm^{-1}, ν (C=O)
1590 cm^{-1}, ν (C=C)

Nuclear magnetic resonance:

^1H NMR Solvent $CDCl_3$: δ ppm

δ: 2.49-2.53: 4H; multiplet; 2 CH_2 α to the nitrogen: morpholine

δ: 2.68: 2H; CH_2-$\underline{CH_2}$ - morpholine; J = 6.3 Hz

δ: 3.54-3.58: 4H; multiplet; 2CH_2 α to the oxygen; morpholine

δ: 4.04: 2H; triplet; $\underline{CH_2}$-CH_2 - morpholine; J = 6.3 Hz

δ: 7.03: 1H; doublet of doublet; aromatic; H_6

δ: 7.38: 1H; doublet of doublet; aromatic; H_7

δ: 8.08: 1H; doublet of doublet; aromatic; H_5

EXAMPLE 5: 3-(2-AMINOETHYL)-3H-OXAZOLO[4,5-b]-PYRIDIN-2-ONE (HYDROCHLORIDE)

0.013 mol of hexamethylenetetramine, dissolved beforehand in 20 cm^3 of chloroform, and 0.01 mol of 3-(2-bromoethyl)-3H-oxazolo[4,5-b]pyridin-2-one, dissolved beforehand in 15 cm^3 of chloroform, are introduced into a round-bottomed flask placed under argon and surmounted by a condenser. The mixture is heated to reflux for one week. The product is drained and dried. The precipitate is introduced into a ground-necked 250-cm^3 flask equipped with a reflux condenser, and 50 cm^3 of absolute alcohol and 10 cm^3 of concentrated hydrochloric acid are added. The mixture is heated to reflux for two hours with magnetic stirring. The solvent is evaporated off on a water bath under vacuum and the product is recrystallized in alcohol at 95°C.

Yield: 70%

Spectral characteristics:

Infrared: 3200-2400 cm^{-1}, ν (NH) and ν (CH)

Nuclear magnetic resonance:

^1H NMR Solvent $CDCl_3$: δ ppm

δ: 7.05 ppm: 1H; aromatic; H_6

δ: 7.38 ppm: 1H; aromatic; H_7

δ: 8.09 ppm: 1H; aromatic; H_5

EXAMPLE 6: 3-[2-(N-METHYL-N-BENZYLAMINO)ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by N-methyl-N-benzylamine, the product of the title is obtained.

Yield: 75%

Spectral characteristics:

Infrared: 3100-2700 cm^{-1}, ν (CH)
1760 cm^{-1}, ν (C=O)

Nuclear magnetic resonance:

^1H NMR Solvent $CDCl_3$: δ ppm

δ: 2.20 ppm, singlet: 3H; $\underline{CH_3}$

δ: 7.03 ppm: 1H; H_6

δ: 7.38 ppm: 1H; H_7

δ: 8.09 ppm: 1H; H_5

δ: 7.27 ppm: 5H; aromatic ($\underline{C_6H_5}$-CH_2)

EXAMPLE 7: 3-[2-(METHYLAMINO)ETHYL]-3H-OXAZOLO-[4,5-b]PYRIDIN-2-ONE

In a 1,000-cm^3 ground-necked flask, 0.02 mol of 3-[2-(N-methyl-N-benzylamino)ethyl]-3H-oxazolo[4,5-b]-pyridin-2-one is dissolved in 250 cm^3 of methanol. 0.2 g of palladinized charcoal is introduced and the mixture is stirred under a hydrogen atmosphere at room temperature and atmospheric pressure. After absorption of the theoretical quantity of hydrogen, the reaction medium is filtered. The filtrate is concentrated on a water bath under vacuum and acidified with a stream of gaseous hydrochloric acid. The precipitate obtained is drained, dried and recrystallized.

Yield: 75%

Spectral characteristics:

Infrared: 3100-2600 cm^{-1}, ν (NH) or ν (CH)
2440 cm^{-1}, ν (NH)
1750 cm^{-1}, ν CO (OCON)
1610 cm^{-1}, ν (C=C) aromatic

Nuclear magnetic resonance:

^1H NMR Solvent $CDCl_3$: δ ppm

δ: 7.05 ppm, doublet of doublet; 1H; H_6

δ: 7.38 ppm, doublet of doublet; 1H; H_7

δ: 8.09 ppm, doublet of doublet; 1H; H_5

EXAMPLE 8: 3-[2-(ISOPROPYLAMINO)ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE (HYDROBROMIDE)

0.1 mol of isopropylamine and 0.01 mol of 3-(2-bromoethyl)-3H-oxazolo[4,5-b]pyridin-2-one, dissolved beforehand in 40 cm^3 of acetonitrile, are introduced into a 100-cm^3 ground-necked round-bottomed flask equipped with a reflux condenser. The mixture is heated to reflux for 15 hours. After cooling, the precipitate obtained is drained, dried and recrystallized.

Yield: 92%

Spectral characteristics:

Infrared: 3100-2650 cm^{-1}, ν (NH) and ν (CH)
2450 cm^{-1}, ν (NH)
1745 cm^{-1}, ν CO

EXAMPLE 9: 3-[2-(CYCLOPROPYLAMINO)ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE (HYDROBROMIDE)

Using the procedure described in Example 8, but replacing isopropylamine by cyclopropylamine, the product of the title is obtained.

EXAMPLE 10: 3-[2-(DIETHYLAMINO)ETHYL]-3H-OXAZOLO-[4,5-b]PYRIDIN-2-ONE (OXALATE)

Using the procedure described in Example 1, but replacing piperidine by diethylamine, the product of the title is obtained in the form of a base. It is dissolved in ethanol and 0.01 mol of oxalic acid is added. The product is drained. It is dried. It is recrystallized.

Melting point: 139°C

EXAMPLE 11: 3-[2-(N-METHYL-N-CYCLOHEXYLAMINO)-ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by N-methyl-N-cyclohexylamine, the product of the title is obtained.

EXAMPLE 12: 3-[2-(4-PHENYLPIPERIDINO)ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but

replacing piperidine by 4-phenylpiperidine, the product of the title is obtained.

Melting point: 88°C

EXAMPLE 13: 3-[2-(1,2,3,4-TETRAHYDRO-1-QUINOLYL)-ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by 1,2,3,4-tetrahydroquinoline, the product of the title is obtained.

EXAMPLE 14: 3-MORPHOLINOMETHYL-3H-OXAZOLO[4,5-b]-PYRIDIN-2-ONE

4.1 g (0.03 mol) of 3H-oxazolo[4,5-b]pyridin-2-one are dissolved in 100 ml of alcohol at 95°C. 2.88 g (0.33 mol) of morpholine and then 3 ml of 30% aqueous formaldehyde solution are added. The mixture is stirred on a water bath at a temperature in the region of 50°C for one hour 30 minutes, stirring being maintained. The mixture is left to stand for one hour at room temperature. The crystals are drained and recrystallized.

Yield: 85%

Spectral characteristics:

Infrared: 3100-2700 cm^{-1}, ν (CH)
1760 cm^{-1}, ν (CO)
1590 cm^{-1}, ν (C=C)

EXAMPLE 15: 3-(1-PYRROLIDINYLMETHYL)-3H-OXAZOLO-[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 14, but replacing morpholine by pyrrolidine, the product of the title is obtained.

EXAMPLE 16: 3-PIPERIDINOMETHYL-3H-OXAZOLO-[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 14, but replacing morpholine by piperidine, the product of the title is obtained.

EXAMPLE 17: 3-(2-PIPERIDINOETHYL)-5-METHYL-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing 3-(2-bromoethyl)-3H-oxazolo[4,5-b]pyridin-2-one by 3-(2-bromoethyl)-5-methyl-3H-oxazolo[4,5-b]pyridin-2-one obtained in Preparation 6, the product of the title

is obtained.

EXAMPLE 18: 3-[2-(4-TRIFLUOROMETHYLBENZYLAMINO)-ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by 4-trifluoromethylbenzylamine, the product of the title is obtained.

EXAMPLE 19: 3-[2-(4-METHYLPIPERIDINO)ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by 4-methylpiperidine, the product of the title is obtained.

EXAMPLE 20: 3-[2-(4-BENZYLPIPERIDINO)ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by 4-benzylpiperidine, the product of the title is obtained.

EXAMPLE 21: 3-[2-(2-CHLOROETHYLAMINO)ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by 2-chloroethylamine, the product of the title is obtained.

EXAMPLE 22: 3-{2-[4-(4,4'-DIFLUOROBENZHYDRYL)-1-PIPERAZINYL]ETHYL}-3H-OXAZOLO-[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by 1-(4,4'-difluorobenzhydryl)-piperazine, the product of the title is obtained.

EXAMPLE 23: 3-[2-(4-BENZHYDRYL-1-PIPERAZINYL)-ETHYL]-3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by 1-benzhydrylpiperazine, the product of the title is obtained.

EXAMPLE 24: 3-{2-[4-(4-CHLOROBENZHYDRYL)-1-PIPERAZINYL]ETHYL}-3H-OXAZOLO-[4,5-b]PYRIDIN-2-ONE

Using the procedure described in Example 1, but replacing piperidine by 1-(4-chlorobenzhydryl)piperazine, the product of the title is obtained.

EXAMPLE 25: 2-(2-PIPERIDINOETHYLAMINO)-3-PYRIDINOL

0.01 mol of 3-(2-piperidinoethyl)-3H-oxazolo-[4,5-b]pyridin-2-one, obtained in Example 1, is placed in 50 ml of 10% sodium hydroxide solution. The mixture is heated to reflux for 4 hours with magnetic stirring. After cooling, the solution is acidified with 30% hydrochloric acid. While cooling, saturated aqueous sodium bicarbonate solution is added until the pH = 7. The precipitate is filtered off and washed three times with water, dried under vacuum in a desiccator and then washed again.

By using the procedure described in Example 25, but employing the compounds obtained in Examples 2 to 24 as starting material, 2-{[(substituted)amino]alkylamino}-3-pyridinols, substituted where appropriate, are obtained.

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

EXAMPLE 26: STUDY OF THE ACUTE TOXICITY

The toxicity was assessed after oral administration of increasing doses (0.1, 0.25, 0.50, 0.75 and 1 g/kg) to batches of five mice (20 ± 2 grams). The animals were observed at regular intervals during the first day, and daily during the two weeks following the treatment.

It is apparent that the compounds of the invention are completely non-toxic.

EXAMPLE 27: STUDY OF THE ANALGESIC ACTIVITY

The activity against pain was investigated in mice (23-25 g) according to a protocol derived from the technique described by SIEGMUND (SIEGMUND E.A., R.A. CADMUS & GOLU, J. Pharm. Exp. Ther. 119, 184, 1957). The mice, randomized in batches of 12 animals, received the treatment orally (excipient for the controls) 1 hour before the intraperitoneal injection of a 0.02% aqueous-alcoholic solution of phenyl-p-benzoquinone. The writhing movements are counted between the 5th and 10th minute after injection.

The percentage activity obtained was evaluated

for each dose (% decrease in the number of writhing movements in the treated animals relative to the controls). An ED_{50}, the dose producing a 50% activity, was determined for each product tested.

EXAMPLE 28: STUDY OF THE ANTI-INFLAMMATORY ACTIVITY

The anti-inflammatory potential of the compounds was investigated on a model of acute inflammation induced by the subcutaneous injection of a solution of carrageenan into the rat hind foot, according to a technique based on the method of WINTER, C.A., E.A. RISLEY and G.N. NUSS - Proc. Soc. Exp. Med. 111, 554, 1962. The rats (100-120 g), randomized in batches of 8, were treated (including the controls, which receive excipient) 1 hour before the local injection of a 0.5% suspension of carrageenan (Sigma type IV; 0.1 ml per rat). The edema is determined 3 hours after injection, by plethysmometric measurement (UGO BASILE water plethysmometer) of the volume of each of the hind feet (edema = volume of the inflamed foot - volume of the non-inflamed foot).

The percentage activity corresponds to the percentage decrease in the mean edema of the batch compared to the mean of the corresponding control batch. An ED_{30}, the dose producing a 30% activity, was determined.

This ED_{30} is equal to 50 $mg.kg^{-1}$ for the compound of Example 6 of Patent US 4,038,396. It is very markedly greater than this value for all the compounds of the invention; up to a dose of 150 $mg.kg^{-1}$, they have no anti-inflammatory activity.

EXAMPLE 29: GASTRIC TOLERANCE TEST

A group of 5 rats is subjected to fasting for 24 hours. The test products are administered orally, in suspension in acacia syrup at a dose of 150 $mg.kg^{-1}$. After administration, the animals are placed under so-called semi-constrained conditions reputed to be ulcerogenic (they are shut up in narrow cages). After 6 hours, they are sacrificed and the stomach wall is examined. Gastric tolerance is defined on the basis of the scoring of SHAY

and LAMBLING. The severity of the irritated areas and of the points of ulceration is scored from 0 to 3. An index of ulceration U and an index of hyperemia or irritation H are defined.

$$U \text{ or } H = \frac{\text{(Sum of the scores)} \times \text{(number of points of stomach tested)}}{\text{Number of animals studied}}$$

Overall index of propensity for attack $G = 3U + H$.

This index G is equal to 1 for the products of the invention, 12 for the control and 74 for aspirin.

EXAMPLE 30: TEST OF BINDING TO RECEPTORS

A study of the binding of the compounds of the invention to different categories of receptors was carried out according to conventional techniques. It is apparent that some compounds of the invention bind with good affinity (10^{-7} M) to MI muscarinic receptors, which does not appear to have been reported hitherto for comparable structures.

EXAMPLE 31: PHARMACEUTICAL COMPOSITION: TABLET

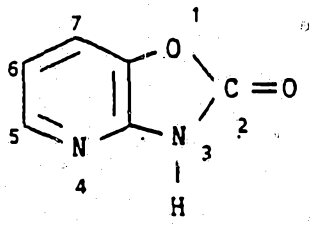
Tablets containing 25 mg of 3-(2-piperidinoethyl)-3H-oxazolo[4,5-b]pyridin-2-one

Preparation formula for 1,000 tablets

3-[2-(1-Pyrrolidinyl)ethyl]-3H-oxazolo-[4,5-b]pyridin-2-one	25 g
Wheat starch	15 g
Corn starch	15 g
Lactose	65 g
Magnesium stearate	1 g
Silica	1 g
Hydroxypropylcellulose	2 g

APPENDIX

Nomenclature

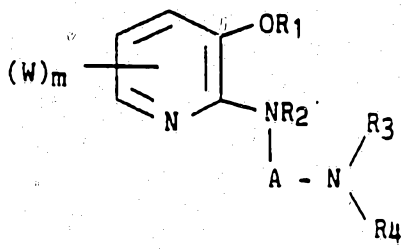


3H-OXAZOLO[4,5-b]PYRIDIN-2-ONE

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

~~CLAIMS~~

1. A compound of formula (I)



(I)

in which:

R_1 and R_2 each represent a hydrogen atom or, with the nitrogen and oxygen which bear them, form an - O - CO - N link,

W represents a halogen atom or a lower alkyl or alkoxy group optionally substituted with one or more halogen atoms, such as trifluoromethyl, and m being between 0 and 3,

A is a linear or branched alkyl radical comprising from 1 to 6 carbon atoms,

R_3 and R_4, which may be identical or different, represent:

- a hydrogen atom,
- a linear or branched lower alkyl group,
- a linear or branched lower alkenyl group,
- a cycloalkyl group having 6 to 10 carbon atoms,
- an aryl or (lower alkyl)aryl group,

each of these groups being optionally substituted with one or more halogen atoms or trifluoromethyl, hydroxyl or lower alkoxy groups,

or alternatively:

R_3 and R_4, with the nitrogen atom to which they are linked, constitute a saturated or unsaturated, mono- or bicyclic nitrogenous heterocyclic system comprising at most 12 atoms - not counting the hydrogen atoms - among which may be included one to three hetero atoms selected from nitrogen, oxygen and sulfur, unsubstituted or substituted with a lower alkyl or phenyl or phenyl(lower alkyl) or diphenyl-(lower alkyl) group, it being possible for the phenyl, phenyl(lower alkyl) or diphenyl(lower alkyl)

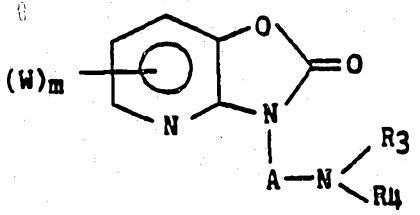
groups to be substituted with one or more halogen atoms or a hydroxyl, lower alkyl, lower alkoxy or trifluoromethyl groups, on condition that R_3 and R_4, with the nitrogen atom to which they are linked, do not constitute a 1-arylpiperazine or 1-heteroaryl-piperazine system,

on the understanding that lower alkyl, lower alkenyl or lower alkyloxy radical is understood to mean a linear or branched group comprising from 1 to 6 carbon atoms, and that aryl or heteroaryl groups are understood to mean unsaturated mono- or bicyclic groups comprising from 5 to 12 carbon atoms - not counting the hydrogen atoms - incorporating or otherwise in their carbon skeleton 1, 2 or 3 hetero atoms selected from nitrogen, oxygen and sulfur,

its isomers, epimers and diastereoisomers,

as well as its addition salts with a pharmaceutically acceptable acid and, when R_1 and R_2 each represent a hydrogen atom, its addition salts with a pharmaceutically acceptable base.

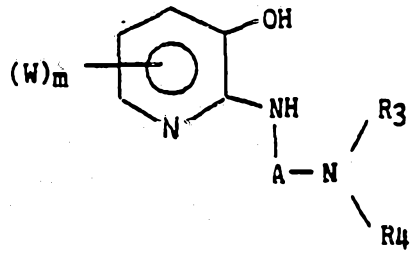
2. A compound as claimed in claim 1 for which R_1 and R_2 together form a CO group, of formula (I/A):



(I/A)

its isomers as well as its addition salts with a pharmaceutically acceptable acid.

3. A compound as claimed in claim 1 for which R_1 and R_2 each represent a hydrogen atom, of formula (I/B):



(I/B)

its isomers as well as its addition salts with a pharmaceutically acceptable acid or with a pharmaceutically acceptable base.

4. A compound as claimed in claim 1 for which R_3 and R_4, with the nitrogen atom which bears them, represent a saturated mono- or bicyclic nitrogenous heterocyclic system comprising from 5 to 12 atoms - not counting the hydrogen atoms - incorporating or otherwise in their carbon skeleton 1, 2 or 3 hetero atoms selected from nitrogen, oxygen and sulfur,
its isomers, epimers and diastereoisomers,
as well as its addition salts with a pharmaceutically acceptable acid and, when R_1 and R_2 each represent a hydrogen atom, its addition salts with a pharmaceutically acceptable base.

5. The compound as claimed in one of claims 1 and 2 which is 3-(2-piperidinoethyl)-3H-oxazolo[4,5-b]pyridin-2-one, as well as its addition salts with a pharmaceutically acceptable acid.

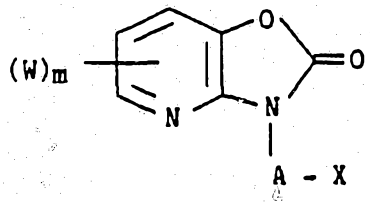
6. The compound as claimed in one of claims 1 and 2 which is 3-[2-(4-methyl-1-piperazinyl)ethyl]-3H-oxazolo [4,5-b]pyridin-2-one, as well as its addition salts with a pharmaceutically acceptable acid.

7. The compound as claimed in one of claims 1 and 2 which is 3-[2-(1-pyrrolidinyl) ethyl]-3H-oxazolo[4,5-b]-pyridin-2-one, as well as its addition salts with a pharmaceutically acceptable acid.

8. The compound as claimed in one of claims 1 and 2 which is 3-(2-morpholinoethyl)-3H-oxazolo[4,5-b]pyridin-2-one, as well as its addition salts with a pharmaceutically acceptable acid.

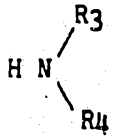
9. The compound as claimed in one of claims 1 and 3 which is 2-(2-piperidinoethylamino)-3-pyridinol, as well as its addition salts with a pharmaceutically acceptable acid or base.

10. A process for obtaining a compound of formula (I) as claimed in claim 1, wherein a compound of formula (II):



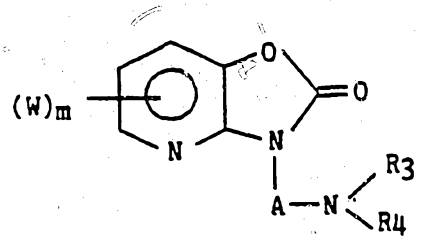
(II)

in which W, m and A have the same meaning as in the formula (I) and X represents a halogen atom,
is reacted, preferably under an inert atmosphere, with a compound of formula (III), preferably in excess:



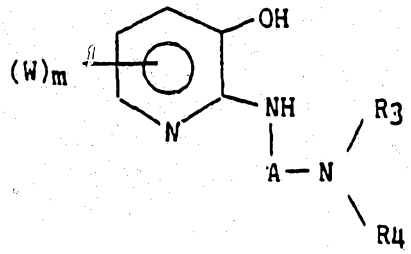
(III)

in which R_3 and R_4 have the same meaning as in the formula (I),
in an organic medium in the presence of a basic agent and at a temperature between room temperature and the refluxing temperature of the chosen solvent, to lead, after cooling, extraction and, where appropriate, purification, to a compound of formula (I/A):



(I/A)

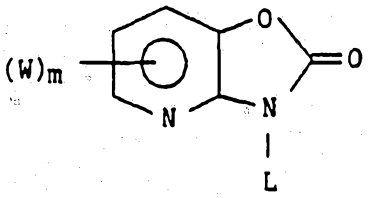
a special case of the compounds of formula (I) for which R_1 with R_2 forms a C = O group,
which may, if so desired, be separated, where applicable, into its isomers and then salified with a pharmaceutically acceptable acid,
which compound of formula (I/A) may be treated, if so desired, with an alkaline agent in aqueous solution, at a temperature between room temperature and the boiling point of the reaction medium, to lead, where appropriate after acidification and/or neutralization of the reaction medium, to a compound of formula (I/B):



(I/B)

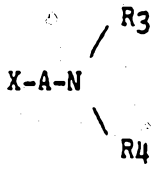
a special case of the compounds of formula (I) in which R_1 and R_2 each represent a hydrogen atom and W, m, A, R_3 and R_4 have the same meaning as above, which is purified, if necessary, by a technique selected from crystallization and chromatography and which is salified, if so desired, with a pharmaceutically acceptable acid or base.

11. A process for preparing a compound of formula (I/A) as claimed in claim 2, wherein a compound of formula (V):



(V)

in which W and m have the same meaning as in the formula (I) and L represents an alkali metal,
is reacted with a compound of formula (VII):

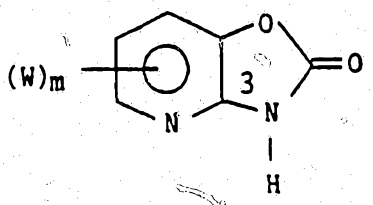


(VII)

in which A, R_3 and R_4 have the same definition as in the formula (I) and X represents a halogen atom, in an organic medium at a temperature between room temperature and the refluxing temperature of the chosen solvent, to lead, where appropriate after cooling, extraction and purification, to a compound of formula (I/A), the isomers of which, where applicable, are separated and which is salified, if so desired, with a pharmaceutically acceptable acid.

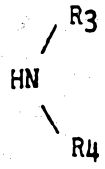
12. A process for preparing a compound of formula

(I/A) as claimed in claim 2 for which A represents a CH_2 group, wherein
on the one hand a compound of formula (IV):



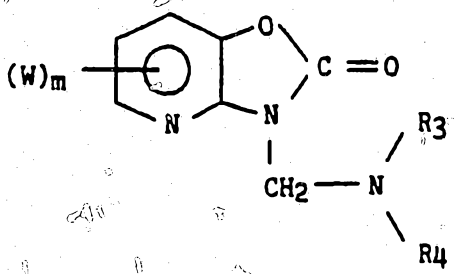
(IV)

in which W and m have the same meaning as in the formula (I),
on the other hand a slight excess of an amine of formula (III):



(III)

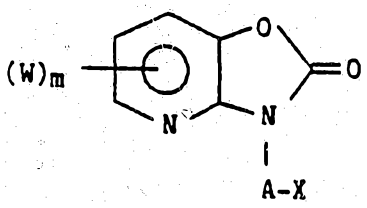
in which R_3 and R_4 have the same meaning as in the formula (I),
and on the other hand an excess of formaldehyde,
are dissolved in an a lower aliphatic alcohol medium, to lead, after heating the solution obtained to a temperature between room temperature and the boiling point, and where appropriate cooling, allowing the mixture to stand for one to two hours, filtration and chromatography on a silica column, to a compound of formula (I/A1):



(I/A1)

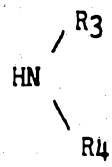
a special case of the compounds of formula (I/A) in which W, m, R_3 and R_4 have the same meaning as in the formula (I) and A represents a CH_2 group,
which may be salified, if so desired, with a pharmaceutically acceptable acid.

13. A process for preparing a compound of formula (I/A) as claimed in claim 2, wherein there is reacted a compound of formula (II):



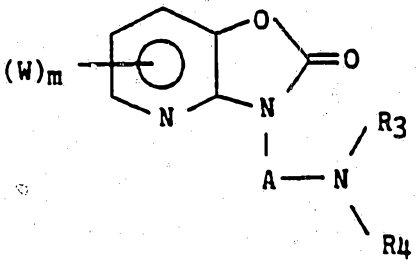
(II)

in which W, m and A have the same meaning as in the formula (I) and X represents a halogen atom,
which is condensed, preferably under an inert atmosphere, with a compound of formula (III), preferably in excess:



(III)

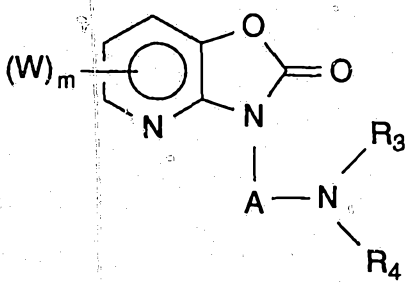
in which R_3 and R_4 have the same meaning as in the formula (I),
in an organic medium, in the optional presence of an excess of a basic agent and at a temperature between room temperature and the refluxing temperature of the chosen solvent, to lead, where appropriate after cooling, extraction and purification, to a compound of formula (I/A):



(I/A)

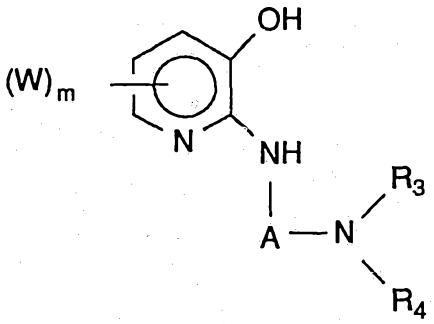
in which W, m, A, R_3 and R_4 have the same definition as in the formula (I),
which may, if necessary, be separated into its isomers and, if so desired, salified with a pharmaceutically acceptable acid.

14. A process for preparing a compound of formula (I/B) as claimed in claim 3, wherein a compound of formula (I/A):



(I/A)

in which W, m, A, R_3 and R_4 have the same meaning as in the formula (I), or one of its addition salts with a pharmaceutically acceptable acid, is subjected to an alkaline agent in aqueous solution, at a temperature between room temperature and the boiling point of the reaction medium, to lead, after neutralization or acidification of the reaction medium, to a compound of formula (I/B):



(I/B)

in which W, m, A, R_3 and R_4 have the same definition as in the formula (I), which is salified, if so desired, with a pharmaceutically acceptable acid or base, where appropriate after purification.

15. A pharmaceutical composition containing as active principle at least one compound as claimed in one of Claims 1 to 9, in combination with one or more pharmaceutically acceptable, non-toxic, inert excipients or vehicles.

16. A method of treating a mammal afflicted with a disorder selected from pain and disorders of cerebral circulatory insufficiency, comprising the step of

administering to the said mammal an amount of a compound as claimed in Claim 1 which is effective for alleviation of said disorder.

DATED this 19th day of January, 1993

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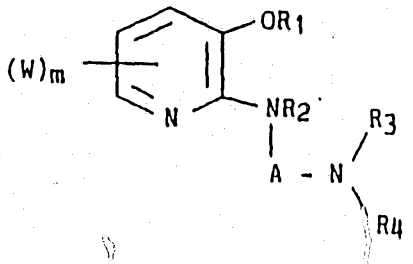
ABSTRACT

A compound of formula (I)



(I)

in which:

R_1 and R_2 each represent a hydrogen atom or, with the nitrogen and oxygen which bear them, form an - O - CO - N link,

W represents a halogen atom or a lower alkyl or alkoxy group optionally substituted with one or more halogen atoms, such as trifluoromethyl, and m being between 0 and 3,

A is a linear or branched alkyl radical comprising from 1 to 6 carbon atoms,

R_3 and R_4, which may be identical or different, represent:

- a hydrogen atom,
- a linear or branched lower alkyl group,
- a linear or branched lower alkenyl group,
- a cycloalkyl group having 6 to 10 carbon atoms,
- an aryl or (lower alkyl)aryl group,

each of these groups being optionally substituted with one or more halogen atoms or trifluoromethyl, hydroxyl or lower alkoxy groups,

or alternatively:

R_3 and R_4, with the nitrogen atom to which they are linked, constitute a saturated or unsaturated, mono- or bicyclic nitrogenous heterocyclic system comprising at most 12 atoms - not counting the hydrogen atoms - among which may be included one to three hetero atoms selected from nitrogen, oxygen and sulfur, unsubstituted or substituted with a lower alkyl or phenyl or phenyl(lower alkyl) or diphenyl(lower alkyl) group, it being possible for the phenyl, phenyl(lower alkyl) or diphenyl(lower alkyl)

groups to be substituted with one or more halogen atoms or a hydroxyl, lower alkyl, lower alkoxy or trifluoromethyl groups, on condition that R_3 and R_4, with the nitrogen atom to which they are linked, do not constitute a 1-arylpiperazine or 1-heteroaryl-piperazine system,

on the understanding that lower alkyl, lower alkenyl or lower alkyloxy radical is understood to mean a linear or branched group comprising from 1 to 6 carbon atoms, and that aryl or heteroaryl groups are understood to mean unsaturated mono- or bicyclic groups comprising from 5 to 12 carbon atoms - not counting the hydrogen atoms - incorporating or otherwise in their carbon skeleton 1, 2 or 3 hetero atoms selected from nitrogen, oxygen and sulfur,

its isomers, epimers and diastereoisomers,

as well as its addition salts with a pharmaceutically acceptable acid and, when R_1 and R_2 each represent a hydrogen atom, its addition salts with a pharmaceutically acceptable base.