

AUSTRALIA
Patents Act

625817

APPLICATION FOR A STANDARD PATENT

Bayer Aktiengesellschaft, a company registered under the laws of the Federal Republic of Germany, of D-5090 Leverkusen, BAYERWERK, FEDERAL REPUBLIC OF GERMANY

hereby applies for the grant of a standard patent for an invention entitled

~~Novel compounds~~ "1,3-Disubstituted Pyrrolidines".

which is described in the accompanying complete specification.

Details of basic application(s):

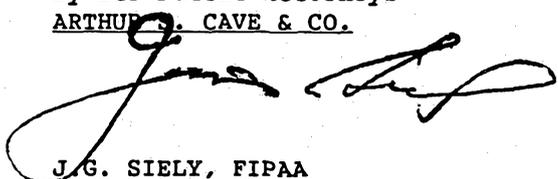
<u>Basic Application:</u>	<u>Country:</u>	<u>Date:</u>
P38 12 989.2	FEDERAL REPUBLIC OF GERMANY	19 April 1988
P38 35 291.5	FEDERAL REPUBLIC OF GERMANY	15 October 1988

The address for service is:

ARTHUR S. CAVE & CO.
Patent & Trade Mark Attorneys
Level 10, 10 Barrack Street
SYDNEY NSW 2000

DATED this TENTH day of APRIL 1989

Bayer Aktiengesellschaft
By Its Patent Attorneys
ARTHUR S. CAVE & CO.



J.G. SIELY, FIPAA

TO:
The Commissioner of Patents
COMMONWEALTH OF AUSTRALIA

FEE: 485.00

5006792 14/04/89



PATENT DECLARATION FORM (CONVENTION)
COMMONWEALTH OF AUSTRALIA
Patents Act 1952

Regulation
12 (2)

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION
FOR A PATENT

To be signed by the applicant(s) or in the case of a body corporate to be signed by a person authorised by the body corporate.

In support of the Convention application made for a patent for an invention entitled

(a) Insert title of invention.

(a) 1,3-Disubstituted pyrrolidines

(b) Insert full name(s) of declarant(s).

I/We (b) Günter Schumacher and Klaus Dänner
both are secretaries

(c) Insert address(es) of declarant(s).

of (c) BAYER AKTIENGESELLSCHAFT, D 5090 Leverkusen, Bayerwerk,
Federal Republic of Germany

do solemnly and sincerely declare as follows:-

~~1. I am/We are the applicant(s) for the patent~~

(OR, IN THE CASE OF AN APPLICATION BY A BODY CORPORATE.)

1. I am/We are authorised by BAYER AKTIENGESELLSCHAFT

the applicant for the patent to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act was/were made in the following country or countries on the following date(s) namely:-

(d) Insert country in which basic application(s) was/were filed.

in (d) the Federal Republic of Germany on (e) April 19, 1988

(e) Insert date of basic application(s).

by (f) Bayer Aktiengesellschaft

(f) Insert full names of basic applicant(s).

in (d) the Federal Republic of Germany on (e) October 15, 1988

by (f) Bayer Aktiengesellschaft

in (d) on (e)

by (f)

~~3. I am/We are the actual inventor(s) of the invention referred to in the basic application~~

(OR, WHERE A PERSON OTHER THAN THE INVENTOR IS THE APPLICANT)

(g) Insert full name(s) of actual inventor(s)

3. (g) 1) Rudolf Schohe 2) Peter-Rudolf Seidel
3) Jörg Traber 4) Thomas Glaser

(h) Insert address(es) of actual inventor(s).

of (h) 1) Pahlkestrasse 5, D 5600 Wuppertal 1, Germany
2) Alte Heide 5D, D 5000 Koeln 90, Germany
3) Loewenburgstrasse 12, D 5204 Lohmar, Germany
4) Koeslinerstrasse 21a, D 5064 Roesrath, Germany

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

(i) Set out how applicant(s) derive(s) title from actual inventor(s) i.e., assignee of the invention from the actual inventor(s).

(i) The company is the Assignee of the said invention from the said inventors

Attestation or legalization not required.

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

To:

Declared at Leverkusen this 7th day of March 1989
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The Commissioner of Patents

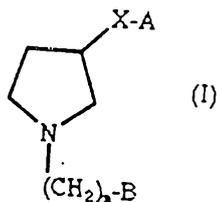
Günter Schumacher
Klaus Dänner
Signature of Declarant(s)

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

(12) PATENT ABRIDGMENT (11) Document No. AU-B-33059/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 625817

- (54) Title
1,3-DISUBSTITUTED PYRROLIDINES
- International Patent Classification(s)
(51)⁴ **C07D 207/12 A61K 031/40 A61K 031/54 C07D 401/06**
C07D 403/06 C07D 417/06 C07D 417/14 A61K 031/425
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- (43) Publication Date : **26.10.89**
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- (71) Applicant(s)
BAYER AKTIENGESELLSCHAFT
- (72) Inventor(s)
RULDOLF SCHOHE; PETER-RUDOLF SEIDEL; JORG TRABER; THOMAS GLASER
- (74) Attorney or Agent
DAVIES COLLISON CAVE , GPO Box 3876, SYDNEY NSW 2001
- (56) Prior Art Documents
AU 599632 69513/87 C07D 211/22 401/06 A61K 31/445
AU 607765 16562/88 C07D 401/06 401/14 A61K 31/55
US 3577432
- (57) Claim

1. 1,3-Disubstituted pyrrolidines of the general formula



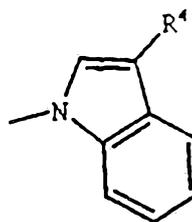
wherein

- A - denotes phenyl or hetaryl, or phenyl fused with aromatic, or with saturated or unsaturated cyclic or heterocyclic hydrocarbons, or A denotes hetaryl fused with aromatic hydrocarbons, wherein radical A can be unsubstituted or substituted,
- X - denotes $-O-CH_2-$, $-CH_2-O-$ or $-O-$,
- and
- B - denotes cyano or a group of the formula $-CO_2R^1$, $-SO_2NR^2R^3$, $-SO_mR^4$, $-NR^5R^6$, or $-C\equiv C-CH_2-NR^5R^6$

where

- R^1 - stands for hydrogen, alkyl, cycloalkyl, alkenyl, aryl or aralkyl,
 R^2 and R^3 are identical or different and
- stand for hydrogen, alkyl, cycloalkyl, aryl or aralkyl, where the aryl radicals can be substituted by halogen, alkoxy or alkoxy-carbonyl,
 R^4 - stands for alkyl, cycloalkyl, aryl or aralkyl, where the aryl radicals can be monosubstituted, disubstituted or trisubstituted by identical or different halogen, cyano, alkyl, alkoxy, trifluoromethyl or trifluoromethoxy, or

- for a group of the formula



- wherein R^4 denotes hydrogen or alkyl,
 m - stands for a number 0, 1 or 2,
 R^5 and R^6 are identical or different and
- stand for hydrogen, alkyl, cycloalkyl, aryl or aralkyl, where the aryl radicals can be substituted by halogen, cyano, alkyl, alkoxy or trifluoromethyl, or
- stand for a group of the formula $-COR^7$ or $-SO_2R^8$,

wherein

- R^7 - denotes hydrogen or
- a group NHR^9 or
- alkyl, cycloalkyl or alkoxy, or
- aryl, aryloxy, aralkyl, aralkoxy or hetero-aryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkylamino or dialkylamino,
 R^8 - denotes cycloalkyl or
- alkyl which can be substituted by cyano,

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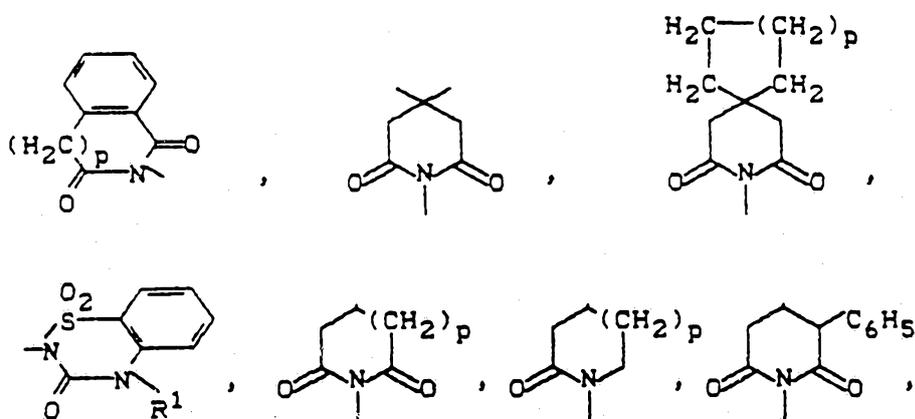
-3-

- halogen, alkoxy or alkoxy carbonyl, or
- aryl, aralkyl or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkylamino or dialkylamino, or
- denotes a group NR^2R^3 , where R^2 and R^3 have the abovementioned meaning and

- R^9
- denotes hydrogen or
 - cycloalkyl or
 - optionally substituted alkyl or
 - aryl, aralkyl or heteroaryl, where the aryl radicals can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkylamino or dialkylamino,

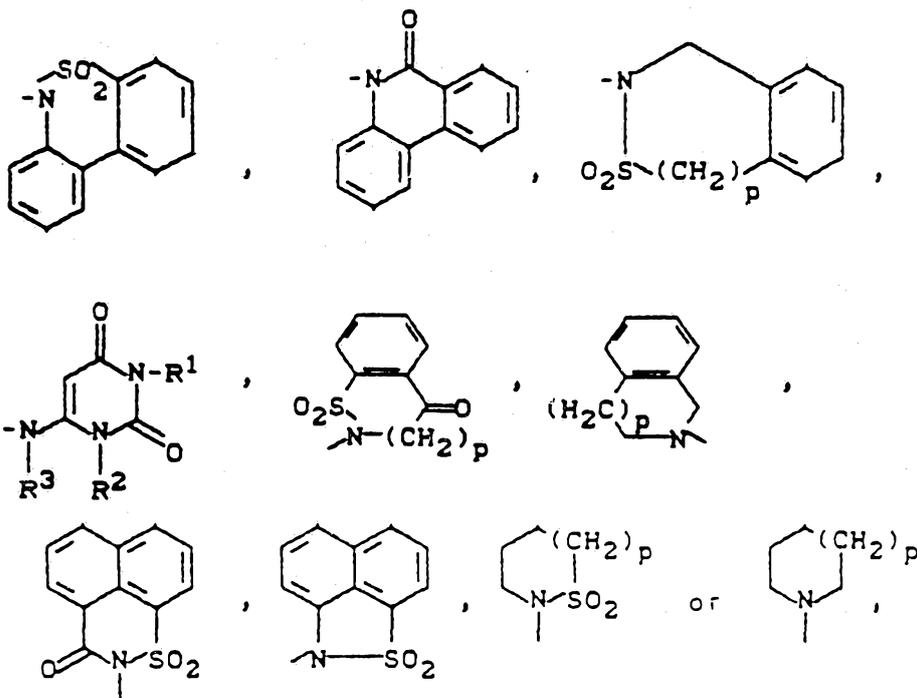
or where

R^5 and R^6 , together with the nitrogen atom, form a ring from the series comprising



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wherein

p - denotes a number 0, 1 and 2,

R^1 , R^2 and R^3 have the abovementioned meaning,

n - denotes a number from 1 to 10 and their salts.

8. Medicaments, containing 1,3-disubstituted pyrrolidines according to any one of claims 1 - 3 and a pharmaceutically acceptable carrier, diluent or excipient.

10. A method for the treatment of a condition of the serotonergic system in a subject which comprises administering to said subject an effective amount of a 1,3 disubstituted pyrrolidine according to any one of claims 1-3.

Our Ref: 260097

625817 FORM 10

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Patents Act

COMPLETE SPECIFICATION

(ORIGINAL)

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:
Related Art:

Applicant(s): Bayer Aktiengesellschaft
D-5090 Leverkusen
BAYERWERK
FEDERAL REPUBLIC OF GERMANY

Address for Service: ARTHUR S. CAVE & CO.
Patent & Trade Mark Attorneys
Level 10, 10 Barrack Street
SYDNEY NSW 2000

Complete specification for the invention entitled "~~Novel compounds~~".
"1,3-Disubstituted Pyrrolidines".

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



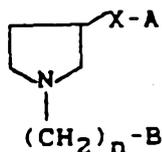
The invention relates to 1,3-disubstituted pyrrolidines, processes for their preparation and their use in medicaments.

Specific pyrrolidines having action on the central nervous system have been disclosed in DE-A 1,964,510. In particular, 1-substituted 3-phenoxy-pyrrolidines which have a pharmacological action on the central nervous system are described in DE-A 1,964,511. The compounds have muscle relaxant properties (page 3, 1st paragraph).

From US 3,642,803, 1-[2-(indol-3-yl)-ethyl]-3-(2-methoxy-phenoxy)pyrrolidine is known which likewise has an action on the central nervous system.

In DE-A 2,315,092, pyrrolidines having antipsychotic and muscle relaxant action are likewise described.

New 1,3-disubstituted pyrrolidines of the general formula (I)



wherein

A - denotes phenyl or hetaryl, which is optionally fused with aromatic, saturated or unsaturated cyclic or heterocyclic hydrocarbons, where this radical can optionally be substituted,

X - denotes -O-CH₂-, -CH₂-O- or -O-,
and

B - denotes cyano or a group of the formula
-COOR¹, -CONR²R³, -SO₂NR²R³, -SO_mR⁴, -NR⁵R⁶,
or -C≡C-CH₂-NR⁵R⁶

where

R¹ - stands for hydrogen, alkyl, cycloalkyl, alkenyl, aryl or aralkyl,

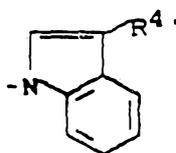
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R^2 and R^3 are identical or different and
- stand for hydrogen, alkyl, cycloalkyl, aryl
or aralkyl, where the aryl radicals can be
substituted by halogen, alkoxy or alkoxy-
carbonyl,

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R^4 - stands for alkyl, cycloalkyl, aryl or aral-
kyl, where the aryl radicals can be mono-
substituted, disubstituted or trisubstituted
by identical or different halogen, cyano,
alkyl, alkoxy, trifluoromethyl or trifluoro-
methoxy, or

10

- for a group of the formula 

- wherein R^4 denotes hydrogen or alkyl,

m - stands for a number 0, 1 or 2,

15

R^5 and R^6 are identical or different and
- stand for hydrogen, alkyl, cycloalkyl, aryl
or aralkyl, where the aryl radicals can be
substituted by halogen, cyano, alkyl, alk-
oxy or trifluoromethyl, or

20

- stand for a group of the formula
 $-COR^7$ or $-SO_2R^8$,

wherein

R^7 - denotes hydrogen or
- a group NHR^9 or
- alkyl, cycloalkyl or alkoxy, or
- aryl, aryloxy, aralkyl, aralkoxy or hetero-
aryl, where the radicals mentioned can be
monosubstituted, disubstituted or trisubsti-
tuted by identical or different alkyl, alk-
oxy, alkylthio, halogen, cyano, trifluoro-
methyl, trifluoromethoxy, trifluoromethyl-
thio, amino, alkylamino or dialkylamino,

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R^8 - denotes cycloalkyl or

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- alkyl which can be substituted by cyano, halogen, alkoxy or alkoxycarbonyl, or
- aryl, aralkyl or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkylamino or dialkylamino, or

5

10

- denotes a group NR^2R^3 , where R^2 and R^3 have the abovementioned meanings and

R^9

- denotes hydrogen or
- cycloalkyl or
- optionally substituted alkyl or
- aryl, aralkyl or heteroaryl, where the aryl radicals can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkylamino or dialkylamino,

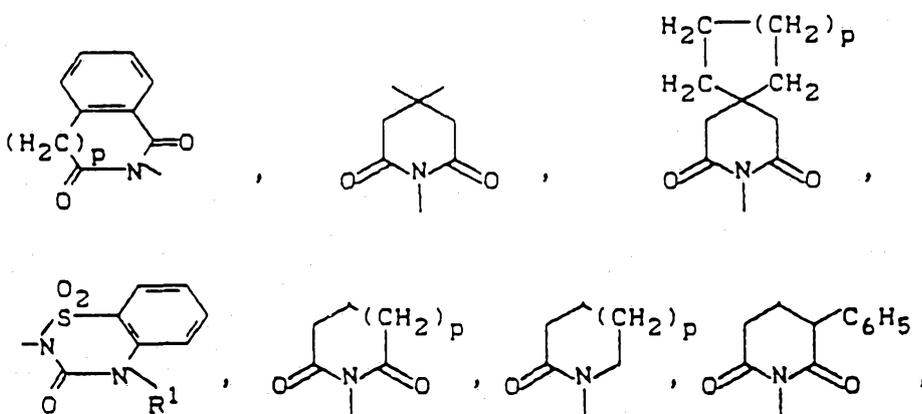
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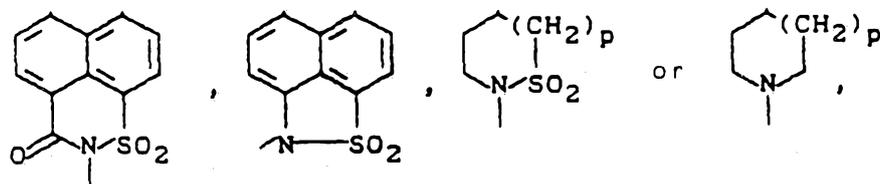
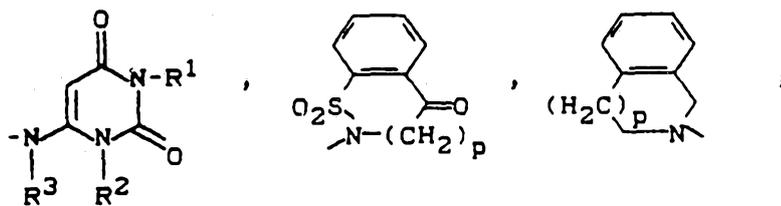
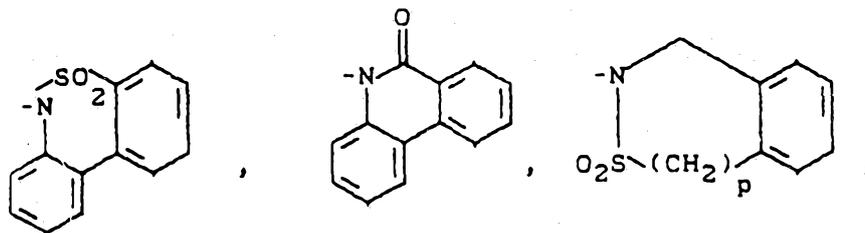
20

or where

R^5 and R^6 , together with the nitrogen atom, form a ring from the series comprising

25





wherein

p - denotes a number 0, 1 or 2,

R¹, R² and R³ have the abovementioned meaning, and

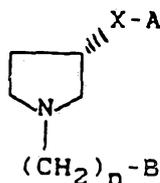
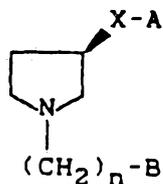
n - denotes a number from 1 to 10

and their salts have been found.

The substances according to the invention surprisingly show a superior action on the central nervous system and can be used for therapeutic treatment in humans and animals.

The substances according to the invention have several asymmetric carbon atoms and can therefore exist in various stereochemical forms. Moreover, compounds having a sulphoxide group can likewise exist in different stereochemical forms. The invention relates both to the individual isomers and to their mixtures. For example, the following isomeric forms of the 1,3-disubstituted pyrrolidines may be mentioned:

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The 1,3-disubstituted pyrrolidines according to the invention can also exist in the form of their salts. In general, salts with inorganic or organic acids may be mentioned here.

In the context of the present invention, physiologically acceptable salts are preferred. Physiologically acceptable salts of the 1,3-disubstituted pyrrolidines can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. For example, hydrochloric acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid or benzoic acid are preferred.

The radical A can be a phenyl or hetaryl radical which is optionally fused with aromatic, saturated, unsaturated or cyclic hydrocarbons or heterocycles. A hetaryl radical in the context of the invention is in general a monocyclic 5- or 6-membered ring having one or two, preferably one, nitrogen, oxygen or sulphur atom as heteroatom. For example, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyridyl, pyranyl, thiopyranyl, pyridazinyl, pyrimidinyl and pyrazinyl may be mentioned.

Further rings can be fused onto the phenyl and hetaryl rings.

Aromatic rings which may be mentioned are aryl

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(C₆ to C₁₂), preferably phenyl.

Unsaturated rings which may be mentioned are five to eight, preferably five- or six-membered hydrocarbons having one or two, preferably one, double bond. For example, cyclopentene may be mentioned.

Saturated rings which may be mentioned are 4- to 8-membered, cyclic hydrocarbons, preferably cyclopentyl and cyclohexyl.

Radicals A which may be mentioned, for example, are: phenyl, 2-fluorophenyl, 2-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-cyano-6-methoxyphenyl, alkenyloxyphenyl, 2-aminocarbonylphenyl, 1-naphthyl, 2-naphthyl, 1-tetralyl, 4-indolyl, 1-isoquinolyl, 2-quinolyl and 8-quinolyl.

Alkyl in general stands for a straight-chain or branched hydrocarbon radical having 1 to 12 carbon atoms. Lower alkyl having 1 to about 6 carbon atoms is preferred. Examples which may be mentioned are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl and isooctyl.

Alkenyl in general stands for a straight-chain or branched hydrocarbon radical having 2 to 12 carbon atoms and one or more, preferably one or two, double bonds. The lower alkyl radical having 2 to about 6 carbon atoms and one double bond is preferred. An alkenyl radical having 2 to 4 carbon atoms and one double bond is particularly preferred. Examples which may be mentioned are allyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, isopentenyl, hexenyl, isohexenyl, heptenyl, isoheptenyl, octenyl and isooctenyl.

Cycloalkyl in general stands for a cyclic hydrocarbon radical having 5 to 8 carbon atoms. The cyclopentane and the cyclohexane ring are preferred. Examples which may be mentioned are cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Aryl in general stands for an aromatic radical

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having 6 to about 12 carbon atoms. Preferred aryl radicals are phenyl, naphthyl and biphenyl.

Aralkyl in general stands for an aryl radical having 7 to 14 carbon atoms bonded via an alkylene chain.

5 Aralkyl radicals having 1 to 6 carbon atoms in the aliphatic moiety and 6 to 12 carbon atoms in the aromatic moiety are preferred. Examples which may be mentioned are the following aralkyl radicals: benzyl, naphthylmethyl, phenethyl and phenylpropyl.

10 Alkoxy in general stands for a straight-chain or branched hydrocarbon radical having 1 to 12 carbon atoms bonded via an oxygen atom. Lower alkoxy having 1 to about 6 carbon atoms is preferred. An alkoxy radical having 1 to 4 carbon atoms is particularly preferred. Examples
15 which may be mentioned are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, isopentoxy, hexoxy, isohexoxy, heptoxy, isoheptoxy, octoxy or isooctoxy.

Aryloxy in general stands for an aromatic radical having 6 to about 12 carbon atoms which is bonded via an
20 oxygen atom. Preferred aryloxy radicals are phenoxy or naphthyloxy.

Aralkoxy in general stands for an aralkyl radical having 7 to 14 carbon atoms, where the alkylene chain is bonded via an oxygen atom. Aralkoxy radicals having 1 to 6
25 carbon atoms in the aliphatic moiety and 6 to 12 carbon atoms in the aromatic moiety are preferred. Examples which may be mentioned are the following aralkoxy radicals: benzyloxy, naphthylmethoxy, phenethoxy and phenylpropoxy.

Alkylthio in general stands for a straight-chain
30 or branched hydrocarbon radical having 1 to 12 carbon atoms bonded via a sulphur atom. Lower alkylthio having 1 to about 6 carbon atoms is preferred. An alkylthio radical having 1 to 4 carbon atoms is particularly preferred. Examples which may be mentioned are methylthio, ethylthio,
35 propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, isopentylthio, hexylthio, isohexylthio, heptylthio,

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isoheptylthio, octylthio or iso-octylthio.

Acyl in general stands for phenyl or straight-chain or branched lower alkyl having 1 to about 6 carbon atoms which are bonded via a carbonyl group. Phenyl and
5 alkyl radicals having up to 4 carbon atoms are preferred. Examples which may be mentioned are: benzoyl, acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl and isobutylcarbonyl.

Alkoxy-carbonyl can, for example, be represented
10 by the formula $\begin{array}{c} -C-Oalkyl \\ || \\ O \end{array}$

Alkyl in this case stands for a straight-chain or branched hydrocarbon radical having 1 to 12 carbon atoms. Lower alkoxy-carbonyl having 1 to about 6 carbon atoms in the alkyl moiety is preferred. An alkoxy-carbonyl having 1 to 4 carbon atoms in the alkyl
15 moiety is particularly preferred. Examples which may be mentioned are the following alkoxy-carbonyl radicals: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl or
20 isobutoxycarbonyl.

Heteroaryl in the context of the abovementioned definition in general stands for a 5- to 6-membered aromatic ring which can contain oxygen, sulphur and/or nitrogen as heteroatoms and onto which a further aromatic ring can be fused. 5- and 6-membered aromatic rings which contain
25 one oxygen, one sulphur and/or up to 2 nitrogen atoms and which are optionally fused onto benzene, and their N-oxides are preferred. The following heteroaryl radicals may be mentioned as particularly preferred:

30 thienyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, thiazolyl, benzothiazolyl, isothiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, imidazolyl, benzimidazolyl, pyrazolyl and indolyl.

35 Halogen in general stands for fluorine, chlorine,
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bromine or iodine, preferably for fluorine, chlorine or bromine. Halogen particularly preferably stands for fluorine or chlorine.

5 Alkylsulphonyl can, for example, denote ethylsulphonyl, methylsulphonyl, 3-chloropropyl-sulphonyl and 4-chlorobutyl-sulphonyl.

Arylsulphonyl can, for example, denote phenylsulphonyl, 4-nitrophenylsulphonyl, 1-naphthylsulphonyl, 2-naphthylsulphonyl or 2,4-dichlorophenylsulphonyl.

10 Alkylarylsulphonyl can, for example, denote 4-methylsulphonyl.

Aralkylsulphonyl can, for example, denote phenylmethylsulphonyl.

15 The radicals mentioned can, of course, be substituted by further radicals, for example lower alkyl (C_1 to about C_6), lower alkoxy (C_1 to about C_6), halogen (in particular fluorine and chlorine) or aryl (in particular phenyl), cyano or alkoxy- (C_4 to C_6)-carbonyl.

20 1,3-Disubstituted pyrrolidines of the general formula (I) are preferred wherein

A stands for phenyl or a monocyclic five- or six-membered hetaryl radical which contains one or two nitrogen and/or oxygen and/or sulphur atoms, onto which are optionally fused one to three aromatic (C_5 to C_8), saturated or unsaturated cyclic (C_5 to C_8) hydrocarbons or five- or six-membered heterocycles (having one or two nitrogen and/or oxygen and/or sulphur atoms), where this radical is optionally monosubstituted or disubstituted by

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lower alkyl, lower alkoxy, lower alkoxy-carbonyl, lower alkenyloxy, acyloxy, benzoyloxy, cyano, phenyl, benzyl, fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, difluoromethoxy or a radical of the formula $-CO-NYZ$, $-NH-SO_2-Y'$, $-SO_2-NYZ$ or $-NH-CO-Y$,
where

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Y and Z are identical or different and stand for hydrogen or alkyl (C₁ to C₆), and
Y' stands for alkyl (C₁ to C₆) or aryl,
and in the case of nitrogen heterocycles is optionally pre-

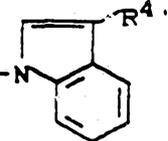
5 sent as the N-oxide,

X - stands for -CH₂-O-, -O-CH₂- or -O-,
B - stands for cyano or a group of the formula
-COOR¹, CONR²R³, -SO₂NR²R³, -SO_mR⁴,
NR⁵R⁶ or -C≡C-CH₂-NR⁵R⁶, where

10 R¹ - stands for hydrogen, alkyl (C₁ to C₁₁),
cycloalkyl (C₅ to C₈), alkenyl (C₂ to C₁₂),
aryl (C₆ to C₁₂) or aralkyl (C₇ to C₁₇),

R² and R³ are identical or different and
- stand for hydrogen, alkyl (C₁ to C₁₂),
15 cycloalkyl (C₅ to C₈), aryl (C₆ to C₁₂)
or aralkyl (C₇ to C₁₄), where the aryl
radicals can be substituted by halogen,
alkoxy or alkoxycarbonyl (C₁-C₆),

R⁴ - stands for alkyl (C₁ to C₁₂), cycloalkyl
20 (C₅ to C₈), aryl (C₆ to C₁₂) or aral-
kyl (C₇ to C₁₄), where the aryl radicals
can be monosubstituted, disubstituted or
trisubstituted by identical or different
halogen, cyano, alkyl (C₁ to C₆), alkoxy
25 (C₁ to C₆), trifluoromethyl or tri-
fluoromethoxy, or

- for a group of the formula 

wherein R⁴ denotes hydrogen or alkyl (C₁-
C₆) or

30 m stands for a number 0, 1 or 2,

R⁵ and R⁶ are identical or different and

- stand for hydrogen, alkyl (C₁ to C₁₂),
cycloalkyl (C₅ to C₈), aryl (C₆ to C₁₂)
or aralkyl (C₇ to C₁₄), where the aryl

radicals can be substituted by halogen, cyano, alkyl (C₁ to C₆), alkoxy (C₁ to C₆) or trifluoromethyl, or

5 - stands for a group of the formula -COR⁷ or -SO₂R⁸ wherein

R⁷ - denotes hydrogen or

- a group NHR⁹ or

- alkyl (C₁ to C₁₁), cycloalkyl (C₅ to C₈) or alkoxy (C₁ to C₁₂), or

10 - aryl (C₆ to C₁₂), aryloxy (C₆ to C₁₂), aralkyl (C₇ to C₁₄), aralkoxy (C₆ to C₁₂) or heteroaryl (five- or six-membered ring having one or two oxygen and/or nitrogen and/or sulphur atoms),

15 where the radicals mentioned can be mono-substituted, disubstituted or trisubstituted by identical or different alkyl (C₁ to C₆), alkoxy (C₁ to C₆), alkylthio (C₁ to C₆), halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkyl-

20 (C₁ to C₆)-amino or dialkyl-(C₁ to C₆)-amino,

R⁸ - denotes cycloalkyl (C₅ to C₈), or

- alkyl (C₁ to C₁₂) which can be substituted by cyano, halogen, alkoxy (C₁ to C₁₂) or alkoxy-(C₁ to C₁₂)-carbonyl or

25 - aryl (C₆ to C₁₂), aralkyl (C₇ to C₁₄) or heteroaryl (five- or six-membered ring having one or two oxygen and/or nitrogen and/or sulphur atoms), where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or

30 different alkyl (C₁ to C₆), alkoxy (C₁ to C₆), alkylthio (C₁ to C₆), halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkyl-

35

(C₁ to C₆)-amino or dialkyl-(C₁ to C₆)-amino or

- denotes a group NR²R³, wherein R² and R³ have the abovementioned meaning and

5

R⁹ - denotes hydrogen, or

- cycloalkyl (C₅ to C₈), or

- optionally substituted alkyl (C₁ to C₁₂), or

10

- aryl (C₆ to C₁₂), aralkyl (C₇ to C₁₄)

or heteroaryl (five- or six-membered ring having one or two oxygen and/or nitrogen

and/or sulphur atoms), where the aryl radicals can be monosubstituted, disubstituted

15

or trisubstituted by identical or different alkyl (C₁ to C₆), alkoxy (C₁ to C₆),

alkylthio (C₁ to C₆), halogen, cyano,

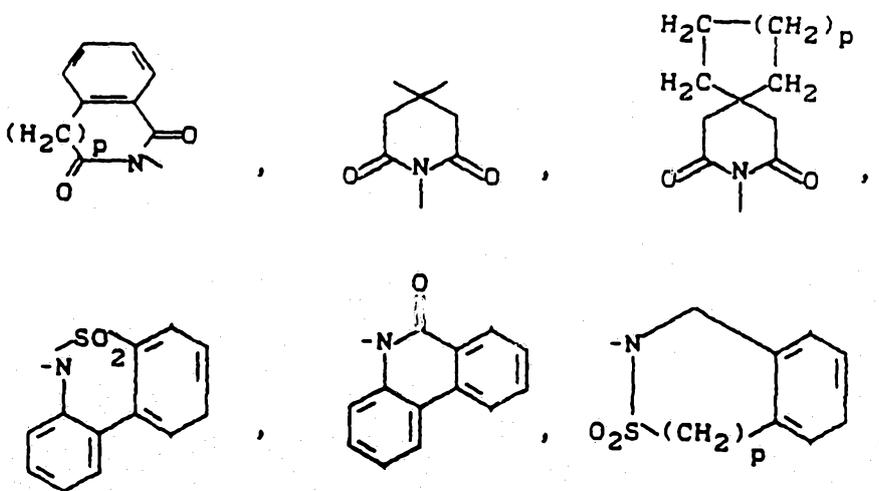
trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkyl-(C₁ to

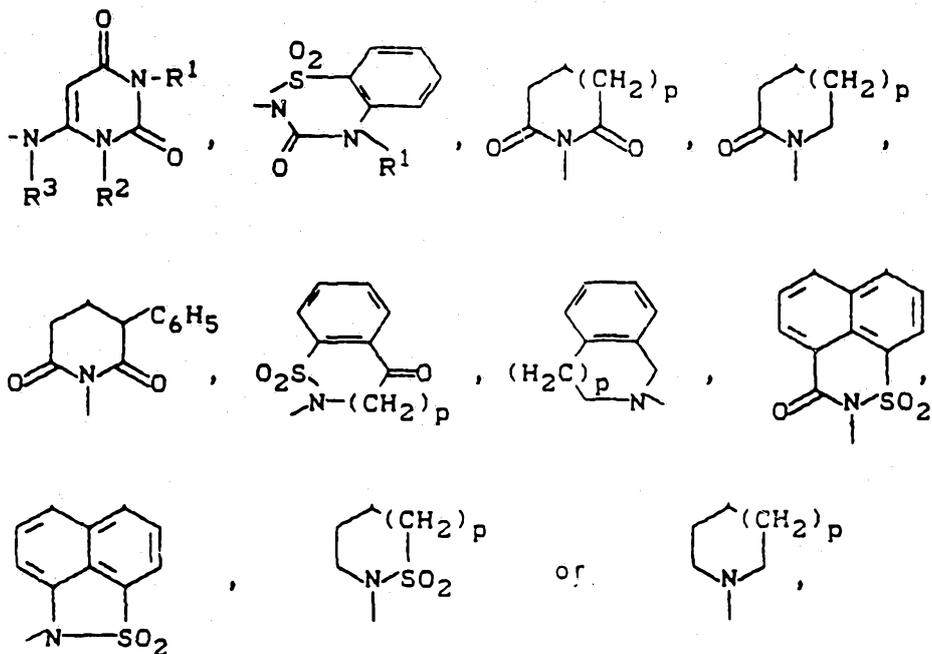
20

C₆)-amino or dialkyl-(C₁ to C₆)-amino,

or where

R⁵ and R⁶, together with the nitrogen atom, form a ring from the series comprising





wherein

p - denotes a number 0, 1 or 2,

R¹, R² and R³ have the abovementioned meaning,

n - denotes a number from 1 to 10

and their salts.

Compounds of the general formula (I) are particularly preferred in which

A stands for phenyl or a monocyclic five- or six-membered hetaryl radical which contains one or two nitrogen and/or oxygen and/or sulphur atoms, onto which one to three aromatic (C₅ to C₈), saturated or unsaturated cyclic (C₅ to C₈) hydrocarbons or five- or six-membered heterocycles (having one or two nitrogen and/or oxygen and/or sulphur atoms) are optionally fused, where this radical is optionally monosubstituted or disubstituted by lower alkyl, lower alkoxy, lower alkoxycarbonyl, lower alkenyloxy, acyloxy, benzoyloxy, cyano, phenyl, benzyl, fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, difluoromethoxy or

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a radical of the formula $-CO-NYZ$, $-NH-SO_2-Y'$,
 $-SO_2-NYZ$ or $NH-Y$, where

Y and Z are identical or different and stand for
hydrogen or alkyl (C_1 to C_6) and

5 Y' stands for alkyl (C_1 to C_6) or aryl,
and in the case of the nitrogen heterocycles is optionally
present as the N-oxide,

X - stands for $-CH_2-O-$, $-O-CH_2-$ or $-O-$,

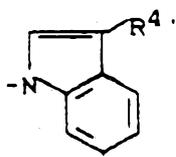
10 B - stands for cyano or a group of the formula
 $-COOR^1$, $CONR^2R^3$, $-SO_2NR^2R^3$,
 $-SO_mR^4$, NR^5R^6 or $-C\equiv C-CH_2-NR^5R^6$,
where

R¹ - stands for hydrogen, lower alkyl or phenyl,

15 R² and R³ are identical or different and
- stand for hydrogen, lower alkyl or phenyl
which, in turn, can be substituted by fluor-
ine, chlorine, bromine, lower alkoxy or
lower alkoxycarbonyl,

20 R⁴ - stands for lower alkyl, or

- for phenyl which can be monosubstituted or
disubstituted by identical or different
fluorine, chlorine, bromine, lower alkyl
or lower alkoxy, or

- for a group of the formula 

25 wherein R⁴ denotes hydrogen or lower alkyl,

m - stands for a number 0, 1 or 2,

R⁵ and R⁶ are identical or different and

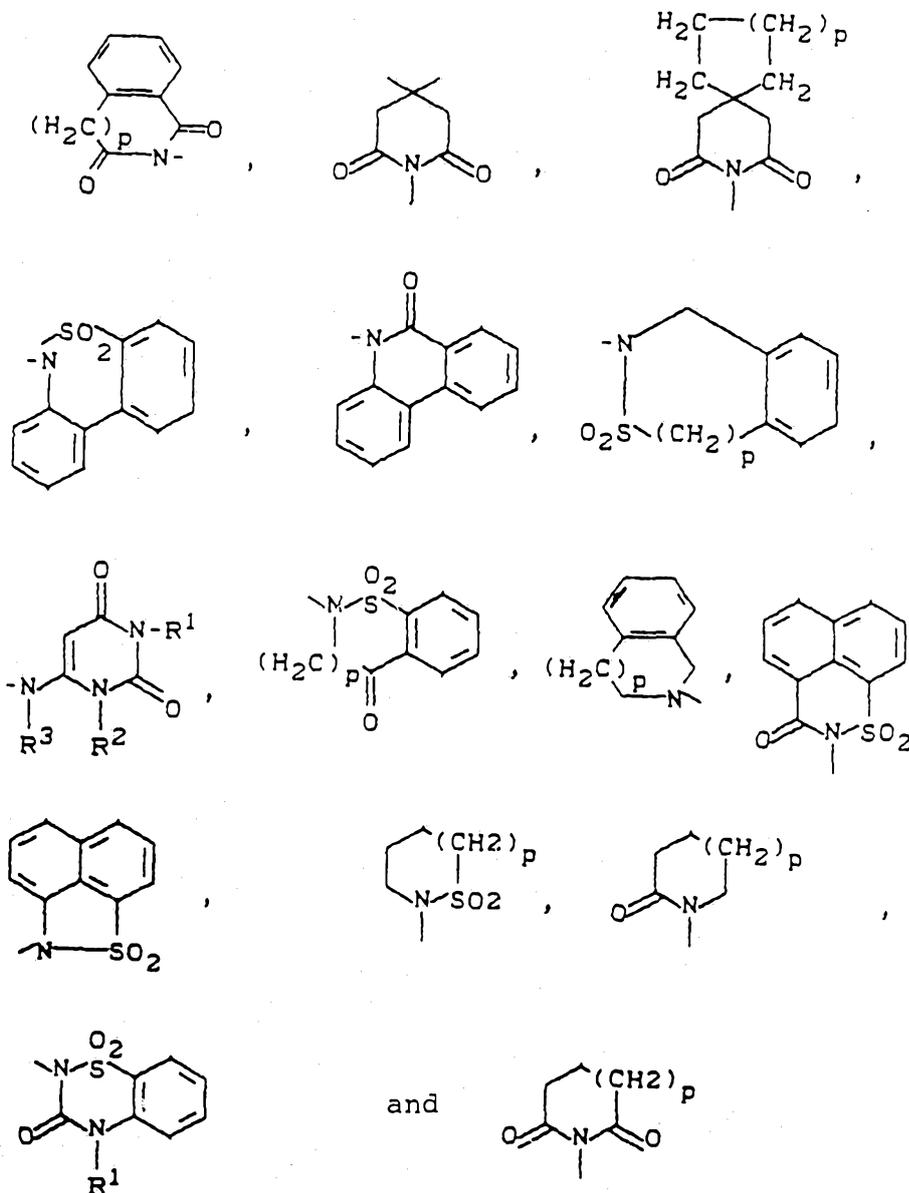
30 - stand for hydrogen, lower alkyl, phenyl or
benzyl, where the phenyl radical can be sub-
stituted by fluorine, chlorine, bromine,
lower alkyl, lower alkoxy or trifluoro-
methyl, or

- stands for a group of the formula
 $-COR^7$ or $-SO_2R^8$,

wherein

- 5
10
15
20
25
30
35
- R⁷
- denotes hydrogen, or
 - denotes a group NHR⁹, or
 - denotes lower alkyl or lower alkoxy, or
 - phenyl, benzyl, benzyloxy, thienyl, furyl, pyridyl, pyrimidyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, thiazolyl, oxazolyl, isoxazolyl or isothiazolyl optionally substituted by lower alkyl, lower alkoxy, fluorine, chlorine, bromine, trifluoromethyl, dimethylamino or diethylamino,
- R⁸
- denotes cyclopropyl, cyclopentyl, cyclohexyl, or
 - lower alkyl which is optionally substituted by cyano, fluorine, chlorine, bromine, trifluoromethyl or lower alkoxy, or
 - denotes phenyl, naphthyl, benzyl, thienyl, furyl, pyrimidyl, pyridyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, thiazolyl, oxazolyl, isoxazolyl or isothiazolyl optionally substituted by lower alkyl, lower alkoxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, dimethylamino or diethylamino, or a group NR²R³, where R² and R³ have the abovementioned meaning, and
- R⁹
- denotes lower alkyl which is optionally substituted by cyano, fluorine, chlorine or bromine, or
 - denotes phenyl, benzyl, thienyl, furyl, pyridyl, pyrimidyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, thiazolyl, oxazolyl, isoxazolyl or isothiazolyl optionally substituted by lower alkyl, lower alkoxy, fluorine, chlorine, bromine, trifluoromethyl, dimethylamino or diethylamino,

or
 R^5 and R^6 , together with the nitrogen atom,
 form a ring from the series comprising



5

wherein

p - denotes a number 0, 1 or 2,

R^1 , R^2 and R^3 have the abovementioned meanings,

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and

n - denotes a number from 1 to 8

and their salts.

Particularly preferred are those compounds of the
5 general formula (I)

in which

A - stands for phenyl or naphthyl optionally
substituted by identical or different lower
10 alkyl, lower alkoxy, lower alkoxycarbonyl,
lower alkenyloxy, acyloxy, benzoyloxy, cyano,
phenyl, benzyl, sulphonylamino, sulphamoyl
(C₁ to C₆), carbamoyl, carbonylamino,
15 fluorine, chlorine, bromine, trifluoro-
methyl, trifluoromethoxy or difluoromethoxy,
furan, thiophene, isoxazole, pyridine,
pyrimidine, indole, indazole, benzofuran,
benzisoxazole, quinoline, isoquinoline,
20 tetralin, indene, chroman, dihydrobenzo-
dioxin, dihydroindole, tetrahydroquinoline
or dihydrobenzofuran,

X - stands for -O-CH₂-, -CH₂-O- or -O-,

B - stands for cyano, or

- a group of the formula
25 -CONR²R³, -NR⁵R⁶, -SO_mR⁴,
-C≡C-CH₂-NR⁵R⁶, -SO₂NR²R³ or
COOR¹,

where

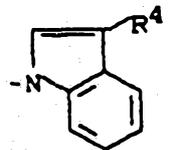
R¹ - denotes hydrogen, methyl, ethyl or phenyl,

R² and R³ are identical or different and

30 - denote hydrogen, methyl, ethyl, propyl, iso-
propyl, butyl or isobutyl or denote phenyl
which can be substituted by methoxycarbonyl

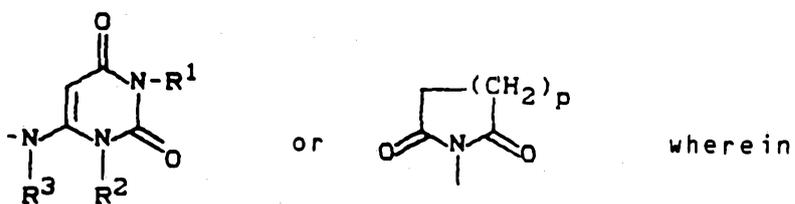
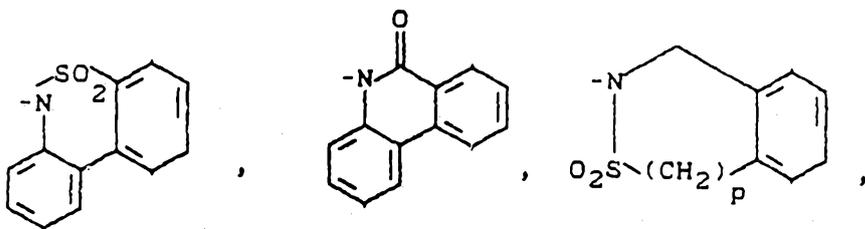
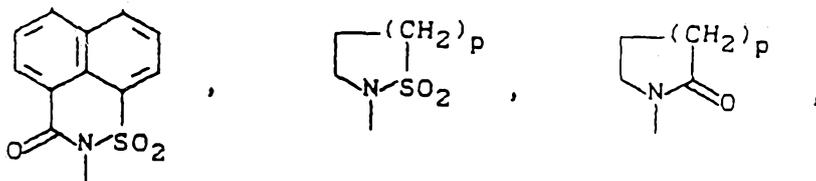
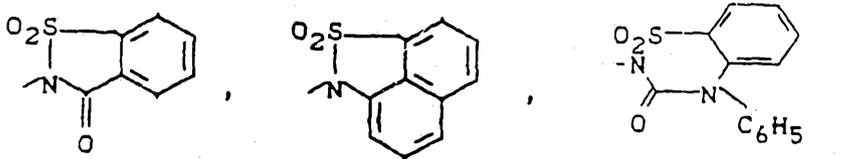
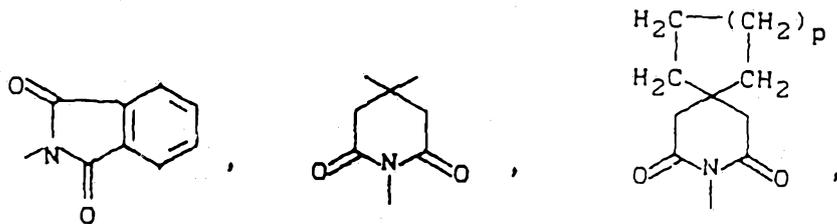
R⁴ - stands for methyl or ethyl or

- for a group of the formula



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wherein R^4 denotes hydrogen or methyl,
 R^5 and R^6 are identical or different, and
 - denote hydrogen, methyl, ethyl, propyl, iso-
 propyl, butyl or isobutyl, or
 5 - phenyl optionally substituted by fluorine,
 chlorine, methyl or methoxy, or
 - denote a group $-COR^7$ or $-SO_2R^8$,
 R^7 - stands for a group NHR^9 , or
 - for methyl, ethyl, propyl, isopropyl, meth-
 10 oxy, ethoxy, propoxy, isopropoxy, tert.but-
 oxy or
 - for phenyl, benzyl, benzyloxy, thienyl,
 furyl, pyridyl, pyrimidyl, quinolyl or iso-
 quinolyl optionally substituted by methyl,
 15 methoxy, fluorine or chlorine,
 R^8 - stands for methyl, ethyl, propyl, isopropyl,
 butyl or isobutyl optionally substituted
 by fluorine, chlorine, methoxycarbonyl,
 ethoxycarbonyl, propoxycarbonyl, isopropoxy-
 20 carbonyl, butoxycarbonyl, isobutoxycarbonyl
 or tert.-butoxycarbonyl,
 - for phenyl, naphthyl, thienyl, furyl, pyr-
 idyl, pyrimidyl, quinolyl or isoquinolyl
 optionally substituted by methyl, ethyl,
 25 propyl, isopropyl, methoxy, fluorine, chlo-
 rine or nitro, or
 - for a group NR^2R^3 , where
 R^2 and R^3 have the abovementioned meaning,
 R^9 - denotes methyl, ethyl, propyl, isopropyl,
 30 butyl, isobutyl, pentyl, isopentyl, hexyl
 or isohexyl optionally substituted by fluo-
 rine or chlorine, or
 - denotes phenyl which can be substituted by
 fluorine, chlorine, methyl or methoxy, or
 35 R^5 and R^6 , together with the nitrogen atom,
 form a ring from the series comprising



p - denotes a number 1 or 2

R¹, R² and R³ have the abovementioned meaning
and

n - denotes a number from 1 to 6,

and their salts.

Examples which may be mentioned are the following
1,3-disubstituted pyrrolidines:

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- 3-(2-methoxyphenoxy)-1-[5-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)pentyl]-pyrrolidine
3-(2-methoxyphenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
5 3-(2-methoxyphenoxy)-1-[3-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)propyl]-pyrrolidine
3-(2-methoxyphenoxy)-1-[2-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)ethyl]-pyrrolidine
3-(3-methoxyphenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
10 3-(3-methoxyphenoxy)-1-[5-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)pentyl]-pyrrolidine
3-(3-methoxyphenoxy)-1-[3-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)propyl]-pyrrolidine
15 3-(3-methoxyphenoxy)-1-[2-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)ethyl]-pyrrolidine
3-(4-methoxyphenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
3-(4-methoxyphenoxy)-1-[5-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)pentyl]-pyrrolidine
20 3-(4-methoxyphenoxy)-1-[3-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)propyl]-pyrrolidine
3-(4-methoxyphenoxy)-1-[2-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)ethyl]-pyrrolidine
25 3-(1-naphthyloxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
3-(1-naphthyloxy)-1-[5-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)pentyl]-pyrrolidine
3-(1-naphthyloxy)-1-[3-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)propyl]-pyrrolidine
30 3-(1-naphthyloxy)-1-[2-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)ethyl]-pyrrolidine
3-(2-naphthyloxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
35 3-(2-naphthyloxy)-1-[5-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)pentyl]-pyrrolidine

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- 3-(2-naphthyloxy)-1-[3-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)propyl]-pyrrolidine
- 3-(2-naphthyloxy)-1-[2-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)ethyl]-pyrrolidine
- 5 3-(2-cyanophenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 3-(2-carbamoylphenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 10 3-(2-cyano-6-methoxy-phenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 3-[(2-fluorophenyl)-methoxy]-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 3-(2-methoxy-phenoxy-methyl)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 15 3-(1-naphthylmethoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 3-(2-naphthylmethoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 3-(1-carbamoyl-2-naphthyloxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 20 3-(2-carbamoyl-1-naphthyloxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 3-[4-(1-methyl)indolyl-oxy]-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 25 3-(2-quinolinyl-oxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 3-(1-isoquinolinyl-oxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 30 3-(5,6,7,8-tetrahydro-1-naphthyloxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 1-[3-(4-fluorophenyl)sulphonamido-propyl]-3-(2-methoxy-phenoxy)-pyrrolidine
- 1-[2-(4-fluorophenyl)sulphonamido-ethyl]-3-(2-methoxy-phenoxy)-pyrrolidine
- 35 1-[4-(4-fluorophenyl)sulphonamido-butyl]-3-(2-methoxy-phenoxy)-pyrrolidine

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- 1-[3-N-phenyl-(methyl)sulphonamido-propyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 1-[3-N-methyl-(4-fluorophenyl)sulphonamido-propyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 5 1-[4-N-methyl-(4-fluorophenyl)sulphonamido-butyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 1-[3-(4-fluorophenyl)sulphonamido-propyl]-3-(1-naphthyl-oxy)-pyrrolidine
- 1-[2-(4-fluorophenyl)sulphonamido-ethyl]-3-(1-naphthyl-oxy)-pyrrolidine
- 10 1-[4-(4-fluorophenyl)sulphonamido-butyl]-3-(1-naphthyl-oxy)-pyrrolidine
- 1-[3-N-methyl-(4-fluorophenyl)sulphonamido-propyl]-3-(1-naphthyloxy)-pyrrolidine
- 15 1-[2-N-methyl-(4-fluorophenyl)sulphonamido-ethyl]-3-(1-naphthyloxy)-pyrrolidine
- 1-[4-N-methyl-(4-fluorophenyl)sulphonamido-butyl]-3-(1-naphthyloxy)-pyrrolidine
- 1-[3-(1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)propyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 20 1-[2-(1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)-ethyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 1-[4-(1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)butyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 25 1-(3-aminopropyl)-3-(2-methoxyphenoxy)-pyrrolidine
- 1-(2-aminoethyl)-3-(2-methoxyphenoxy)-pyrrolidine
- 1-[3-(1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)propyl]-3-(1-naphthyloxy)-pyrrolidine
- 1-[2-(1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)-ethyl]-3-(1-naphthyloxy)-pyrrolidine
- 30 1-[4-(1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)butyl]-3-(1-naphthyloxy)-pyrrolidine
- 1-[3-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)propyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 35 1-[2-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)ethyl]-3-(2-methoxyphenoxy)-pyrrolidine

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- 1-[4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)butyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 1-[3-(1,1-dioxido-3,4-dihydro-4-phenyl-2H-1,2,4-benzothiadiazin-3-on-2-yl)-propyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 5 1-[2-(1,1-dioxido-3,4-dihydro-4-phenyl-2H-1,2,4-benzothiadiazin-3-on-2-yl)-ethyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 10 1-[4-(1,1-dioxido-3,4-dihydro-4-phenyl-2H-1,2,4-benzothiadiazin-3-on-2-yl)-butyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 1- (2-cyanoethyl)-3-(2-methoxyphenoxy)-pyrrolidine
- 1-cyanomethyl-3-(2-methoxyphenoxy)-pyrrolidine
- 3-(1-naphthyloxy)-1-[4-(2-oxopyrrolidin-1-yl)but-2-in-1-yl]-pyrrolidine
- 15 1-[2-(N,N-dimethylsulphamoyl)ethyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 1-[2-(N,N-diethylsulphamoyl)ethyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 20 1-[2-(N-(2-methoxycarbonyl)phenylsulphamoyl)ethyl]-3-(2-methoxyphenoxy)-pyrrolidine
- R(-)-3-(2-methoxyphenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- S(+)-3-(2-methoxyphenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydrobenzisothiazol-2-yl)butyl]-pyrrolidine
- 25 3-(2-methoxyphenoxy)-1-[4-(1,1-dioxido-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine
- 3-(2-methoxyphenoxy)-1-[2-(3-methylindol-1-yl)-sulphonyl-ethyl]-pyrrolidine
- 30 3-(2-methoxyphenoxy)-1-[4-(6(5H)-phenanthridinon-5-yl)-butyl]-pyrrolidine
- 1-[4-(5,5-dioxido-6H-dibenzo[c,e][1,2]thiazin-6-yl)butyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 1-[3-(1,3-dimethyl-uracil-6-yl)aminopropyl]-3-(2-methoxyphenoxy)-pyrrolidine
- 35 1-[2-(prop-2-enyloxy)phenoxy]-1-[4-(1,1-dioxido-3-oxo-

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2,3-dihydrobenzothiazol-2-yl)butyl]-pyrrolidine

The following are particularly preferred:

3-(2-methoxyphenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-
benzothiazol-2-yl)butyl]-pyrrolidine

5 3-(3-methoxyphenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-
benzothiazol-2-yl)butyl]-pyrrolidine

3-(1-naphthyl)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benz-
isothiazol-2-yl)butyl]-pyrrolidine

10 3-(2-cyano-6-methoxy-phenoxy)-1-[4-(1,1-dioxido-3-oxo-
2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine

1-[2-(4-fluorophenyl)sulphonamido-ethyl]-3-(2-methoxy-
phenoxy)-pyrrolidine

1-[3-(4-fluorophenyl)sulphonamido-propyl]-3-(2-methoxy-
phenoxy)-pyrrolidine

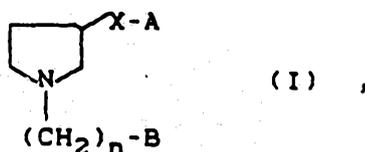
15 1-[4-(1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)butyl]-
3-(2-methoxyphenoxy)-pyrrolidine

1-[4-(1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)butyl]-
3-(1-naphthyloxy)-pyrrolidine

20 R(-)-3-(2-methoxyphenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-
dihydrobenzothiazol-2-yl)butyl]pyrrolidine

3-(2-methoxyphenoxy)-1-[4-(2,3-dihydro-benzisothiazol-2-
yl)butyl]-pyrrolidine

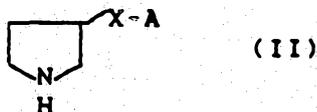
25 Furthermore, a process has been found for the pre-
paration of the 1,3-disubstituted pyrrolidines of the
general formula (I) according to the invention



wherein

A, B, X and n have the abovementioned meaning,
which is characterized in that

30 3-substituted pyrrolidines of the general formula (II)



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in which

A and X have the abovementioned meaning,
or their salts
are reacted in a first step with alkyl derivatives of the
5 general formula (III)



wherein

n - has the abovementioned meaning,

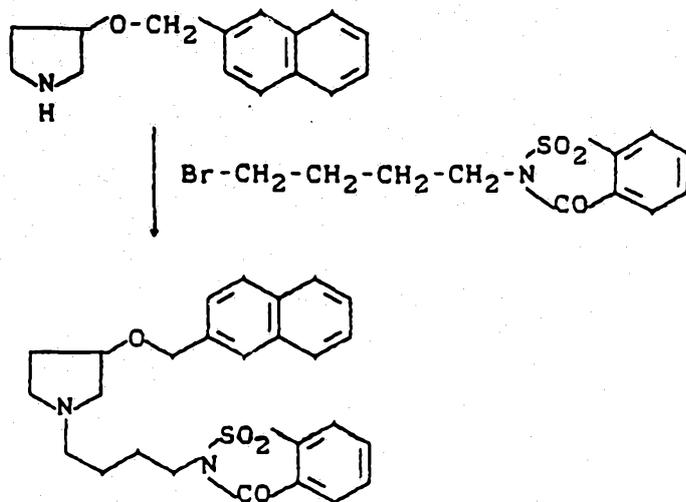
10 B' corresponds to the range of meaning of B,
where, however, R⁵ and R⁶ do not stand
simultaneously for hydrogen or simultaneously
for hydrogen and alkyl or aryl,

15 R - stands for chlorine, bromine, iodine, methyl-
sulphonyloxy, phenylsulphonyloxy, tolyl-
sulphonyloxy, trifluoroacetoxy or trifluoro-
methylsulphonyloxy,

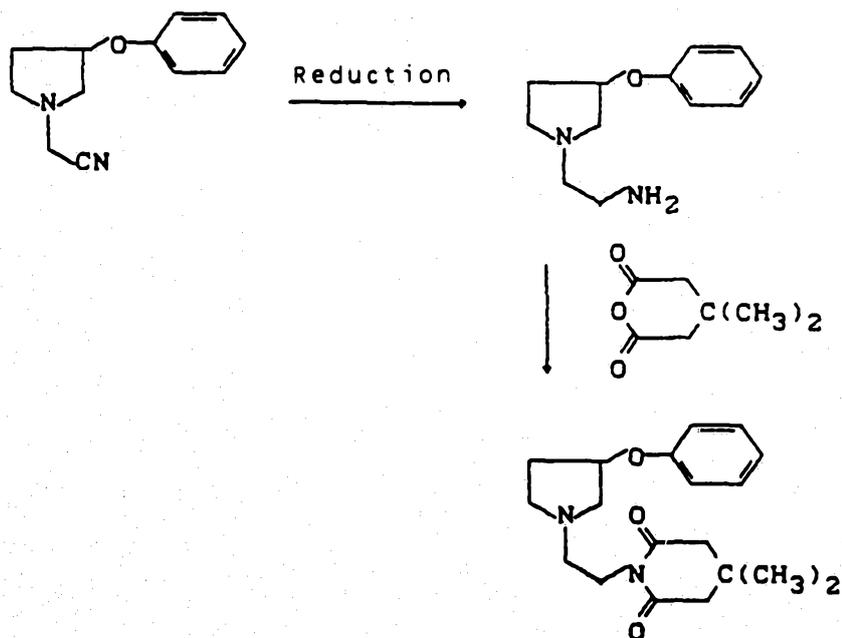
in inert solvents, if appropriate in the presence of
bases,

20 then, if desired, functional groups are converted into
other functional groups by reduction, oxidation, hydrolysis
or reaction with electrophiles or nucleophilic reagents
and then, in the case of the preparation of the salts, if
desired, the products are reacted with the corresponding acid.

25 The first step of the process according to the in-
vention (known as method M 1 in the following) can be des-
cribed by way of example by the following reaction equation:



A possible subsequent reaction (known as method M 2 in the following) may be illustrated by way of example by the following reaction equation, in which the nitrile can be prepared according to M 1:



The alkyl compounds of the general formula (III) employed are known or can be prepared by known methods (for example J. March; "Advanced Organic Chemistry", second edition, p. 1170, 1189).

5 Suitable inert solvents for the process according to method M 1 are the customary organic solvents which do not change under the reaction conditions. These preferably include alcohols such as methanol, ethanol, propanol or isopropanol, or ethers such as diethyl ether, butyl methyl
10 ether, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, or halogenated hydrocarbons such as, for example, methylene chloride, chloroform or carbon tetrachloride, or hydrocarbons such as benzene, toluene, xylene, or petroleum fractions, or amides
15 such as dimethylformamide or hexamethylphosphoric triamide. In addition, it is possible to use mixtures of the solvents mentioned.

 The acids formed in the reaction can be bound by the use of excess pyrrolidine (II) or by the use of bases.
20 Alkali metal carbonates and alkaline earth metal carbonates such as sodium carbonate, potassium carbonate, calcium carbonate, hydrogen carbonates such as sodium hydrogen carbonate, metal oxides such as silver oxide, or other inorganic compounds such as silver carbonate can serve as
25 bases. Organic amines can also be employed. Triethylamine, diisopropylamine, 1,8-bis-(dimethylamino)naphthalene may be mentioned by way of example. Triethylamine and potassium carbonate are preferred as bases.

 The reaction can be carried out in the absence and
30 in the presence of catalysts. In this connection, alkali metal iodides such as sodium iodide or potassium iodide, which are added to the reaction batch in amounts between 0.5 and 150 moles per cent, preferably 5 to 50 moles per cent, are particularly suitable.

35 The reaction is in general carried out in a temperature range from -20°C to $+150^{\circ}\text{C}$, preferably from
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+20°C to +100°C. The reaction can be carried out at atmospheric, elevated and reduced pressure. In general, the reaction is carried out at atmospheric pressure.

When carrying out the reaction, the starting materials are in general employed in a molar ratio of pyrrolidine (II) to alkyl compound (III) of 0.5:1 to 1.1:1. The base added to bind the reaction product HR is in this case employed in an equimolar amount or in an up to 20-fold excess. The reaction is preferably carried out using a ratio of pyrrolidine:alkyl compound:base of 1:1:1 to 1:1:4. If the reaction is carried out without base, the molar ratio of pyrrolidine (II) to alkyl compound (III) is 1:1 to 5:1. The reaction is preferably carried out using a molar ratio of 2:1.

The conversion of functional groups into other functional groups by method M 2 is carried out, depending on the functional groups, by oxidation, reduction, hydrolysis or by reaction with electrophilic or nucleophilic reagents and is illustrated in the following.

20 M 2.1.

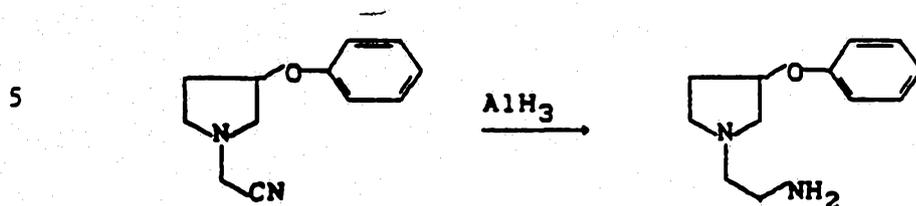
The reduction of the nitrile group to the amino group is in general carried out using metal hydrides, preferably using lithium aluminium hydride, aluminium hydride (prepared, for example, by reaction of lithium aluminium hydride with 100% strength sulphuric acid or with aluminium chloride) or their mixtures in inert solvents such as ethers or chlorinated hydrocarbons, preferably in ethers such as, for example, tetrahydrofuran, diethyl ether or dioxane in a temperature range from -20°C to +100°C, preferably from 0°C to +50°C at atmospheric pressure.

Reduction is additionally possible by hydrogenating the nitriles in inert solvents such as alcohols, for example methanol, ethanol, propanol or isopropanol in the presence of a noble metal catalyst such as platinum, palladium, palladium on animal charcoal or Raney nickel, in a temperature range from 0°C to +150°C, preferably from

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room temperature to +100°C at atmospheric pressure or at overpressure.

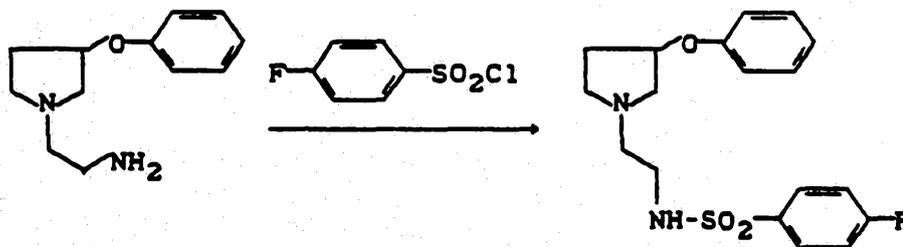
The reaction can be illustrated by the following equation:



M 2.2.

The reaction of compounds with R⁵ = meaning as above, R⁶ = H, with acylating agents such as acid chlorides is in general carried out in inert solvents such as ethers, hydrocarbons or halogenated hydrocarbons or their mixtures, preferably in ethers such as, for example, diethyl ether, tetrahydrofuran, or halogenated hydrocarbons such as methylene chloride or chloroform, if appropriate in the presence of bases such as alkali metal carbonates, for example, sodium carbonate or potassium carbonate, or organic amines such as, for example, triethylamine or pyridine, in a temperature range from -20°C to +100°C, preferably from 0°C to +60°C at atmospheric pressure.

The reaction can be illustrated by the following equation:



If the reaction is carried out without organic or inorganic bases, the compounds according to the invention

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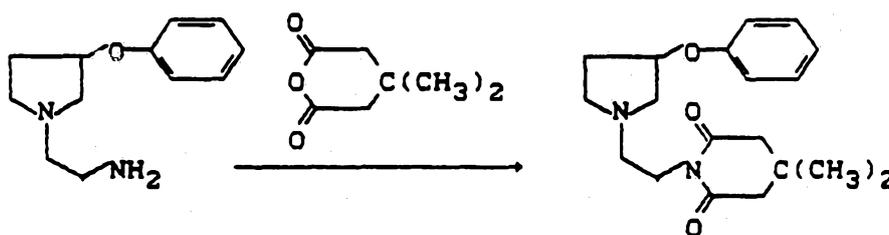
are obtained in the form of their salts, from which the free base is accessible, for example by treating with bicarbonate.

M 2.3.

5 Cyclic imides of the general formula (I) are in general prepared by the reaction of amino compounds of the type I ($R^5 = H$, $R^6 = H$) with cyclic anhydrides in inert solvents such as ethers, hydrocarbons or halogenated hydrocarbons or their mixtures, preferably in hydrocarbons
 10 such as benzene, toluene, xylene, if appropriate in the presence of organic bases, preferably triethylamine or tri-butylamine, if appropriate with removal of the water of reaction, preferably by azeotropic distillation or by the addition of activated molecular sieve, in a temperature
 15 range from $+20^{\circ}\text{C}$ to $+150^{\circ}\text{C}$, preferably $+20^{\circ}\text{C}$ to the boiling point of the solvent. Working without solvent at elevated temperature is likewise possible.

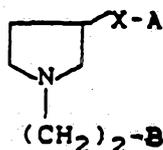
The process may be illustrated by the following example:

20



Compounds in which n is equal to 2 and B stands for cyano or a group of the formula $-\text{SO}_2\text{NR}^2\text{R}^3$ or $-\text{SO}_m\text{R}^4$, where R^2 , R^3 , R^4 and m have the abovementioned meaning, can be prepared by a particular process variant (known as
 25 method M 3 in the following).

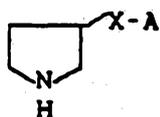
A process has now been found for the preparation of 1,3-disubstituted pyrrolidines of the general formula (I)



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wherein

A and X have the abovementioned meaning, and B stands for cyano or a group of the formula $-SO_2NR^2R^3$ or $-SO_mR^4$, wherein R^2 , R^3 , R^4 and m have the abovementioned meaning, characterized in that 3-substituted pyrrolidines of the general formula (II)

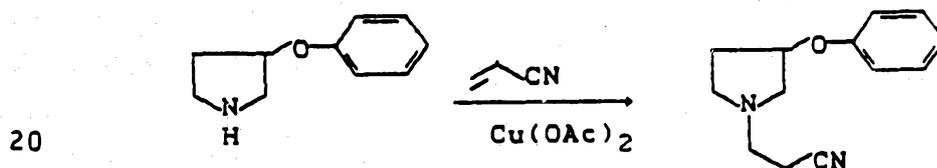


wherein

A and X have the abovementioned meaning, or their salts, are reacted with acrylonitrile or with a group of the formula $CH_2=CH-SO_2NR^2R^3$ or $CH_2=CH-SO_mR^4$, wherein R^2 , R^3 , R^4 and m have the abovementioned meaning, in the presence of catalysts (method M 3).

Of course, it is possible to prepare, according to method M 2, further pyrrolidines according to the invention from the nitriles.

The following reaction equation illustrates this process (method M 3):



Salts of the pyrrolidines of the formula II for the process according to the invention are, for example, hydrohalides (such as hydrochlorides) or trifluoroacetates.

Catalysts for the process variant according to the invention are, for example, copper salts, preferably copper(II) acetate.

The variant is in general carried out in a temperature range from $+50^{\circ}C$ to $+150^{\circ}C$, preferably from $+90^{\circ}C$ to $+110^{\circ}C$, at atmospheric, elevated or reduced pressure, preferably at atmospheric pressure.

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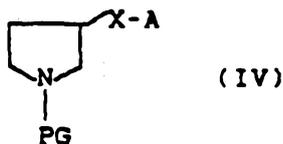
The pyrrolidines of the formula II and the olefin are in general employed in the ratio 0.5 to 20, preferably 1 to 5, mole equivalents.

The amount of copper salt employed is 0.5 to 10, preferably 1 to 5, mole %, relative to the pyrrolidine of the formula II.

If salts of the pyrrolidines II are used, 1 to 10, preferably 1 to 3, mole equivalents of base, relative to II, can be employed. Inorganic and organic bases, preferably triethylamine, are used as bases.

The process variant can, of course, be carried out in inert solvents.

The 3-substituted pyrrolidines of type II used for the preparation of the compounds (I) according to the invention according to methods M 1 to M 3 are either known [J. Med. Chem. 12, 435 to 441 (1969)] or can be prepared according to method P from pyrrolidines of the formula IV



wherein

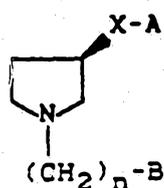
A and X have the abovementioned meaning, and PG stands for a nitrogen-protecting group which can be eliminated by customary methods of organic chemistry (Th. Greene, "Protective Groups in Organic Synthesis", 1st edition, J. Wiley and Sons, New York, 1981). The protecting groups can be eliminated, for example, by hydrolysis or hydrogenolysis.

For the case in which the radical X-A stands for O-aryl, the pyrrolidines (IV) are accessible from the corresponding hydroxypyrrolidines and the corresponding hydroxyaromatics in a manner known per se. If X-A stands for -O-CH₂-aryl, these compounds can be obtained from the corresponding aryl-methyl halides and the corresponding hydroxypyrrolidines in a manner known per se.

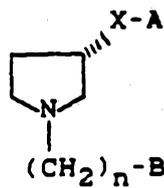
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3-Hydroxymethyl-pyrrolidines yield pyrrolidines of the formula (IV), in which X-A stands for -CH₂-O-aryl, by reaction with the corresponding hydroxyaromatics in a manner known per se.

5 The invention includes both enantiomers of the pyrrolidines of the type I (= Ia, Ib)



Ia



Ib

wherein

A, B, X and n have the abovementioned meaning, and their mixtures.

The mixtures deviating from the ratio Ia/Ib = 1:1 and the pure isomers are expediently obtained by the use of customary methods for the synthesis of optically active compounds.

15 Examples which may be mentioned are the formation and resolution of diastereomeric salts (with optically active acids) of the compounds I, II, IV, (inasmuch as PG is not acyl or alkoxy-carbonyl), with subsequent release of the base and the use of optically active starting materials [D. Flanagan + M. Joullie, Heterocycles 26, 2247 (1987)].

20 The pyrrolidines according to the invention have a superior pharmacological action, in particular on the central nervous system, and can be employed as active compounds in medicaments.

25 In particular, the pyrrolidines according to the invention have a high affinity for cerebral 5-hydroxy-tryptamine receptors of the 5-HT₁ type. Connected with this are agonistic, partially agonistic or antagonistic actions on the serotonin receptor.

The high affinity ligands for the serotonin-1

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receptor described in the present invention thus represent active compounds for combating diseases which are distinguished by disturbances of the serotonergic system, in particular with the involvement of receptors which have a high affinity for 5-hydroxytryptamine (5-HT₁ type). They are therefore suitable for the treatment of diseases of the central nervous system such as anxiety, tension and depressive states, sexual dysfunctions caused by the central nervous system and disturbances of sleep and nutritional absorption. Furthermore, they are suitable for the elimination of cognitive deficits, for the improvement of powers of learning and memory and for the treatment of Alzheimer's disease. Furthermore, these active compounds are also suitable for the modulation of the cardiovascular system. They also intervene in the regulation of the cerebral circulation and thus represent powerful agents for combating migraine. They are also suitable as prophylactics and for combating the consequences of the occurrence of cerebral infarcts (Apoplexia cerebri) such as strokes and cerebral ischaemia. The compounds according to the invention can also be used for combating pain states. They can also be used for combating diseases of the intestinal tract which are distinguished by disturbances of the serotonergic system, and disturbances of the carbohydrate metabolism.

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, dragees, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, non-toxic, pharmaceutically suitable excipients or solvents. In these formulations, the therapeutically active compound should in each case be present in a concentration of about 0.5 to 90 % by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by

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extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where, for example, in the case of the use of water as a diluent, if necessary organic solvents can be used as
5 auxiliary solvents.

Examples of auxiliaries which may be mentioned are: water, non-toxic organic solvents, such as paraffins (for example mineral oil fractions), vegetable oils (for example groundnut/sesame oil), alcohols (for example: ethyl alcohol, glycerol), excipients, such as, for example, ground
10 natural minerals (for example kaolins, argillaceous earths, talc, chalk), ground synthetic minerals (for example highly disperse silica, silicates), sugars (for example sucrose, lactose and dextrose), emulsifiers (for example polyoxyethylene fatty acid acid esters), polyoxyethylene fatty alcohol ethers (for example lignin-sulphite waste liquors,
15 methylcellulose, starch and polyvinylpyrrolidone) and lubricants (for example magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

Administration is carried out in a customary
20 manner, preferably orally or parenterally, in particular perlingually or intravenously. In the case of oral administration, tablets can, of course, also contain additions, such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives, such as starch,
25 preferably potato starch, gelatin and the like in addition to the excipients mentioned. Furthermore, lubricants, such as magnesium stearate, sodium lauryl sulphate and talc can be additionally used for tableting. In the case of aqueous suspensions, various flavour-improvers or
30 colourants can be added to the active compounds in addition to the abovementioned auxiliaries.

In the case of parenteral administration, solutions of the active compounds can be employed using suitable liquid excipients.

35 In general, it has proved advantageous on

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intravenous administration to administer amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg of body weight to attain effective results, and on oral administration the dosage is about 0.01 to 20 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

5 In spite of this, it may be necessary to deviate from the amounts mentioned, depending on the body weight or the type of administration route, on individual behaviour towards the medicament, the nature of its formulation and the point in time or interval at which administration is
10 carried out. Thus, in some cases it may be sufficient to manage with less than the previously mentioned minimum amount, whereas in other cases the upper limit mentioned must be exceeded. In the case of the administration of
15 larger amounts, it may be advisable to divide these into a number of individual doses over the day.

Preparation Examples

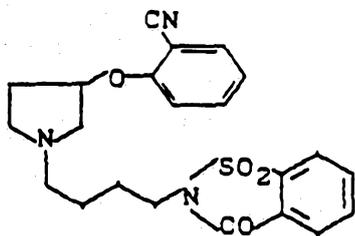
The R_f values mentioned in each case were determined - unless stated otherwise - by thin layer chromatography on silica gel (aluminium foil, silica gel 60 F 254,
20 E. Merck). The visualization of the substance spots took place by examination under UV light and/or by spraying with 1 % strength potassium permanganate solution.

Flash chromatography was carried out on silica gel 60, 0.040 - 0.064 mm, E. Merck (see Still et al., J.
25 Org. Chem. 43, 2923, 1978; for simpler separation problems see Aldrichimica Acta 18, 25, 1985). Elution with solvent gradients means: beginning with the pure, non-polar solvent mixture component, the polar solvent component is ad-
30 mixed to an increasing extent, until the desired product is eluted (checked by TLC).

In all products, the solvent was finally distilled off at about 0.1 Torr. Salts were stored at this pressure overnight over potassium hydroxide and/or phosphorus pentoxide.

Example 1 (method M 1)

3-(2-Cyanophenoxy)-1-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]-pyrrolidine oxalate



5 1.88 g (10 mmol) of 3-(2-cyanophenoxy)-pyrrolidine,
3.18 g (10 mmol) of 2-(4-bromobutyl)-benzisothiazol-3(2H)-
one 1,1-dioxide and 1.01 g (10 mmol) of triethylamine were
dissolved in 40 ml of dry dimethylformamide and the mix-
10 ture was stirred for 20 hours at 45°C with the exclusion
of moisture. The solvent was removed in a high vacuum and
the remaining residue was purified by flash chromatography
(toluene-ethyl acetate and toluene-ethanol gradients).
The product (2.90 g) was obtained as a yellow oil.

 The ¹H-NMR spectrum indicated the presence of
15 about 10 % of dimethylformamide in this product.
¹H-NMR (CDCl₃): δ = 1.65 (quintet, 2H); 1.95 (quintet,
2H); 2.1 (m, 1H); 2.35 (m, 1H); 2.6 - 3.0 (m, also contains
signals from dimethylformamide); 3.3 (dd, 1H); 3.8 (t, 2H);
4.95 (m, 1H); 6.9 (d, 1H); 7.0 (dd, 1H); 7.5 (m, 2H);
20 7.8 - 8.1 (m, contains signals from dimethylformamide).
Yield: 61%.

R_f = 0.48 (toluene/methanol 4:1; silica gel plates).

 The oxalate was obtained from this by treating
with anhydrous oxalic acid in warm, anhydrous ethanol.
25 Recrystallization from acetone/ethyl acetate/tert.butyl
methyl ether gave colourless crystals (1.68 g) of melting
point 135 - 139°C.

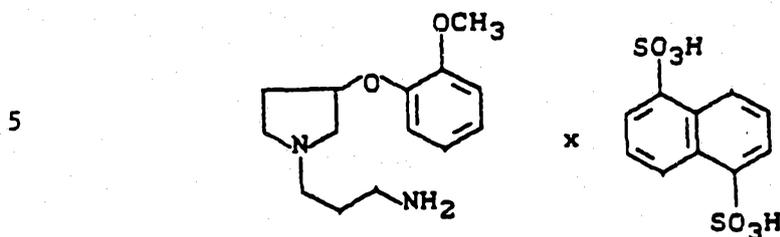
 This method was employed in a similar manner to
obtain the compounds I of Table 1 (method M 1). If pyrrol-
30 idines of the type II were used in the form of their hydro-
chlorides, a 2- to 3-fold amount of triethylamine was

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used.

Example 2 (method M 2.1.)

1-(3-Aminopropyl)-3-(2-methoxyphenoxy)-pyrrolidine 1,5-naphthalenedisulphonate



2.06 g of a mixture of 95 % strength sulphuric acid and 20 % strength oleum in the ratio 1:1 was cautiously added to a suspension of 1.6 g (42 mmol) of lithium aluminium hydride in 50 ml of ether at 0°C. After 1 h at room temperature, 3.5 g (14 mmol) of 1-(2-cyanoethyl)-3-(2-methoxyphenoxy)-pyrrolidine in 70 ml of ether were added dropwise. The mixture was heated to reflux for 2 h. 9.3 ml of water and 18.6 ml of 10 % strength sodium hydroxide solution were added with ice cooling. Stirring with kieselguhr, filtering off with suction over kieselguhr, subsequently washing the filter cake with ethyl acetate, drying and evaporating gave 3.4g of the free base as a yellow oil (96%).

MS (FAB): 251 (M + 1).

¹H-NMR (CDCl₃): δ = 1.2 - 1.5 (broad signal, about 2H; -NH₂); 1.65 (quintet, 2H); 2.05 (m, 1H); 2.25 (m, 1H); 2.5 - 2.8 (m, 7H); 3.0 (dd, 1H); 3.75 (s, 3H); 4.85 (m, 1H); 6.75 - 6.95 (m, 4H).

R_f = 0.1 (toluene/methanol 4:1; silica gel plates).

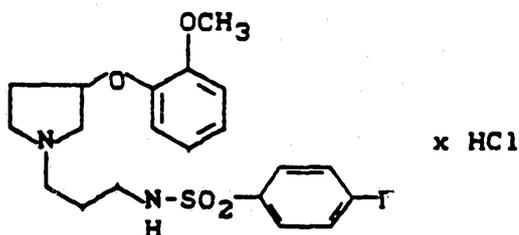
The salt (1:1 adduct) was obtained from 1.2 g of this product with 1,5-naphthalenedisulphonic acid in hot ethanol in the form of beige crystals (1.7 g).

Melting point: from 187°C with foaming.

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Example 3 (method M 2.2.)

1-[3-(4-Fluorophenyl)sulphonamido-propyl]-3-(2-methoxyphenoxy)-pyrrolidine hydrochloride



5 0.78 g (4.0 mmol) of 4-fluorophenylsulphonyl chloride in 15 ml of ether were added dropwise to a solution of 1.0 g (4.0 mmol) of 1-(3-aminopropyl)-3-(2-methoxyphenoxy)-pyrrolidine in 20 ml of anhydrous ether at 0°C. After 2 h at room temperature, the mixture was freed from solvent in vacuo and the remaining oily residue was brought to crystallization by trituration with diethyl ether/hexane. In this manner, 1.1 g (62 %) of title compound were obtained as a slightly reddish, hygroscopic solid. It melted from 50°C.

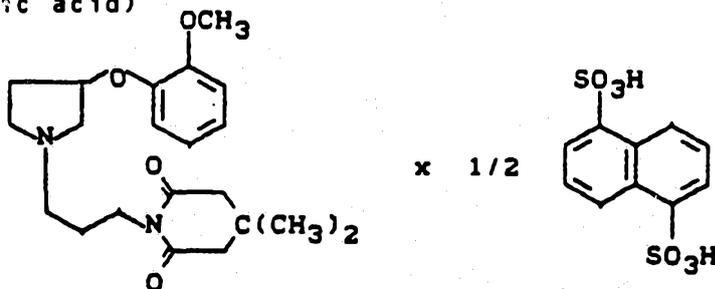
15 MS (FAB): 409 (M + 1)

R_f = 0.2 (toluene/methanol 4:1, silica gel plates)

[free base]

Example 4 (method M 2.3.)

20 1-[3-(4,4-Dimethyl-2,6-dioxo-piperidin-1-yl)-propyl]-3-(2-methoxyphenoxy)-pyrrolidine (salt with 1,5-naphthalenedisulphonic acid)



A solution of 1.0 g (4.0 mmol) of 1-(3-amino-propyl)-3-(2-methoxyphenoxy)-pyrrolidine, 0.57 g (4.0 mmol) of 3,3-dimethylglutaric anhydride and 4 drops of tributylamine were heated to reflux in the presence of 2 g of
25 Le A 25 921

molecular sieve (3Å). After 2 h, the mixture was filtered and freed from solvent in vacuo. The residue obtained in this way was purified by flash chromatography (toluene-ethyl acetate and ethyl acetate-ethanol gradient).

5 1.0 g (67 %) of free base was obtained as a yellow oil.

$R_f = 0.6$ (toluene/methanol 4:1, silica gel plates)

IR (CHCl₃): 3008, 2965, 2814, 1727, 1672, 1593, 1503.

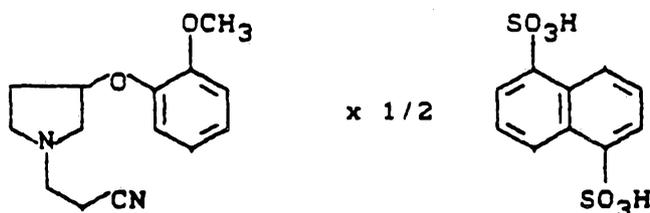
The salt (as the 2:1 compound) was precipitated from this in hot ethanol using 1,5-naphthalenedisulphonic acid.

Melting point: 195 - 200°C (colourless crystals)

Example 5 (method M 3)

1-(2-Cyanoethyl)-3-(2-methoxyphenoxy)pyrrolidine (as the salt of 1,5-naphthalenedisulphonic acid).

15



0.1 g of copper (II) acetate was added to 5.0 g (22 mmol) of 3-(2-methoxyphenoxy)-pyrrolidine hydrochloride, 2.43 g (24 mmol) of triethylamine and 5.8 g (109 mmol) of acrylonitrile and the mixture was stirred for 4 hours at 110°C. The reaction batch was purified by flash chromatography (silica gel, toluene/ethyl acetate gradient). 5.0 g (93 %) of the free base were obtained as a yellowish oil.

MS (m/z): 246, 206, 123, 83, 82

$R_f = 0.3$ (toluene/methanol 4:1, silica gel plates)

25 IR (CHCl₃): 3030, 3003, 2951, 2822, 2254, 1593, 1503.

Treating the free base with 1,5-naphthalenedisulphonic acid in hot ethanol gave the 2:1 salt of the title compound as a colourless solid.

Melting range: 85 - 95°C.

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Examples 6 to 45

The examples are summarized in Table 1:

Legend to Table 1:

- a) Abbreviations used in column B:
- 5 SACCH = 1,1-dioxido-2,3-dihydro-3-oxo-benzisothiazol-2-yl
FSULF = [(4-fluorophenyl)sulphonyl]amino
NPSULF = [N-phenyl-N-methylsulphonyl]amino
TDIAZ = 1,1-Dioxido-3-oxo-4-phenyl-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl
NAPHT = 1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl
DMP = 4,4-dimethyl-2,6-dioxo-piperidin-2-yl
- 10 NH₂ = amino
CN = cyano
PYRR = 3-(2-oxopyrrolidin-1-yl)prop-1-ynyl
DES = N,N-diethylsulphamoyl
DMS = N,N-dimethylsulphamoyl
- 15 BITZ = 1,1-Dioxido-2,3-dihydro-benzthiazol-2-yl
SANTH = N-(2-methoxycarbonylphenyl)sulphamoyl
SIND = 3-methyl-indol-1-yl-sulphonyl
PHEN = 6(5H)-phenanthridinon-5-yl
DBTH = 5,5-dioxido-6H-dibenzo[c,e][1,2]thiazin-6-yl
- 20 DMUR = (1,3-dimethyl-uracil-6-yl)amino
- b) Abbreviations used for the eluents
- KTM = toluene/methanol 4:1; silica gel plates
KDM = dichloromethane/methanol 10:1; silica gel plates
ADM = dichloromethane/methanol 100:1; alumina plates
- 25 AE = ethanol; alumina plates
KTE = toluene/ethyl acetate 1:1, silica gel plates
- c) Abbreviations used for the salts
- OX = salt of oxalic acid
NS = salt of 1,5-naphthalenedisulphonic acid (stoichiometry = 2 moles of base/1 mole of acid)
- 30 NDS = salt of 1,5-naphthalenedisulphonic acid
(1 mole of base/1 mole of acid)
Cl = salt of hydrochloric acid
W = salt of L-tartaric acid
- 35 F = free base

- d) Abbreviations used for the educts
- A = 2-(4-bromobutyl)-2H-benzisothiazol-3-one 1,1-dioxide
- B = chloroacetonitrile
- 5 C = acrylonitrile
- D = 2-(4-bromobutyl)-2H-naphth[1,8-cd]isothiazole 1,1-dioxide
- E = 2-(4-bromobutyl)-3,4-dihydro-4-phenyl-2H-1,2,4-benzothiadiazin-3-one 1,1-dioxide
- 10 F = (4-fluorophenyl)sulphonyl chloride
- G = 3,3-dimethylglutaric anhydride
- H = aluminum hydride
- I = N-(4-bromobutyl)-N-phenyl-methanesulphonamide
- K = 2-(3-bromopropyl)-2H-benzisothiazol-3-one 1,1-dioxide
- 15 L = N,N-dimethyl-vinylsulphonamide
- M = N,N-diethyl-vinylsulphonamide
- N = 2-(4-bromobutyl)-2,3-dihydrobenzisothiazole-1,1-dioxide
- O = methyl 2-(ethenesulphonylamino)benzoate [from methyl anthranilate and 2-chloroethanesulphonyl chloride in the presence of excess triethylamine]
- 20 P = 3-methyl-1-vinylsulphonyl-indole [from 3-methyl-indole and 2-chloroethanesulphonyl chloride in the presence of excess triethylamine]
- 25 R = 5-(4-bromobutyl)-6(5H)-phenanthridinone
- S = 6-(4-bromobutyl)-6H-dibenzo[c,e][1,2]-thiazine 5,5-dioxide
- T = 6-(3-chloropropyl)amino-1,3-dimethyluracil
- e) $^1\text{H-NMR}$ (CD_3OD): δ = 1.8 - 2.0 (m, 4H); 2.1 - 2.4 (m, 1H); 2.5 - 2.8 (m, 1H); 3.2 - 3.5 (m, contains signals from the solvent); 3.7 - 4.2 (m, 4H); 5.2 (m, 1H); 6.85 - 7.0 (m, 3H); 7.2 - 7.4 (m, 2H); 7.75 - 8.15 (m, 4H).
- f) R(-)-enantiomer from Example 8; $\alpha_{\text{D}}^{20} = -7.0$ (c = 1, CH_3OH)
- 35 g) syrupy, solidifies after digestion with diethylether,
- h) $^1\text{H-NMR}$ (CD_3OD): δ = 1.05 (s, 6H); 2.1 - 2.7

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(m, 6H); 3.3 - 3.6 (m, contains signals from the solvent);
3.7 - 4.2 (m, among them: 3.75, s, OCH₃; 7H); 5.1 (m,
1H); 6.85 - 7.1 (m, 4H).

i) elemental analysis C₂₃H₂₈N₂O₅S x C₄H₆O₆

5 k) ¹³C-NMR (CDCl₃) 25.4 (t). 26.5 (t). 32.1 (t). 36.9
(q). 50.4 (t). 52.8 (t). 55.6
(t). 55.9 (q). 60.3 (t). 77.6
(d). 112.1 (d). 114.8 (d). 120.8
(d). 121.3 (d). 128.0 (d). 128.5
10 (d). 129.5 (d). 139.1 (s). 147.4
(s). 150.0 (s).

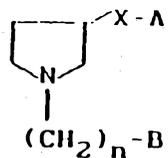
l) from Example 57 by reaction with 1-(prop-2-ynyl)-
2-pyrrolidone and paraformaldehyde in the presence of
copper(II) acetate

15 m) S(+)-enantiomer from Example 8 $\alpha_D^{20} = + 7.1$
(c = 1, CH₃OH)

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Table 1: Compounds of the general formula (I)



Ex.	-X-(A)	-A	-B ^{a)}	n	R _f / Solvent ^{b)}	Salt ^{c)} / Melting point ^{c)}	prepared from ^{d)}	Method
6	-O-	Phenyl	SACCH	4	0.35 (KTM)	Cl; amorphous ^{e)}	Ex. 48 + A	M 1
7	-OCH ₂ -	Phenyl	SACCH	4	0.4 (KDM)	NS; 155-158	Ex. 49 + A	M 1
8	-O-	2-Methoxyphenyl	SACCH	4	0.35 (KTM)	OX; 134	Ex. 50 + A	M 1
9 ^{f)}	-O-	2-Methoxyphenyl	SACCH	4	0.52 (KDM)	F; g)	Ex. 55 + A	M 1
10	-O-	3-Methoxyphenyl	SACCH	4	0.52 (KDM)	NS; 173-178	Ex. 51 + A	M 1
11	-O-	2-Methoxyphenyl	NH ₂	2	0.1 (KTM)	NDS; >220	Ex. 14 + II	M 2.1.
12	-O-	2-Methoxyphenyl	FSULF	2	0.4 (KTM)	Cl; 98-110	Ex. 11 + F	M 2.2.
13	-O-	2-Methoxyphenyl	DMP	2	0.3 (KTM)	Cl; hydr. ^{h)}	Ex. 11 + G	M 2.3.
14	-O-	2-Methoxyphenyl	CN	1	0.57 (KTM)	F; 73-76	Ex. 50 + B	M 1
15	-CH ₂ O-	2-Methoxyphenyl	SACCH	4	0.34 (ADM)	W; amorphous ⁱ⁾	Ex. 46 + A	M 1
16	-O-	2-Methoxyphenyl	NFSULF	4	0.24 (KTM)	F; k)	Ex. 50 + I	M 1
17	-O-	2-Methoxyphenyl	NAPHT	4	0.35 (KTM)	NS; 115-117	Ex. 50 + D	M 1

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Continuation of Table 1

Ex.	-X-(A)	-A	B ^{a)}	n	R _f / Solvent ^{b)}	Salt ^{c)} /Melting point(°C)	prepared from ^{d)}	Method
18	-O-	2-Methoxyphenyl	TDIAZ	4	0.38 (KDM)	Cl; amorphous	Ex. 50 + E	M I
19	-O-	(2-Carbamoyl)-phenyl	SACCH	4	0.75 (AE)	NDS; >220	Ex. 53 + A	M I
20	-O-	(2-Methoxy-6-cyano)phenyl	SACCH	4	0.38 (KTM)	NS; 165(dec.)	Ex. 47 + A	M I
21	-O-	(1-Cyano)-naphth-2-yl	SACCH	4	0.59 (KDM)	F; 132-134	Ex. 54 + A	M I
22	-O-	(2-Carbamoyl)-naphth-1-yl	SACCH	4	0.44 (KDM)	NS; >167 (sintering)	Ex. 56 + A	M I
23	-O-	Naphth-1-yl	SACCH	4	0.50 (KDM)	NS; 209-215	Ex. 57 + A	M I
24	-O-	Naphth-2-yl	SACCH	4	0.53 (KDM)	OX; 142-149	Ex. 58 + A	M I
25	-OCH ₂ -	Naphth-1-yl	SACCH	4	0.35 (KDM)	OX; amorphous	Ex. 59 + A	M I
26	-OCH ₂ -	Naphth-2-yl	SACCH	4	0.4 (KDM)	NS; 138	Ex. 60 + A	M I
27	-OCH ₂ -	2-Fluorphenyl	SACCH	4	0.23 (KTM)	NS; 143-148	Ex. 61 + A	M I
28	-O-	(1-Methyl)indol-4-yl	SACCH	4	0.44 (KDM)	NS; >162(dec.)	Ex. 62 + A	M I

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Continuation of Table 1

Ex..	-X-(A)	-A	B ^{a)}	n	R _f /Solvent ^{b)}	Salt ^{c)} /Melting point _(°C)	prepared from ^{d)}	Method
29	-0-	Naphth-1-yl	NAPHT	4	0.64 (KDM)	Cl; 192-193	Ex.57 + D	M 1
30	-0-	4-Methoxyphenyl	SACCH	4	0.6 (KDM)	NS; 192-196	Ex.63 + A	M 1
31	-0-	5,6,7,8-Tetrahydro-naphth-1-yl	SACCH	4	0.38 (KDM)	NS; 190-192	Ex.64 + A	M 1
32	-0-	Chinolin-2-yl	SACCH	4	0.28 (KTM)	NDS; 200(dec.)	Ex. 65 + A	M 1
33	-0-	Isochinolin-1-yl	SACCH	4	0.63 (KDM)	NDS; 180(dec.)	Ex. 66 + A	M 1
34	-0-	Naphth-1-yl	PYRR	1	0.75 (KTM)	Cl; 138-140		1)
35	-0-	2-Methoxyphenyl	SACCH	3	0.44 (KTM)	NS; ab 225 (dec.)	Ex. 50 + K	M 1
36	-0-	2-Methoxyphenyl	DMS	2	0.24 (KTM)	NS; 162-164	Ex. 50 + L	M 3
37	-0-	2-Methoxyphenyl	DES	2	0.30 (KTM)	NS; 145-150	Ex. 50 + M	M 3
38 ^{m)}	-0-	2-Methoxyphenyl	SACCH	4	0.50 (KDM)	F; 70-73	Ex. 67 + A	M 1
39	-0-	2-Methoxyphenyl	BITZ	4	0.44 (KDM)	NS; 150-156	Ex. 50 + N	M 1
40	-0-	2-Methoxyphenyl	SANTH	2	0.36 (KTE)	NS; 168-170	Ex. 50 + O	M 3

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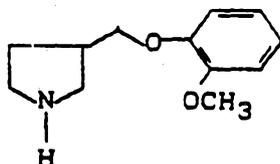
Continuation of Table 1

Ex. .	-X-(A)	-A	B ^{a)}	n	R _f / Solvent ^{b)}	Salt ^{c)} / Melting point (°C)	prepared from ^{d)}	Method
41	-O-	2-Methoxyphenyl	SIND	2	0.46 (KTE)	F; 156-158	Ex. 50 + P	M 3
42	-O-	2-Methoxyphenyl	PHEN	4	0.31 (KDM)	Cl; 169-170	Ex. 50 + R	M 1
43	-O-	2-Methoxyphenyl	DBTH	4	0.48 (KDM)	NS; 182-186	Ex. 50 + S	M 1
44	-O-	2-(Prop-2-enyl-oxy)phenyl	SACCH	4	0.46 (KDM)	NS; 138-142	Ex. 68 + A	M 1
45	-O-	2-Methoxyphenyl	DMUR	3	0.35 (KDM)	NDS; 199(dec.)	Ex. 50 + T	M 1

Starting compounds

Example 46

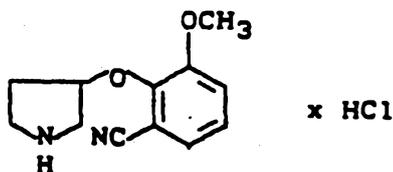
3-(2-Methoxyphenoxy)methyl-pyrrolidine



- 5 5.0 g of 10 % palladium on activated carbon were added to a solution of 5.0 g (17 mmol) of 1-benzyl-3-(2-methoxyphenoxy)methyl-pyrrolidine and 10.6 g (0.17 mol) of ammonium formate in 300 ml of methanol and the mixture was heated to reflux for 1 hour. After cooling, the solution was separated from the catalyst by filtration and the filtrate was freed from solvent in vacuo. The residue was rendered basic using 1N NaOH and the mixture was extracted using ether. After drying and evaporating, 1.5 g (43 %) of the title compound were obtained as an oil.
- 10
- 15 $R_f = 0.35$ (dichloromethane/methanol 20:1; alumina plates) (cf. DE-A 2,315,092)

Example 47

3-(2-Cyano-6-methoxy)phenoxy-pyrrolidine hydrochloride



- 20 14.8 ml (59.4 mmol) of 4 M hydrogen chloride in anhydrous dioxane were added at 0°C to 6.3 g (19.8 mmol) of 1-tert.butoxycarbonyl-3-(2-cyano-6-methoxy-phenoxy)-pyrrolidine. After 2 hours at room temperature, 7.4 ml of 4 M hydrogen chloride in dioxane were again added. After
- 25 a further 2 hours, the mixture was concentrated. The residue was triturated with toluene and allowed to crystallize overnight under toluene. In this manner, 4.2 (83 %) of light reddish crystals were obtained.

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Melting point: 132°C (from 98°C: sintering)

R_f = 0.14 (dichloromethane/methanol 10:1, silica plates)

[free base]

Examples 48 to 68

5 Examples 48 to 68 are summarized in Table 2; they are obtained analogously to Example 46 and 47.

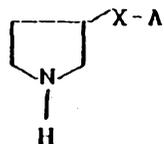
Legend to Table 2

- a) TLC system: silica gel plates
 Eluent:
10 TET = toluene/ethanol/triethylamine 5:3:1
 DM = dichloromethane/methanol 10:1
- b) salts:
 Cl = hydrochloride; F = free base
- c) preparation from Ex. 72 using trifluoroacetic acid
15 at 0°C/45 min and subsequent release of the base with
 alkali.
 ¹H-NMR (CDCl₃): δ = 2.0 - 2.3 (m, about 4H, also contains signal from -NH and traces of water); 2.9 - 3.3 (m, 4H); 4.9 (m, 1H); 6.85 - 7.1 (m, 2H); 7.45 - 7.6 (m, 2H).
- 20 d) sintering from 98°C
 e) from Ex. 52
 f) reacted further as a crude product to give Example 9
- g) amorphous, hygroscopic solid
25 ¹H-NMR (CD₃OD): δ = 2.0 - 2.5 (m, 2H); 3.4 - 3.8 (m, 4H); 5.15 (m, 1H); 7.5 - 8.3 (m, 6H).
- h) dihydrochloride; directly reacted further to give Example 28.
- i) 3 equivalents of HCl in dioxane employed;
30 dihydrochloride, amorphous, hygroscopic
 ¹H-NMR (CD₃OD): δ = 2.5 (mc, 2H); 3.55 (mc, 2H); 3.75 (mc, 2H); 5.9 (m, 1H); 7.4 (d, 1H); 7.6 (m, 1H); 7.8 - 8.1 (m, 3H); 8.6 (d, 1H).
- 35 k) S(+)-enantiomer; α_D²⁰ (hydrochloride) + 22.6 (c = 1; CH₃OH)

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Table 2: Compounds of the general formula (II)



Ex.	-X-(A)	-A	R _f / Solvent a)	Salt ^{b)} / Melting point (°C)	prepared from
48	-O-	Phenyl	[cf. DE 19 64 511]		
49	-OCH ₂ -	Phenyl	0.41 (TET)	Cl; Syrup	Ex. 71
50	-O-	2-Methoxyphenyl	[cf. US 430 60 65]		
51	-O-	3-Methoxyphenyl	[cf. DE 19 64 511]		
52	-O-	2-Cyanophenyl	0.35 (TET)	F; Syrup ^{c)}	Ex. 72
53	-O-	2-Carbamoylphenyl	[cf. DE 19 64 510]		
54	-O-	(1-Cyano)naphth-2-yl	0.11 (DM)	Cl; 204-208	Ex. 70
55	-O-	2-Methoxyphenyl	f)	-	Ex. 74

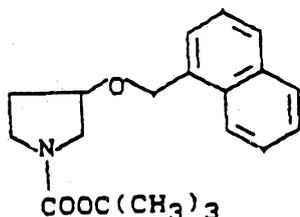
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Continuation of Table 2

Ex.	-X-(A)	-A	R _f / Solvent ^{a)}	Salt ^{b)} / Melting point(°C)	prepared from
56	-O-	(2-Carbamoyl)-naphth-1-yl	<0.1 (TET)	Cl; g)	Ex. 75
57	-O-	Naphth-1-yl	0.42 (TET)	Cl; 223-226	Ex. 77
58	-O-	Naphth-2-yl	0.5 (TET)	Cl; 168-170	Ex. 78
59	-OCH ₂ -	Naphth-1-yl	0.25 (TET)	Cl; 117-124	Ex. 69
60	-OCH ₂ -	Naphth-2-yl	0.28 (TET)	Cl; 128-130	Ex. 79
61	-OCH ₂ -	2-Fluorophenyl	0.5 (TET)	Cl; Syrup	Ex. 80
62	-O-	(1-Methyl)-indol-4-yl	<0.1 (TET)	Cl; Syrup ^{h)}	Ex. 81
63	-O-	4-Methoxyphenyl	[compare J. Med. Chem. <u>12</u> , 435 (1969)]		
64	-O-	5,6,7,8-Tetrahydro-naphth-1-yl	0.52 (TET)	Cl; 196-200	Ex. 83
65	-O-	Quinolin-2-yl	0.42 (TET)	i)	Ex. 84
66	-O-	Isoquinolin-1-yl	0.38 (TET)	Cl; foam	Ex. 85
67 ^{k)}	-O-	2-Methoxyphenyl	0.22 (TET)	Cl; 145-147	Ex. 86
68	-O-	2-(Prop-2-en-1-yl-oxy)phenyl	0.2 (TET)	Cl; Syrup	Ex. 87

Example 69

1-tert.Butoxycarbonyl-3-(1-naphthyl)methoxy-pyrrolidine

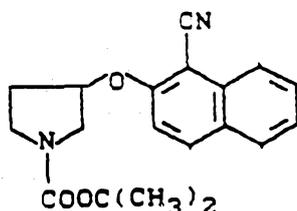


1.27 g of an 80% strength suspension of sodium hydride in paraffin (44 mmol) were added in small portions at 0°C to a solution of 7.49 g (40 mmol) of 1-tert.butoxycarbonyl-3-hydroxy-pyrrolidine in 40 ml of dry dimethyl sulphoxide. 7.77 g (44 mmol) of 1-chloromethyl-naphthalene were subsequently slowly added dropwise. After 3 hours at room temperature, the mixture was poured into 200 ml of saturated ammonium chloride solution, extracted a number of times using ether, dried (MgSO₄) and concentrated. Flash chromatography (petroleum ether-toluene, then toluene-ethyl acetate gradients) gave 10.5 g of the title compound (76%) as a yellowish oil.

R_f = 0.46 (toluene-ethyl acetate 3:1)

Example 70

1-tert.Butoxycarbonyl-3-[(1-cyano)-2-naphthyloxy]pyrrolidine



20

7.66 g (44 mmol) of diethyl azodicarboxylate in 20 ml of dry tetrahydrofuran were added dropwise at 0°C to a solution of 6.2 g (37 mmol) of 1-cyano-2-hydroxy-naphthalene, 8.2 g (44 mmol) of 1-tert.butoxycarbonyl-3-hydroxy-pyrrolidine and 11.5 g (44 mmol) of triphenylphosphine in 100 ml of dry tetrahydrofuran. After 2 hours at room temperature, the mixture was concentrated and the residue was purified twice by flash chromatography

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(toluene-ethyl acetate gradient). 7.3 g of a reddish oil, which was brought to crystallization by trituration with ether, were obtained.

Yield: 4.7 g (40 %)

5 Melting point: 145-148°C

R_f = 0.33 (toluene/ethyl acetate 3:1, silica gel plates)

Examples 71 to 87

Examples 71 to 87 are summarized in Table 3; they are obtained analogously to Examples 69/70.

10 Legend to Table 3

a) Abbreviations used:

BN = phenylmethyl

BOC = tert.butoxycarbonyl

b) Unless stated otherwise, the products occurred as oils.

Abbreviations used for the TLC systems: silica gel plates,

eluent TE 31 = toluene/ethyl acetate 3:1

TE 11 = toluene/ethyl acetate 1:1

TM 41 = toluene/methanol 4:1

20 c) Abbreviations used:

X = 1-tert.butoxycarbonyl-3-hydroxy-pyrrolidine

(obtained by reaction of 3-hydroxypyrrolidine with di-tert.butyl pyrocarbonate in tetrahydrofuran/methanol 5:1)

A has the meaning indicated in column "A"

25 d) (-)-Enantiomer; $[\alpha]_D^{20} = -6.8$ (CH₃OH; c = 0.93)

e) (-)-1-Benzyl-3-hydroxy-pyrrolidine

[J. Med. Chem. 29, 2504 (1986)].

f) Reaction of Example 76 with ammonia (gaseous) in ethanol at 0°C to room temperature.

30 g) Still contains unreacted 2-naphthol; further reacted as a mixture.

h) Reaction of Example 82 with dimethyl sulphate and sodium hydride in dimethylformamide at 0°C → room temperature.

35 i) Melting point 160-162°C

k) Silica gel plates; eluent = ethyl acetate;

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MS (m/e) = 314, 257, 241, 169

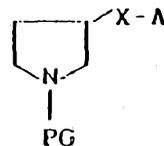
l) Carried out in THF/acetonitrile 1:2.5 at 40° to 50°C

m) S(+)-enantiomer; $\alpha_D^{20} = +32.4$ (c=1; CH₃OH)

n) R(-)-1-tert.-butoxycarbonyl-3-hydroxy-pyrrolidine
[$\alpha_D^{20} = -25.4$ (c=1; CH₃OH)], Heterocycles 1987, 2247;

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Table 3: Compounds of the general formula (IV)



Ex.	-X-(A)	-A	PG ^{a)}	R _f /Solvent ^{b)}	Prepared from
71	-OCH ₂ -	Phenyl	BOC	0.49 (TE 31)	X + Λ-CH ₂ Br
72	-O-	2-Cyanophenyl	BOC	0.27 (TE 31)	X + Λ-OH
73	-O-	(2-Methoxy-6-cyano)-phenyl	BOC	0.42 (TE 31)	X + Λ-OH
74 ^{d)}	-O-	2-Methoxyphenyl	BN	0.38 (TE 11)	e), Λ-OH
75	-O-	(2-Carbamoyl)-naphth-1-yl	BOC	0.3 (TM 41)	Ex. 76 + NH ₃ ^{f)}
76	-O-	(2-Phenoxycarbonyl)-naphth-1-yl	BOC	0.46 (TE 31)	X + Λ-OH
77	-O-	Naphth-1-yl	BOC	0.63 (TE 31)	X + Λ-OH
78	-O-	Naphth-2-yl	BOC	0.69 ^{g)} (TE 31)	X + Λ-OH
79	-OCH ₂ -	Naphth-2-yl	BOC	0.43 (TE 31)	X + Λ-CH ₂ Cl

Continuation of Table 3

Ex.	-X-(A)	-A	PG ^{a)}	R _f /Solvent ^{b)}	Prepared from
80	-OCH ₂ -	2-Fluorophenyl	BOC	0.48 (TE 31)	X + A-CH ₂ Br
81	-O-	(1-Methyl)indol-4-yl	BOC	0.48 (TE 31)	Ex. 82 + ^{h)} (CH ₃) ₂ SO ₄
82	-O-	Indol-4-yl	BOC	0.42 (TE 31) ⁱ⁾	X + A-OH
83	-O-	5,6,7,8-Tetrahydro-naphth-1-yl	BOC	0.58 (TE 31)	X + A-OH
84	-O-	Quinolin-2-yl	BOC	0.87 ^{k)}	X + A-OH
85	-O-	Isoquinolin-1-yl	BOC	0.58 (TM 41)	X + A-OH ^{l)}
86 ^{m)}	-O-	2-Methoxyphenyl	BOC	0.49 (TE 31)	n) + A-OH
87	-O-	2-(Prop-2-en-1-yloxy)-phenyl	BOC	0.52 (TE 31)	X + A-OH

Use Example

Example 69

Affinity for the 5-HT₁ receptor

The high affinity of the compound according to the invention for 5-hydroxytryptamine receptors of the subtype 1 is represented by way of example in Table 4. The values indicated are data which have been determined from receptor binding studies using calf hippocampus membrane preparations. For this purpose, ³H-serotonin was used as a radioactively labelled ligand.

Table 4

Compound from

<u>Example No.</u>	<u>Ki (nmol/L)</u>
1	2
6	9
8	1.3
10	6
19	7
23	0.3

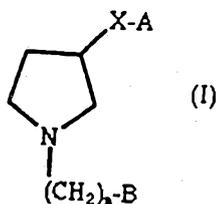
Comparison:

In DE-A 1,964,511 pyrrolidines with
A equal to o-methoxy-phenyl,
X equal to oxygen,
B equal to 2-propyl and
n equal to 0
were described.

This compound has a Ki value of 1.0 μmol/L.

The claims defining the invention are as follows:

1. 1,3-Disubstituted pyrrolidines of the general formula



wherein

A - denotes phenyl or hetaryl, or phenyl fused with aromatic, or with saturated or unsaturated cyclic or heterocyclic hydrocarbons, or A denotes hetaryl fused with aromatic hydrocarbons, wherein radical A can be unsubstituted or substituted,

X - denotes $-O-CH_2-$, $-CH_2-O-$ or $-O-$,

and

B - denotes cyano or a group of the formula $-COOR^1$, $-SO_2NR^2R^3$, $-SO_mR^4$, $-NR^5R^6$, or $-C\equiv C-CH_2-NR^5R^6$

where

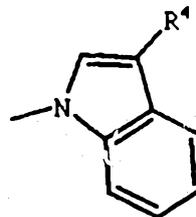
R^1 - stands for hydrogen, alkyl, cycloalkyl, alkenyl, aryl or aralkyl,

R^2 and R^3 are identical or different and

- stand for hydrogen, alkyl, cycloalkyl, aryl or aralkyl, where the aryl radicals can be substituted by halogen, alkoxy or alkoxy-carbonyl,

R^4 - stands for alkyl, cycloalkyl, aryl or aralkyl, where the aryl radicals can be monosubstituted, disubstituted or trisubstituted by identical or different halogen, cyano, alkyl, alkoxy, trifluoromethyl or trifluoromethoxy, or

- for a group of the formula



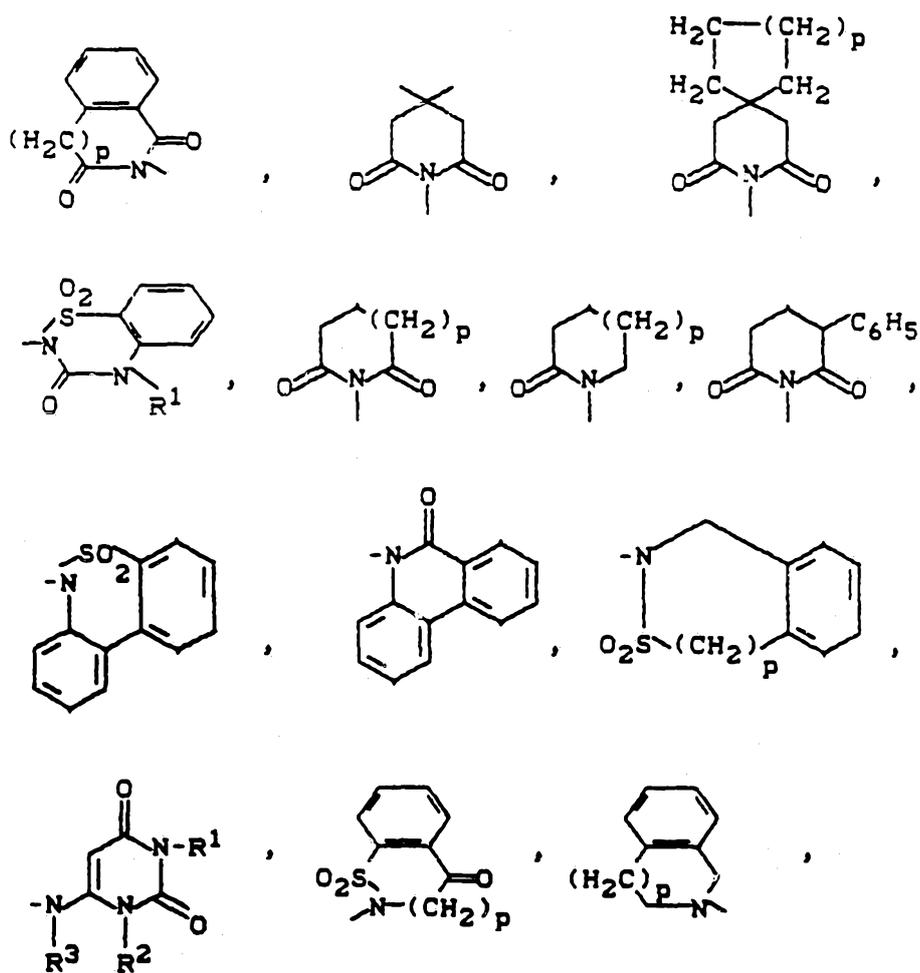
- wherein R^4 denotes hydrogen or alkyl,
- m - stands for a number 0, 1 or 2,
- R^5 and R^6 are identical or different and
 - stand for hydrogen, alkyl, cycloalkyl, aryl or aralkyl, where the aryl radicals can be substituted by halogen, cyano, alkyl, alkoxy or trifluoromethyl, or
 - stand for a group of the formula $-COR^7$ or $-SO_2R^8$,

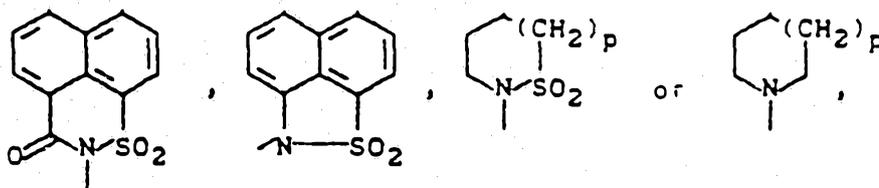
wherein

- R^7
 - denotes hydrogen or
 - a group NHR^9 or
 - alkyl, cycloalkyl or alkoxy, or
 - aryl, aryloxy, aralkyl, aralkoxy or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkylamino or dialkylamino,
- R^8
 - denotes cycloalkyl or
 - alkyl which can be substituted by cyano, halogen, alkoxy or alkoxycarbonyl, or
 - aryl, aralkyl or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkylamino or dialkylamino, or
 - denotes a group NR^2R^3 , where R^2 and R^3 have the abovementioned meaning and
- R^9
 - denotes hydrogen or
 - cycloalkyl or
 - optionally substituted alkyl or
 - aryl, aralkyl or heteroaryl, where the aryl

radicals can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkylamino or dialkylamino,

or where R^5 and R^6 , together with the nitrogen atom, form a ring from the series comprising





wherein

- p - denotes a number 0, 1 and 2,
 R^1 , R^2 and R^3 have the abovementioned meaning,
 n - denotes a number from 1 to 10 and their salts.

2. 1,3-Disubstituted pyrrolidines of the general formula (I) according to Claim 1,

A stands for phenyl or a monocyclic five- or six-membered hetaryl radical, or phenyl fused with one to three aromatic (C_5 to C_8) hydrocarbons, or with saturated or unsaturated cyclic (C_5 to C_8) hydrocarbons, or with five- or six-membered heterocycles having one or two nitrogen and/or oxygen and/or sulfur atoms, or A stands for five- or six-membered hetaryl fused with one to three aromatic (C_5 to C_8) hydrocarbons, wherein radical A can be unsubstituted or substituted by lower alkyl, lower alkoxy, lower alkoxy carbonyl, lower alkenyloxy, acyloxy, benzoyloxy, cyano, phenyl, benzyl, fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, difluoromethoxy or radical of the formula $-CO-NYZ$, $-NH-SO_2-Y'$, $-SO_2-NYZ$ or $-NH-CO-Y$,

where

Y and Z are identical or different and stand for hydrogen or alkyl (C_1 to C_6), and Y' stands for alkyl (C_1 to C_6) or aryl,

and in the case of nitrogen heterocycles is optionally present as the N-oxide,

X - stands for $-CH_2-O-$, $-O-CH_2-$ or $-O-$,

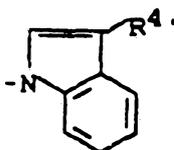


B - stands for cyano or a group of the formula
-COOR¹, -SO₂NR²R³, -SO_mR⁴,
NR⁵R⁶ or -C≡C-CH₂-NR⁵R⁶, where

R¹ - stands for hydrogen, alkyl (C₁ to C₁₁),
cycloalkyl (C₅ to C₈), alkenyl (C₂ to C₁₂),
aryl (C₆ to C₁₂) or aralkyl (C₇ to C₁₇),

R² and R³ are identical or different and
- stands for hydrogen, alkyl (C₁ to C₁₂),
cycloalkyl (C₅ to C₈), aryl (C₆ to C₁₂)
or aralkyl (C₇ to C₁₄), where the aryl
radicals can be substituted by halogen,
alkoxy or alkoxycarbonyl (C₁-C₆),

R⁴ - stands for alkyl (C₁ to C₁₂), cycloalkyl
(C₅ to C₈), aryl (C₆ to C₁₂) or aral-
kyl (C₇ to C₁₄), where the aryl radicals
can be monosubstituted, disubstituted or
trisubstituted by identical or different
halogen, cyano, alkyl (C₁ to C₆), alkoxy
(C₁ to C₆), trifluoromethyl or tri-
fluoromethoxy, or

- for a group of the formula 

wherein R⁴ denotes hydrogen or alkyl (C₁-
C₆) or

m stands for a number 0, 1 or 2,

R⁵ and R⁶ are identical or different and

- stand for hydrogen, alkyl (C₁ to C₁₂),
cycloalkyl (C₅ to C₈), aryl (C₆ to C₁₂)
or aralkyl (C₇ to C₁₄), where the aryl
radicals can be substituted by halogen,
cyano, alkyl (C₁ to C₆), alkoxy (C₁ to
C₆) or trifluoromethyl, or

- stands for a group of the formula
-COR⁷ or -SO₂R⁸ wherein

R⁷ - denotes hydrogen or

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- a group NHR^9 or
 - alkyl (C_1 to C_{11}), cycloalkyl (C_5 to C_8) or alkoxy (C_1 to C_{12}), or
 - aryl (C_6 to C_{12}), aryloxy (C_6 to C_{12}), aralkyl (C_7 to C_{14}), aralkoxy (C_6 to C_{12}) or heteroaryl (five- or six-membered ring having one or two oxygen and/or nitrogen and/or sulphur atoms),
- where the radicals mentioned can be mono-substituted, disubstituted or trisubstituted by identical or different alkyl (C_1 to C_6), alkoxy (C_1 to C_6), alkylthio (C_1 to C_6), halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkyl- (C_1 to C_6)-amino or dialkyl- (C_1 to C_6)-amino,

- R^8
- denotes cycloalkyl (C_5 to C_8), or
 - alkyl (C_1 to C_{12}) which can be substituted by cyano, halogen, alkoxy (C_1 to C_{12}) or alkoxy- (C_1 to C_{12})-carbonyl or
 - aryl (C_6 to C_{12}), aralkyl (C_7 to C_{14}) or heteroaryl (five- or six-membered ring having one or two oxygen and/or nitrogen and/or sulphur atoms), where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl (C_1 to C_6), alkoxy (C_1 to C_6), alkylthio (C_1 to C_6), halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkyl- (C_1 to C_6)-amino or dialkyl- (C_1 to C_6)-amino or
 - denotes a group NR^2R^3 , wherein R^2 and R^3 have the abovementioned meaning and

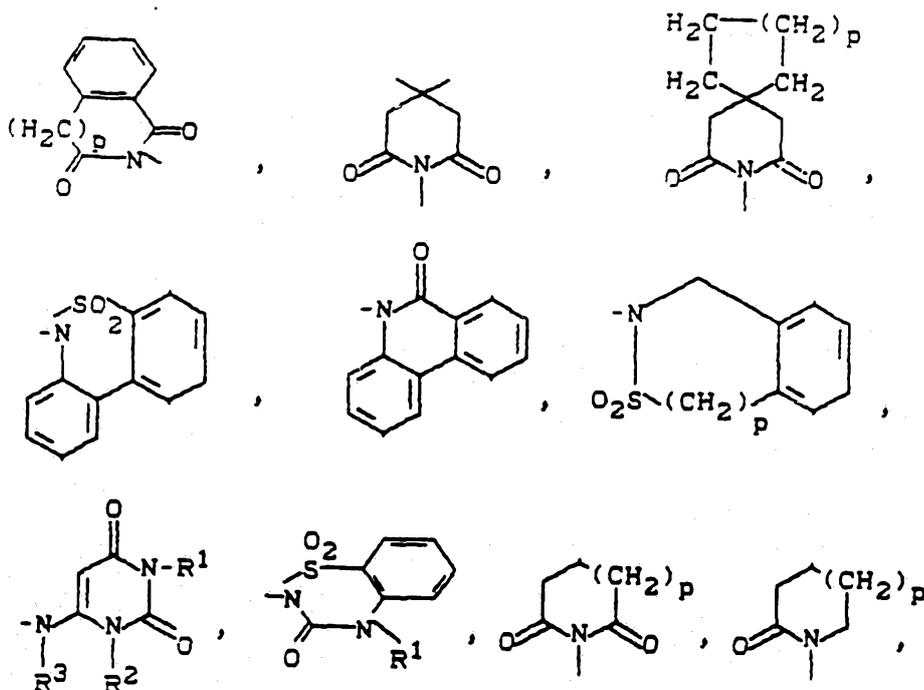
- R^9
- denotes hydrogen, or

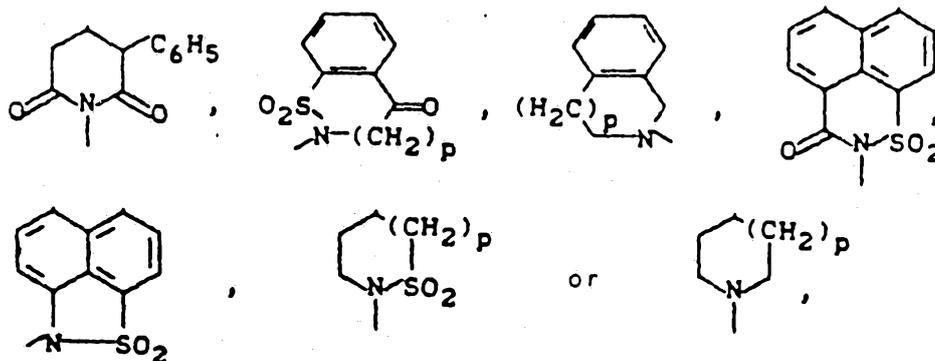
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- cycloalkyl (C₅ to C₈), or
- optionally substituted alkyl (C₁ to C₁₂),
or
- aryl (C₆ to C₁₂), aralkyl (C₇ to C₁₄)
or heteroaryl (five- or six-membered ring
having one or two oxygen and/or nitrogen
and/or sulphur atoms), where the aryl radi-
cals can be monosubstituted, disubstituted
or trisubstituted by identical or different
alkyl (C₁ to C₆), alkoxy (C₁ to C₆),
alkylthio (C₁ to C₆), halogen, cyano,
trifluoromethyl, trifluoromethoxy, trifluoro-
methylthio, nitro, amino, alkyl-(C₁ to
C₆)-amino or dialkyl-(C₁ to C₆)-amino,

or where

R⁵ and R⁶, together with the nitrogen atom,
form a ring from the series comprising





wherein

P - denotes a number of 0, 1 or 2,

R¹, R² and R³ have the abovementioned meaning,

n - denotes a number from 1 to 10 and their salts.

3. 1,3-Disubstituted pyrrolidines according to Claims 1 and 2,

wherein

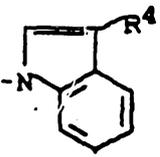
A stands for phenyl, or a monocyclic five- or six-membered hetaryl radical which contains one or two nitrogen and/or oxygen and/or sulfur atoms, or phenyl fused with one to three aromatic (C₅ to C₈) hydrocarbons, or with saturated or unsaturated cyclic (C₅ to C₈) hydrocarbons, or with five- or six-membered heterocycles having one or two nitrogen and/or oxygen and/or sulfur atoms, or A stands for a monocyclic five- or six-membered hetaryl radical which contains one or two nitrogen and/or oxygen and/or sulfur atoms fused with one to three aromatic (C₅ to C₈) hydrocarbons, wherein radical A can be unsubstituted or monosubstituted or disubstituted by lower alkyl, lower alkoxy, lower alkoxy carbonyl, lower alkenyloxy, acyloxy, benzyloxy, cyano, phenyl, benzyl, fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, difluoromethoxy or a radical of the formula -CO-NYZ, -NH-SO₂Y', -SO₂-NYZ or NH-Y, where Y and Z are identical or different and stand for hydrogen or alkyl (C₁ to C₆) and Y' stands for alkyl (C₁ to C₆) or aryl, and in the case of the nitrogen heterocycles is optionally present as the N-oxide,



- X - stands for $-\text{CH}_2\text{-O-}$, $-\text{O-CH}_2-$ or $-\text{O-}$,
 B - stands for cyano or a group of the formula
 $-\text{COOR}^1$, $-\text{SO}_2\text{NR}^2\text{R}^3$,
 $-\text{SO}_m\text{R}^4$, NR^5R^6 or $-\text{C}\equiv\text{C-CH}_2\text{-NR}^5\text{R}^6$,
 where

- R^1 - stands for hydrogen, lower alkyl or phenyl,
 R^2 and R^3 are identical or different and
 - stand for hydrogen, lower alkyl or phenyl
 which, in turn, can be substituted by fluorine,
 chlorine, bromine, lower alkoxy or
 lower alkoxycarbonyl,

- R^4 - stands for lower alkyl, or
 - for phenyl which can be monosubstituted or
 disubstituted by identical or different
 fluorine, chlorine, bromine, lower alkyl
 or lower alkoxy, or

- for a group of the formula 
 wherein R^4 denotes hydrogen or lower alkyl,

- m - stands for a number 0, 1 or 2,
 R^5 and R^6 are identical or different and
 - stand for hydrogen, lower alkyl, phenyl or
 benzyl, where the phenyl radical can be substituted
 by fluorine, chlorine, bromine,
 lower alkyl, lower alkoxy or trifluoromethyl, or

- stands for a group of the formula
 $-\text{COR}^7$ or $-\text{SO}_2\text{R}^8$,
 wherein

- R^7 - denotes hydrogen, or
 - denotes a group NHR^9 , or
 - denotes lower alkyl or lower alkoxy, or
 - phenyl, benzyl, benzyloxy, thienyl, furyl,
 pyridyl, pyrimidyl, quinolyl, isoquinolyl,
 benzothiazolyl, benzoxazolyl, thiazolyl,

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- oxazolyl, isoxazolyl or isothiazolyl optionally substituted by lower alkyl, lower alkoxy, fluorine, chlorine, bromine, trifluoromethyl, dimethylamino or diethylamino,
- R^8 - denotes cyclopropyl, cyclopentyl, cyclohexyl, or
- lower alkyl which is optionally substituted by cyano, fluorine, chlorine, bromine, trifluoromethyl or lower alkoxy, or
 - denotes phenyl, naphthyl, benzyl, thienyl, furyl, pyrimidyl, pyridyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, thiazolyl, oxazolyl, isoxazolyl or isothiazolyl optionally substituted by lower alkyl, lower alkoxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, dimethylamino or diethylamino, or a group NR^2R^3 , where R^2 and R^3 have the abovementioned meaning, and
- R^9 - denotes lower alkyl which is optionally substituted by cyano, fluorine, chlorine or bromine, or
- denotes phenyl, benzyl, thienyl, furyl, pyridyl, pyrimidyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, thiazolyl, oxazolyl, isoxazolyl or isothiazolyl optionally substituted by lower alkyl, lower alkoxy, fluorine, chlorine, bromine, trifluoromethyl, dimethylamino or diethylamino.
- or
- R^5 and R^6 , together with the nitrogen atom, form a ring from the series comprising

4. Process for the preparation of 1,3-disubstituted pyrrolidines of the general formula



wherein

A - denotes phenyl or hetaryl, or phenyl fused with aromatic, or with saturated or unsaturated cyclic or heterocyclic hydrocarbons, or A denotes hetaryl fused with aromatic hydrocarbons, wherein radical A can be unsubstituted or substituted,

X - denotes -O-CH₂-, -CH₂-O- or -O-,

and

B - denotes cyano or a group of the formula
 -COOR¹, -SO₂NR²R³, -SO_mR⁴, -NR⁵R⁶,
 or -C≡C-CH₂-NR⁵R⁶

where

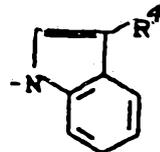
R¹ - stands for hydrogen, alkyl, cycloalkyl, alkenyl, aryl or aralkyl,

R² and R³ are identical or different and

- stand for hydrogen, alkyl, cycloalkyl, aryl or aralkyl, where the aryl radicals can be substituted by halogen, alkoxy or alkoxy-carbonyl,

R⁴ - stands for alkyl, cycloalkyl, aryl or aralkyl, where the aryl radicals can be monosubstituted by identical or different halogen, cyano, alkyl, alkoxy, trifluoromethyl or trifluoromethoxy, or

for a group of the formula



- wherein R^4 denotes hydrogen or alkyl,
- m - stands for a number 0, 1 or 2,
- R^5 and R^6 are identical or different and
 - stand for hydrogen, alkyl, cycloalkyl, aryl or aralkyl, where the aryl radical can be substituted by halogen, cyano, alkyl, alkoxy or trifluoromethyl, or
 - stand for a group of the formula $-COR^7$ or $-SO_2R^8$,

wherein

- R^7
 - denotes hydrogen or
 - a group NHR^9 or
 - alkyl, cycloalkyl or alkoxy, or
 - aryl, aryloxy, aralkyl, aralkoxy or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkylamino or dialkylamino,
- R^8
 - denotes cycloalkyl or
 - alkyl which can be substituted by cyano, halogen, alkoxy or alkoxycarbonyl, or
 - aryl, aralkyl or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, amino, alkylamino or dialkylamino, or
 - denotes a group NR^2R^3 , where R^2 and R^3 have the abovementioned meaning and
- R^9
 - denotes hydrogen or
 - cycloalkyl or
 - optionally substituted alkyl or
 - aryl, aralkyl or heteroaryl, where the aryl

wherein

p - denotes a number 0, 1 or 2,

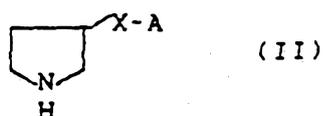
R¹, R² and R³ have the abovementioned meaning,

n - denotes a number from 1 to 10

and their salts,

characterized in that

3-substituted pyrrolidines of the general formula (II)



in which

A and X have the abovementioned meaning,

or their salts

are reacted in a first step with alkyl derivatives of the general formula (III)



wherein

n - has the abovementioned meaning,

B' corresponds to the range of meaning of B, where, however, R⁵ and R⁶ do not stand simultaneously for hydrogen or simultaneously for hydrogen and alkyl or aryl,

R - stands for chlorine, bromine, iodine, methylsulphonyloxy, phenylsulphonyloxy, tolylsulphonyloxy, trifluoroacetoxy or trifluoromethylsulphonyloxy,

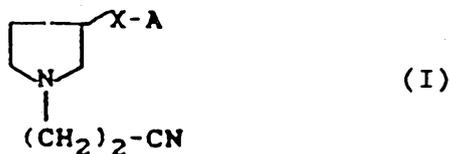
in inert solvents, if appropriate in the presence of bases,

then, if desired, functional groups are converted into other functional groups by reduction, oxidation, hydrolysis or reaction with electrophiles or nucleophilic reagents and then, in the case of the preparation of the salts, if desired, the products are reacted with the corresponding acid.

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5. Process according to Claim 4, characterized in that the reaction is carried out in the temperature range from -20°C to $+150^{\circ}\text{C}$.

6. Process for the preparation of 1,3-disubstituted pyrrolidines of the general formula



wherein

A - denotes phenyl or hetaryl, or phenyl fused with aromatic, or with saturated or unsaturated cyclic or heterocyclic hydrocarbons, or A denotes hetaryl fused with aromatic hydrocarbons, wherein radical A can be unsubstituted or substituted,

X - denotes $-0-\text{CH}_2$, $-\text{CH}_2-0-$ or $-0-$,
characterized in that 3 substituted pyrrolidines of the general formula (II)



wherein

A and X have the abovementioned meaning and B stands for cyano or for a group of the formula $-\text{SO}_2\text{NR}^2\text{R}^3$ or SO_mR^4 , wherein R^2 , R^3 , R^4 and m have the meaning given in Claim 1,

or their salts,

are reacted with acrylonitrile or a group of the formula $\text{CH}_2=\text{CH}-\text{SO}_2\text{NR}^2\text{R}^3$ or $\text{CH}_2-\text{CH}=\text{SO}_m\text{R}^4$, wherein R^2 , R^3 , R^4 and m have the abovementioned meaning, in the presence of catalysts.

7. Process according to Claim 6, characterized in that the reaction is carried out in the temperature range from $+50^{\circ}\text{C}$ to $+150^{\circ}\text{C}$.



8. Medicaments, containing 1,3-disubstituted pyrrolidines according to any one of claims 1 - 3 and a pharmaceutically acceptable carrier, diluent or excipient.
9. Medicaments according to claim 8, containing 0.5 to 90% by weight of 1,3-disubstituted pyrrolidines, relative to the total mixture.
10. A method for the treatment of a condition of the serotonergic system in a subject which comprises administering to said subject an effective amount of a 1,3 disubstituted pyrrolidine according to any one of claims 1-3.
11. A method according to claim 10 wherein the condition involves receptors which have a high affinity for 5-hydroxytryptamine (5-HT₁ type).
12. A method according to claim 10 wherein the said condition is: a disorder of the central nervous system, or a cognitive deficit, or responsive to modulation of the cardiovascular system, or responsive to the regulation of the cerebral circulation, or the consequence of the occurrence of cerebral infarcts, or a disease of the intestinal tract.
13. A method according to claim 10 wherein the said condition is: anxiety, or tension and depressive states, or sexual dysfunction or disturbances of sleep, or disturbances of nutritional absorption or Alzheimers disease, or deficiencies in powers of learning and memory, or a migraine, or the consequences of strokes or cerebral ischaemia.
14. A 1,3-Disubstituted pyrrolidine compound of the general formula shown in claim 1, said compound substantially as herein described with reference to any one of the preparation examples.
15. A medicament substantially as herein described with reference to the use examples.

DATED this 13th day of February, 1992.

BAYER AKTIENGESELLSCHAFT
By Its Patent Attorneys
ARTHUR S. CAVE & CO.

