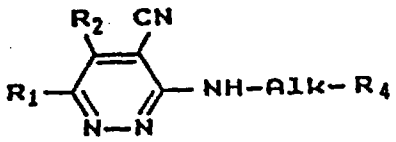
The present invention relates, by way of new products, to pyridazine derivatives.

It also relates to a process for the preparation of these compounds and the medicaments which contain at least one of the said derivatives as the active principle.

The compounds according to the invention correspond to the general formula:



in which:

R_1 denotes hydrogen, a C_1-C_4 alkyl group, a phenyl group, a phenyl group monosubstituted by a halogen, or a nitro group, or a C_1-C_4 alkyl group or a C_1-C_4 alkoxy group or a hydroxy group or a trifluoromethyl group, a phenyl group disubstituted by a halogen, a naphthyl group, a cyclohexyl group, a thien-2-yl group, a thien-3-yl group or an indol-3-yl group;

R_2 represents hydrogen, a C_1-C_4 alkyl group, or a phenyl group;

Alk represents a group $(CH_2)_n$, in which n is an integer equal to 2,3,4 or a 1,2-propynyl group $-CH_2-C{\equiv}C-$

R^4 represents: -COOH

-COO-(C_1-C_4)alkyl

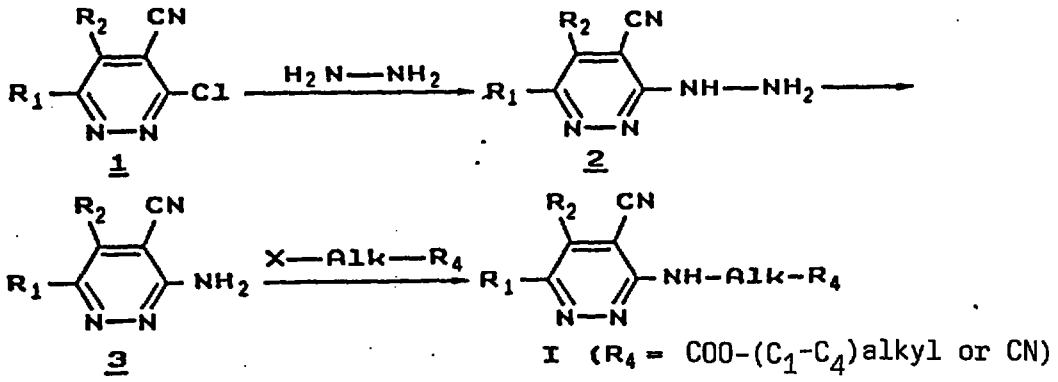
$-CONH_2$

-C≡N

The compounds I are capable of giving addition salts with mineral or organic acids. The present invention also relates to the addition salts which the compounds (I) give with pharmaceutically acceptable acids.

The compounds according to the invention can be obtained from the appropriately substituted 3-chloropyridazines 1 according

to the following reaction scheme:



The pyridazines chlorinated in the 3-position are used as starting materials for preparing the corresponding 3-aminopyridazines 3. In practice, as direct conversion of the chlorinated derivatives to the amino derivatives is found to be impracticable, it is carried out via the hydrazine derivatives 2, which are obtained with good yields by heating the chlorinated derivatives 1 with excess hydrazine hydrate under reflux. On hydrogenation in the presence of a catalyst such as Raney nickel, the compounds 2 lead to the compounds 3.

Reaction of an ω-halogenoester X-Alk-R_4, in which X represents a halogen, preferably bromine, and R_4 represents a COO-(C_1-C_4)alkyl group or the cyano group, with 3 gives the compounds (I) in which R_4 represents a COO-(C_1-C_4)alkyl group or the cyano group. The reaction is carried out by heating the reactants in a solvent such as dimethylformamide, at a temperature of between 50 and 100°C.

The compounds (I) in which R_4 represents a -COOH group are obtained from the compounds in which R_4 represents a COO-(C_1-C_4) alkyl group by saponification in an acid medium, preferably by heating with a hydracid such as hydrochloric acid or

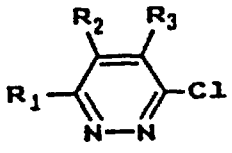
hydrobromic acid, in acetic acid, at a temperature of between 20 and 100°C. The acid is isolated directly, in the form of the salt corresponding to the hydracid used, by evaporation to dryness.

Finally, the compounds (I) in which R_4 represents a carboxamido group may be prepared either from the corresponding esters (I) by reaction with a solution of ammonia in an aliphatic alcohol such as methanol, or from the nitriles (I).

In the particular case where Alk represents 1,2-propynyl group, the acids (I) are obtained by carbonating the pyridazine substituted in the 3-position by a group -NH-Alk in which Alk is a 1,2-propynyl group.

The invention also relates to the pyridazine derivatives active on the central nervous system, obtained by the process comprising the steps of:

1) reacting a pyridazine chlorinated in the 3-position, of the formula 1:



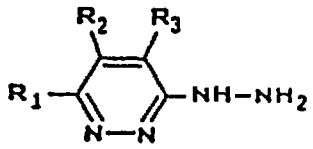
in which:

R_1 denotes hydrogen, a C_1-C_4 alkyl group, a phenyl group, a phenyl group monosubstituted by a halogen, or a nitro group, or a C_1-C_4 alkyl group or a C_1-C_4 alkoxy group or a hydroxy group or a trifluoromethyl group, a phenyl group disubstituted by a halogen, a naphthyl group, a cyclohexyl group, a thien-2-yl group, a thien-3-yl group or an indol-3-yl group;

R_2 represents hydrogen, a C_1-C_4 alkyl group, a phenyl group;

R_3 represents hydrogen, a C_1-C_4 alkyl group, a phenyl group;

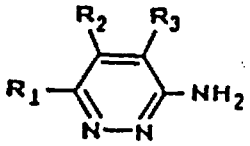
with an excess of hydrazine hydrate NH_2-NH_2, to form the pyridazine of the formula 2:



2

in which R_1, R_2 and R_3 are as defined above;

2) converting the pyridazine of the formula 2 to the corresponding 3-aminopyridazine of the formula 3 by catalytic hydrogenation:



3

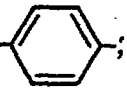
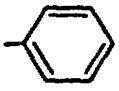
in which R_1, R_2 and R_3 are as defined above;

3) reacting the said 3-aminopyridazine with an ω-halogeno compound of the formula X-Alk-R_4, in which X is a halogen atom and R_4 is a COO-(C_1-C_4)alkyl group or the cyano group;

4) optionally converting the resulting compound by saponification or by reaction of ammonia in an aliphatic alcohol;

5) optionally converting the derivatives obtained to one of their addition salts with acids.

The invention concerns in particular pyridazine derivatives obtained according to the process described hereinabove, using in step 1) a pyridazine of formula 2 in which

R_1 is Cl-; R_2 and R_3 are hydrogen or R_1 is 

R_2 is hydrogen and R_3 is the methyl group, and in step 3) the ω-halogenated compound of the formula X-Alk-R_4 in which Alk is $(CH_2)_3$ and R_4 is the $-COOC_2H_5$ group, the resulting compounds then being converted by saponification in the corresponding acid.

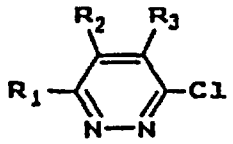
The invention also concerns pyridazine derivatives obtained by the process which consists in reacting 3-amino-pyridazine of formula 3 with an X-Alk halide in which Alk is a 1,2-propynyl group and to subject the resulting product to a carbonatation.

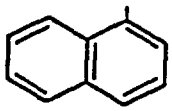
The 3-chloropyridazines used as starting materials are known compounds or may be prepared by known processes, in particular by reacting excess phosphorus oxychloride with the corresponding 2H-pyridazin-3-ones.

The non-limiting examples which follow are given by way of illustration of the present invention.

Example 1

Compound obtained from the pyridazine of formula

(1)  in which $R_2 = H$; $R_3 = CH_3$;

(I) $R_1 =$ 

and from a -halogenoester of formula X-Alk-R_4 in which Alk $=(CH_2)_3$ and $R_4 =$ $-COOC_2H_5$

a) 3-Hydrazino-4-methyl-6-(naphth-1-yl)!-pyridazine.

A mixture of 6.0 g of 3-chloro-4-methyl-6-(naphth-1-yl)-pyridazine and 4.8 g of hydrazine hydrate is heated under reflux for 4 hours. On cooling, a precipitate forms, which is filtered off and washed with water. It is recrystallised from methanol. Melting point: 206°C.

b) 3-Amino-4-methyl-6-(naphth-1-yl)-pyridazine.

2 g of Raney nickel are added to a methanol solution of 5.0 g of the hydrazino derivative obtained above, and hydrogenation is carried out at ambient temperature under one atmosphere for 72 hours. The catalyst is filtered off and the solvent is then evaporated off to dryness in vacuo. The residue is recrystallized from methanol. Melting point: 110°C.

c) 1.18 g of the amino derivative of paragraph b) are dissolved in the minimum quantity of dimethylformamide, and 1.46 g of ethyl ω-bromobutyrate are then added. The mixture is heated at 80°C for 3 hours. After cooling, it is diluted with water and rendered alkaline with 1 N sodium hydroxide solution. Extraction is

carried out with ethyl acetate and the organic phase is dried over magnesium sulphate. It is evaporated to dryness in vacuo. The oily residue is taken up in a small quantity of methanol, and hydrogen chloride is bubbled into the solution until the pH is acid. Anhydrous ether is added and the precipitate is filtered off. It is recrystallised from isopropanol. Melting point: 168°C.

Examples 2 to 26

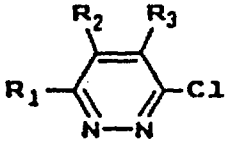
By proceeding as indicated above, but by varying the starting 3-chloropyridazines  and/or the corresponding halogenoesters X-Alk-R_4 which are opposed thereto, other compounds are obtained collated below in Table I.

TABLE 1

Example No.	R_1	R_2	R_3	Alk	R_4	physical characteristic of the resulting pyridazine derivative: Base or salt melting point °C
2	O_2N-C$_6$H$_4$-	H	H	$(CH_2)_3$	$COOC_2H_5$	Hydrobromide 196 (95° Ethanol-Ether
3	"	H	CH_3	"	"	Hydrobromide (1)
4	H_3CO-C$_6$H$_4$-	H	CH_3	"	"	Hydrobromide 250 (Dimethylformamide)
5	Cl-C$_6$H$_4$-	H	H	"	"	Hydrobromide 250 (Isopropanol)
6	"	H	CH_3	"	"	Hydrobromide (1)
7	Cl-C$_6$H$_3$Cl-	H	H	"	"	Hydrobromide 220 (Isopropanol)
8	Cl-C$_6$H$_4$-	H	H	"	"	Hydrobromide 250 (Precipitate)
9	C$_6$H$_5$-	CH_3	H	"	"	Hydrobromide 140 (Ethyl acetate)
10	Cl-C$_6$H$_4$-	H	CH_3	"	"	Hydrobromide (1)
11	H_3C-C$_6$H$_4$-	H	CH_3	"	"	Hydrobromide 260
12	C$_6$H$_5$-	H	CN	"	$COOCH_3$	Base 152 * (Chromatographed)
13	C$_6$H$_5$-	H	C$_6$H$_5$-	"	$COOC_2H_5$	Hydrochloride 204 (Isopropanol ether)
14	C$_6$H$_5$-	H	CH_3	"	"	Hydrochloride 248

* In the case of example 12 the resulting product corresponds to the formula :

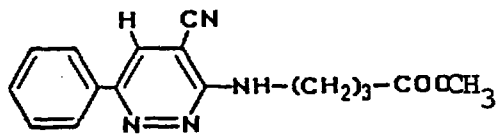
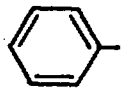
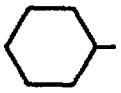
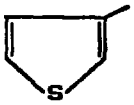
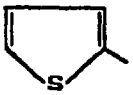
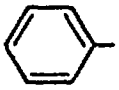
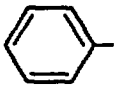
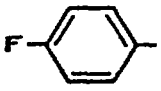


TABLE I (continued)

15		H	H	"	"	Hydrochloride 245
16	"	H	CH_3	$(CH_2)_2$	"	Hydrobromide (1)
17	"	H	CH_3	$(CH_2)_4$	"	Hydrobromide (1)
18		H	H	$(CH_2)_3$	"	Hydrobromide 149 (Isopropanol ether)
19		H	H	"	"	Hydrobromide 243 (Absolute ethanol)
20		H	H	"	"	Hydrobromide 250 (Precipitate)
21	CH_3		H	"	"	Hydrobromide 174 (Isopropanol)
22	H		H	"	"	Hydrobromide (1)
23		H	H	"	"	Hydrobromide (1)

(1) used as such for saponification into acid.

Example 24

1.8 g of the ester obtained in Example 1 are dissolved in a mixture of 81 ml of acetic acid and 9 ml of concentrated hydrochloric acid. The mixture is heated at 100°C for 9 hours and then evaporated to dryness in vacuo. The solid residue is recrystallised from isopropanol and gives the corresponding product in which R_4 has been converted to a COOH group.

Melting point:

260°C.

Examples 25 to 46:

Following the procedure of Example 24, from the various esters of Example 1, the corresponding acids are obtained whose physical characteristics and, if appropriate, their structure are shown in Table II below.

TABLE II

Example No.	R1	R2	R3	Alk	Physical characteristics of the resulting acid: Melting point (°C) solvent
25	O_2N-C$_6$H$_4$-	H	H	$(CH_2)_3$	Hydrobromide 204 (Ethanol-Ether)
26	"	H	CH_3	"	Hydrochloride 258
27	H_3CO-C$_6$H$_4$-	H	CH_3	"	Hydrobromide 255 (Precipitate)
28	2-Cl-C$_6$H$_4$-	H	H	"	Hydrobromide 226 (Isopropanol)
29	"	H	CH_3	"	Hydrochloride 0.5 H_2O 221 (Ethanol-Ether)
30	2,4-Cl$_2$-C$_6$H$_3$-	H	H	"	Hydrochloride >260
31	4-Cl-C$_6$H$_4$-	H	H	"	Hydrobromide 250 (Isopropanol-Water)
32	C$_6$H$_5$-	CH_3	H	"	Hydrobromide 0.25 H_2O 165 (Isopropanol-Isopropyl ether)
33	2-Cl-C$_6$H$_4$-	H	CH_3	"	Hydrobromide 235 (Precipitate)
34	4-H_3C-C$_6$H$_4$-	H	CH_3	"	Hydrobromide 264 (Isopropanol-Water)
35	C$_6$H$_5$-	H	CN	"	Hydrochloride 0.5 H_2O * (precipitated)
36	"	H	C$_6$H$_5$-	"	Hydrochloride 204 (Isopropanol-Ether)

* the obtained compound has the following formula:

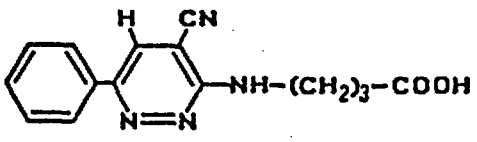
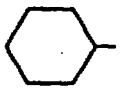
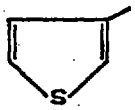
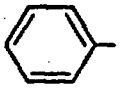
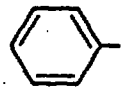
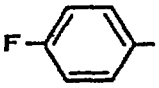


TABLE II (continued)

37	"	H	CH_3	$(CH_2)_3$	Hydrochloride 238 (Acetic acid-Ether)
38	"	H	H	"	Hydrochloride 240
39	"	H	CH_3	$(CH_2)_2$	Hydrobromide 210 (Acetic acid-Ether)
40	"	H	CH_3	$(CH_2)_4$	Hydrochloride 236
41		H	H	$(CH_2)_3$	Hydrobromide 170 (Isopropanol -Ether)
42		H	H	"	Hydrobromide 252 (95° Ethanol-Ether)
43		H	H	"	Hydrobromide 228 (Isopropanol-Water)
44	CH_3		H	"	Hydrobromide 186 (Isopropanol-Ether)
45	H		H	"	Hydrochloride 238
46		H	H	"	Hydrochloride 240

Example 47

A solution of 2 g of the acid of Example 27 in 20 ml of 48% hydrobromic acid is heated under reflux for 15 hours. After cooling, the solid which has formed is filtered off and washed with isopropanol and then with ether.

The solid is dried at 70°C in vacuo to give 2 g of the expected product. Melting point $> 260^{\circ}C$.

Example 48

4-Methyl-6-phenyl-3-(prop-2-ynylamino)-pyridazine is prepared by heating 7 g of 3-amino-4-methyl-6-phenylpyridazine and 9 ml of propargyl bromide at 60°C for 2 hours. After evaporation of

the excess propargyl bromide, the residue is taken up in 300 ml of anhydrous benzene, and 1.77 g of sodium are added. The mixture is heated under reflux for 15 hours and the solution is then poured onto excess solid carbon dioxide and left in contact therewith for several hours.

The solvent is evaporated off, the residue is taken up in isopropanol and a stream of hydrogen chloride is passed in. The solid is filtered off and recrystallised twice from isopropanol. Melting point: 101°C.

Example 49

1.3 g of the ester of Example 8, in the form of the base, are dissolved in 100 ml of methanol, the solution is then cooled in ice and 13 g of ammonia are dissolved in the solution. The mixture is stirred for 6 days at ambient temperature and then evaporated to dryness in vacuo. The residue is recrystallised from acetonitrile. This gives the expected product (0.7 g). Melting point: 170 and then 180°C.

Example 50

2.47 g of 3-amino-4,6-diphenylpyridazine are dissolved in 5 ml of dimethylformamide, and 1.63 g of 4-bromobutyronitrile are added. The mixture is heated at 60°C for 2 hours and left to cool. The crystals formed are filtered off and recrystallised from isopropanol. Melting point: = 202-204°C.

Examples 51 and 52

The compounds below are obtained in the same manner by following the same procedure, but by varying the starting 3-aminopyridazine:

from 3-amino-4-methyl-6-phenylpyridazine a product is obtained with a melting point $>265^{\circ}C$ and from 3-amino-6-phenylpyridazine a product is obtained with a melting point: 265-264°C.

Example 53

3.33 g of the hydrobromide of the nitrile of Example 51 are dissolved in 100 ml of dry formic acid, and a stream of dry hydrogen chloride is then bubbled into the solution for 4 hours at a rate of about 5 litres/hour, with stirring. The mixture is

RECEIVED 19 NOV 1990 TRADE MARKS & PATENTS

evaporated to dryness in vacuo by heating as little as possible. The residue is taken up in ethanol, and anhydrous ether is added. The crystals are filtered off and recrystallised from isopropanol. Melting point: 130-132° C.

The products according to the invention were studied for their activity on the central nervous system. Activity on the displacement of γ-aminobutyric acid from its post-synaptic receptor.

Method:

The neurochemical activity of the derivatives of the present invention on the GABA-ergic system was evaluated by measuring the displacement of γ-aminobutyric acid (GABA) from its post-synaptic receptor.

The study was carried out by the method of ENNA and SNYDER (Brain Res. 100, 81-97, 1975).

The displacement experiment was carried out in vitro in the presence of a suspension of synaptic membranes and tritiated GABA at a final concentration of 3.6 nM.

Results:

Product of Example No.	Median effective concentration (EC_{50}) for displacement of tritiated GABA, in μM
37	2.8
38	1.34
24	2.9
39	10
33	0.70
31	1.25
27	5.0
42	2.4
41	10.5
47	3.0
43	0.83
30	7.0
29	3.2
34	

RECEIVED 19 NOV 1980

Remarks:

The products of the invention have the ability to displace GABA from its synaptic receptor.

This in vitro study was complemented by an in vivo study.

The following tests were used.

1 - Activity on the motility of mice.

Method:

The tranquillising-sedative activity of the derivatives of the present invention was evaluated by measuring the spontaneous motility of mice by means of the actimetric test (J.R. BOISSIER and P.SIMON, Arch. Int. Pharmacodyn. 1965, 158, 212-221).

The equipment consisted of actimetric stages of the Apelab type (length = 26cm; width = 21.5 cm; height = 10cm), through which two rays of light pass, acting on a photoelectric cell.

The animals were placed individually in the cages 45 minutes after oral administration of the product: each crossing of a light beam was counted by an individual counter. The scores corresponding to the movements of the animals were recorded for 10 minutes. The batches consisted of 12 mice per dose.

2 - Effect on the antagonism of reserpine-induced ptosis.

Method:

The antidepressive activity of the compounds was evaluated in the test for the antagonism of reserpine-induced ptosis in mice.

This study was carried out on batches of 10 female mice weighing 20 ± 1 g. The products were administered intraperitoneally at the same time as the reserpine (2 mg/kg, administered intravenously). The mice were observed individually 1 hour after the administrations. The animals which did not exhibit ptosis during the 15 seconds of the observation were considered as antagonised. All the control animals, who had only received the vehicle and the reserpine, exhibited ptosis. The median effective dose for antagonism (ED_{50}) was evaluated by the probit method.

3 - Effect on the rotatory behaviour of mice after unilaterial lesion of the nigro-striated passage by 6-(OH)- dopamine.

Method

The influence of the derivatives of the present invention on the central dopaminergic system was evaluated on the rotatory behaviour of mice after unilateral lesion of the nigro-striated passage by 6-(OH)-dopamine (P. PROTAIS and J. COSTENTIN, J. Pharmacol, 7 (2), 251-255, 1976).

CD1 Charles River female mice, weighing 20 to 24 g, have previously undergone unilateral lesion of the striatum by the stereotaxic injection of 6-(OH)-dopamine at a dose of 8 µg per animal. One week after this operation, the product to be studied was administered intraperitoneally to groups of 7 mice. The number of rotations was evaluated over 2 minutes, 1 hour after the administration of the product. The rotations on the same side as the lesion were counted as positive and those on the opposite side were counted as negative. The algebraic sum of the rotations for a group of treated animals was compared with that for the group of control animals which had only received the vehicle (physiological serum).

The results obtained with one of the products representative of the invention, namely the product of Example No. 40, are shown in Table III below.

TABLE III

Motility of the mice		Antagonism of the reserpine-induced ptosis	Rotatory behaviour of mice	
Dose in mg/kg	Effect	ED_{50} mg/kg	Dose in mg/kg	Effect
100	-48%**	29	0.5	-50%**
50	-33%*	(26-32)	2	-62%**

* : p 0.05

**: p 0.01

RECEIVED 19 NOV 1990 SINGAPORE

The tests carried out in this way show that the products according to the invention act on the neuron by occupying the γ-aminobutyric acid receptor site. They have pharmacological properties in animals which make them suitable for use in human therapy for the treatment of neurological or neuromuscular psychic complaints.

In particular, the products according to the invention can be used for humour or behaviour disorders such as depressive states, asthenia, Parkinson's disease, disturbances in eating habits, or insomnia.

These products can be administered orally or by injection. The pharmaceutical compositions can be solid or liquid and can be presented, for example, in the form of tablets, capsules, granules, suppositories or injectable preparations.

The dosage can vary within wide limits depending, in particular, on the type and seriousness of the complaint to be treated and according to the method of administration. When administered orally to adults, it is most frequently between 0.050 to 0.500 g per day, divided up into several individual doses if appropriate.

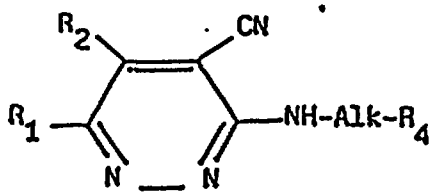
The following galenical preparation may be indicated as an example:

Capsules

Product of Example No. 40	100 mg
Aerosil	0.5 mg
Magnesium stearate	1.5 mg
STA RX 1500 starch	40 mg
	150 mg

CLAIMS for contracting States:BE,CH,DE,FR,GB,IT,LU,NL,SE

1. Pyridazine derivatives amino-substituted in the 3-position, characterized in that they correspond to the general formula:



(I)

in which:

R_1 denotes hydrogen, a C_1-C_4 alkyl group, a phenyl group, a phenyl group monosubstituted by a halogen, a nitro group, or a C_1-C_4 alkyl group or a C_1-C_4 alkoxy group or a hydroxy group or a trifluoromethyl group, a phenyl group disubstituted by a halogen, a naphthyl group, a cyclohexyl group, a thien-2-yl group, a thien-3-yl group or an indol-3-yl group;

R_2 represents hydrogen, a C_1-C_4 alkyl group, a phenyl group;

Alk represents a group $(CH_2)_n$, in which n is an integer equal to 2,3 , 4, or a 1,2-propynyl group $-CH_2C{\equiv}C-$; and

R_4 represents: -COOH

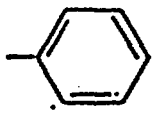
-COO-(C_1-C_4)alkyl

$-CONH_2$

$-C{\equiv}N$

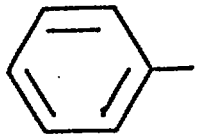
and the addition salts of the said derivatives with acids.

2. Pyridazine derivatives according to claim 1, characterized in that:

R_1 is the group 

R_2 is hydrogen,
Alk is the group $-(CH_2)_3-$
R_4 is the group $-COOCH_3$.

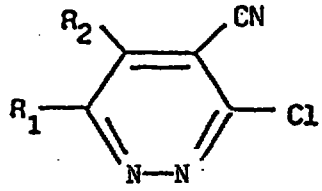
3. Pyridazine derivative according to claim 1, characterized in that:

R_1 is the group 

R_2 is hydrogen
Alk is the group $-(CH_2)_3-$ and
R_4 is the group -COOH.

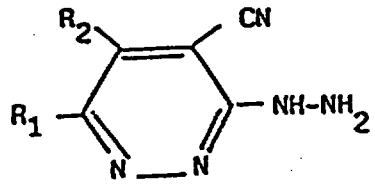
4. Process for the preparation of the pyridazine derivatives of the formula (I) in which Alk is a group $(CH_2)_n$, according to claim 1, characterized in that it consists in:

1) reacting a pyridazine chlorinated in the 3-position, of the formula 1:



1

with an excess of hydrazine hydrate NH_2-NH_2, to form the pyridazine of the formula 2:



2

2) converting the pyridazine of the formula 2 to the corresponding 3-aminopyridazine by catalytic

* C L M S *

hydrogenation;

3) reacting the said 3-aminopyridazine with an ω-halogeno compound of the formula X-Alk-R_4, in which X is a halogen atom and R_4 is a group COO-(C_1-C_4)alkyl or the cyano group, to give the compound of the formula (I) in which R_4 is as defined above;

4) optionally converting the resulting compound of the formula (I) to a compound of the formula(I) in which R_4 is the COOH or $CONH_2$ group; and

5) optionally converting the derivatives obtained to addition salts with acids.

5. Process according to claim 4, characterized in that step 4) consists in saponifying the compound of the formula (I) in which R_4 is the group COO-(C_1-C_4) alkyl to form the corresponding acid, namely the compound of the formula (I) in which R_4 is -COOH.

6. Process according to claim 5, characterized in that the saponification is carried out in an acid medium by known means.

7. Process according to claim 6, characterized in that the saponification is carried out by heating with a hydracid, in acetic acid, at a temperature of between 20 and 100°C.

8. Process according to claim 7, characterized in that the hydracid is hydrochloric or hydrobromic acid.

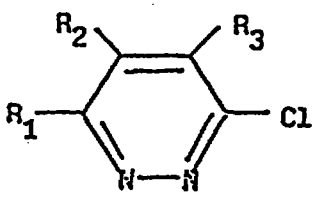
9. Process according to claim 4, characterized in that step 4) consists in converting the compound of the formula (I) in which R_4 is the group COO-(C_1-C_4)alkyl or the cyano group to the compound of the formula (I) in which R_4 is a carboxamido group.

10. Process for the preparation of the pyridazine derivatives of the formula (I) in which R_1, R_2 and R_4 are as defined in claim 1, and Alk is a 1,2-propynyl group, characterized in that it consists in carbonating the corresponding pyridazine substituted in the 3-position by the group -NH-Alk in which Alk is a 1,2-propynyl group.

11. Pyridazine derivatives active on the central nervous system, characterized in that they are obtained by the process comprising the steps of:

* C L M S *

1) reacting a pyridazine chlorinated in the 3-position, of the formula 1:



1

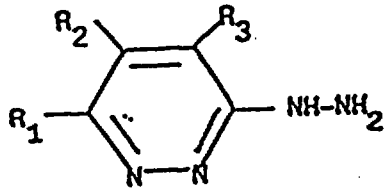
in which:

R_1 denotes hydrogen, a (C_1-C_4) alkyl group, a phenyl group, a phenyl group monosubstituted by a halogen or a nitro group or a C_1-C_4 alkyl group or a (C_1-C_4) alkoxy group or a hydroxyl group or a trifluoromethyl group, a phenyl group disubstituted by a halogen, a naphthyl group, a cyclohexyl group, a thien-2-yl group, a thien-3-yl group or an indol-3-yl group;

R_2 represents hydrogen, a (C_1-C_4) alkyl group, a phenyl group;

R_3 represents hydrogen, a (C_1-C_4) alkyl group, a phenyl group;

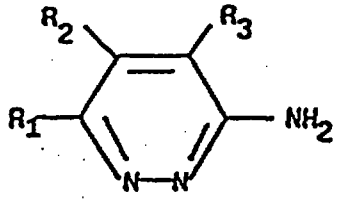
with an excess of hydrazine hydrate, NH_2-NH_2, to form the pyridazine of the formula 2:



2

in which R_1, R_2 and R_3 are as above defined;

2) converting the pyridazine of the formula 2 to the corresponding 3-aminopyridazine of the formula 3 by catalytic hydrogenation:



3

* C L M S *

in which R_1, R_2 and R_3 are as defined above;

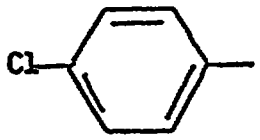
3) reacting the said 3-aminopyridazine with an ω-halogeno compound of the formula X-Alk-R_4, in which X is a halogen atom and R_4 is a group COO-(C_1-C_4) alkyl or the cyano group;

4) optionally converting the resulting compound by saponification or by action of ammonia in an aliphatic alcohol.

5) optionaly converting the derivatives obtained to addition salts with acids.

12. Derivative according to claim 11, characterized in that step 1) uses the pyridazine of formula 2 in which

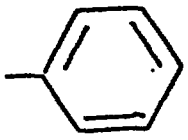
R_1 is the radical



R_2 and R_3 denote hydrogen and in that in step 3) the ω-halogeno compound of formula X-Alk-R_4 in which Alk is the group $-(CH_2)_3-$ is used; X is a halogen and R_4 is the group $-COOC_2H_5$ and in that the resulting compound is converted by saponification into the corresponding acid.

13. Derivative according to claim 11, characterized in that in step 1) the pyridazine of formula 2 in which

R_1 is the radical



R_2 is hydrogen and

R_3 is the methyl group, is used and in that

in step 3) is used the ω-halogeno compound of formula

X-Alk-R_4 in which Alk is the group $-(CH_2)_3-$; X is a halogen and R_4

is the group $-COOC_2H_5$ and in that the resulting compound is converted by saponification into the corresponding acid.

14. Pyridazine derivatives, characterized in that they are obtained by the process consisting in reacting the 3-amino pyridazine of formula 3 with an halide X-Alk in which Alk is a 1,2-propynyl group and in subjecting the resulting product to a carbonating treatment.

15. Medicines, characterized in that they contain one of the pharmaceutically acceptable derivative of pyridazine according to any one of claims 1 to 3 and 11 to 14.

16. Medicines according to claim 15, characterized in that they are active on the central nervous system.

17. Medicines according to one of claims 15 or 16, characterized in that they are packed for oral administration or for injectable administration.

* C L M S *