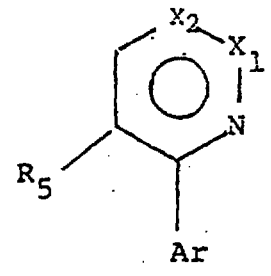
Description

The present invention relates to novel heterocyclic compounds presenting interesting therapeutic properties on the central nervous system.

The compounds according to the invention are described by the general formula :



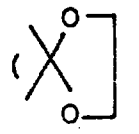
in which :

- X_1 represents N or the $C-N<^{R_1}_{R_2}$ group;
- X_2 represents N or the $C-N<^{R_1}_{R_2}$ group provided that X_1 and X_2 are different from each other;
- R_1 and R_2 represent $-(CH_2)_nOH$; n = 1 to 4 or $-N<^{R_1}_{R_2}$ constitutes a saturated heterocycle with 5 or 6 groupings containing one nitrogen atom as heteroatom and bearing a substituent in 3 or 4 position selected from :

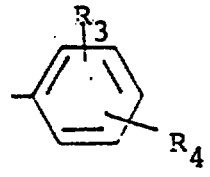
i) a $-(CH_2)_mOR_6$ group where m is equal to 0,1 or 2 and R_6 represents hydrogen or a $-\overset{O}{\overset{\|}{C}}-R_7$ group or $-\overset{O}{\overset{\|}{C}}-N<^{R_8}_{R_9}$ group in which R_7 represents a straight or branched alkyl group, having from 1 to 5 carbon atoms, a cyclopropyl group or a phenyl group possibly substituted by an atom of halogen and R_8 and R_9 considered independently each represents hydrogen or a straight or branched alkyl group having from 1 to 5 carbon atoms,

ii) an oxo (=O) group;

iii) a spiro-1,3-dioxolane-2-yl


group;

- Ar represents:

. a  group

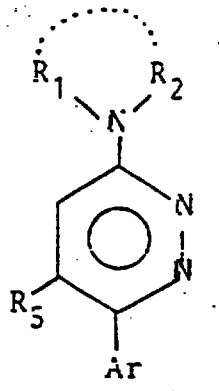
in which :

R_3 designates hydrogen, an atom of halogen a straight or branched alkyl group, having from 1 to 5 atoms of carbon a straight or branched alkoxy group, having from 1 to 5 atoms of carbon, a trifluoromethyl group, a hydroxy group, a nitro group or a cyano group and R_4 designates hydrogen or an atom of halogen ;

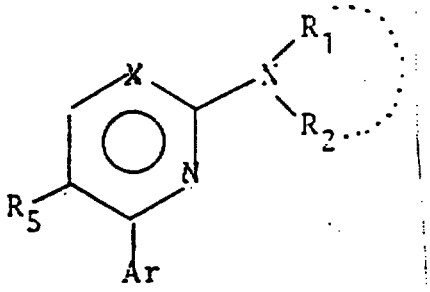
a naphthyl group non-substituted or monosubstituted by an atom of halogen ;

R_5 designates hydrogen or an atom of chlorine, it being understood that R_5 be an atom of chlorine, only if X_2 represents an atom ofnitrogen,

More precisely, the compounds according to the invention are represented by one of the following two formulae :



Ia

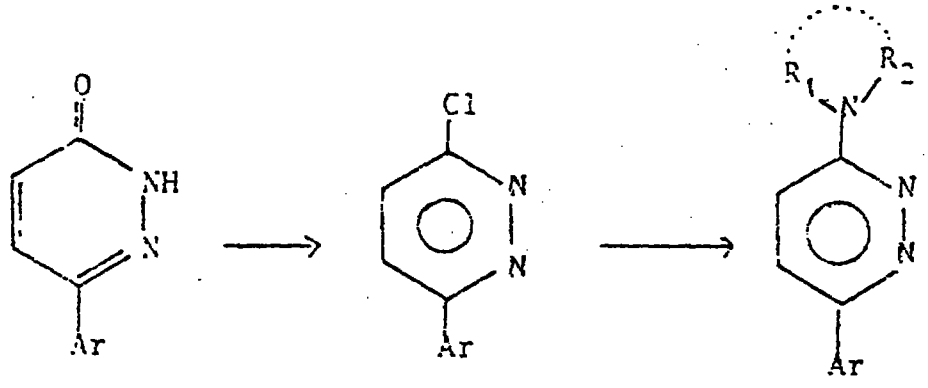


Ib

Compounds I yield salts with organic or inorganic acids. These salts, with the pharmaceutically acceptable acids, are an integral part of the invention.

Compounds I are prepared from the corresponding ketonic derivative obtained according to the methods described in the prior art. The ketonic derivative is converted into the corresponding chlorinated aromatic compound; then the latter is converted into corresponding aminated compound.

Preparation of Ia:

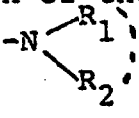


Ia

The 3-pyridazinones are prepared in accordance with the methods described in: Journal of the American Chemical Society, 1953, pp1117-1119 and Journal of Organic Chemistry, 1973, 38, pp 4044-4048.

The 6-aryl-3-chloro-pyridazines are known compounds; they may be prepared for example according to the method described in : Journal of Heterocyclic Chemistry, 1973, 38, 881-892.

When one of the substituents R_3 or R_4 is hydroxyl, the latter must be blocked, for example by ethyl chloroformate, during preparation of the 6-aryl-3-chloro-pyridazine.

The substitution of the pyridazine by the hydroxylated amine group  is effected by

heating 6-aryl-3-chloro-pyridazine and HNR_1R_2 amine in an alkanol at boiling temperature.

The product may then possibly be esterified by action of an acid chloride in the presence of a tertiary amine by heating the mixture in an aprotic solvent, for example tetrahydrofuran.

The N-monosubstituted carbamate may also possibly be prepared by addition on the hydroxylated amine of an isocyanate and heating in an aprotic solvent, for example tetrahydrofuran.

Similarly, the disubstituted N,N-carbamates are obtained by action of a carbamoyl chloride within a solvent such as dioxane at reflux and in the presence of a hydracid acceptor, such as triethylamine.

Finally, when the cyclic amine is substituted by an oxo group, compound I is obtained by acid hydrolysis of the corresponding cyclic acetal.

EXAMPLE 1:

3-(4-hydroxy-piperidino)-6-(2-nitro-phenyl)-pyridazine; SR 41673

By using the methods described in the prior art, the 3-chloro-6-(2-nitro-phenyl)-pyridazine is prepared (m.p. : 138-140°C). 3 g of this product are mixed with 3.86 g of 4-hydroxy-piperidine in 60 ml of normal butanol and heated with stirring to 100°C for 5 hours.

The reaction mixture is concentrated in vacuo to dryness, then the residue is taken up in water and extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulfate then concentrated to dryness. The residual oil is chromatographed over silica gel by using a chloroform/methanol (90/10 vol:vol) mixture as eluent. After evaporation of the solvents, the residual oil crystallizes. Recrystallization is carried out in acetonitrile to

obtain 2.6 g of the expected product.

m.p. 138-139°C.

EXAMPLE 2:

3-(4-hydroxy-piperidino)-6-(2-chloro-phenyl)pyridazine. CM 40907.

Operation is carried out in accordance with the methods mentioned for preparing 3-chloro-6-(2-chloro-phenyl)pyridazine (m.p.: 146-147°C). 5 g of this product are dissolved in 120 ml of normal butanol and mixed with 6.74 g of 4-hydroxy-piperidine, then heated to reflux. By following the modus operandi described for the previous Example, 5 g of CM 40907 are obtained after recrystallization in absolute ethanol.

m.p. : 154-155°C.

EXAMPLE 3:

3-(4-butyroyloxy-piperidino)-6-(2-chloro-phenyl)-pyridazine; SR 41172

2.9 g of CM 40907 are dissolved in 100ml of tetrahydrofuran, 3.5 ml of triethylamine and 2.6 g of butyryl chloride are added, then the mixture is heated to reflux for 3 days. 0.7 ml of triethylamine and 0.52 ml of butyryl chloride are added and the mixture is again heated to reflux for 24 hours. The reaction medium is then concentrated to dryness and the residue is taken up in normal hydrochloric acid and washed with ether.

After addition of sodium carbonate, the mixture is extracted with ethyl acetate. The organic phase is dried over sodium sulfate and concentrated to dryness. The residual oil is chromatographed over silica gel, using ethyl acetate as eluent. After concentration and recrystallization in isopropyl ether, 2.7 g of SR 41172 are obtained.

m.p. 89-90°C.

EXAMPLE 4:

3-(4-methylcarbamoyloxy-piperidino)-6-(2-chloro-phenyl)pyridazine; SR 41820.

A solution of 2.7 g of CM 40907 in 50ml of tetrahydrofuran is prepared. It is heated to reflux for 48 hours in the presence of 1.65 ml of methyl isocyanate; after having added 1.65 ml of ethyl isocyanate, heating is resumed for 48 hours.

The reaction medium is concentrated under vacuum, the residue is chromatographed over silica gel using ethyl acetate as eluent. After concentration, the product is recrystallized in ethyl acetate. 1 g of SR 41 820 is obtained.

m.p. 134-136°C.

EXAMPLE 5:

4-(dimethylcarbamoyl-4-oxy-piperidino)-6-(2,4-dichloro-phenyl)pyridazine; SR 42432.

a) 3-(4-hydroxy-piperidino)-6-(2,4-dichloro-phenyl)pyridazine; SR 41378

Operation is carried out as in Example 1 from 3-chloro-6-(2,4-dichloro-phenyl)pyridazine and 4-hydroxy-piperidine.

The expected product is obtained in the same way. m.p. 151 3°C (ethanol).

b) SR 42432

4.7 g of the product obtained hereinabove are dissolved in 60 ml of dioxane then 6.3 ml of triethylamine and 4.1 ml of dimethylcarbamoyl chloride are added. The mixture is heated to reflux for 7 days then the solvent is evaporated to dryness under vacuum. The residue is taken up in an aqueous solution of 10% sodium carbonate and extracted with ethyl acetate. The organic layer is separated, dried over sodium sulfate and the solvent is evaporated to dryness in vacuo. The

residue is chromatographed over silica gel, eluting with ethyl acetate. A product is obtained which crystallizes. After recrystallization in ethyl acetate, m.p. 196 :198°C; weight 2.8:g.

EXAMPLE 6:

3-[1,4-dioxa-8-aza-spiro[4,5]decane-8-yl]-6-(2-chloro-phenyl)pyridazine; SR 42487

The mixture of 4.5 g of 3-chloro-6-(2-chloro-phenyl)pyridazine and 8.2 g of 1,4-dioxa-8-aza-spiro[4,5]decane in 100 ml of butanol is heated to reflux for 18 hours.

The butanol is evaporated to dryness in vacuo and the residue is taken up in water. The mixture is extracted with ethyl acetate and the organic solution is dried over sodium sulfate. The solvent is evaporated to dryness under vacuum and the residue is recrystallized in ethyl acetate, m.p. : 156-158°C; weight:5.2 g.

EXAMPLE 7:

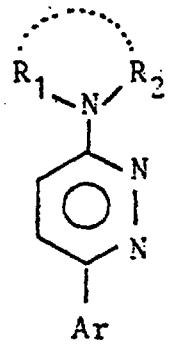
3-(4-oxo-piperidono)-6-(2-chloro-phenyl)pyridazine; SR. 42488

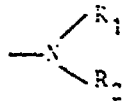
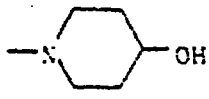
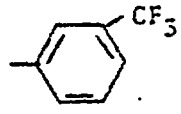
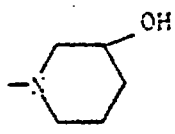
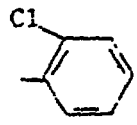
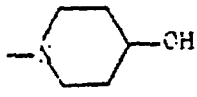
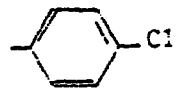
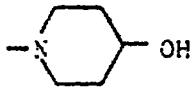
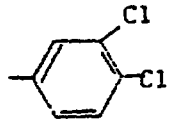
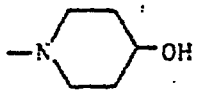
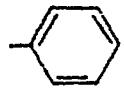
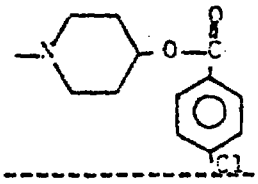
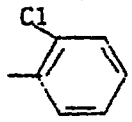
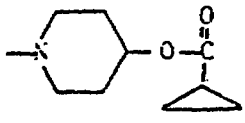
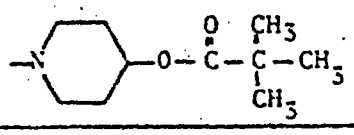
4 g of the product of Example 6 in the mixture of 40 ml of formic acid and 60 ml of water are heated to reflux for 4 hours. The reaction mixture is poured over a solution of sodium hydroxide in excess to which ice has been added. The mixture is extracted with methylene chloride, the organic layer is separated and dried over sodium sulfate.

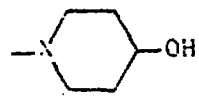
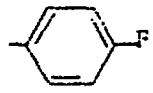
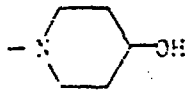
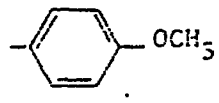
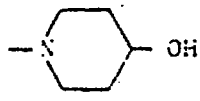
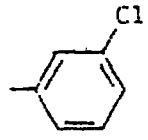
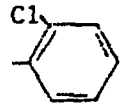
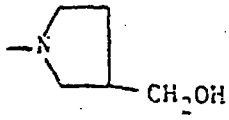
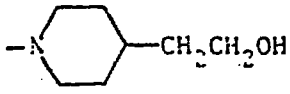
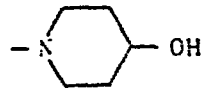
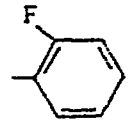
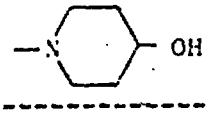
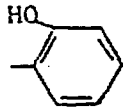
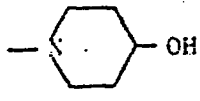
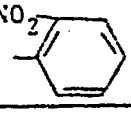
The solvent is evaporated to dryness under vacuum then the residue is recrystallized in absolute ethanol. m.p. : 158-160°C; Weight: 3.2 g.

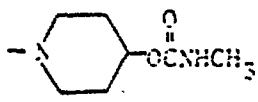
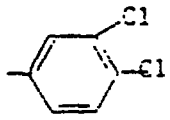
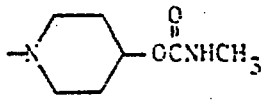
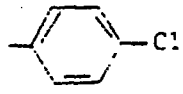
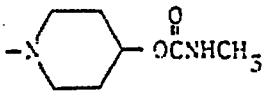
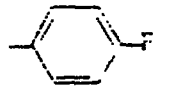
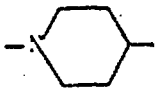
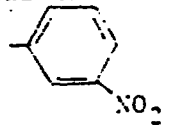
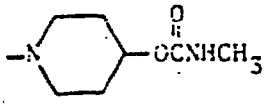
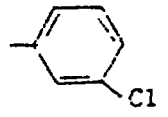
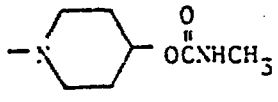
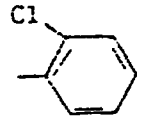
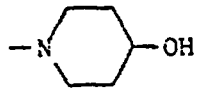
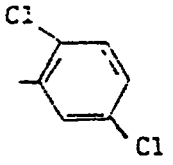
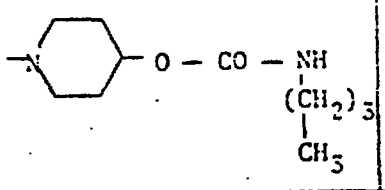
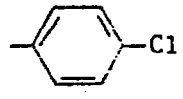
By using similar methods, the compounds according to the invention described in Table 1 hereinbelow are prepared.

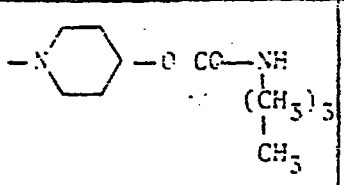
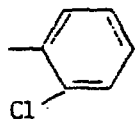
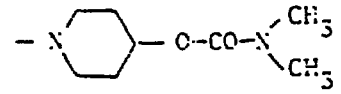
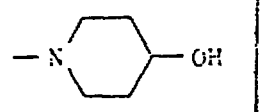
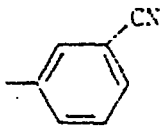
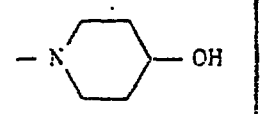
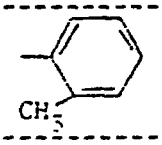
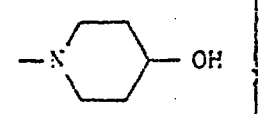
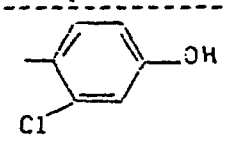
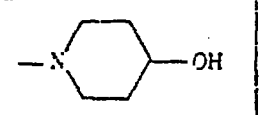
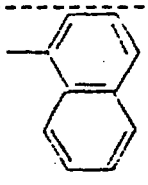
TABLE I



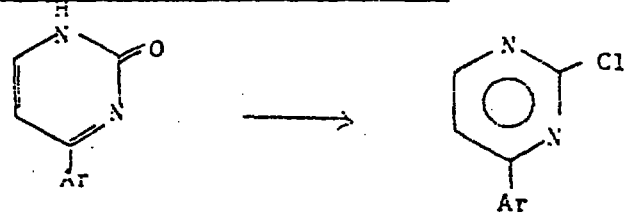
No. of Product		Ar	m.p. °C Solvent of crystallization
CM 40857			130°C ethyl acetate
CM 41096			134°C ethyl acetate
CM 41127			174-176°C absolute ethanol
SR 41155			150-152°C ethyl acetate
SR 41171			150°C (acetonitrile)
SR 41173			142-144°C (aceto-nitrile)
SR 41174		" "	88-90°C methylene chloride-iso-propyl ether
SR 41175		" "	145°C (aceto-nitrile)

SR 41184			162-164°C ethyl alcohol
SR 41185			182-184°C ethyl alcohol
SR 41188			152-154°C ethyl acetate
SR 41254			170-172°C ethyl alcohol
SR 41259		" "	136-138°C ethyl alcohol isopropyl ether
SR 41261		" "	88-90°C (isopropanol-isopropyl ether
SR 41553			132-134°C (ethanol-isopropyl ether
SR 41559			141-143°C (aceto-nitrile)
SR 41673			138-139°C (aceto-nitrile)

SR 41900			168-170°C (acetonitrile)
SR 41915			216-218°C (aceto-nitrile)
SR 41917			170-172°C (aceto-nitrile)
SR 41930			230°C ethanol
SR 41931			165°C (aceto-nitrile)
SR 41935			164-166 ethyl acetate
SR 41965			166-167°C ethyl acetate
SR 41932			172-173°C (ethanol)
SR 42087			156-158°C ethyl acetate

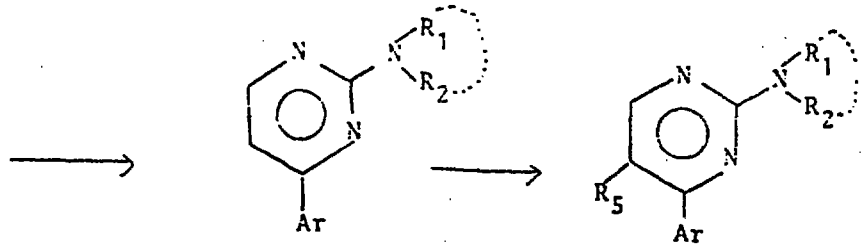
SR 42095			154-155°C ethyl acetate-isopropyl ether
SR 42095		" "	131°C ethyl acetate-isopropyl ether
SR 42159			136-138°C ethyl acetate-isopropyl ether
SR 42356			187-188°C (methanol)
SR 42368			176-178°C ethyl acetate
SR 42399			148-150°C ethyl acetate

Preparation of Ib: Reaction scheme



IIb

IIIb



IVb

The 6-aryl-pyrimidine-2-ones (11b) are prepared in accordance with the method described in : Journal of Organic Chemistry, 1953, 18, pp 588-593.

Compounds 111 b and IV b are obtained by using the same methods as those used for the similar compounds in pyridazine series.

If R_5 is a halogen, halogenation of the pyrimidine nucleus for obtaining 1 b is effected by N-chloro-succinimide according to the method described in : Tetrahedron, 1966, 22, 2401.

EXAMPLE 8

2-(4-hydroxy-piperidino)-4-(2-chloro-phenyl)pyrimidine; CM 40724.

a) 4-(2-chloro-phenyl)-pyrimidine-2-one

The 2-chloro-benzoyl acetaldehyde is prepared according to the method described in : Berichte der Deutschen Chemischen Gesellschaft, 1901, 34, 3889-3897.

53.6 g of this product are dissolved in 2.5 l of absolute alcohol to which are added 17.63 g of urea and 29.35 ml of concentrated hydrochloric acid. After heating to reflux for one night, the reaction mixture is concentrated. The residue is taken up in diluted sodium hydroxide and extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulfate and concentrated to dryness.

The crystallized residue is chromatographed, then 10.1 g are dissolved in 500 ml of ethanol. 4.54 g of potassium hydroxide dissolved in 50 ml of water are added, then the mixture is heated to reflux for 30 minutes. After having concentrated the reaction mixture under vacuum, the residue is neutralized by dilute hydrochloric acid.

The organic phase is extracted with methylene chloride, washed with water, dried over

sodium sulfate then concentrated. The crystallized residue is washed with 50 ml of ethyl acetate to yield 6 g of white product.

m.p.: 210-212°C.

b) 2-chloro-4-(2-chloro-phenyl)pyrimidine

This product is obtained by action of phosphorus oxychloride hot according to the method mentioned for the preparation of 1 a.

m.p. : 100°C (hexane)

c) CM 40724

The modus operandi described in Example 1 is used for adding 4-hydroxy-piperidine.

m.p.: 102-104°C (isopropyl ether).

EXAMPLE 9

Hydrobromide of 5-chloro-6-(2-chloro-phenyl)-2-(4-hydroxy-piperidino)pyrimidine; SR 40858

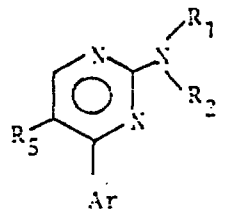
2.7 g of CM 40724 are dissolved in 50 ml of chloroform. 1.37 g of N-chloro-succinimide are added and the reaction mixture is heated to reflux for one night, then concentrated under vacuum. The residue is taken up in 50 ml of boiling water, the slightly cooled mixture is extracted with ethyl acetate. The organic phase is decanted, dried over sodium sulfate then concentrated. The residual oil is chromatographed over silica gel using as eluent a cyclohexane-ethyl acetate (50/50vol:vol) mixture. After elimination of impurities at the head of the column, the product described is eluted. The concentration of the fractions yields 1.9 g of oil which is taken up in 100 ml of ether.

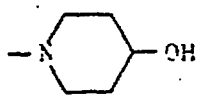
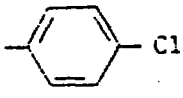
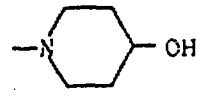
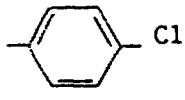
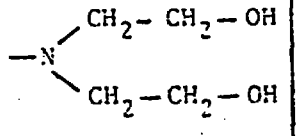
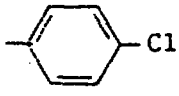
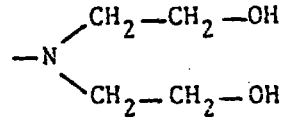
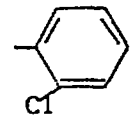
After bubbling hydrobromic gas up to acid pH, the hydrobromide of the product crystallizes. It is recrystallized in acetonitrile.

m.p. 192.194°C.

By following the methods of preparation indicated, the compounds according to the invention described in Table II hereinbelow are obtained.

TABLE II



No. of product	$-N(R_1)(R_2)$	R_5	Ar	m.p. °C solvent of crystallization
SR 41554		H		140-142°C isopropyl ether
SR 41556		Cl		144°C isopropyl ether
SR 41590		H		114°C isopropyl ether
SR 41591		H		106-108°C isopropyl ether

The products according to the invention have been assessed for their hypnogenic and sedative effects, as well as for their anti-epileptic activity.

I - ASSESSMENT OF THE HYPNOGENIC AND SEDATIVE EFFECT OF THE PRODUCTS

a. Effect of the products on the spontaneous motility.

The sedative effect is translated by the reduction of the spontaneous motility of the animals. This was measured by the actimeter test developed by BOISSIER and SIMON (1965). The equipment was composed of actimetric cages, of the Apelab type (26 x 21.5 x 10 cm), through which pass two light rays which act on a photoelectric cell. The batches were constituted by 12 female Charles River CD1 mice weighing between 20 and 24 g. The animals were placed individually in the cages 45 minutes after the oral administration of the products at the dose of 250 mg/kg or at the dose of 100 mg/kg. Each passage through a light beam was counted by an individual meter. The scores corresponding to the movements of the animals were recorded for 10 minutes and compared with the scores made by the batches of control animals, treated solely by the vehicle (0.1 N HCl).

Comments :

After administration, at the oral dose of 100 mg/kg or of 250 mg/kg, the products of the invention reveal a powerful sedative effect characterized by a considerable reduction in the motility of the animals.

On the other hand, at the dose of 100 mg/kg, the CM 41378 provokes a loss of turn-around reflex characteristic of a sleep-inducing effect in 60% of the animals treated.

TABLE III

Products	Dose p.o. mg/kg	Locomotor activity. Score (p.cent/controls)
CM 40857	100	- 57 % **
CM 40907	100	- 66 % **
CM 41127	100	- 68 % **
SR 41155	100	- 82 % **
SR 41171	100	- 54 %
SR 41172	100	- 32 % **
SR 41184	100	- 91 % **
SR 41188	100	- 77 % **
SR 41254	100	- 34 % *
SR 41259	100	- 19 %
SR 41261	100	- 27 % *
CM 40858	250	- 20 %
SR 41185	250	- 78 % **
SR 41554	250	- 26 % *
SR 41556	250	- 29 % **
SR 41558	250	- 93 % **
SR 41559	250	- 66 % **
SR 41654	250	- 57 % **
SR 41673	250	- 61 % **
SR 41174	100	- 15 %
SR 41932	150	- 59 % **
SR 42095	10	- 28 % *
SR 42487	100	- 42 % **

* p 0,05 (Student test)

** p 0,01 " "

b. Potentialization of narcosis by pentobarbital

With a view to assessing the hypnogenic power of the products, we have studied their capacity to potentialize the effects of a subnarcotic dose of pentobarbital in the mouse. The batches were constituted by 10 Charles River CD1 mice, weighing between 20 and 24 g. The pentobarbital (20 mg/kg, i.p.) was administered 60 minutes after administration of the products. The criterion of sleep-induction retained was the loss of the turn-around reflex. The animals which did not present this reflex were counted.

Products	Potentialization of pentobarbital ED_{50} (mg/kg, p.o.)
CM 40907	96
SR 41155	20
SR 41378	21
SR 41554	66
SR 42095	7,4
SR 42488	67

The products according to the invention are capable of potentializing narcosis by pentobarbital; this property is predictive of a hypnogenic effect.

II - ASSESSMENT OF THE ANTI-EPILEPTIC ACTIVITY OF THE PRODUCTS

The anti-epileptic effect of the products in the mouse was assessed on a model of convulsions provoked by an electric shock, and on a model of convulsions induced by a chemical agent : bicuculline.

a. Antagonism of the convulsions induced by an electric shock.

The test was slightly modified from that of SWINYARD et al (1952) and ASAMI et al (1974). The equipment was composed of a Racia shock generator provided with two ocular electrodes delivering a current of 12.5 volts for 0.3 seconds. The batches were constituted by 10 Charles River CD1 mice, weighing between 20 and 24 g. The products were administered by the oral route, 60 minutes before the electric shock. The animals presenting no tonic extension of the rear limbs were considered as being protected from the convulsive crisis.

b. Antagonism of the convulsions provoked by bicuculline

The batches were constituted by 10 Charles River CD1 mice, weighing between 20 and 22g. The products were administered by the oral route, 60 minutes before the bicuculline (0.8 mg/kg, i.v.). The appearance of tonic convulsions was noted during the 60 minutes following the injection of the bicuculline.

Comments :

After oral administration in the mouse, the products according to the invention show anti-epileptic properties both with respect to electric shock and bicuculline.

TABLE IV

Products	Median effective dose (ED_{50}) (mg/kg, p.o.)	
	Antagonism of the electric shock	Antagonism of Bicuculline
CM 40857	63	
CM 40858	49	
CM 40907	16	38
CM 41127	28	98
SR 41171	86	83
SR 41172	28	39
SR 41184	48	
SR 41188	45	
SR 41378	30	5,7
SR 41554	145	147
SR 41558	115	30
SR 41673	27	81
SR 41820	10	13
SR 41174	92	
SR 41932	30	131
SR 42095	2	1,6
SR 42399	38	
SR 42487	57	
SR 42488	40	35

III - DETERMINATION OF THE LETHAL DOSE IN THE MOUSE AFTER ACUTE ADMINISTRATION OF THE PRODUCTS

The products were administered by the oral route to batches of 5 female Charles River CD1 mice, weighing between 20 and 24 g. They were solubilized in 0.1 N HCl.

Toxicity was noted during the 72 hours following administration of the products. The LD_{50} was calculated for two products.

TABLE V

Products	% of toxicity or LD_{50}		
	250 mg/kg p.o.	500 mg/kg p.o.	1000 mg/kg p.o.
CM 40858	0	0	0
CM 40907		DL_{50} = 807	
CM 41127	0	0	
SR 41155	0	100	100
SR 41171	0	0	100
SR 41172	0	0	100
SR 41184	0	60	100
SR 41185	0	0	0
SR 41188	0	0	60
SR 41254	0	0	20
SR 41378		DL_{50} = 423	
SR 41554	0	0	0

TABLE V (cont.)

Products	% of toxicity or LD_{50}		
	250 mg/kg p.o.	500 mg/kg p.o.	1000 mg/kg p.o.
SR 41556	0	0	0
SR 41558	0	0	80
SR 41559	0	0	0
SR 41590	0	0	40
SR 41591	0	0	0
SR 41654	0	0	60
SR 41673	0	0	20
SR 41932	0	0	100
SR 42094	0	0	0
SR 42399	0	0	
SR 42487	0	0	0
SR 42488	0	0	0

The results expressed in percentage of animals which die in the 71 hours consecutive to the oral administration of the products are noted in the preceding Table.

The tests thus effected show that the products according to the invention present interesting pharmacological properties and a low toxicity. They may be used in human therapeutics, particularly for the treatment of psychic, neurological or neuromuscular disorders.

The products according to the invention may be used in particular for the treatment of disorders in mood or in the behaviour: nervosity, irritability as well as for the treatment of anxious states, insomnias and epilepsy.

These products may be administered by the oral route or by the injectable route. The pharmaceutical compositions may be solid or liquid and may be in the form for example of tablets, capsules, granules, suppositories or injectable preparations.

Posology may vary in large proportions, in particular, depending on the type and seriousness of the disorder to be treated and depending on the mode of administration. In the adult by the oral route, it is most often included between 1 mg and 500 mg per day, possibly spread out in several doses.

By way of example, the following Galenic preparation may be indicated :

Capsules

CM 40907	100 mg
Aerosil	0.5 mg
Magnesium stearate	1.5 mg
Starch STA RX 1500	48 mg
	150 mg