

DESCRIPTION

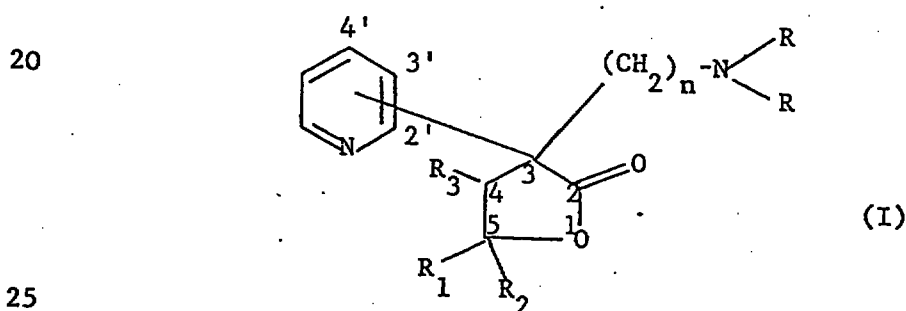
The present invention relates as new industrial products to derivatives of γ -butyrolactone as well as to the methods for preparing them and to the application thereof to therapeutics.

Said derivatives which are protectors of the myocardium and present an anti-arrythmic activity are substituted by a pyridine group.

In patent EP 27142 derivatives of pyridine have already been described as myocardium protectors having an anti-arrythmic activity. Said derivatives are pyridines substituted by an alkyl group carrying an amide function and an amine function.

On the contrary, the compounds of the invention can be considered, as shown by the following general formula, as being pyridines covering a butyrolactone cycle substituted by an alkyl amino group.

The novel compounds according to the invention respond to the following general formula :



in which :

. R represents a straight or branched alkyl group having from 2 to 5 atoms of carbon,

or the group $\begin{array}{c} \text{R} \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{R} \end{array}$ represents a morpholino or piperidino group

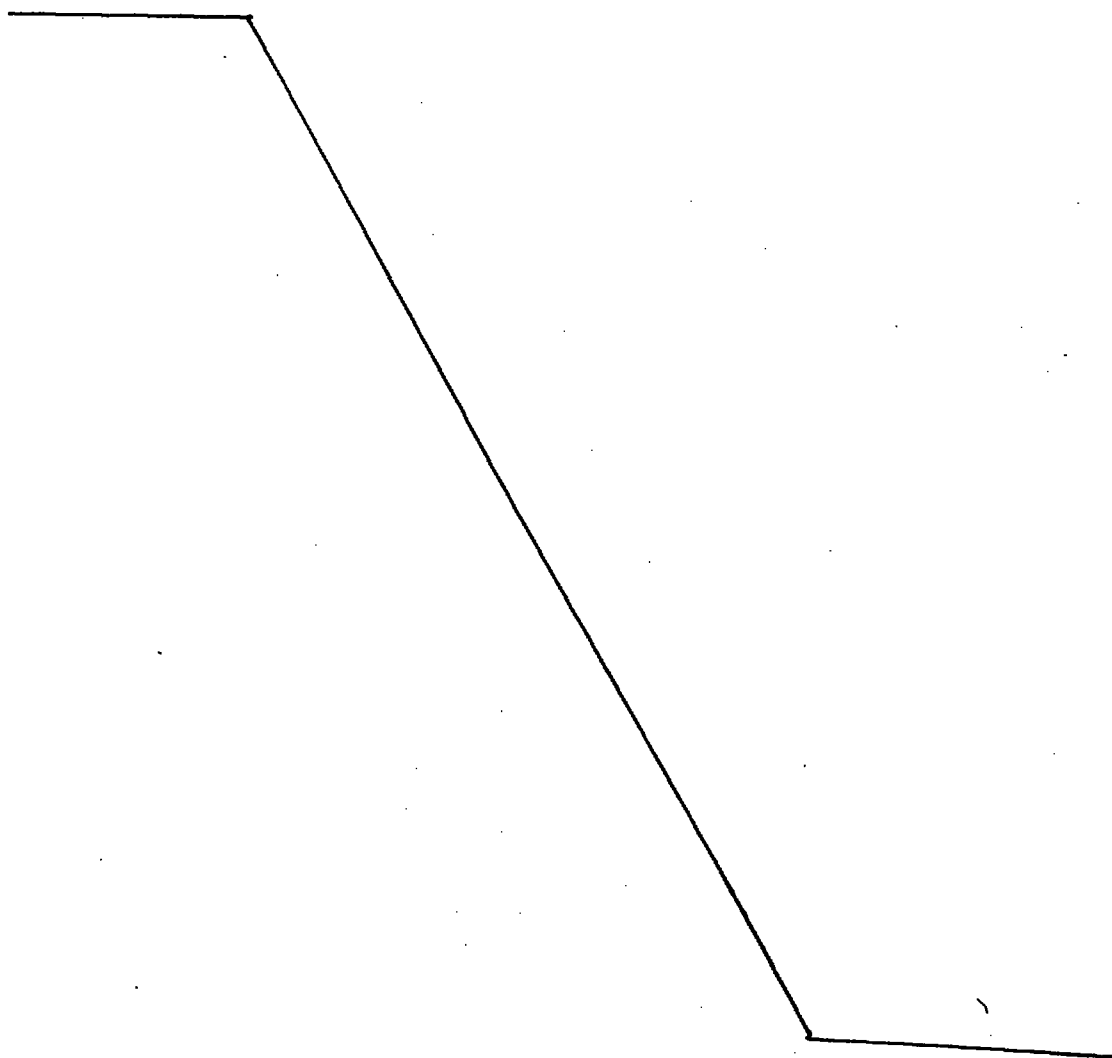
possibly substituted by 1 to 4 methyl groups ;

. n = 2 or 3 ;

. R₁ and R₂ considered independently each represent hydrogen or a lower alkyl group (1 to 4 carbon atoms) or R₁ and R₂ taken

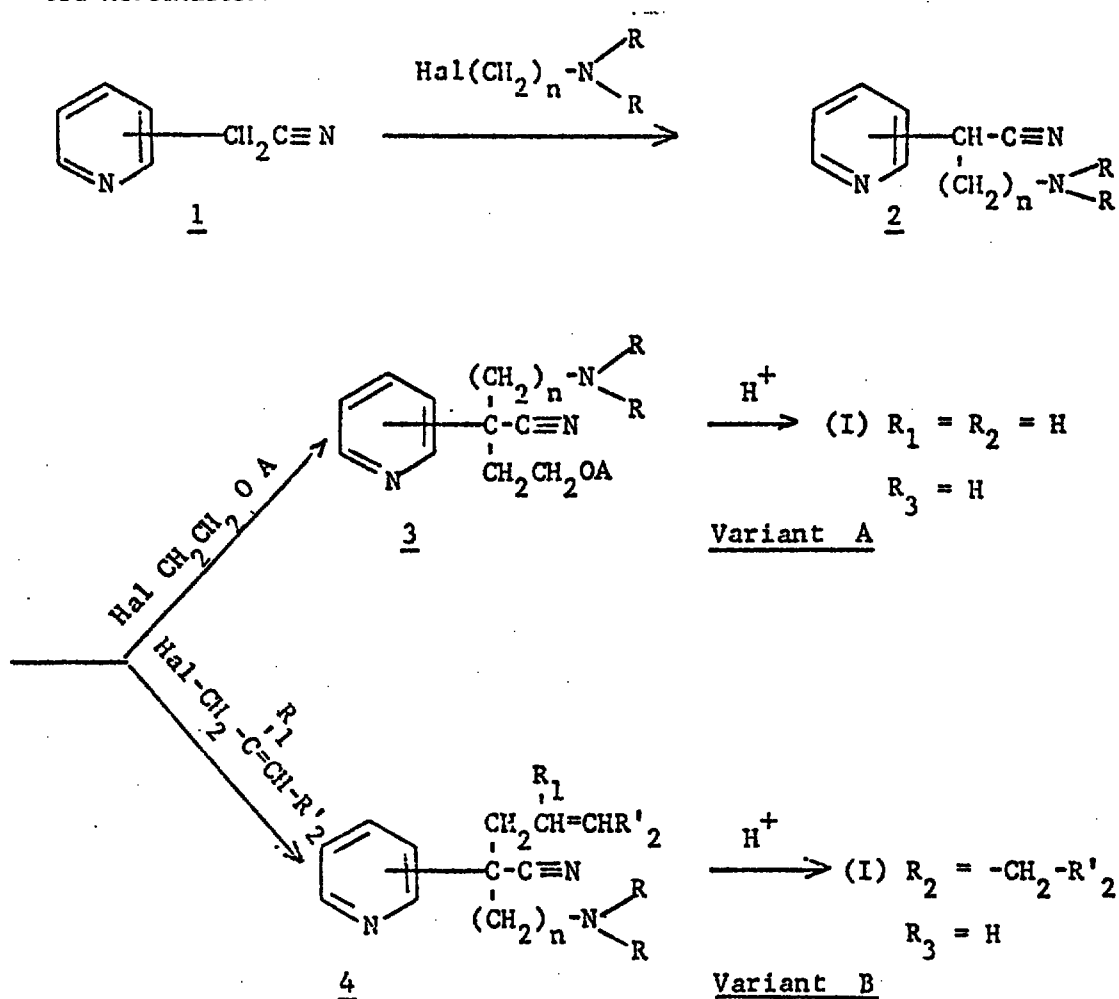
together represent a $(CH_2)_m$ group where $m = 4$ or 5 ; in these two cases R_3 being equal to H or R_1 represent H and R_2 and R_3 considered together represent $(CH_2)_p$ where p is 3 or 4 .
5 the butyrolactone cycle substitutes the pyridyl group in $2'$, $3'$, $4'$ position.

Compounds (I) furnish with the inorganic or organic acids soluble salts. These salts, with pharmaceutically acceptable acids, form an integral part of the invention.



Compounds (I) always have an asymmetrical carbon atom, namely atom 3 of the γ -butyrolactone cycle. If substituents R_1 and R_2 are different, the carbon atom 5 which carries them is also an asymmetrical carbon atom. Consequently, compounds (I) may exist in the form of diastereoisomers and optical isomers. These isomers as well as the mixtures thereof form part of the invention.

The compounds of the invention where R_3 is H are obtained from a pyridylacetonitrile in accordance with the reaction diagram indicated hereinafter:



The pyridylacetonitrile 1 is firstly subjected to a reaction of alkylation by a compound $\text{Hal}-(\text{CH}_2)_n-\text{N} \begin{smallmatrix} \text{R} \\ \text{R} \end{smallmatrix}$ (Hal representing a halogen), in the presence of an organic or inorganic base to lead to compound 2. From the latter, two variants are possible:

5 Variant A:

Compound 2 is again substituted by a compound $\text{Hal}-\text{CH}_2\text{CH}_2\text{OA}$ in which Hal represents a halogen and A represents a group protecting the hydroxyl function which is easy to eliminate in acid medium and in particular a tetrahydropyranyl group.

10 Operation is carried out in an inert solvent such as a benzene hydrocarbon in the presence of sodium hydride, at a temperature of between 80 and 120°C.

Compound 3 thus obtained is treated by a concentrated inorganic acid such as 85% phosphoric acid to lead to compound (I) where

15 $\text{R}_1 = \text{R}_2 = \text{H}$.

Variant B:

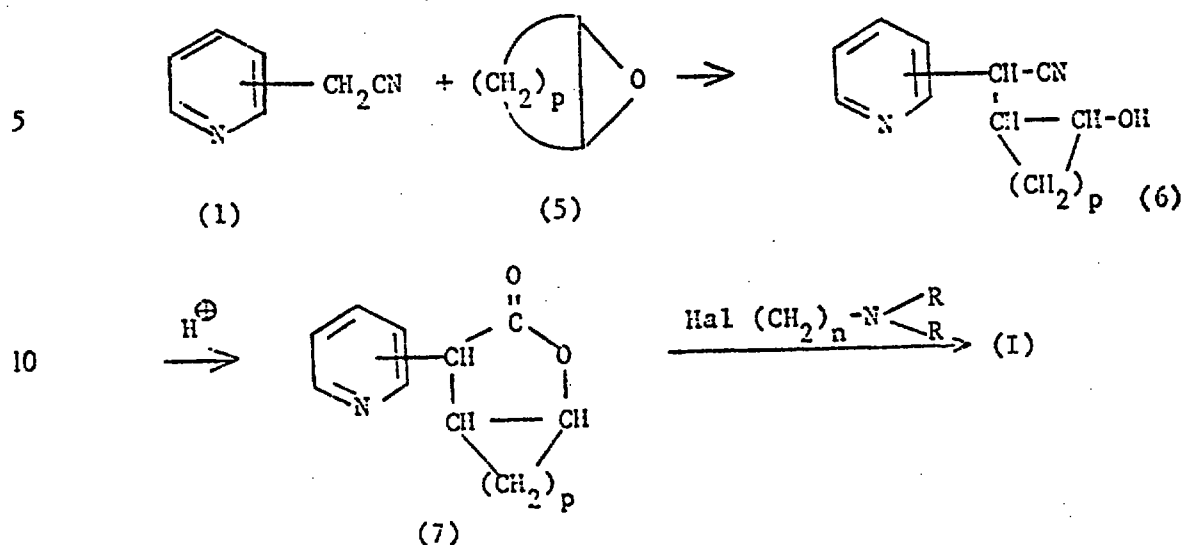
Compound 2 is again substituted by an unsaturated derivative

20 $\text{Hal}-\text{CH}_2-\overset{\text{R}_1}{\underset{|}{\text{C}}}=\text{CH}-\text{R}'_2$, in which Hal represents a halogen and R'_2 represents hydrogen or an alkyl group with 1 to 3 carbon atoms, or $\text{R}_1 + \text{R}_2$ represents a group $(\text{CH}_2)_{m'}$, with $m' = 3$ or 4.

Reaction takes place within a solvent such as dimethylformamide in the presence of sodium amide at a temperature of between 20 and 80°C.

25 Compound 4 thus obtained is treated by a concentrated inorganic acid and in particular by concentrated sulfuric acid to lead to compound (I) in which substituent R_2 represents $\text{CH}_2\text{R}'_2$.

When R_1 represents H and R_2 and R_3 represent, together, a $(\text{CH}_2)_p$ group, compounds (I) may be obtained in accordance with the following
30 reaction diagram:



The opening of epoxide 5 by the anion of the pyridylacetonitrile (I) leads to hydroxynitrile (6).

To obtain the pyridylacetonitrile anion, lithium diisopropylamide is used (prepared in situ by the action of diisopropylamine on butyllithium) within an inert solvent such as tetrahydrofuran and operating at low temperature (-6° to -80°C). Hydroxynitrile 6 leads to the ketone 7 by hydrolysis in acid medium and to this end a concentrated inorganic acid such as 85% phosphoric acid is preferably used. Finally, compound (I) is obtained by substitution of compound 7 with a derivative of formula $\text{Hal}(\text{CH}_2)_n-\text{N}(\text{R})_2$ (in which Hal is a halogen) in the presence of a sodation agent such as sodium hydride within a solvent such as tetrahydrofuran.

The salts of compounds (I) are obtained by the conventional methods of salification.

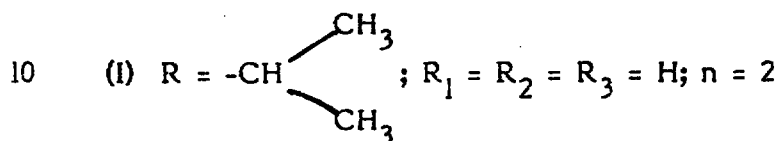
When R_1 and R_2 are different, products (I) exist in the form of diastereoisomers. The process according to the invention leads to a mixture of diastereoisomers. This mixture may be used as such

or separated into its constituents by the conventional methods and, in particular, by chromatography.

The following examples, which are in no way limiting, are given by way of illustration for the preparation of the compounds according to the invention.

Example 1

3-(2-diisopropylamino ethyl) 3-(2-pyridyl) γ -butyrolactone, phosphate (SR 41340)



a) 4-diisopropylamino 2-(2-pyridyl) butyronitrile

8 g of 2-pyridyl acetonitrile, 8.8 g of 1-chloro 2-diisopropylamino ethane and 0.27 g of benzyltrimethylammonium chloride are mixed, then, maintaining the temperature below 35°C, 35 ml of 50% sodium hydroxide solution are added. The mixture is heated to 35°C for 5 hours. After cooling, it is diluted with water and extracted with ether. The organic phase is separated and dried over sodium sulfate, then the solvent is evaporated to dryness.

20 By distilling the residue, a yellow oil (9.36 g) is obtained; b.p. / 8Pa 0.06 mm Hg : 132-134°C.

b) 2-(2-diisopropylamino ethyl) 2-(2-pyridyl) 4-(2-tetrahydropyranyloxy) butyronitrile

25 The mixture of 9.3 g of the nitrile obtained above, 7.5 g of 1-chloro 2-(2-tetrahydropyranyloxy) ethane and 1.75 g of sodium hydride in 200 ml of toluene is taken to reflux for 18 hours. After cooling, water is added, then the organic phase is decanted. The substance is dried over sodium sulfate and the solvent is evaporated to dryness.

30 An oil is obtained (14 g) used as such for the following operation.

c) SR 41340

The product obtained in paragraph b) is dissolved in 70 ml of 85% phosphoric acid and the mixture is heated to 90-100°C for 1 hour. The mixture is poured over ice and extracted with ether. The organic phase is separated and the aqueous phase is rendered alkaline

with a solution of potassium carbonate. It is extracted again with ether and the organic extracts are collected. The substance is dried over sodium sulfate, then the solvent is evaporated to dryness and the residue is distilled under reduced pressure.

5 An oil is obtained (7.5 g); b.p./ 13.33Pa 0.1 mm Hg: 149-152°C.

Phosphate

5.5 g of the above product are dissolved in 50 ml of ethanol and 2.18 g of an 85% phosphoric acid solution are added. Evaporation takes place, the residue is taken up in ether and left to crystallize.

10 The solid is drained and washed with ether.

Weight: 5.95 g; m.p.: 107-109°C.

EXAMPLE 2

5-cyclohexanespiro 3-(2-diisopropylamino ethyl) 3-(2-pyridyl) γ -butyrolactone (SR 41412)

15 (I) $R = -CH \begin{array}{l} \nearrow CH_3 \\ \searrow CH_3 \end{array}$; $n = 2$; $R_1 + R_2 = (CH_2)_5$; $R_3 = H$

a) 2-(1-cyclohexenyl methyl) 4-diisopropylamino 2-(2-pyridyl) butyronitrile

In a three-necked bottle, 1.45 g of sodium hydride and 20 ml of dimethylformamide are introduced in an atmosphere of nitrogen. The solution of 12.25 g of 4-diisopropylamino 2-(2-pyridyl) butyronitrile (Example 1 a)) in 20 ml of dimethylformamide is added drop by drop, then, after the end of introduction, the mixture is stirred for 1 hour at ambient temperature.

25 9.6 g of 1-bromomethyl cyclohexene dissolved in 20 ml of dimethylformamide are then added and the mixture is stirred again for 2 hours at ambient temperature. The solvent is evaporated in vacuo and the residue is taken up in water and ether. The organic layer is separated and the aqueous phase is re-extracted with ether. The ethereal
30 extracts are collected, dried over sodium sulfate and the solvent is evaporated to dryness.

18 g of crude product are obtained, used as such for the following step.

b) SR 41412

35 The compound obtained hereinabove is dissolved in 150

ml of 85% phosphoric acid and the mixture is heated to 130°C for 3 hours.

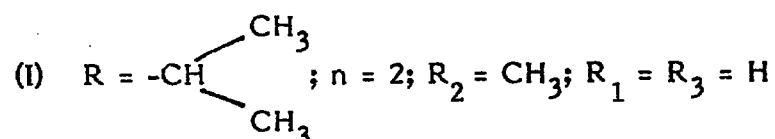
The reaction mixture is poured over ice and ether is added, then the aqueous phase is rendered alkaline by a 40% sodium hydroxide solution with cooling so that the temperature remains less than 20°C.

The ethereal layer is separated and re-extracted with ether. The ethereal extracts are dried over sodium sulfate and the solvent is evaporated to dryness.

The residue (8.7 g) is chromatographed over a column of alumina. By eluting with the pentane-ethyl acetate (97-3) vol/vol mixture, 3.1 g of the expected product are obtained, which crystallize. m.p.: 42-44°C.

EXAMPLE 3

3-(2-diisopropylamino ethyl) 5-methyl 3-(2-pyridyl) γ -butyrolactone, phosphate (SR 41653)



Mixture of the diastereoisomers.

Operation is carried out as in Example 2 from the same starting product but by replacing in step a) 1-bromomethyl cyclohexene by an equivalent quantity of allyl bromide. Cyclization is effected as in Example 2 b) by heating to 150°C for 6 hours. The crude product thus obtained is distilled under reduced pressure.

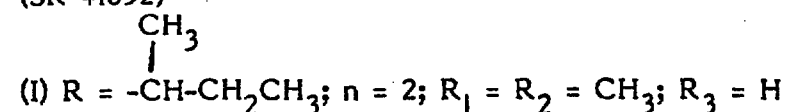
b.p./20 Pa 0.15 mm Hg : 120-124°C.

The phosphate is prepared as in Example 1 c). m.p. :

157-159°C.

EXAMPLE 4

5,5-dimethyl 3-(2-di-sec-butylamino ethyl) 3-(2-pyridyl) γ -butyrolactone (SR 41652)



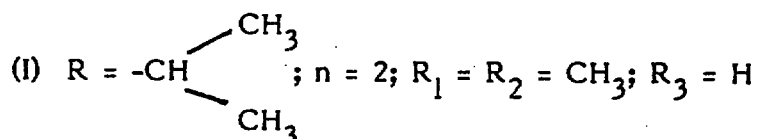
The starting product is prepared as in Example 1 a), replacing 1-chloro 2-diisopropylamino ethane by an equivalent quantity of 1-chloro 2-di-sec-butylamino ethane. b.p./13.33 Pa 0.1 mm Hg : 120-125°C.

From this product, operation is carried out as in Example 2 a), replacing the 1-bromomethyl cyclohexene by an equivalent quantity of 3-chloro 2-methyl propene.

The crude product thus obtained is cyclized as in Example 2 b). After chromatography over a column of alumina, eluting with the pentane-ethyl acetate (95-5) vol/vol mixture, the expected product is obtained. m.p. : 67-68°C.

EXAMPLE 5

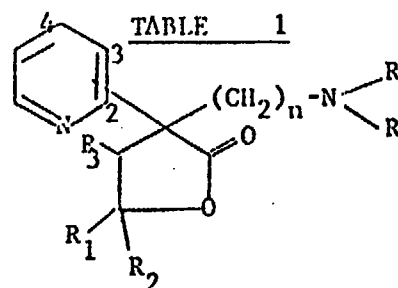
3-(2-diisopropylamino ethyl) 5,5-dimethyl 3-(2-pyridyl) γ -butyrolactone, SR 41098



From the starting product of Example 1 a), operation is carried out as in Example 4 with 3-chloro 2-methyl propene. The crude product thus obtained is cyclized by heating to 50°C for 30 mins. with concentrated sulfuric acid (d : 1.83). Treatment is as described in Example 2 b) and, after chromatography over alumina, eluting with the pentane-ethyl acetate (90-10) vol/vol mixture, the expected product is obtained. m.p. : 58-59°C.

EXAMPLES 6 to 21

By operating as in Example 1 a), but by varying the halogen derivative used, various substituted nitriles 2 are obtained. By action thereon of a suitably selected unsaturated derivative and by operating as in Examples 2, 4 and 5, corresponding compounds 4 are obtained which are directly cyclized into compound (I) either by phosphoric acid according to Example 4 or by sulfuric acid according to Example 5. Products (I) thus prepared are collected in Table I hereinafter.



Ex ^a m- ple n°	n° code product	Position substitution pyridine	n		R ₁	R ₂	R ₃	Cyclization	Base or salt m.p., °C (solvent)
6	SR 41696	2	2		-CH ₃	-CH ₃	H	SO ₄ H ₂	Basemp.: 58-59
7	SR 41816	2	3	-N[CH-(CH ₃) ₂] ₂	-CH ₃	-CH ₃	H	SO ₄ H ₂	Dihydrochloride 11/2 O m.p.: 158-160 (isopropanol)
8	SR 41913	2	2		-CH ₃	-CH ₃	H	SO ₄ H ₂	Dihydrochloride m.p.: 201-202 (acetone)
9	SR 41914	2	2		-CH ₃	-CH ₃	H	PO ₄ H ₃	Dihydrochloride 0,5 H ₂ O m.p.: 140-142 (isopropanol)
10	SR 41941	2	2		-CH ₃	-CH ₃	H	SO ₄ H ₂	Oxalate m.p.: 103-105 (acetone)
11	SR 41942	2	2	-N[CH(CH ₃) ₂] ₂	-C ₂ H ₅	-C ₂ H ₅	H	PO ₄ H ₃	Oxalate m.p.: 128-130 (ether)

TABLE 1 (cont. 1)

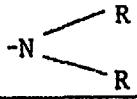
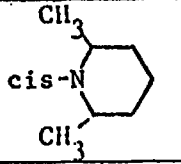
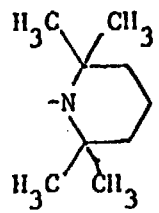
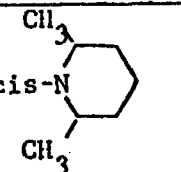
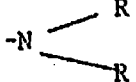
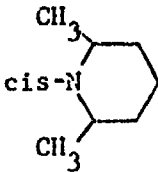
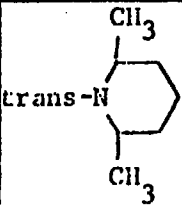
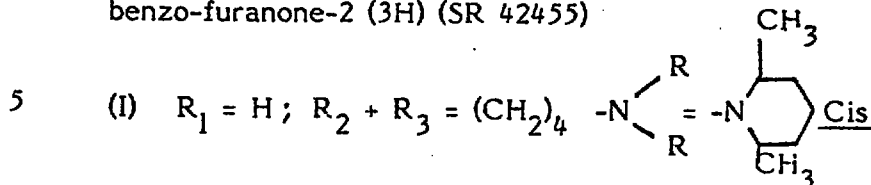
Example n°	n° code product	Position substitution pyridine	n		R ₁	R ₂	R ₃	Cycli- zation	Base or salt m.p., °C (solvent)
12	SR 41943	2	2		-CH ₃	-CH ₃	H	PO ₄ H ₃	Oxalate m.p.: 188-189 (ethanol)
13	SR 41944	2	2		-CH ₃	-CH ₃	H	PO ₄ H ₃	Base m.p.: 55-57 (hexane)
14	SR 42167	2	2		(CH ₂) ₅		H	PO ₄ H ₃	hydrochloride 0,75 H ₂ O m.p.: 135-137 (butanone-2)
15	SR 42180	2	2		-CH ₃	-CH ₃	H	PO ₄ H ₃	Base m.p.: 87-88 (ethanol-water)
16	SR 42205	2	2	-N[CH(CH ₃) ₂] ₂	-C ₃ H ₇	-C ₃ H ₇	H	PO ₄ H ₃	Oxalate m.p.: 121-123 (acetone)
17	SR 42206	3	2		-CH ₃	-CH ₃	H	PO ₄ H ₃	Base (liquid)
18	SR 42298	2	2	"	-C ₂ H ₅	-C ₂ H ₅	H	PO ₄ H ₃	Oxalate, 0,75 H ₂ O m.p.: 80-82 (ethyl acetate)

TABLEAU 1 (cont. 2)

Exa- m- ple n°	n° code product	Position substitution pyridine	n		R ₁	R ₂	R ₃	Cycli- zation	Base or salt m.p. °C (solvent)
19	SR 42408	2	2		-C ₃ H ₇	-C ₃ H ₇	H	PO ₄ H ₃	Dihydrochloride m.p.: 189-190 (isopropanol)
20	SR 42435	2	3	"	-CH ₃	-CH ₃	H	PO ₄ H ₃	Phosphate m.p.: 165-167 (isopropanol)
21	SR 42483	2	2		-CH ₃	-CH ₃	H	SO ₄ H ₂	Base (liquid.)

EXAMPLE 22

3-[2-(2,6-cis-dimethyl piperidino) ethyl] 3-(2-pyridyl) hexahydro trans-benzo-furanone-2 (3H) (SR 42455)



a) α -(trans-hydroxy-2 cyclohexyl) 2-pyridyl acetonitrile.

To the mixture of 45.45 g of diisopropylamine and 200 ml of anhydrous tetrahydrofuran cooled to -20°C are added, in an atmosphere of nitrogen and with stirring, 300 ml of a 1.6 M solution of butyllithium in hexane. The mixture is then cooled to -70°C , then the solution of 53.1 g of 2-pyridyl acetonitrile in 200 ml of anhydrous tetrahydrofuran is added. The mixture is stirred for 15 minutes at a temperature less than or equal to -70°C , then the solution of 48.5 g of epoxycyclohexane in 200 ml of anhydrous tetrahydrofuran is added at the same temperature. The temperature is allowed to rise up to ambient temperature (about 20°C) and the mixture is stirred for 15 hours at this temperature.

The mixture is cooled by an ice bath and 300 ml of water are added. The organic phase is decanted then the aqueous phase is re-extracted twice with ether.

The organic phases are collected, washed twice with a saturated solution of sodium chloride then the solution is dried over sodium sulfate. The solvents are evaporated to dryness and the residue is crystallized in isopropanol.

74.6 g of the expected product are obtained. m.p.: $110-112^{\circ}\text{C}$.

b) 3-(2-Pyridyl) hexahydro-trans-benzofuranone-2 (3 H)

The mixture of 32.4 g of the product obtained above and 160 ml of 85% phosphoric acid is heated to 90°C for 30 minutes. The reaction mixture is poured over ice then rendered alkaline by adding a 30% sodium hydroxide solution, maintaining the temperature below 25°C .

The mixture is extracted with ethyl acetate and the solution is dried over sodium sulfate. The solvent is evaporated to dryness and the solid residue is taken up in isopropyl ether. The solid is drained and the expected product is obtained (31 g). m.p.: $124-125^{\circ}\text{C}$.

c) SR 42455

100 ml of anhydrous tetrahydrofuran and 2.5 g of a 55% suspension in the oil of sodium hydride are introduced in a flask in an atmosphere of nitrogen. The mixture is heated to reflux then the solution in 250 ml of anhydrous tetrahydrofuran of 10.85 g of the product obtained above and 917 g of 1-(2-chloro ethyl) 2,6-cis-dimethyl piperidine is added drop by drop. After the end of the addition, reflux is maintained for 1 hour then the tetrahydrofuran is evaporated. The residue is taken up in water and extracted with ether. The solution is dried over sodium sulfate then the solvent is evaporated and the oily residue is chromatographed over a column of alumina.

By eluting with a pentane-ethyl acetate (95-5) vol/vol mixture, an oil is obtained (6.7 g).

Pentane is added and the mixture is left to crystallize slowly at 0°C. The solid is drained and washed with a little pentane cooled to 0°C. Crystals are finally obtained (3.5 g). m.p.: 81-82°C.

The products of the invention have been studied in pharmacology, particularly with a view to demonstrating their anti-arrhythmic properties.

Protocol

The anti-arrhythmic power of these molecules was assessed on an animal model of ventricular arrhythmia.

Mongrel dogs are anaesthetized then subjected to the positioning, by retrograde catheterism, of a metal turn in the coronary bed.

At the same time, a frequency modulator micro-emitter is fixed to the animal's back and connected to two precordial electrodes.

The animal, returned to its cage, then shows a progressive thrombosis of the anterior interventricular artery. A localized, transmural myocardial infarction is thus constituted, generating an abnormal but repetitive electrical activity: ventricular tachycardia.

In this state, 24 hours after the turn has been positioned, the drugs are administered per os and the telemetered system enables the development of the arrhythmia of the alert dog to be followed in real time.

The systolic, sinus and pathological complexes are perma-

nently metered by electronic processes. The quality and duration of action of the product may thus be quantified. The animal's behaviour is observed.

Results

A product is considered active if it eliminates at least 60% of the abnormal complexes or if it induces a sinusal rhythm.

The results obtained with various products of the invention are shown in Table 2.

TABLE 2

	Product SR Code No.	Dose mg/kg per os	Number of animals	Duration of action
10	41098	50	2	3 hours
	41412	50	1	1 hour
	41652	50	1	1 hour 50.
15	41653	50	1	1 hour 25.
	41696	20	1	longer than 24 hrs.
		5	1	3 hrs. 30.
		3	1	2 hours
	41816	50	2	longer than 24 hrs.
20	41913	50	1	longer than 24 hrs.
	41942	50	1	longer than 24 hrs.
	42180	50	1	8 hours

These results show that the products according to the invention have a considerable activity on the arrhythmia.

Furthermore, the compounds according to the invention are relatively non-toxic and, in particular, present no sign of toxicity at doses where they manifest their anti-arrhythmic activity.

Consequently, products (I) may be used in human therapeutics as protector of the myocardium for correcting disorders of the ventricular rhythm of ischemic origin.

The products may be presented in the galenic forms for administration by the oral route (tablets, capsules, ...) and for administra-

tion by the parenteral route (injectable ampoules).

The dose necessary for restoring the sinusal rhythm in man is included between about 5 and 150 mg by the intravenous route and between about 40 and 800 mg by the oral route, per day.

5 The following galenic preparation is indicated by way of example:

Compounds

SR 41696	0.200 g
Microcrystalline cellulose	0.140 g
Lactose	0.140 g
Magnesium stearate	0.020 g
	0.500 g

10