DESCRIPTION

The present invention relates to new substituted 1H-imidazoles, and their pharmaceutically acceptable non-toxic acid addition salts, as well as to processes for their preparation and to their therapeutic use.

It also concerns pharmaceutical compositions containing the said compounds.

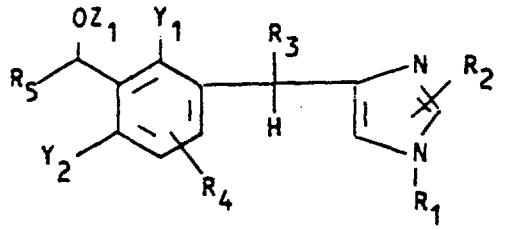
According to European Patent No. 24,829, 4-benzyl-1H-imidazoles are known, in which the benzyl group contains in the phenyl nucleus various substituents selected from hydrogen and chloro, bromo, fluoro, methyl, ethyl, methoxy, amino, hydroxyl and nitro groups. These compounds have antihypertensive, anti-ulcer, diuretic, sedative, analgesic, anti-inflammatory and tranquillizing properties. European Patent No. 58,047 describes similar 4-(phenylalkyl)-1H-imidazoles but in which the alkyl radical of the phenylalkyl group contains 1-6 carbon atoms; in most of the compounds, the imidazole ring is additionally substituted by an alkyl radical containing 1 to 7 carbon atoms, a phenyl group or a substituted or unsubstituted benzyl radical. These compounds possess antithrombotic, antihypertensive, antimicrobial and antifungal activities. European Patent No. 72,615 also describes similar 4-benzyl-1H-imidazoles but in which the benzyl group is substituted in the alpha position by an alkyl radical. The benzyl group contains in the phenyl ring various substituents selected from hydrogen, a halogen, methyl, ethyl, hydroxy and methoxy radicals and the methylenedioxy radical between two adjacent carbon atoms. The pharmacological trials described in this latter patent demonstrate that the compounds have antihypertensive, antithrombotic and diuretic properties. J.M. SAVOLA in Naunyn-Schmiedeberg's Arch. Pharmacol. 334,(1986),423-9 [Chem. Abstr.106,(1987),95591n], studied, in the rat, the hypotensive and bradycardic activities of some 4-(phenylalkyl)-H-imidazoles in which the phenyl nucleus was substituted in the 2-, 2,3- or 2,6- positions by methyl radicals. It was shown in this study that, among other things, the introduction of a hydroxyl radical in the alpha position

on the alkyl bridge situated between the imidazole and phenyl nuclei, always brought about a reduction in hypotensive and bradycardic activities.

There was no mention however of anti-ischaemic properties in the aforementioned documents.

The present invention provides new substituted 1H-imidazoles having excellent cardiac, cerebral and tissular anti-ischaemic properties. These compounds can therefore be used, among other things, for the prevention and treatment of disorders induced by ischaemias in general. Among these disorders, angina pectoris is the clinical expression of an acute myocardial ischaemia which is the result of a momentary imbalance between the myocardial oxygen demand and the oxygen supply by the coronary circulation, an imbalance which can lead, in severe cases, to myocardial infarction. It is for this reason that compounds according to the invention are particularly well suited to to the treatment of angina pectoris and myocardial infarction. In addition, it has been found that certain of these compounds possess a not insignificant hypotensive activity.

The new compounds of the present invention are substituted 1H-imidazoles corresponding to the general formula




(I)

in which

$R_1$, $R_2$, $R_3$ and $R_5$, which may be identical or different, each represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms,

$R_4$ represents a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms or an alkoxy radical containing 1 to 4 carbon atoms,

one of the radicals $Y_1$ and $Y_2$ represents hydrogen and the other an $OZ_2$ radical, and

$Z_1$ and $Z_2$ taken separately both represent hydrogen or an alkyl radical containing 1 to 4 carbon atoms and taken together represent a $-CH_2$ or $-C(CH_3)_2-$ group,

as well as their pharmaceutically acceptable non-toxic acid addition salts.

When the molecule contains a single asymmetrical carbon atom, compounds of formula I may be either in a racemic form or in the form of one or other enantiomer. When the molecule contains two asymmetrical carbon atoms, these compounds are generally in the form of a mixture of diastereoisomers. These various forms also fall within the scope of the present invention.

When in formula I, the symbols $Z_1$ and $Z_2$ each represent a hydrogen atom, a specific representative of the compounds of the invention is for example 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol, whilst when in formula I, the symbols $Z_1$ and $Z_2$ each represent an alkyl radical having 1 to 4 carbon atoms, a specific compound according to the invention is for example 4-[(2,6-dimethoxy-3-methoxymethylphenyl)methyl]-1H-imidazole. In the case where the symbols $Z_1$ and $Z_2$ together represent a $-CH_2$ or $-C(CH_3)_2-$ group, there may be mentioned as specific examples of compounds according to the invention

4-[(4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole ($Y_1 = OZ_2$, $Y_2 = H$),

4-[(4H-1,3-benzodioxin-6-yl)methyl]-1H-imidazole ($Y_1 = H$, $Y_2 = OZ_2$) and

4-[1-(2,2 dimethyl-4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole ($Y_1 = OZ_2$; $Y_2 = H$).

Preferred compounds of the present invention are the 1H-imidazoles of general formula I wherein

$R_1$, $R_2$, $R_4$ and $R_5$ represent a hydrogen atom,

$R_3$ represents hydrogen or an alkyl radical having 1 to 4 carbon atoms and

$Z_1$ and $Z_2$ taken separately represent hydrogen and together represent a $-CH_2-$ or $-C(CH_3)_2-$ group,

as well as their pharmaceutically acceptable non-toxic acid addition salts.

Compounds particularly preferred according to the invention are :

3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol;

3-[(1H-imidazol-4-yl)methyl]-6-hydroxybenzenemethanol;

3-[1-(1H-imidazol-4-yl)ethyl]-2-hydroxybenzenemethanol;

3-[1-(1H-imidazol-4-yl)pentyl]-2-hydroxybenzenemethanol;

4-[(4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole and its hydrochloride;

4-[1-(4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole:

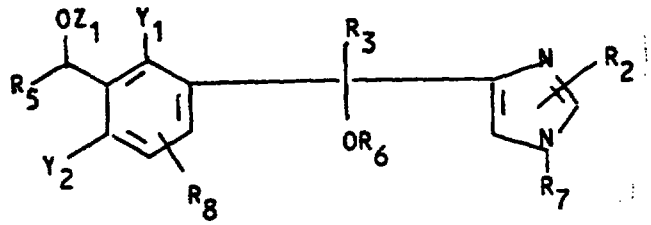
4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole;

4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole;

4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)pentyl]-1H-imidazole.

The present invention also concerns the pharmaceutically acceptable non-toxic acid addition salts of the 1H-imidazoles of formula I. Examples of pharmaceutically acceptable acids that may be mentioned are inorganic acids such as hydrochloric, hydrobromic, sulphuric, nitric and phosphoric acids etc, and organic acids, such as acetic, citric, tartaric, benzoic, salicylic and maleic acids etc.

The substituted 1H-imidazoles of formula I, in which $Z_1$ and $Z_2$ taken separately represent an alkyl radical having 1 to 4 carbon atoms and together represent a $-CH_2-$ or a $-C(CH_3)_2-$ group, are prepared by reducing, according to conventional methods, an imidazole compound of formula :



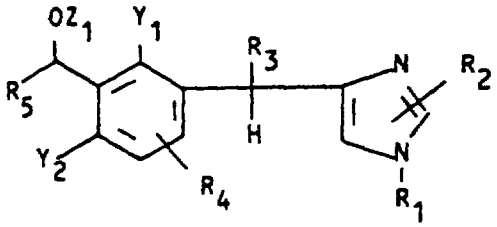

(II)

in which $R_2$, $R_3$, and $R_5$ have the meanings given above. $R_6$ represents a hydrogen atom or an alkyl radical having 1 to 4

carbon atoms, $R_7$ represents a radical $R_1$ such as defined above or a radical which may be easily removed by reduction, such as a benzyl or triphenylmethyl radical, $R_8$ represents a radical $R_4$ such as defined above or a chlorine atom, one of the radicals $Y_1$ and $Y_2$ represents hydrogen and the other an $OZ_2$ radical, $Z_1$ and $Z_2$ having the meaning given above.

This reduction is generally carried out in either glacial acetic acid or methanol, in the presence of a catalyst, such as for example palladium on carbon, at a temperature of 20 to 80°C, preferably at about 80°C, and under an atmosphere of hydrogen at a pressure of between 2 and 5 bar, or in liquid ammonia, in the presence of an alkali metal such as lithium or preferably sodium, and an auxiliary solvent such as toluene or an ether such as for example tetrahydrofuran. In the case where a chlorine atom is present on the phenyl nucleus of the starting compounds of formula II ($R_8$ = Cl), this chlorine atom is eliminated in the course of the reduction.

Substituted 1H-imidazoles of formula I, in which $Z_1$ and $Z_2$ are hydrogen, may be prepared by hydrolysis in an aqueous acid medium of a 4-[[2,2-dimethyl-4H-1,3-benzodioxin-6(or8)-yl]methyl]-1H-imidazole of formula :



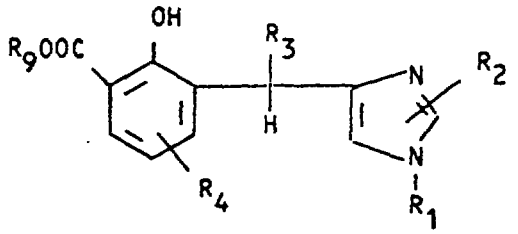

(III)

in which $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ have the meanings given above, one of the radicals $Y_1$ and $Y_2$ represents a hydrogen and the other an $OZ_2$ radical, $Z_1$ and $Z_2$ together being the $-C(CH_3)_2-$group.

This hydrolysis is carried out by means of a mineral acid such as aqueous hydrochloric acid (pH 2 to 3), at a temperature of between 20 and 100°C for about one to two hours.

The reaction medium is then made alkaline to pH 8 to 8.6 by means of an inorganic base such as sodium hydroxide and the reaction product is recovered by filtration. It is washed with water to remove inorganic salts and recrystallized from a suitable solvent.

According to a variant, substituted 1H-imidazoles of formula I, in which $Y_1 = OZ_2$ and $Y_2$, $Z_1$, $Z_2$ and $R_5$ are hydrogen, may also be prepared by reduction, according to conventional methods, of an alkyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoate of formula :




(IV)

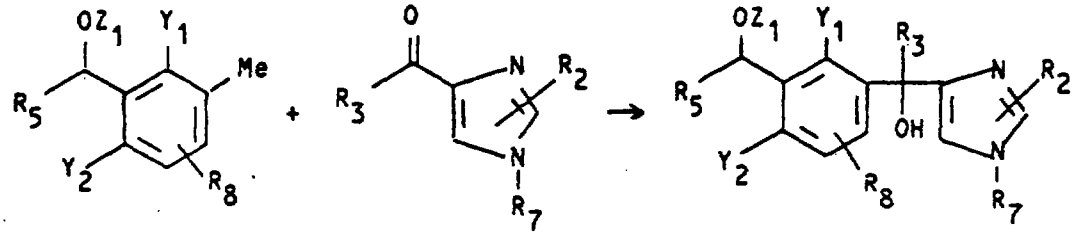
in which $R_1$, $R_2$, $R_3$ and $R_4$ have the meanings given above and $R_9$ represents an alkyl radical containing 1 to 4 carbon atoms, preferably methyl or ethyl.

This reduction may be carried out by means of various hydrides, preferably lithium-aluminium hydride, at reflux temperature in an inert organic solvent such as for example tetrahydrofuran. The latter has the advantage of giving a rapid, clean and complete reaction.

Pharmaceutically acceptable non-toxic acid addition salts may be prepared starting from 1H-imidazoles of formula I by known methods.

The starting compounds of formula II, in which $R_6$ = H and $R_7$ represents an alkyl radical containing 1 to 4 carbon atoms or a radical which may be easily removed by reduction, and which are also new compounds, may be prepared according to one or other of the following procedures :

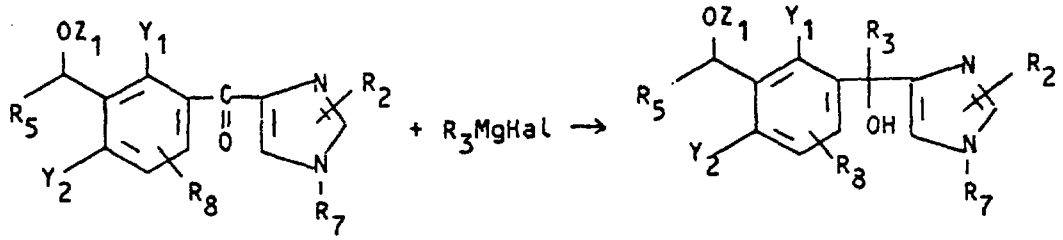
a) An organometallic derivative of formula V is reacted with a 4-($R_3$-CO)-1H-imidazole of formula VI, according to the equation



(V) (VI) (II) with $R_6$ = H and $R_7$ different from H

$R_2$, $R_3$, $R_5$, $R_7$, $R_8$, $Y_1$, $Y_2$, $Z_1$ and $Z_2$ in these formulae having the meanings given above, $R_7$ being other than hydrogen and Me representing MgBr or Li.

b) A ketone of formula VII is reacted with an organomagnesium compound of formula VIII according to the equation



(VII) (VIII) (II) with $R_6$ = H and $R_7$ different from H

$R_2$, $R_5$, $R_7$, $R_8$, $Y_1$, $Y_2$, $Z_1$ and $Z_2$ in these formulae having the meanings given above, $R_3$ being an alkyl radical having 1 to 4 carbon atoms, $R_7$ being other than hydrogen and Hal representing a halogen atom.

Procedures a) and b) above are preferably carried out in tetrahydrofuran under an inert atmosphere. In the case of compounds in which $Z_1$ and $Z_2$ together represent the $-CH_2-$ group, the temperature at which this exothermic reaction is carried out may reach 50°C. In the case of compounds in which $Z_1$ and $Z_2$ taken separately represent an alkyl radical with 1 to

4 carbon atoms and together the $-C(CH_3)_2-$ group, which are more sensitive to heat, the reaction temperature is generally maintained between 0 and 20°C and in any case must not exceed 40°C.

Compounds of formula II prepared according to procedures a) and b) above in which $R_8$ represents a chlorine atom, may possibly be converted by reduction, according to conventional methods, into the corresponding compounds of formula II in which $R_8$ represents hydrogen.

The organometallic derivatives of formula V are obtained in a known manner by reacting the corresponding bromine derivatives with magnesium or lithium. In the case of compounds in which $Z_1$ and $Z_2$ together represent the $-CH_2-$ group, the temperature of formation of the organometallic derivative of formula V may reach 50°C. In the case of compounds in which $Z_1$ and $Z_2$ taken separately represent an alkyl radical containing 1 to 4 carbon atoms and together the $-C(CH_3)_2-$ group, this temperature should be maintained below 40°C.

When the bromine derivatives are brominated 4H-1,3-benzodioxins ($Z_1$ and $Z_2$ = $-CH_2-$) they may be prepared by reacting paraformaldehyde with an appropriate bromophenol, whilst when these derivatives are brominated 2,2-dimethyl-4H-1,3-benzodioxins ($Z_1$ and $Z_2$ = $-C(CH_3)_2-$) they may be obtained by reacting 2,2-dimethoxypropane with brominated 2-hydroxybenzenemethanol, suitably substituted, itself prepared starting from an appropriate bromophenol and an aqueous solution of formaldehyde.

Bromine derivatives in which $Z_1$ and $Z_2$ represent an alkyl radical with 1 to 4 carbon atoms, may be prepared by alkylation of the corresponding bromophenols, according to known methods.

The 4-($R_3$-CO)-1H-imidazoles of formula VI may be obtained, in a general manner, by oxidizing the corresponding 1H-imidazole-4-methanols by means of activated $MnO_2$ according to the method described by J.L.KELLEY, C.A.MILLER and E.W.McLEAN (J.Med.Chem. 20, (1977), 721-723).

Ketones of formula VII are prepared by oxidation of a corresponding alcohol of formula II, in which $R_3$ and $R_6$ are hydrogen, for example by the action of manganese oxide in a chlorinated solvent, preferably chloroform, at the boiling point, the starting alcohol of formula II being itself prepared by process a) described above.

The organomagnesium compounds of formula VIII, are obtained in a known manner by the reaction of magnesium on the corresponding alkyl halide.

The starting compounds of formula II in which $R_6$ and $R_7$ are hydrogen, which are also new compounds, are prepared by reduction of a corresponding compound of formula II in which $R_6$ represents a hydrogen atom and $R_7$ a radical which can easily be removed by reduction (eg. benzyl or triphenylmethyl). This reduction may be carried out in liquid ammonia in the presence of sodium. However, it is not easy to follow the course of the reaction and thus it is preferable to carry out hydrogenolysis in the presence of palladium on carbon in an alcohol, at a temperature which may vary between 20°C and 80°C and under an atmosphere of hydrogen at a pressure of between 2 and 5 bar.

The starting compounds of formula II in which $R_6$ represents an alkyl radical with 1 to 4 carbon atoms and $R_7$ is hydrogen, are obtained by reduction in an alcohol of formula $R_6OH$ ($R_6$ equals an alkyl with 1 to 4 carbon atoms) of the corresponding compound of formula II in which $R_6$ represents a hydrogen atom and $R_7$ a radical which can be easily removed by reduction.

In most cases, this reduction does not lead solely to the desired alkoxylated compound of formula II ($R_6$ = alkyl, $R_7$ = H), but a mixture is obtained of this alkoxylated compound and the corresponding alcohol of formula II ($R_6 = R_7 =$ H). This mixture is generally used as it is to carry out the following stage of eliminating the $OR_6$ group by reduction. However, if so desired, the alcohol of formula II ($R_6 = R_7 =$ H) and the alkoxylated compound of formula II ($R_6$ = alkyl, $R_7$ = H)

may be isolated in a pure state, for example by chromatography of the mixture.

Furthermore, hydrochlorides of the alcohols of formula II ($R_6$ = $R_7$ = H) may be easily converted into the hydrochlorides of the alkoxylated compounds of formula II ($R_6$ = alkyl, $R_7$ = H) by simply heating in the corresponding alcohol of formula $R_6OH$.

When a chlorine atom is present on the phenyl nucleus of the starting compounds of formula II ($R_8$ = Cl), it is generally eliminated at the same time as the easily removable $R_7$ radical during the reduction processes which have just been described.

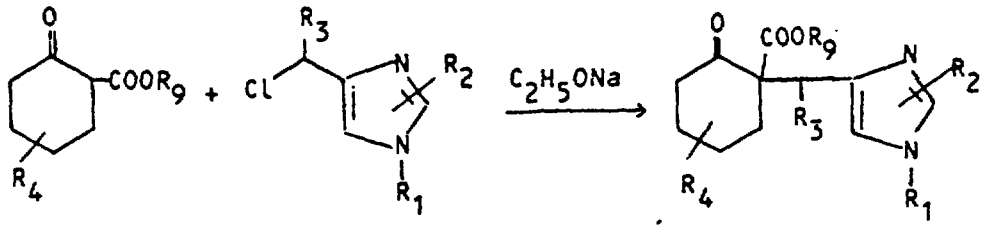
The 4-[[2,2-dimethyl-4H-1,3-benzodioxin-6(or 8)-yl]methyl]-1H-imidazoles of formula III are prepared by reduction, according to conventional methods, of a compound of formula II, in which $R_2$, $R_3$, $R_5$, $R_6$, $R_7$, $R_8$, $Y_1$ and $Y_2$ have the meanings given above and $Z_1$ and $Z_2$ represent together the $-C(CH_3)_2-$ group.

This reduction is generally carried out either in glacial acetic acid or in methanol, in the presence of a catalyst, such as for example palladium on carbon, at a temperature of 20 to 80°C, preferably at about 80°C, and under an atmosphere of hydrogen at a pressure of between 2 and 5 bar or in liquid ammonia, in the presence of an alkali metal such as lithium or preferably sodium, and an auxiliary solvent such as toluene or an ether as for example tetrahydrofuran. The chlorine atom which may possibly be present on the phenyl nucleus of the starting compounds of formula II ($R_8$ = Cl) is eliminated during this reduction.

The starting alkyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoates of formula IV may be prepared by a multi-stage process :

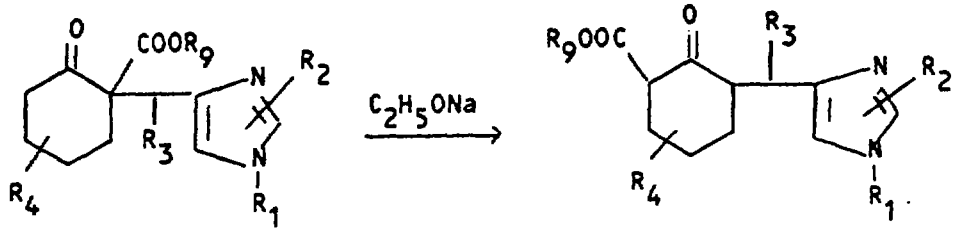
a) reaction in the presence of sodium ethoxide of an alkyl 2-oxo-cyclohexanecarboxylate of formula IX with a 4-chloromethyl-1H-imidazole of formula X, to obtain an alkyl 1-[(1H-imidazol-4-yl)methyl]-2-oxo-

cyclohexanecarboxylate of formula XI according to the equation



(IX) (X) (XI)

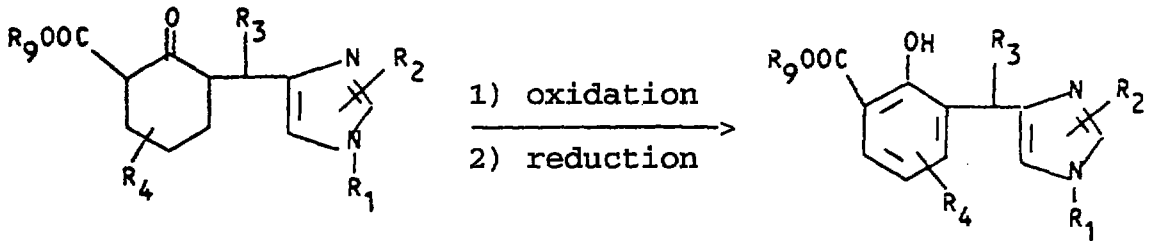
b) heating the alkyl 1-[(1H-imidazol-4-yl)methyl]-2-oxo-cyclohexanecarboxylate of formula XI for several hours at a temperature of approximately 100 to 105°C, in the presence of an excess of sodium ethoxide, which leads by molecular rearrangement, to the alkyl 3-[(1H-imidazol-4-yl)methyl]-2-oxo-cyclohexanecarboxylate of formula XII according to the equation



(XI) (XII)

c) oxidation of the alkyl 3-[(1H-imidazol-4-yl)methyl]-2-oxo-cyclohexanecarboxylate of formula XII by bromine in acetic acid at reflux temperature for several hours, to obtain a mixture of alkyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoate and its derivatives brominated in the 2 and/or 5 positions of imidazole, followed by

hydrogenolysis of the mixture obtained in the presence of palladium on carbon and rhodium on carbon, under a hydrogen pressure of 3.5 bar, which finally leads to the alkyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoate of formula IV, according to the equation




(XII) (IV)

with $R_1$, $R_2$, $R_3$ and $R_4$ in these formulae having the meanings given above and $R_9$ representing an alkyl radical with 1 to 4 carbon atoms, preferably methyl or ethyl.

4-chloromethyl-1H-imidazoles of formula X may be prepared starting from the corresponding 1H-imidazole-4-methanols by chlorination according to known methods.

As has been indicated above, the substituted 1H-imidazoles of formula I as well as their pharmaceutically acceptable non-toxic acid addition salts have excellent cardiac cerebral and tissular anti-ischaemic properties. The pharmacological trials described below provide evidence of these valuable properties.

The following products of the present invention were subjected to pharmacological trials :

- 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol (product A)
- 3-[(1H-imidazol-4-yl)methyl]-2-hydroxy-5-methyl-benzenemethanol (product B)
- 3-[(1H-imidazol-4-yl)methyl]-6-hydroxybenzenemethanol (product C)

- 4-[(6-methyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole hydrochloride (compound D)
- 4-[(4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole hydrochloride (compound E)
- 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole (product F)
- 4-[(2,2,6-trimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole (product G)
- 4-[1-(4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole (product H)
- 4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)pentyl]-1H-imidazole (product I)
- 3-[1-(1H-imidazol-4-yl)pentyl]-2-hydroxybenzenemethanol (product J)
- 4-[[2,6-dimethoxy-3-(1-methoxyethyl)phenyl]methyl]-1H-imidazole hydrochloride (product K)
- 4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole (product L)
- 3-[1-(1H-imidazol-4-yl)ethyl]-2-hydroxybenzenemethanol (product M)
- d-4-[1-(4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole (product N)

1. <u>Cardiac ischaemic activity</u>

1.1. In the rat

In an anaesthetized and thoracotomized rat, a coronary ligature induced a stable cardiac ischaemia (see H.SELYE et al. Angiology,11,(1960),398-407) which resulted in an elevation of the R wave of the epicardial electrocardiogram (see L.G.T.RIBEIRO et al., J.Electrocardiol.12,(1979), 89-95). The anti-ischaemic activity of a product was revealed by a reduction in the elevation of the R wave.

Table I shows, for the products subjected to the trial, the dose ($DE_{20}$ in mg/kg) which, administered intravenously to a group of 5 rats, produced a mean reduction in the elevation of the R wave of at least 20%

for the group of animals. The following compounds were used as reference substances :

- Propranolol : 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol
- Verapamil : alpha-[3-[[2-(3,4-dimethoxyphenyl)ethyl] methylamino]propyl]-3,4-dimethoxy-alpha-(1-methylethyl)benzeneacetonitrile;
- Nifedipine : dimethyl ester of 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid.

Table I.

| Products | $DE_{20}$ (in mg/kg) |
|---|---|
| A | 0.006 |
| B | 0.22 |
| C | 0.20 |
| D | 0.09 |
| E | 0.25 |
| F | 0.24 |
| G | 0.26 |
| J | 0.26 |
| L | 0.03 |
| M | 0.02 |
| N | < 0.23 |
| Propranolol | 9.47 |
| Verapamil | 0.32 |
| Nifedipine | 1.70 |

1.2 In the dog

In an awake dog bearing a coronary pneumatic obstructor (occluder), coronary occlusion produced an elevation of the ST-segment of the epicardial electrocardiogram. The anti-ischaemic action of a compound resulted in a reduction of the magnitude of the ST-segment elevation. (P.R. MAROKO and E.BRAUNWALD, Circ. 53, (1976, Suppl.I)162-168; S.E. EPSTEIN et al., Circ.53, (1976, Suppl.I),191-197). Table II shows, for the products submitted to the test, the dose ($DE_{20}$ in mg/kg) which, when administered intravenously to groups of ten animals, produced a mean reduction of at least 20% of the ST-segment elevation on the whole group of animals.

Table II.

| Products | $DE_{20}$ (in mg/kg) |
|---|---|
| A | 0.002 |
| B | 0.02 |
| C | 0.02 |
| D | 0.09 |
| E | 0.01 |
| F | 0.24 |
| G | 0.26 |
| H | 0.007 |
| I | 0.1 |
| J | 0.03 |
| K | 0.31 |
| L | 0.008 |
| M | 0.0007 |
| Propranolol | 0.53 |

In these tables, it can be seen that the products of the invention are very active and superior to the reference substances.

2. Cerebral anti-ischaemic activity

Ligature of the two carotids in anaesthetized mice progressively produced the death of at least half of the animals after 90 minutes.

In this test, a 0.2 mg/kg dose of compound A dissolved in 10 ml of a normal saline solution was administered by the intraperitoneal route to a group of 18 animals, 30 minutes before making the ligatures. At the same time, a control group also consisting of 18 animals, only received the normal saline solution (0.9% aqueous solution of sodium chloride). The number of animals surviving in the control group and the treated group was then noted, 30 minutes and 90 minutes after the ligatures were applied. The results obtained are given in Table III.

TABLE III

| Product | Number of animals surviving | | Period |
|---|---|---|---|
| | Control group | Treated group | (min) |
| A | 12/18 | 17/18 | 30 |
| A | 9/18 | 15/18 | 90 |

This table shows that compound A significantly increased the number of animals surviving in the group treated with compound A compared with the number of animals surviving in the control group. The protection achieved and calculated according to the ABBOTT formula (see FINNEY, Statist.Meth.in Biol.Assay, 2nd Ed. 1964) was 66% after 90 minutes.

3. Tissular ischaemic activity

In animal pathology, the accumulation of $Ca^{++}$ ions in ischaemic tissues is an indication of the degree of suffering of the cells (see A.D.SHARMA et al., J.Clin.Invest,72,(1983),802-818). Long duration coronary occlusion (150 minutes) carried out on anaesthetized rats, brought about an accumulation of calcium ions (+250%) in tissues of the necrotized region.

In this test, the compound studied was administered intravenously over a period of one minute, ten minutes before coronary occlusion, to a group of at least 6 rats at a dose of 100 µg/kg dissolved in 0.8 ml of normal saline solution. This administration was immediately followed by a slow infusion of the test compound at a dose of 100 µg/kg per hour for two and a half hours. After having dissected the necrotized region, the tissular accumulation of $Ca^{++}$ was measured by atomic absorption spectrometry according to the procedure described by Hideto OHHARA et al., (J.Mol.Cell.Cardiol. 14,(1982),13-20). A control group consisting of at least 6 rats only received the normal saline solution.

The activity of compound A was compared with that of Verapamil administered under the same conditions but a dose of 320 μg/kg of Verapamil was used instead of 100μg/kg.

Table IV below shows the reduction in % of the mean $Ca^{++}$ ion concentration in ischaemic tissues of the treated group compared with the mean $Ca^{++}$ ion concentration in ischaemic tissues of the control group. The results show that, although administered at a dose 3 times lower than that of Verapamil, compound A was more than twice as active in combatting the infiltration of calcium into the tissues of the necrotized region.

TABLE IV

| Products | Reduction in concentration of tissular $Ca^{++}$ (in %) |
|---|---|
| Verapamil | 18 |
| A | 40 |

4. Toxicity

The toxicity of products of the invention was determined with NMRI male mice by means of Irwin's test (S.IRWIN,Psychopharmacologia,13,(1968),222-257).

Progressive doses of the product studied were administered intraperitoneally to groups of three mice until the lethal dose was obtained (causing the death of two animals out of three in 48 hours).

Table V below gives the observed lethal dose for the products of the invention. It follows from this table that the products of the invention are not very toxic, the lethal dose being well above the active doses.

TABLE V

| Product | Lethal dose (in mg/kg) |
|---|---|
| A | 204 |
| B | > 218 |
| C | 613 |
| D | 80 |
| E | 253 |
| F | 73 |
| G | 258 |
| H | 69 |
| I | 300 |
| J | 260 |
| K | 31.2 |
| L | 25.8 |

The pharmaceutical compositions containing the products of the invention may be administered orally, parenterally or rectally.

The pharmaceutical compositions which can be used for oral administration may be solid or liquid, for example in the form of tablets (coated or uncoated), pills, dragees, gelatine capsules, solutions, syrups, and the like. Similarly, the compositions which can be used for parenteral administration are the pharmaceutical compositions known for this mode of administration, for example solutions, suspensions, or aqueous or oily emulsions. For rectal administration, the compositions containing the compounds of the invention are generally used in the form of suppositories.

The pharmaceutical forms such as injectable solutions, injectable suspensions, tablets, drops, suppositories and the like are prepared by the methods currently used by pharmacists. The compounds of the invention are mixed with a solid or liquid, non-toxic, pharmaceutically acceptable carrier, and optionally with a dispersing agent, a disintegrating agent, a stabilizing agent etc. If desired,

sweetening and colouring agents and the like may also be added.

The percentage of active compound in the pharmaceutical compositions may vary within very wide limits, according to the patient and the mode of administration, and in particular according to the frequency of administration. As far as the daily dose is concerned, it may vary within a very wide range of dosage units, for example from 0.1 μg to 1mg of active product according to the mode of administration. Thus, for example it may be between 0.1μg and 160 μg, preferably from 1μg to 80μg, when the compound is administered intravenously. As a non-limiting example of a composition containing a compound of the invention, an example is given hereinafter of a sterile solution for intravenous injection :

| | |
|---|---|
| Product A | 250 μg |
| Sodium acetate | 19.15 mg |
| Sodium chloride | 81 mg |
| Acetic acid | 3.59 mg |
| Water for injection ad | 10 ml |

Non-limiting examples are given hereinafter of the preparation of 1H-imidazoles according to the invention as well as their intermediate compounds. In these examples, nuclear magnetic resonance spectra (NMR) were taken with a Perkin Elmer apparatus at 60 MHz using tetramethylsilane as an internal reference; the chemical shifts are indicated in delta (ppm). The letters s, d, t, q, m and J denote singlet, doublet, triplet, quartet, multiplet and coupling constants in Hertz respectively.

Example 1. Preparation of starting compounds of formula II ($R_6$ = H, $R_7$ = alkyl with 1 to 4 carbon atoms or triphenylmethyl) by procedure a).

A. Preparation of bromine derivatives as precursors of the organometallic derivatives of formula V.

1. 8-bromo-6-chloro-4H-1,3-benzodioxin.

1a. 2-bromo-4-chlorophenol.
This product was prepared according to the method of I.I.LAPKIN et al. (see Zh.Obshch.Khim.35(2),(1965),251-253; Chem.Abstr. 62,(1965),13111).

1b. 8-bromo-6-chloro-4H-1,3-benzodioxin.
311 g of paraformaldehyde (previously washed with 200 ml of acetic acid) were added all at once to a mixture of 229 ml of concentrated sulphuric acid and 620 ml of acetic acid cooled to 15°C followed by 462.6 g (2.23 mole) of 2-bromo-4-chlorophenol. Stirring was maintained for 148 hours at 15°C. The reaction medium was neutralized with 3.1 litres of a 7.8N aqueous solution of sodium hydroxide. The precipitate which formed was filtered off, dried and then dissolved in toluene. The solution was dried over sodium sulphate and then distilled. The residue was stirred in hexane and allowed to recrystallize. 364 g of 8-bromo-6-chloro-4H-1,3-benzodioxin were obtained.
Yield : 65.5%; MPt : 108-110°C
Analysis for $C_8H_6BrClO_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 38.47 | H 2.40 |
| Found : | 38.9 | 2.51 |

2. 6-bromo-4H-1,3-benzodioxin

This product was prepared as indicated in 1b. above from the following quantities of reagents : 3.8 litres of acetic acid, 654 ml of concentrated sulphuric acid, 1kg (5.78 mole) of 4-bromophenol and 870 g (28.9 mole) of paraformaldehyde. The reaction time was 120 hours at 0°C. Following neutralization of the reaction mixture with a solution containing 1350 g of sodium hydroxide in 13 litres of water, the precipitate which formed was

filtered off and then dissolved in 7 litres of toluene. The organic phase was dried by azeotropic distillation, filtered hot to remove polymers of formaldehyde and evaporated under reduced pressure. The residue was distilled under reduced pressure. 933 g of 6-bromo-4H-1,3-benzodioxin were obtained.
Yield : 75%. BPt : 80-90°C/0.13 mbar.
The product was crystallized by stirring in an isopropyl ether-hexane mixture. MPt : 43-47°C.
NMR spectrum ($CDCl_3$) : delta 4.88 (2H, s, Ar-$CH_2$), 5.24 (2H, s, -$OCH_2O$-), 6.39 (1H, d, J = 8.7 Hz, ArH), 7.13 (1H, m, ArH), 7.31 (1H, dd, J, = 8.7 and 2.4 Hz, ArH).

3. 8-bromo-6-chloro-2,2-dimethyl-4H-1,3-benzodioxin.

3.a. 3-bromo-5-chloro-2-hydroxybenzenemethanol.
880 g (4.241 mole) of 2-bromo-4-chlorophenol were dissolved in 8.2 litres of a 38% aqueous solution of formaldehyde (approximately 100 moles). After cooling the mixture in an ice bath, 1380 g (24 mole) of potassium hydroxide were added in 100 g portions. The addition was carried out over 150 minutes at a temperature of between 18 and 23°C. Stirring was maintained for 2 hours at ambient temperature and the mixture was then heated progressively to 40°C on a water bath. The reaction was slightly exothermic and the temperature of the medium became stable at about 45°C. Stirring was maintained for 178 hours at 40°C.
The reaction medium was then cooled, 2 litres of water were added and the mixture was acidified to pH 3 using 1420 ml of concentrated hydrochloric acid. The mixture was extracted with 2 litres of dichloromethane and then again 6 times with a litre of dichloromethane. The organic phase was washed with 2 litres of water and dried over sodium sulphate and the solvent was evaporated under reduced pressure.

The crude residue obtained (1490 g) contained approximately 68.8% of 3-bromo-5-chloro-2-hydroxybenzenemethanol, approximately 23.8% of the starting 2-bromo-4-chlorophenol not having reacted. This mixture was used as such in the following stage.

3.b. 8-bromo-6-chloro-2,2-dimethyl-4H-1,3-benzodioxin.
The crude residue (1490 g) separated in the preceding stage was dissolved in 20 litres of toluene and 4.68 litres of 2,2-dimethoxypropane in the presence of 296 g of K10 montmorillonite (freshly dehydrated by azeotropic distillation with toluene). The temperature of the mixture rose by itself to 30°C and stirring was maintained at this temperature for 115 hours. The reaction medium was filtered and toluene removed under reduced pressure. The residue obtained was purified by distillation under reduced pressure. 527 g of 90% pure 8-bromo-6-chloro-2,2-dimethyl-4H-1,3-benzodioxin were obtained (analysis by HPLC chromatography).
BPt : 100-112°C/0.026 mbar. Overall yield : 75% (calculated on the 2-bromo-4-chlorophenol used).
NMR spectrum ($CDCl_3$) : delta 1.55 (6H, s, $C(CH_3)_2$), 4.78 (2H, s, $CH_2$), 6.9 (1H, m, ArH), 7.4 (1H, m, ArH).

4. 6-bromo-2,2-dimethyl-4H-1,3-benzodioxin.

4.a. 5-bromo-2-hydroxybenzenemethanol.
This compound was prepared as indicated in 3.a above from 4-bromophenol.
Following evaporation of the dichloromethane used for extraction, 709 g of residue were obtained which were subjected to chromatography on 1.2 kg of silica (eluent : dichloromethane). Following evaporation of the solvent, 602 g of residue were obtained containing approximately 50% of the desired 5-bromo-2-hydroxybenzenemethanol (analysis by HPLC chromatography). This residue was used as such in the following stage.

4.b. 6-bromo-2,2-dimethyl-4H-1,3-benzodioxin.

572 g of the residue obtained in the previous stage were dissolved in 12.5 litres of dry toluene and 2.94 litres of 2,2-dimethoxypropane. 186 g of K10 montmorillonite were added and the mixture was stirred for 25 hours at ambient temperature.

The mixture was filtered, the organic phase was distilled under reduced pressure and the residue redissolved in 600 mls of toluene. This solution was passed through a column containing 3 kg of alumina (eluent : 6 litres of toluene). The eluate was evaporated under reduced pressure and gave 180 g of residue which was distilled under reduced pressure. 60 g of 6-bromo-2,2-dimethyl-4H-1,3-benzodioxin were obtained.

B.Pt : 110-130°C/0.027 mbar.

The yield calculated on the 4-bromophenol used was approximately 10%.

NMR spectrum ($CDCl_3$): delta 1.52 (6H, s, $C(CH_3)_2$), 4.80 (2H, s, $CH_2$), 6.71 (1H, d, J = 7.9 Hz, ArH), 7.07-7.5 (2H, m, ArH).

5. 8-Bromo-2,2,6-trimethyl-4H-1,3-benzodioxin.

This compound was prepared according to the method of H.E. KATZ and D.J. CRAM (J.Am.Chem.Soc.,106,(1984),4977. It was isolated in the form of a residue which was used as such in the following stage.

6. 1-bromo-2,6-dimethoxy-3-methoxymethylbenzene.

6.a. 3-bromo-2-hydroxy-4-methoxybenzenemethanol.

28 g (0.12 mole) of methyl 3-bromo-2-hydroxy-4-methoxybenzoate (prepared according to the method of T.M. CRESP et al., J.Chem.Soc.Perkin Trans., Part 1, (1973),340-345) dissolved in 250 ml of tetrahydrofuran, were added dropwise over 75 minutes at 0°C to a

suspension of 6.06 g (0.159 mole) of lithium aluminium hydride in 100 ml of tetrahydrofuran. The mixture was stirred for three hours at ambient temperature. A mixture of 11.5 ml of water and 12 ml of tetrahydrofuran was added and the mixture was acidified using 28.6 ml of concentrated hydrochloric acid dissolved in 300 ml of water. The mixture was extracted with dichloromethane. The organic phases were washed with water, dried over sodium sulphate and evaporated under reduced pressure. The residue (22.9 g) was used as such in the following stage. Yield : 91%.
NMR spectrum ($CDCl_3$): delta 3.8 (3H, s, $OCH_3$), 4.72 (2H, s, $CH_2$), 6.45 (1H, d, J = 8.6 Hz, Arh), 7.1 (1H, d, J = 8.6 Hz, ArH).

6.b. 2-bromo-3-methoxy-6-methoxymethylphenol.
A mixture of 22.8 g of 3-bromo-2-hydroxy-4-methoxybenzenemethanol, 230 ml of 2,2-dimethoxypropane and 23 g of K10 montmorillonite (freshly dehydrated by azeotropic distillation with toluene) in 200 ml of toluene were stirred at ambient temperature for 90 minutes. After filtration and elimination of the solvent, 24.1 g of 2-bromo-3-methoxy-6-methoxymethylphenol were obtained which could be recrystallized from diisopropyl ether.
Yield : 99% M.Pt. : 98-100°C.
Analysis for $C_9H_{11}BrO_3$ in % :

| | | |
|---|---|---|
| Calculated : | C 43.72 | H 4.45 |
| Found : | 44.32 | 4.49 |

6.c. 1-Bromo-2,6-dimethyoxy-3-methoxymethylbenzene.

24.1 g (0.098 mole) of 2-bromo-3-methoxy-6-methoxymethylphenol and 27.7 g of methyl iodide were dissolved in 200 ml of acetone in the presence of 14.82 g (0.107 mole) of potassium carbonate. This solution was heated at reflux temperature with stirring, for two and a

half hours. The mixture was cooled, mineral salts were filtered off and the acetone distilled. The residue was taken up in water and extracted with dichloromethane. The organic phase was dried over sodium sulphate and distilled under reduced pressure.
13.1 g of 1-bromo-2,6-dimethoxy-3-methoxymethylbenzene were obtained.
Yield : 51%. B.Pt.: 92-115°C/0.005 mbar.
NMR spectrum ($CDCl_3$): delta 3.4 (3H, s, $OCH_3$), 3.88 (3H, s, $OCH_3$), 3.9 (3H, s, $OCH_3$), 4.48 (2H, s, $CH_2$), 6.74 (1H, s, J = 8.6 Hz, ArH), 7.33 (1H, d, J = 8.6 Hz, ArH).

7. 1-Bromo-2,6-dimethoxy-3-(1-methoxyethyl)benzene.

7.a. 3-bromo-2-hydroxy-4-methoxy-alpha-methylbenzenemethanol.
64.3 g (0.262 mole) of 3'-bromo-2'-hydroxy-4'-methoxyacetophenone (prepared according to the method of T.M.CRESP et al., J.Chem.Soc.Perkin Trans. Part 1, (1973),340-345) dissolved in 560 ml of tetrahydrofuran were added dropwise over 80 minutes at a temperature of between 13 and 18°C, to a suspension of 13.89 g (0.367 mole) of sodium borohydride in 300 ml of tetrahydrofuran. Stirring was then maintained for 2 hours at ambient temperature. The reaction mixture was decomposed by the addition of 140 ml of tetrahydrofuran containing 3 ml of water and a further 60 ml of water were added. The medium was acidified by the addition of 415 ml of a 1N aqueous solution of hydrochloric acid. Tetrahydrofuran was removed under reduced pressure and the aqueous phase was extracted four times with dichloromethane. The organic phases were dried over sodium sulphate and distilled. The residue (70 g) was used as such in the following stage.

7.b. 2-bromo-3-methoxy-6-(1-methoxyethyl)phenol.
This compound was prepared as indicated in 6.b. above starting from 65 g of 3-bromo-2-hydroxy-4-methoxy-alpha-

methylbenzenemethanol obtained in the previous stage. The crude product obtained in quantitative yield was used as such in the following stage.
NMR spectrum ($CDCl_3$) : delta 1.48 (3H, d, J = 6.6 Hz, $CH_3$), 3.35 (3H, s, $OCH_3$), 3.88 (3H, s, $OCH_3$), 4.54 (1H, q, J = 6.6 Hz, CH), 6.48 (1H, d, J = 8.6 Hz, ArH), 7.02 (1H, d, J = 8.6 Hz, ArH).

7.c. 1-bromo-2,6-dimethoxy-3-(1-methoxyethyl)benzene.
This compound was prepared as indicated in 6.c. above starting from 2-bromo-3-methoxy-6-(1-methoxyethyl)phenol isolated in the preceding stage. 56 g of 1-bromo-2,6-dimethoxy-3-(1-methoxyethyl)benzene were obtained.
Yield : 77%. BPt. 95-120°C/0.001 mbar.
NMR spectrum ($CDCl_3$) : delta 1.42 (3H, d, J = 6.6 Hz, $CH_3$), 3.23 (3H, s, $OCH_3$), 3.88 (3H, s, $OCH_3$) 3.90 (3H, s, $OCH_3$), 4.68 (1H, q, J = 6.6 Hz, CH), 6.79 (1H, d, J = 8.6 Hz, ArH), 7.38 (1H, d, J = 8.6 Hz, ArH).

B. Preparation of 4-($R_3$-CO)-1H-imidazoles of formula VI.

1. 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde.

1.a. 1-triphenylmethyl-1H-imidazole-4-methanol.
This compound was prepared according to the method described by J.L.KELLEY et al. (J.Med.Chem.,20,(1977), 721-723).
Yield : 71.3% MPt : 236°C.

1.b. 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde.
This compound was prepared according to the method described by J.L.KELLEY et al. (loc.cit.) with a yield of 87.5%.
MPt. : 190-198°C.

2. 1-methyl-1H-imidazole-4-carboxaldehyde.
This product was prepared according to the method of G.LINDGREN et al. (J.Het.Chem.17,(1980),679).

3. 5-methyl-1-triphenylmethyl-1H-imidazole-4-carboxaldehyde.

3.a. 5-methyl-1H-imidazole-4-methanol.
This compound was prepared according to the method described in Belgian Patent 878,490. Yield : 59.3%.

3.b. 5-methyl-1-triphenylmethyl-1H-imidazole-4-methanol.
230 ml (1.659 mole) of triethylamine were added over 15 minutes to a solution of 100 g (0.673 mole) of 5-methyl-1H-imidazole-4-methanol in 1.5 litre of dimethyl formamide, held at between 10 and 14°C. Subsequently, a solution containing 192 g (0.69 mole) of triphenylmethyl chloride in 2 litres of dimethylformamide, were added at between 8 and 11°C.
The reaction mixture was stirred for 2 hours and was then poured onto 14 litres of ice. Stirring was maintained for one hour and the precipitate was filtered, washed with 6 litres of water and dried. This precipitate was then taken up in 4 litres of ethanol at the boiling point and the non-soluble fraction was separated by hot filtration. A first crop of the desired product was thus recovered (19 g; MPt : 255-260°C). The alcoholic filtrate was filtered hot through Norit, and then was concentrated and cooled with stirring. A second crop of the desired product crystallized and was separated by filtration : 28.3 g (MPt : 255-262°C). Finally, the filtrate was distilled under reduced pressure and the residue dissolved in 1 litre of a 95:5 mixture of dichloromethane-methanol and the solution obtained was purified by passing through a column of 1.8 kg of silica (0.2-0.5 mm) (eluent : 80:20 mixture of dichloromethane - methanol. A further 72.1 g of the desired product were recovered. In total, 119.4 g were obtained containing

practically only one of the two possible isomers in the 4 and 5 positions, that is, 5-methyl-1-triphenylmethyl-1H-imidazole-4-methanol. Yield : 50.1%. The product obtained was used as such in the following stage.

3.c. 5-methyl-1-triphenylmethyl-1H-imidazole-4-carboxaldehyde.

A solution of 19 g (0.0536 mole) of the product prepared in the preceding stage, in 400 ml of chloroform, was heated under reflux for 85 minutes in the presence of 32.65 g (0.375 mole) $MnO_2$. The manganese salts were removed by filtration through Dicalite and the filtrate was distilled. The residue was recrystallized from 200 ml of ethyl acetate. A first crop of 4.37 g of the desired product was obtained. A second crop of 9.43 g was in addition obtained following concentration of the mother liquors to a volume of 60 ml and crystallization. Yield : 73.5%.

MPt : 195-196°C.

The product obtained contained only one position isomer.

Analysis for $C_{24}H_{20}N_2O$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 81.18 | H 5.68 | N 7.95 |
| Found : | 81.37 | 6.25 | 7.95 |

4. 1-(1-triphenylmethyl-1H-imidazol-4-yl)-1-ethanone.

4.a. alpha-methyl-1-triphenylmethyl-1H-imidazole-4-methanol.

This compound was prepared by the method described by J.L.KELLEY et al. (J.Med.Chem.,20,(1977),721-723).

4.b. 1-(1-triphenylmethyl-1H-imidazole-4-yl)-1-ethanone.

A mixture of 221.3 g (2.544 mole) of manganese dioxide and 56.9 g (0.161 mole) of alpha-methyl-1-triphenylmethyl-1H-imidazole-4-methanol dissolved in 2.5 litres of chloroform were heated under reflux for 90 minutes. The solution was then cooled to about 50°C,

filtered and the chloroform removed by distillation. The residue was dissolved in 400 ml of isopropyl alcohol and the solution filtered through Norit.
The product crystallized on cooling. 32.8 g of 1-(1-triphenylmethyl-1H-imidazol-4-yl)-1-ethanone were obtained.
Yield : 58%. MPt : 158-160°C.
Analysis for $C_{24}H_{20}N_2O$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 81.82 | H 5.68 | N 7.95 |
| Found : | 81.89 | 5.65 | 7.90 |

5. 1-(1-triphenylmethyl-1H-imidazol-4-yl)-1-pentanone.

5.a. alpha-n-butyl-1-triphenylmethyl-1H-imidazole-4-methanol.
A solution of 0.22 mole of n-butylmagnesium bromide in 75 ml of tetrahydrofuran was added slowly, under an atmosphere of argon, to 67.6 g (0.2 mole) of 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde (obtained as indicated in 1.b. above) in 500 ml of tetrahydrofuran. The temperature of the mixture was maintained at about 20°C by cooling in an ice bath. When addition was complete, stirring was maintained for a further 30 minutes at ambient temperature and then 11 g of ammonium chloride and 100 ml of water were added successively. The mixture was extracted with dichloromethane. The organic phases were dried over sodium sulphate and then evaporated under reduced pressure. The residue was recrystallized from a 2:1 mixture of ethyl acetate-diethyl ether. 45.8 g of alpha-n-butyl-1-triphenylmethyl-1H-imidazole-4-methanol were obtained.
Yield : 58%. MPt : 119-120°C.
Analysis for $C_{27}H_{28}N_2O$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 81.82 | H 7.07 | N 7.07 |
| Found : | 79.13 | 6.82 | 6.65 |

5.b. 1-(1-triphenylmethyl-1H-imidazol-4-yl)-1-pentanone.
This compound was prepared as indicated in 4.b. above, from alpha-n-butyl-1-triphenylmethyl-1H-imidazole-4-methanol obtained in the previous stage.
The oily residue obtained after evaporation of the chloroform was purified by chromatography on silica (eluent : dichloromethane).
39 g of 1-(1-triphenylmethyl-1H-imidazole-4-yl)-1-pentanone were obtained.
Yield : 85.3% M.Pt: 115-118°C.
Analysis for $C_{27}H_{26}N_2O$ in % :

| | | | |
|---|---|---|---|
| calc : | C 82.23 | H 6.60 | N 7.11 |
| found : | 82.18 | 6.61 | 7.14 |

C. Reaction of an organometallic derivative of formula V with the 4-($R_3$-CO)-1H-imidazoles of formula VI.

1. alpha-(6-chloro-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol.
121 g (0.485 mole) of 8-bromo-6-chloro-4H-1,3-benzodioxin, dissolved in 400 ml of dry tetrahydrofuran, were added dropwise under an atmosphere of nitrogen to a suspension of 12.16 g (0.5 mole) of magnesium in 430 ml of anhydrous tetrahydrofuran under reflux.
When was the addition was completed, reflux was continued for half an hour and the mixture was cooled to about 40°C. The organomagnesium compound thus formed was added rapidly to 164 g (0.485 mole) of 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde dissolved in 2 litres of tetrahydrofuran preheated to 40°C.
The temperature rose by itself to 50°C during the addition. Stirring was maintained for one hour at 40°C. The reaction mixture was then cooled to 0°C and decomposed by the addition of a litre of a saturated solution of ammonium chloride. The precipitate formed was filtered off and washed with methanol and ether. 140.7 g of the product were collected. The product was further

purified by stirring in 1 litre of water. It was filtered off and washed with ethanol and then with diethyl ether. 121.3 g of alpha-(6-chloro-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol were obtained.
Yield : 49.2%. MPT : 233-235°C.
Analysis for $C_{31}H_{25}ClN_2O_3$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 73.15 | H 4.91 | N 5.50 |
| Found : | 73.21 | 4.94 | 5.48 |

2. alpha-(4H-1,3-benzodioxin-6-yl)-1-triphenylmethyl-1H-imidazole-4-methanol.
This compound was prepared in a similar manner to the preceding compound but starting from 6-bromo-4H-1,3-benzodioxin and 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde. Following decomposition of the reaction medium, the reaction product was extracted with dichloromethane and recrystallized from isopropyl alcohol. A second crop was further recovered by chromatography of the residue obtained following evaporation of the mother liquors.
Yield : 53%. MPt : 165-167°C.
Analysis for $C_{31}H_{26}N_2O_3$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 78.48 | H 5.48 | N 5.91 |
| Found : | 78.19 | 5.82 | 5.84 |

3. alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol.
2 ml of dibromoethane were added to a suspension of 26.73 g (1 mole + 10% excess) of magnesium in 250 ml of anhydrous tetrahydrofuran and the mixture was heated to 30°C in order to initiate the reaction. 277.5 g (1 mole) of 8-bromo-6-chloro-2,2-dimethyl-4H-1,3-benzodioxin dissolved in 250 ml of tetrahydrofuran were next added dropwise in such a way that the temperature of the medium did not exceed 40°C.

The addition took about 150 minutes. The organomagnesium compound was cooled to about 10°C (partial precipitation) and was then added to a solution of 338 g (1 mole) of 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde in 2.8 litres of tetrahydrofuran, previously cooled to 0°C. During the addition, the temperature of the mixture rose progressively to 20°C. Stirring was maintained for a further hour at this temperature and then 53.5 g (1 mole) of ammonium chloride were added.
After stirring for 1 hour, a further 18 ml of water were added and stirring was continued for an additional one hour. The tetrahydrofuran was removed under reduced pressure. The residue was taken up in 5 litres of dichloromethane and washed with 2 litres of water containing 30 g of sodium bisulphite. The aqueous phase was separated and washed with 1 litre of dichloromethane. The organic phases were again washed with water and then dried over sodium sulphate and the solvent removed under reduced pressure. The residue was recrystallized from about 4 litres of toluene at 80°C and filtered hot through Norit. 335.6 g of alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol were thus obtained, containing 1 molecule of toluene.
MPt : 120°C followed by 188°C.
Analysis for $C_{33}H_{29}ClN_2O_3 + C_7H_8$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 76.81 | H 5.78 | N 4.37 |
| Found : | 74.78 | 5.24 | 4.73 |

The following compounds were prepared by the method described in 3. above.

4. alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-methyl-1H-imidazole-4-methanol.
Starting from 8-bromo-6-chloro-2,2-dimethyl-4H-1,3-benzodioxin and 1-methyl-1H-imidazole-4-carboxaldehyde.
The addition of the organomagnesium compound was made at 0°C.

Yield : 63.5%. MPt : 131-136°C (ethyl acetate).
Analysis for $C_{17}H_{17}ClN_2O_3$ in % :

| | | | | |
|---|---|---|---|---|
| Calculated : | C 58.35 | H 5.51 | N 9.08 | Cl 11.55 |
| Found : | 58.47 | 5.54 | 8.97 | 11.49 |

5. alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-5-methyl-1-triphenylmethyl-1H-imidazole-4-methanol.
Starting from 8-bromo-6-chloro-2,2-dimethyl-4H-1,3-benzodioxin and 5-methyl-1-triphenylmethyl-1H-imidazole-4-carboxaldehyde.
Addition of the organomagnesium compound was carried out at 0°C.
Yield : 50%. MPt : 100-120°C (acetonitrile).
NMR spectrum ($CDCl_3$) : delta 1.4 (6H, m, $CH_3$-C-$CH_3$), 1.94 (3H, s, $CH_3$), 4.79 (2H, s, $CH_2$), 5.98 (1H, s, CHOH), 6.65-7.70 (18H, m, ArH + ImH).

6. alpha-(2,2,6-trimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol.
Starting from 8-bromo-2,2,6-trimethyl-4H-1,3-benzodioxin and 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde. The organomagnesium compound was added at ambient temperature. The reaction product was purified by chromatography on silica (15µm) (eluent : 98:2 dichloromethane-methanol).
Yield : 31%. MPt : 205-215°C (acetonitrile).
NMR spectrum ($CDCl_3$) : delta 1.3 (3H, s, $CH_3$-C-$CH_3$), 1.38 (3H, s, $CH_3$-C-$CH_3$), 2.21 (3H, s, $CH_3$), 4.78 (2H, s, $CH_2$), 6.02 (1H, broad s, CHOH), 6.72 (2H, m, ImH + OH), 7.0 - 7.65 (18H, m, ArH + ImH).

7. alpha-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1-triphenylmethyl-1H-imidazole-4-methanol.
Starting from 6-bromo-2,2-dimethyl-4H-1,3-benzodioxin and 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde. The temperature of the reaction medium did not exceed 40°C.
Yield : 54.5% MPt : 155-162°C (acetonitrile).

NMR spectrum (DMSO) : delta 1.43 (6H, s, $CH_3$-C-$CH_3$), 4.77 (2H, s, $CH_2$), 5.53 (2H, s, CH and OH), 6.6-7.7 (20H, m, ArH + ImH).

8. alpha-(2,6-dimethoxy-3-methoxymethylphenyl)-1-triphenylmethyl-1H-imidazole-4-methanol.
Starting from 1-bromo-2,6-dimethoxy-3-methoxymethylbenzene and 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde. The reaction product was purified by chromatography on silica and formed in a glassy lac.
Yield : 48%.
NMR spectrum ($CDCl_3$) : delta 3.36 (3H, s, $OCH_3$), 3.7 (6H, s, 2 x $OCH_3$), 4.43 (2H, s, $CH_2$), 6.0-6.4 (1H, m, CH), 6.5-7.6 (20H, m, ArH + ImH + OH).

9. alpha-[2,6-dimethoxy-3-(1-methoxyethyl)phenyl]-1-triphenylmethyl-1H-imidazole-4-methanol.
Starting from 1-bromo-2,6-dimethoxy-3-(1-methoxyethyl)benzene and 1-triphenylmethyl-1H-imidazole-4-carboxaldehyde. The reaction product was purified by chromatography on silica (eluent : 98:2 dichloromethane-methanol mixture).
Yield : 49.7%. MPt : 96-99°C (acetonitrile).
Analysis for $C_{34}H_{34}N_2O_4$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 76.4 | H 6.36 | N 5.24 |
| Found : | 76.37 | 6.31 | 5.29 |

10. alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-alpha-methyl-1-triphenylmethyl-1H-imidazole-4-methanol.
The organomagnesium compound of 8-bromo-6-chloro-2,2-dimethyl-4H-1,3-benzodioxin was prepared as indicated in 3. above. Next, 15 g (0.046 mole) of this organomagnesium compound were added over 20 minutes at a temperature not exceeding 25°C, to 15 g (0.0426 mole) of 1-(1-triphenylmethyl-1H-imidazol-4-yl)-1-ethanone dissolved in 150 ml of tetrahydrofuran. The reaction medium was stirred for 165 minutes and then decomposed

with 2.5 g of ammonium chloride dissolved in 50 ml of water and extracted with dichloromethane. The organic phase was dried over sodium sulphate and then distilled. The residue was purified by chromatography on silica (eluent: 98:2 dichloromethane-methanol mixture). 5.68 g of alpha-(6-chloro-2,2-dimethyl-4H-1-,3-benzodioxin-8-yl)-alpha-methyl-1-triphenylmethyl-1H-imidazole-4-methanol were obtained.
MPt : 182-184°C (ethyl acetate). This compound was identical to that prepared in example 2.B.2.

11. alpha-n-butyl-alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol.
This compound was prepared in the same manner as the preceding compound by reacting the organomagnesium compound of 8-bromo-6-chloro-2,2-dimethyl-4H-1,3-benzodioxin with 1-(1-triphenylmethyl-1H-imidazol-4-yl)-1-pentanone.
Yield : 54.6%. MPt : 124°C (petroleum ether).
NMR spectrum ($CDCl_3$) : delta 0.6-3.3 (15H, m, $C_4H_9$ and $CH_3$-C-$CH_3$), 4.26 (1H, broad s, OH), 4.78 (2H, s, $CH_2$), 6.7-8.0 (19H, m, ArH + ImH).

12. alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-methyl-1H-imidazole-4-methanol (hydrochloride).
15.88 g of alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-methyl-1H-imidazole-4-methanol (prepared in 4. above) dissolved in 160 ml of methanol were subjected to hydrogenolysis in the presence of 3 g of 10% palladium on carbon at a hydrogen pressure of 3.5 bar at 50°C for 150 minutes. The catalyst was then filtered off, the solvent was removed and the residue was stirred in diethyl ether. The ether phase was decanted off and the residue obtained was used as such in the following stage.

Example 2. Preparation of starting compounds of formula II ($R_6$ = H, $R_7$ = alkyl with 1 to 4 carbon atoms or triphenylmethyl) by procedure b)

A. Preparation of ketones of formula VII.

1. (6-chloro-4H-1,3-benzodioxin-8-yl)(1-triphenylmethyl-1H-imidazol-4-yl)ketone

This compound was prepared according to the procedure described in example 1.B.4.b. starting from alpha-(6-chloro-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.1).
Yield : 95%. MPt : 175-182°C. A sample recrystallized from ethanol melted at 182-185°C and 203°C.
Analysis for $C_{31}H_{23}ClN_2O_3$ in %

| | | | | |
|---|---|---|---|---|
| Calculated : | C 73.45 | H 4.54 | N 5.53 | Cl 7.01 |
| Found | 72.48 | 4.48 | 5.18 | 6.96 |

2. (6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)(1-triphenylmethyl-1H-imidazol-4-yl)ketone

This compound was prepared according to the procedure described in example 1.B.4.b. starting from alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.3).
Yield : 88% (practically pure product). MPt : 200-205°C.
Analysis for $C_{33}H_{27}ClN_2O_3$ in %

| | | | | |
|---|---|---|---|---|
| Calculated : | C 74.08 | H 5.05 | N 5.24 | Cl 6.64 |
| Found | 74.17 | 5.03 | 5.22 | 6.73 |

B. Reaction of a ketone of formula VII with an organomagnesium compound of formula VIII.

1. alpha-(6-chloro-4H-1,3-benzodioxin-8-yl)-alpha-methyl-1-triphenylmethyl-1H-imidazole-4-methanol.

A suspension of 0.148 mole of methylmagnesium iodide in 150 ml of diethyl ether at 30°C, was added at ambient temperature to 17.3 g (0.033 mole) of (6-chloro-4H-1,3-benzodioxin-8-yl)(1-triphenylmethyl-1H-imidazol-4-yl)ketone dissolved in 200 ml of tetrahydrofuran. The temperature of the reaction medium rose to 40°C. When the addition was complete, stirring was maintained for one hour at ambient temperature. 8 g of ammonium chloride were added and stirring was maintained for a further hour. 100 ml of water were then added and the reaction medium was extracted twice with dichloromethane. The organic phases were dried over sodium sulphate and the solvent was removed under reduced pressure. The residue was recrystallized from 100 ml of ethyl acetate. 13.77 g of alpha-(6-chloro-4H-1,3-benzodioxin-8-yl)-alpha-methyl-1-triphenylmethyl-1H-imidazole-4-methanol were obtained.
Yield : 80%. MPt : 248-250°C (decomposition).
Analysis for $C_{32}H_{27}ClN_2O_3$ in % :

| | | | | |
|---|---|---|---|---|
| Calculated : | C 73.49 | H 5.16 | N 5.36 | Cl 6.7 |
| Found : | 73.41 | 5.05 | 5.26 | 6.93 |

2. alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-alpha-methyl-1-triphenylmethyl-1H-imidazole-4-methanol.

This compound was prepared in the same way as the preceding compound from methylmagnesium iodide and (6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)(1-triphenylmethyl-1H-imidazol-4-yl)ketone. The residue obtained after evaporation of dichloromethane crystallized on stirring in diethyl ether.

Yield 80%. MPt : 182-184°C (ethyl acetate).
Analysis for $C_{34}H_{31}ClN_2O_3$ in % :

| | | | | |
|---|---|---|---|---|
| Calculated : | C 74.11 | H 5.63 | N 5.08 | Cl 6.45 |
| Found : | 73.98 | 5.65 | 5.00 | 6.49 |

This compound was identical to that prepared in example 1.C.10.

Example 3. Preparation of the starting compounds of formula II ($R_6$ = H or an alkyl with 1 to 4 carbon atoms, $R_7$ = H.

1. 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)(methoxy)methyl]-1H-imidazole (hydrochloride) and alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1H-imidazole-4-methanol (hydrochloride).

125.4 g (0.23 mole) of alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.3) partially dissolved in 1250 ml of methanol, were subjected to hydrogenolysis, in the presence of 6 g of 10% palladium on carbon under an initial hydrogen pressure of 2.7 bar.

The reaction was carried out at a temperature of 60°C. The catalyst was then filtered off through Hyflo-cel and the methanol was removed under reduced pressure. The residue was taken up in 100 ml of methanol and cooled in an ice bath. Triphenylmethane which had crystallized was removed by filtration and the filtrate was then evaporated. The residue obtained was stirred for at least 12 hours in 650 ml of diethyl ether. The precipitate was filtered off and washed with diethyl ether. 64.59 g of an amorphous powder was obtained which was formed of a mixture of the desired alcohol and the O-methyl derivative in a ratio of 35/65 determined by NMR. This mixture was used as such in the following stage. A 5.36 g sample of this mixture of products was recrystallized from 20 ml of a mixture of 1:1 ethanol-ether. 1.35 g of pure alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1H-imidazole-4-methanol hydrochloride were isolated. The product did not have a sharp melting point (decomposition).

Analysis for $C_{14}H_{16}N_2O_3$.HCl in %.

| | | | | |
|---|---|---|---|---|
| Calculated : | C 56.66 | H 5.40 | N 9.44 | $Cl^-$ 11.97 |
| Found : | 55.81 | 5.77 | 8.94 | 11.83 |

The O-methyl derivative which formed during hydrogenolysis, was separated from the reaction medium, neutralized by the addition of ammonia and at the same time purified by chromatography. The 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)(methoxy)methyl]-1H-imidazole obtained was converted into the hydrochloride by addition of a solution of hydrochloric acid in methanol. MPt : 150-155°C (decomposition).

Analysis for $C_{15}H_{18}N_2O_3$.HCl in %.

| | | | | |
|---|---|---|---|---|
| Calculated : | C 57.97 | H 6.12 | N 9.02 | $Cl^-$ 11.43 |
| Found : | 58.12 | 6.08 | 9.10 | 11.40 |

2. alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-5-methyl-1H-imidazole-4-methanol (hydrochloride) and 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)(methoxy)methyl]-5-methyl-1H-imidazole (hydrochloride).

17.5 g (0.032 mole) of alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-5-methyl-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.5) dissolved in 300 ml of methanol, were subjected to hydrogenolysis, in the presence of 1.5 g of 10% palladium on carbon under a hydrogen pressure of 3.5 bar at 50°C for 3 hours. The catalyst was then filtered off, the solvent was removed and the residue was stirred with diethyl ether to remove triphenylmethane. The residue obtained following decantation of the ether phase was characterized by its NMR spectrum and was a mixture comprising 65% of the hydrochloride of the O-methyl derivative and 35% of the alcohol hydrochloride. This mixture was used as such in the following stage.

3. 4-[(2,2,6-trimethyl-4H-1,3-benzodioxin-8-yl)(methoxy)methyl]-1H-imidazole and 4-[(2,2,6-trimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole.

9.45 g (0.0183 mole) of alpha-(2,2,6-trimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.6) dissolved in 300 ml

of methanol, were subjected to hydrogenolysis, in the presence of 0,6 g of 10% palladium, for 4 hours at 80°C on carbon under a hydrogen pressure of 2 bar. The catalyst was then filtered off and the solvent removed. The residue was stirred with diethyl ether to remove triphenylmethane and then subjected to chromatography on 700 g of silica (10µm) (eluent 95:5 dichloromethane-methanol). A 40:60 mixture of 4-[(2,2,6-trimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole and 4-[(2,2,6-trimethyl-4H-1,3-benzodioxin-8-yl)(methoxy)methyl]-1H-imidazole were isolated, identified with NMR by the peak corresponding to the methoxy radical (DMSO : delta 3.13). This mixture was used as such in the following stage.

4. alpha-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1H-imidazole-4-methanol.
The process used was the same as that described in 2. above, but starting from alpha-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.7.). The residue obtained was subjected to chromatography on silica (15µm) (eluent : 95:5 dichloromethane-methanol). The alpha-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1H-imidazole-4-methanol which was isolated was recrystallized from ethyl acetate.
MPt : 96°C.
Analysis for $C_{14}H_{16}N_2O_3$ in %

| | | | |
|---|---|---|---|
| Calculated : | C 64.62 | H 6.15 | N 10.77 |
| Found : | 64.37 | 6.40 | 10.68 |

5. alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1H-imidazole-4-methanol.
5.75 g (0.25 mole) of sodium were added piece by piece to a suspension of 21.46 g (0.04 mole) of alpha-(6-chlor-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.3) in 2 litres of ammonia and 200 ml of toluene. Stirring was maintained for 40 minutes and the reaction medium was

then decomposed by the addition of 6.42 g (0.12 mole) of ammonium chloride. 500 ml of toluene containing 10% methanol were added, the ammonia was evaporated and a further 500 ml of water were added. The toluene phase was decanted, dried over sodium sulphate and then distilled. The residue containing triphenylmethane was partially dissolved in 50 ml of water containing 3.3 ml of concentrated hydrochloric acid and the suspension obtained was extracted with ether. The aqueous phase was then adjusted to pH 8 by the addition of sodium bicarbonate and then extracted with dichloromethane. The solvent was then removed by distillation and 3.5 g of alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1H-imidazole-4-methanol were obtained.

Yield : 33%

The product formed a hydrochloride (recrystallizable from a 1:1 ethanol-ether mixture) which had a glassy appearance and no sharp melting point.

Analysis for $C_{14}H_{16}N_2O_3$.HCl in %.

| | | | | |
|---|---|---|---|---|
| Calculated : | C 56.66 | H 5.40 | N 9.44 | $Cl^-$ 11.97 |
| Found : | 55.81 | 5.77 | 8.94 | 11.83 |

6. alpha-(2,6-dimethoxy-3-methoxymethylphenyl)-1H-imidazole-4-methanol.

The procedure was as in 1. above, but at 80°C starting with alpha-(2,6-dimethoxy-3-methoxymethylphenyl)-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.8). After removal of the crystallized triphenylmethane and evaporation of methanol, the residue obtained was purified by chromatography on silica (eluent: 80:20 dichloromethane-methanol mixture). An oil was obtained, characterized by its nuclear magnetic resonance spectrum.

Yield : 68%.

NMR spectrum ($CDCl_3$) : delta 3.38 (3H, s, $OCH_3$), 3.66 (3H, s, $OCH_3$), 3.76 (3H, s, $OCH_3$), 4.43 (2H, s, $CH_2$), 6.28 (1H, s, CH), 6.69-7.70 (6H, m, ArH + ImH + OH + NH).

7. alpha-[(2,6-dimethoxy-3-(1-methoxyethyl)phenyl]-1H-imidazole-4-methanol.
The procedure was as in 6. above by hydrogenolysis of alpha-[(2,6-dimethoxy-3-(1-methoxyethyl)phenyl]-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.9.).
Yield : 79.6% MPt : 138-145°C (tetrahydrofuran-ether).
Analysis for $C_{15}H_{20}N_2O_4$ in %.

| | | | | |
|---|---|---|---|---|
| Calculated : | C 61.64 | H 6.85 | N 9.59 | |
| Found : | 61.48 | 7.0 | 9.38 | |

8. alpha-n-butyl-alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1H-imidazole-4-methanol.
The procedure was as in 1. above, but at 80°C, starting from alpha-n-butyl-alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.11). The residue obtained after filtering the triphenylmethane and evaporating the methanol, was used as such in the following stage.

9. alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-alpha-methyl-1H-imidazole-4-methanol hydrochloride.
The procedure was as in 2. above, but at 20°C, starting from alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-alpha-methyl-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 2.B.2). The yield was practically quantitative. MPt : 85-100°C (decomposition).
An analytical sample was prepared by stirring in diethyl ether. MPt : 72-90°C (decomposition).
Analysis for $C_{15}H_{18}N_2O_3.HCl$ in %.

| | | | | |
|---|---|---|---|---|
| Calculated : | C 57.97 | H 6.12 | N 9.01 | $Cl^-$ 11.43 |
| Found : | 57.94 | 6.95 | 8.12 | 9.51 |

Example 4. Preparation of 1H-imidazoles of formula I ($Z_1$ = $Z_2$ = alkyl and $Z_1 + Z_2$ = $-CH_2-$

1. 4-[(4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole hydrochloride.

50.85 g (0.1 mole) of alpha-(6-chloro-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.1) dissolved in 500 ml of acetic acid, were subjected to hydrogenolysis in the presence of 3 g of 10% palladium on carbon for 2 hours at 80°C under a hydrogen pressure of 2.41 bar. The catalyst was then removed by filtration and the solvent distilled under reduced pressure. The residue obtained was extracted three times with diethyl ether to remove the triphenylmethane which formed. It was then recrystallized from 50 ml of acetonitrile. 21.2 g of 4-[(4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole hydrochloride were obtained.

Yield : 83%. MPt : 168-173°C.

Analysis for $C_{12}H_{12}N_2O_2.HCl$ in % :

| | | | | |
|---|---|---|---|---|
| Calculated : | C 57.03 | H 5.15 | N 11.09 | $Cl^-$ 14.06 |
| Found : | 57.01 | 5.20 | 11.02 | 13.83 |

2. 4-[(4H-1,3-benzodioxin-6-yl)methyl]-1H-imidazole.

This compound was prepared in a similar manner to the previous compound, but from 25 g (0.052 mole) of alpha-(4H-1,3-benzodioxin-6-yl)-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 1.C.2). The triphenylmethane formed was extracted several times with hexane and the residue purified by chromatography on silica (eluent : 95:5 dichloromethane-methanol). Fractions containing the product were evaporated and the residue taken up in a dilute solution of ammonia in methanol. This solution was distilled and the residue recrystallized from ethyl acetate.

3.5 g of 4-[(4H-1,3-benzodioxin-6-yl)methyl]-1H-imidazole were obtained .
Yield : 31.2% MPt : 145°C.
Analysis for $C_{12}H_{12}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 66.66 | H 5.55 | N 12.96 |
| Found : | 66.14 | 5.62 | 12.69 |

3. 4-[(2,6-dimethoxy-3-methoxymethylphenyl)methyl]-1H-imidazole (hydrochloride).
6.75 g (0.0243 mole) of alpha-(2,6-dimethoxy-3-methoxymethylphenyl)-1H-imidazole-4-methanol (prepared in example 3.6.) previously dissolved in 200 ml of tetrahydrofuran, were added to 1 litre of liquid ammonia. First of all, 1.3 g (0.0243 mole) of ammonium chloride were added and then, over 30 minutes, 1.12 g (0.0486 mole) of sodium piece by piece. After the sodium had completely disappeared, 1.3 g of ammonium chloride were added and the reaction medium was stirred for 30 minutes. 300 ml of toluene containing 10 ml of methanol were added. Ammonia was then evaporated off on a water bath. A further 100 ml of water were added and the organic phase was decanted off. The latter was dried over sodium sulphate and the solvent evaporated under reduced pressure.
The product obtained was purified by chromatography on silica (eluent : 95:4.5:0.5 mixture of dichloromethane-methanol-ammonia). 1.81 g were obtained in the form of a lac (yield 28.4%). It was dissolved in isopropyl ether and converted into the hydrochloride by adding one equivalent of a solution of hydrochloric acid in isopropyl alcohol. MPt : 130-135°C.
Analysis for $C_{14}H_{18}N_2O_3.HCl$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 56.28 | H 6.36 | N 9.38 |
| Found : | 56.13 | 6.39 | 9.10 |

4. 4-[[(2,6-dimethoxy-3-(1-methoxymethyl)phenyl]methyl]-1H-imidazole (hydrochloride).
The procedure was as in 3. above, but starting from alpha-[2,6-dimethoxy-3-(1-methoxymethyl)phenyl]-1H-imidazole-4-methanol (prepared in example 3.7.). The oil obtained after evaporation of toluene was taken up in ether and converted into the hydrochloride by the addition of a solution of hydrochloric acid in methanol.
Yield : 68.5%. MPt : 168-170°C.
Analysis for $C_{15}H_{20}N_2O_3$.HCl in % :

| | | | | |
|---|---|---|---|---|
| Calculated : | C 57.6 | H 6.72 | N 8.96 | $Cl^-$ 11.36 |
| Found : | 57.52 | 6.84 | 8.89 | 11.27 |

5. 4-[1-(4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole.
The procedure was as in 1. above, but starting from alpha-(6-chloro-4H-1,3-benzodioxin-8-yl)-alpha-methyl-1-triphenylmethyl-1H-imidazole-4-methanol (prepared in example 2.B.1.). After removal of triphenylmethane, the residue obtained was dissolved in water and the solution was made alkaline to pH 8 by the addition of a saturated solution of sodium carbonate. The precipitate which formed was dissolved in dichloromethane. The organic phase was dried over sodium sulphate and the solvent evaporated under reduced pressure. The residue was subjected to chromatography on silica (eluent : 95:4.5:0.5 dichloromethane-methanol-ammonia mixture)
Yield : 52%. MPt : 145-148°C (ethyl acetate).
Analysis for $C_{13}H_{14}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 67.83 | H 6.09 | N 12.17 |
| Found : | 67.68 | 6.11 | 12.10 |

The compound thus obtained was in the racemic form. It was resolved into its two enantiomers by the following method.
7.57 g ((0.0329 mole) of racemic 4-[1-(4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole were dissolved in 263 ml of hot isopropyl alcohol. 2.47 g (0.0165 mole) of d-tartaric acid dissolved in 33 ml of isopropyl alcohol

were added. A flocculant precipitate formed. The suspension was stirred for 16 hours at ambient temperature and the liquid phase was removed by decantation. The residue obtained was taken up in 300 ml of boiling isopropyl alcohol. The insoluble fraction crystallized. The mixture was cooled to 45°C, was stirred at this temperature for 4 hours and was then filtered hot (45°C). 3.21 g of crystalline salt (hemitartrate) were obtained.

MPt : 164°C. $[\alpha]_D^{25}$ = + 40.8 (c = 1, methanol).

The filtrate resulting from the separation of the crystals wil be dealt with under b) below.

a) The crystals obtained above were first recrystallized twice from isopropyl alcohol.
MPt : 178°C. $[\alpha]_D^{25}$ = + 53.3 (c = 1, methanol).
Next, 1 g of this salt were dissolved in 33 ml of water and the solution made alkaline to pH 9.5 by addition of a 1N aqueous solution of sodium hydroxide. A precipitate formed which was filtered off and recrystallized from 1 ml of ethyl acetate. 0.457 g of the dextro-rotatory isomer d-4-[1-(4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole were thus obtained.
MPt : 113.7°C. $[\alpha]_D^{25}$ = + 69.8 (c = 1, methanol).
Analysis for $C_{13}H_{14}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 67.83 | H 6.09 | N 12.17 |
| Found : | 67.88 | 6.06 | 12.13 |

b) The filtrate was evaporated under reduced pressure to remove isopropyl alcohol. The residue obtained was dissolved in water and the solution made alkaline to pH 9.5 by the addition of a 1N aqueous solution of sodium hydroxide. The liberated base precipitated, was filtered off and was treated in isopropyl alcohol with half an equivalent of l-tartaric acid. The salt which formed precipitated from the medium, was filtered off and was recrystallized from isopropyl alcohol. MPt : 178°C.

$[\alpha]_D^{25}$ = -51.57 (c = 1, methanol).
It was then redissolved in water and the solution made alkaline to pH 9.5 by addition of a 1N aqueous solution of sodium hydroxide. A precipitate formed which was recrystallized twice from ethyl acetate. 0.296 g of the laevorotatory isomer 1-4-[1-(4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole were obtained.
MPt : 114.4°C. $[\alpha]_D^{25}$ = - 72.6 (c = 1, methanol).
Analysis for $C_{13}H_{14}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 67.83 | H 6.09 | N 12.17 |
| Found : | 67.78 | 6.10 | 12.24 |

6. 4-[(6-methyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole hydrochloride.
This compound was prepared in a similar manner.
MPt : 175-183°C (decomposition).
Analysis for $C_{13}H_{14}N_2O_2$.HCl in % :

| | | | |
|---|---|---|---|
| Calculated : | C 58.58 | H 5.63 | N 10.51 |
| Found : | 56.47 | 5.63 | 9.93 |

Example 5. Preparation of 4-[1-[2,2-dimethyl-4H-1,3-benzodioxin-6(or 8)-yl]alkyl]-1H-imidazoles of formulae I and III ($Z_1 + Z_2 = -C(CH_3)_2-$)

1. 4-[(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)methyl]-1H-imidazole.
3.4 g (0.013 mole) of alpha-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1H-imidazole-4-methanol (prepared in example 3.4) were subjected to hydrogenolysis in methanol at 80°C for 5 hours, in the presence of 10% palladium on carbon and under a hydrogen pressure of 2.8 bar. The catalyst was then filtered off and the solvent removed under reduced pressure. The residue obtained was subjected to chromatography on silica (eluent : 90:10 dichloromethane-methanol). 3 g of 4-[(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)methyl]-1H-imidazole were obtained.
Yield : 94%. MPt : 150-170°C.

NMR spectrum (DMSO) : delta 1.45 (6H, s, $CH_3$-C-$CH_3$), 3.78 (2H, s, $CH_2$), 4.77 (2H, s, $CH_2$) , 6.5-7.7 (5H, m, ArH + ImH)

2a. 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole.

94.13 g (0.317 mole) of alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1H-imidazole-4-methanol hydrochloride (prepared in example 3.1 or 3.5) were added to one litre of anhydrous liquid ammonia. Solubilization of the reagent was completed by addition of one litre of tetrahydrofuran. 14.6 g (0.634 mole) of sodium were then added piece by piece. Five minutes after the sodium had disappeared, 34 g of ammonium chloride were added and the reaction medium was stirred for half an hour. 1.56 litres of a 10% solution of methanol in toluene were added. Ammonia was then evaporated off on a water bath. 780 ml of water were then added and the organic phase separated. The aqueous phase was extracted twice with 500 ml of toluene. The organic phases were combined and washed with 1 litre of water, then dried over sodium sulphate and distilled under reduced pressure.

The residue obtained was recrystallized from 900 ml of boiling acetone. 57.8 g of 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole were thus obtained, melting between 160 and 170°C.

Yield : 74.6%.

Analysis for $C_{14}H_{16}N_2O_2$ in %.

| | | | |
|---|---|---|---|
| Calculated : | C 68.85 | H 6.56 | N 11.48 |
| Found : | 69.15 | 6.70 | 11.53 |

2.b. The same product could be prepared starting from 0.8 g (0.0015 mole) of alpha-(6-chloro-2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-triphenylmethyl-1H-imidazole-4-methanol (obtained in example 1.C.3) and 0.245 g (0.0106 mole) of sodium according to the procedure described in example 3.5. The residue obtained after evaporation of the toluene phase was subjected to chromatography on

150 g of silica (10 μm) (eluent : 95:5 ethyl acetate-methanol). 123 mg of the product were obtained corresponding to that isolated in 2.a above.

The following products were obtained by the method described in 2.a above.

3. 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1 methyl-1H-imidazole.
This compound was prepared starting from alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1-methyl-1H-imidazole-4-methanol hydrochloride (prepared as in 1.C.12). The residue obtained was purified by chromatography on silica (eluent : 98:2 dichloromethane-methanol).
Yield : 67%. MPt : 67-72°C (isopropyl ether-hexane).
Analysis for $C_{15}H_{18}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 69.74 | H 7.02 | N 10.84 |
| Found : | 69.93 | 7.54 | 10.78 |

4. 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-5-methyl-1H-imidazole.
This compound was prepared starting from 9.68 g of the mixture of the hydrochlorides of the O-methylated and alcohol derivatives prepared in example 3.2. It was purified by chromatography on silica (eluent : 90:10 dichloromethane-methanol). 4 g of the desired product were obtained.
MPt : 172-178°C (dichloromethane).
Analysis for $C_{15}H_{18}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 69.74 | H 7.02 | N 10.84 |
| Found : | 67.55 | 6.98 | 10.38 |

5. 4-[(2,2,6-trimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole.
This compound was prepared from 2.3 g of the mixture containing the O-methyl derivative prepared in example 3.3. 0.9 g of the desired product were isolated.

MPt : 152-155°C (ethyl acetate).
Analysis for $C_{15}H_{18}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 69.74 | H 7.02 | N 10.84 |
| Found : | 69.82 | 7.04 | 10.64 |

6. 4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole.
This compound was prepared starting from alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-alpha-methyl-1H-imidazole-4-methanol hydrochloride (prepared in example 3.9). The residue obtained following evaporation of toluene crystallized on stirring at 60°C in isopropyl ether.
Yield : 60%. MPt : 118 and 130°C.
Analysis for $C_{15}H_{18}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 69.74 | H 7.02 | N 10.84 |
| Found : | 69.64 | 6.95 | 10.72 |

7. 4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)pentyl]-1H-imidazole.
This compound was prepared by reduction of alpha-n-butyl-alpha-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)-1H-imidazole-4-methanol (prepared in example 3.8).
Yield : 23.6%. MPt : 108-12°C (cyclohexane).
Analysis for $C_{18}H_{24}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 72.0 | H 8.0 | N 9.33 |
| Found : | 72.08 | 8.15 | 9.32 |

Example 6. Preparation of 3-[1-(1H-imidazol-4-yl)alkyl]-2 (or 6)-hydroxybenzenemethanols of formula I ($Z_1$ = $Z_2$ = H).

1. 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol.
82.83 g (0.339 mole) of 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole (prepared in example 5.2) were suspended in 1645 ml of water (pH = 7.9) and dissolved by adding 349 ml of a 1N aqueous

solution of hydrochloric acid, over the course of 80 minutes. At the end of this addition, the pH of the solution was 2.5. The reaction medium was then heated for one hour in an oil bath at 120°C. The solution was cooled, treated with 5 g of Norit and filtered on Hyflo-cel. This solution was then made alkaline by addition of 242.5 ml of a 1N aqueous solution of sodium hydroxide (pH = 8.5). The precipitate was filtered off, washed with water and dried. This precipitate was then dissolved in 3.3 litres of ethyl acetate in the presence of Norit and a few grammes of sodium sulphate. The solution was then filtered, concentrated to a volume of 400 ml and left to crystallize. 55.67 g of 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol were obtained.
Yield : 80.4%. MPt : 152-155°C.
Analysis for $C_{11}H_{12}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 64.69 | H 5.92 | N 13.72 |
| Found : | 65.05 | 5.69 | 13.72 |

The following compounds were prepared by the method described above.

2. 3-[(1-methyl-1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol.
This compound was prepared starting from 7 g of 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1-methyl-1H-imidazole (prepared in example 5.3).
5.6 g of the desired product were obtained.
Yield : 73%. MPt : 139-144°C (acetonitrile).
Analysis for $C_{12}H_{14}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 66.03 | H 6.46 | N 12.83 |
| Found : | 65.81 | 6.65 | 12.55 |

3. 3-[(5-methyl-1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol.
This compound was prepared starting from 4 g of 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-5-methyl-1H-

imidazole (prepared in example 5.4). 2.7 g of the desired product were obtained.
Yield : 80%. MPt : 126-130°C (acetonitrile).
Analysis for $C_{12}H_{14}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 66.03 | H 6.46 | N 12.83 |
| Found : | 66.25 | 6.44 | 12.76 |

4. 3-[(1H-imidazol-4-yl)methyl]-2-hydroxy-5-methylbenzenemethanol.
This compound was prepared starting from 3 g of 4-[(2,2,6-trimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole (prepared in example 5.5). 2.4 g of the desired product were obtained.
Yield : 95%. MPt : 170-175°C (decomposition).
Analysis for $C_{12}H_{14}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 66.03 | H 6.46 | N 12.83 |
| Found : | 66.02 | 6.56 | 12.73 |

5. 3-[1-(1H-imidazol-4-yl)ethyl]-2-hydroxybenzenemethanol.
This compound was prepared by hydrolysis of 4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole (prepared in example 5.6).
Yield : 60%. MPt : 135-136°C
Analysis for $C_{12}H_{14}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 66.03 | H 6.46 | N 12.83 |
| Found : | 65.97 | 6.44 | 12.80 |

6. 3-[1-(1H-imidazol-4-yl)pentyl]-2-hydroxybenzenemethanol.
This compound was prepared by hydrolysis of 4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)pentyl]-1H-imidazole (prepared in example 5.7).
Yield : 94%. MPt : 93°C.
Analysis for $C_{15}H_{20}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 69.23 | H 7.69 | N 10.77 |
| Found : | 69.30 | 7.70 | 10.81 |

7. 3-[(1H-imidazol-4-yl)methyl]-6-hydroxybenzenemethanol.
This compound was prepared starting from 4 g of 4-[(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)methyl]-1H-imidazole (prepared in example 5.1). 1.6 g of the desired product were obtained.
Yield : 48%. MPt : 149-155°C (decomposition).
Analysis for $C_{11}H_{12}N_2O_2$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 64.70 | H 5.88 | N 13.72 |
| Found : | 65.11 | 6.11 | 13.45 |

Example 7. Preparation of starting alkyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoates of formula IV.

Ethyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoate.

a. Ethyl 3-[(1H-imidazol-4-yl)methyl]-2-oxo-cyclohexanecarboxylate.
A solution of sodium ethoxide was prepared, under a nitrogen atmosphere, by dissolving 58.2 g (2.53 mole) of sodium in 2 litres of absolute ethanol. The solution was cooled to 10°C and 195.5 g (1.15 mole) of ethyl 2-oxo-cyclohexanecarboxylate were added with vigorous stirring. The sodium salt precipitated and the mixture was stirred at 20°C for one hour and was then cooled to -10°C. 193.5 g (1.26 mole) of 4-chloromethyl-1H-imidazole hydrochloride dissolved in 1 litre of absolute alcohol were added dropwise. The temperature of the reaction mixture was maintained at -10°C for one hour and was then allowed to return to ambient temperature and stirring was maintained for 20 hours. 2 litres of solvent were distilled off at atmospheric pressure and a solution of sodium ethoxide, formed by dissolving 79.35 g (3.45 mole) of sodium in 1.2 litres of absolute ethanol, was added at between 30 and 40°C. Distillation of the solvent was continued until the reaction medium reached a temperature of 100-105°C. Distillation of the solvent was stopped and reflux was maintained for 10 hours. The mixture was then

cooled to ambient temperature and 200 ml of absolute ethanol were added. The mixture was then cooled to -10°C and 400 ml of a 9.9N methanolic solution of hydrochloric acid was then added dropwise. The temperature was allowed to rise to 10°C and sodium chloride was removed by centrifuging. Following evaporation of the solvent under reduced pressure, 180 g of a brown oil were obtained. The sodium chloride deposit removed by centrifuging was washed twice with a litre of dichloromethane. This solvent was then removed under reduced pressure and a further 60 g of oil were recovered.

The oil was purified by chromatography on silica (80 mm diameter column, Merck TLC 60 H 15 $\mu$m silica; eluent 93:6.5:0.5 mixture of dichloromethane-ethanol-ammonia). 138 g of ethyl 3-[(1H-imidazol-4-yl)methyl]-2-oxo-cyclohexanecarboxylate were finally obtained in the form of an oil which slowly solidified (mixture of diastereoisomers).

Yield : 48%.

The ethyl 2-oxo-cyclohexanecarboxylate used as the starting product was prepared according to the method described by H.R.SNYDER et al. (Organic Syntheses, Coll. Vol.II.(1943), 531-534).

The 4-chloromethyl-1H-imidazole hydrochloride used as a starting product was prepared according to the method described by R.A.TURNER et al. (J.Am.Chem.Soc.71,(1949), 2801-2803).

b. Ethyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoate.

176 g (56.5 ml, 1.1 mole) of bromine dissolved in 400 ml of glacial acetic acid were added dropwise at between 17 and 20°C over a period of 30 minutes, under an argon atmosphere, to a solution containing 37.5 g (0.55 mole) of ethyl 3-[(1H-imidazol-4-yl)methyl]-2-oxo-cyclohexanecarboxylate in 1.5 litres of glacial acetic acid. The mixture was then heated under reflux for 4 hours. The red solution blackened progressively. The

mixture was cooled to 20°C and evaporated under reduced pressure. The residue was taken up in 1.2 litre of 50% aqueous acetic acid solution. A spatula tip of anion exchanged resin (Amberlite IR 45 acetate) was then added, together with 25 g of 10% palladium on carbon and 25 grams of 10% rhodium on carbon and the mixture was stirred for 150 minutes under a hydrogen pressure of 3.5 bar. The mixture was filtered on Celite and evaporated under reduced pressure. The oil obtained was dissolved in 1 litre of a mixture of ice and water, the solution was adjusted to pH 8 by addition of a 2 N aqueous solution of sodium hydroxide and was rapidly extracted 5 times with 400 ml of ethyl acetate. The organic phases were combined, dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica (eluent : 93.5:6:0.5 dichloromethane-ethanol-ammonia mixture). 75.9 g of ethyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoate were obtained in the form of an oil which slowly crystallized.

Yield : 55%. MPt : 133°C

Analysis for $C_{13}H_{14}N_2O_3$ in % :

| | | | |
|---|---|---|---|
| Calculated : | C 63.41 | H 5.69 | N 11.38 |
| Found : | 63.72 | 5.80 | 11.32 |

Example 8. Preparation of 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanols of formula I ($Y_1 = OZ_2$, $Y_2 = Z_1$ $Z_2 = R_5 = H$).

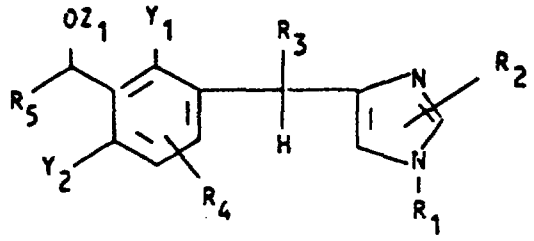
3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol.

22.8 g (0.6 mole) of lithium-aluminium hydride were added in small portions, under an argon atmosphere, to a solution of 73.9 g (0.3 mole) of ethyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoate (prepared in example 7) in 4 litres of anhydrous tetrahydrofuran. The temperature rose progressively and when the addition was completed, the mixture was refluxed

for 3 hours. The mixture was cooled to 10°C and 200 ml of ethyl acetate were added dropwise. The mixture was evaporated under reduced pressure and the residue was taken up in 1 litre of an ice and water mixture. The suspension was adjusted to pH 7.5 by addition of concentrated hydrochloric acid. 700 ml of ethyl acetate were added, the mixture was stirred vigorously for 30 minutes and then filtered. The filtrate was decanted off and the aqueous phase was extracted 3 times with 500 ml of ethyl acetate. The organic phases were combined, dried over magnesium sulphate, filtered and then evaporated under reduced pressure. 61 g of an oil were obtained which crystallized. The filter cake was carefully washed with ethyl acetate.
This cake was taken up in 1.5 litre of ethyl acetate and extracted under reflux for 3 hours. The mixture was filtered and after evaporation of the solvent under reduced pressure, a further 7 g of oil were recovered. The product was purified by chromatography on silica (eluent : 91.5:8:0.5 dichloromethane-ethanol-ammonia mixture) and recrystallized from ethyl acetate. 33.8 g of 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol were obtained, identical to the product obtained in example 6.1.
Yield : 55%.

CLAIMS for contracting states : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

1. Substituted 1H-imidazoles, their optical isomers and their racemic mixtures corresponding to the general formula



(I)

in which

$R_1$, $R_2$, $R_3$ and $R_5$, which may be identical or different, each represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms.

$R_4$ represents a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms or an alkoxy radical containing 1 to 4 carbon atoms,

one of the radicals $Y_1$ and $Y_2$ represents hydrogen and the other an $OZ_2$ radical, and

$Z_1$ and $Z_2$ taken separately both represent hydrogen or an alkyl radical containing 1 to 4 carbon atoms and together represent a $-CH_2-$ or $-C(CH_3)_2-$ group,

as well as their pharmaceutically acceptable non-toxic acid addition salts.

2. 1H-imidazoles corresponding to the general formula I given in Claim 1, in which

$R_1$, $R_2$, $R_4$ and $R_5$ each represents hydrogen,

$R_3$ represents hydrogen or an alkyl radical containing 1 to 4 carbon atoms and

$Z_1$ and $Z_2$ taken separately represent hydrogen and together represent a $-CH_2-$ or $-C(CH_3)_2-$ group,

as well as their pharmaceutically acceptable non-toxic acid addition salts.

* C L M S *

3. 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzenemethanol and its pharmaceutically acceptable non-toxic acid addition salts according to Claim 1.

4. 3-[(1H-imidazol-4-yl)methyl]-6-hydroxybenzenemethanol and its pharmaceutically acceptable non-toxic acid addition salts according to Claim 1.

5. 3-[1-(1H-imidazol-4-yl)ethyl]-2-hydroxybenzenemethanol and its pharmaceutically acceptable non-toxic acid addition salts according to Claim 1.

6. 3-[1-(1H-imidazol-4-yl)pentyl]-2-hydroxybenzenemethanol and its pharmaceutically acceptable non-toxic acid addition salts according to Claim 1.

7. 4-[(4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole and its pharmaceutically acceptable non-toxic acid addition salts according to Claim 1.

8. 4-[1-(4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole and its pharmaceutically acceptable non-toxic acid addition salts according to Claim 1.

9. 4-[(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)methyl]-1H-imidazole and its pharmaceutically acceptable non-toxic acid addition salts according to Claim 1.

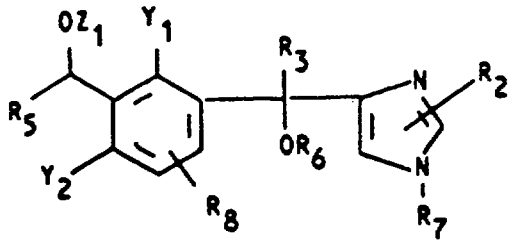
10. 4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)ethyl]-1H-imidazole and its pharmaceutically acceptable non-toxic acid addition salts according to Claim 1.

11. 4-[1-(2,2-dimethyl-4H-1,3-benzodioxin-8-yl)pentyl]-1H-imidazole and its pharmaceutically acceptable non-toxic acid addition salts according to Claim 1.

* C L M S *

12. Process for the preparation of substituted 1H-imidazoles and their salts such as defined in Claim 1, characterized in that :

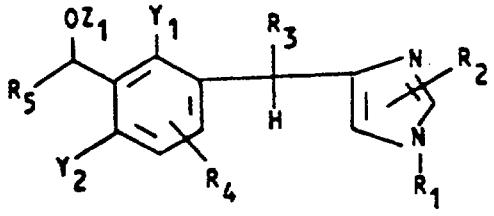
a) in order to prepare 1H-imidazoles corresponding to the general formula I, in which $Z_1$ and $Z_2$ taken separately represent an alkyl radical having 1 to 4 carbon atoms and together represent a $-CH_2-$ or a $-C(CH_3)_2$-group, an imidazole compound having the following formula :



(II)

in which $R_2$, $R_3$, and $R_5$ have the meanings given in Claim 1, $R_6$ represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms, $R_7$ represents an $R_1$ radical such as defined in Claim 1 or a radical which can be easily removed by reduction, $R_8$ represents an $R_4$ radical such as defined in Claim 1 or a chlorine atom, one of the radicals $Y_1$ and $Y_2$ represents hydrogen and the other an $OZ_2$ radical, $Z_1$ and $Z_2$ having the meanings given above, is reduced; or

b) in order to prepare 1H-imidazoles corresponding to the general formula I in which $Z_1$ and $Z_2$ are hydrogen, a 4-[[2,2-dimethyl-4H-1,3-benzodioxin-6(or8)-yl]methyl]-1H-imidazole having the formula

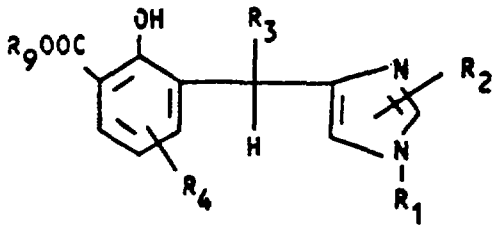


(III)

* C L M S *

in which $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ have the meanings given in Claim 1, one of the radicals $Y_1$ and $Y_2$ represents hydrogen and the other an $OZ_2$ radical, $Z_1$ and $Z_2$ together representing the $-C(CH_3)_2-$ group is hydrolysed in an aqueous acid medium; or

c) in order to prepare 1H-imidazoles corresponding to the general formula I in which $Y_1 = OZ_2$ and $Y_2$, $Z_1$, $Z_2$ and $R_3$ are hydrogen, an alkyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoate of formula :




(IV)

in which $R_1$, $R_2$, $R_3$ and $R_4$ have the meanings given in Claim 1 and $R_9$ represents an alkyl radical containing 1 to 4 carbon atoms is reduced; and

d) in that, optionally, the 1H-imidazoles of formula I thus obtained are converted into their pharmaceutically acceptable non-toxic acid addition salts.

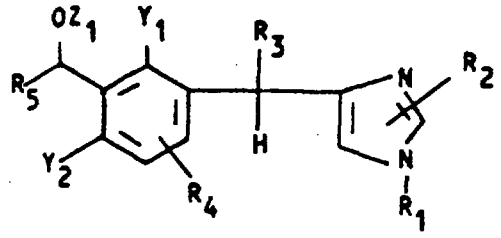
13. 1H-imidazoles according to any of Claims 1 to 11 or one of their pharmaceutically acceptable non-toxic acid addition salts for therapeutic use as an anti-ischaemic agent.

14. Therapeutic compositions containing a therapeutically effective quantity of a 1H-imidazole according to any of Claims 1 to 11 or one of its pharmaceutically acceptable non-toxic acid addition salts, in association with solid or liquid pharmaceutical excipients.

* C L M S *

CLAIMS for contracting states : ES, GR

1. Process for the preparation of 1H-imidazoles, their optical isomers and their racemic mixtures corresponding to the general formula



(I)

in which

$R_1$, $R_2$, $R_3$ and $R_5$, which may be identical or different, each represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms.

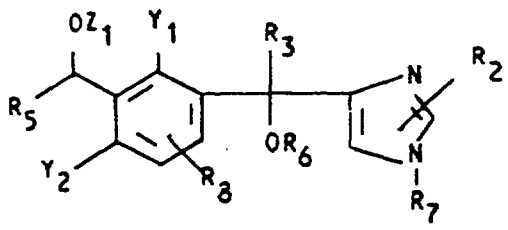
$R_4$ represents a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms or an alkoxy radical containing 1 to 4 carbon atoms,

one of the radicals $Y_1$ and $Y_2$ represents hydrogen and the other an $OZ_2$ radical, and

$Z_1$ and $Z_2$ taken separately both represent hydrogen or an alkyl radical containing 1 to 4 carbon atoms and together represent a $-CH_2-$ or $-C(CH_3)_2-$ group,

as well as their pharmaceutically acceptable non-toxic acid addition salts, characterized in that :

a) in order to prepare 1H-imidazoles corresponding to the general formula I, in which $Z_1$ and $Z_2$ taken separately represent an alkyl radical having 1 to 4 carbon atoms and together represent a $-CH_2-$ or a $-C(CH_3)_2-$ group, an imidazole compound of the following formula :

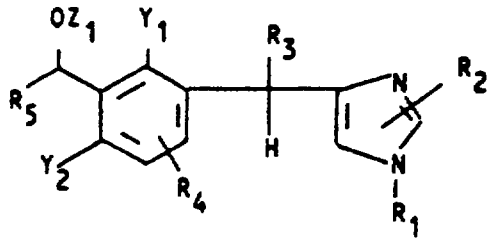


(II)

* C L M S *

in which $R_2$, $R_3$, and $R_5$ have the meanings given above, $R_6$ represents a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms, $R_7$ represents an $R_1$ radical such as defined above or a radical which can be easily removed by reduction, $R_8$ represents an $R_4$ radical such as defined above or a chlorine atom, one of the radicals $Y_1$ and $Y_2$ represents hydrogen and the other an $OZ_2$ radical, $Z_1$ and $Z_2$ having the meaning given above, is reduced; or

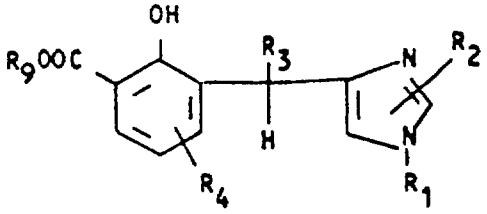
b) in order to prepare 1H-imidazoles corresponding to the general formula I in which $Z_1$ and $Z_2$ are hydrogen, a 4-[[2,2-dimethyl-4H-1,3-benzodioxin-6(or8)-yl]methyl]-1H-imidazole having the formula



(III)

in which $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ have the meanings given above, one of the radicals $Y_1$ and $Y_2$ represents a hydrogen and the other an $OZ_2$ radical, $Z_1$ and $Z_2$ together being the $-C(CH_3)_2-$ group, is hydrolysed in an aqueous acid medium ; or

c) in order to prepare 1H-imidazoles corresponding to the general formula I in which $Y_1$ = $OZ_2$ and $Y_2$, $Z_1$, $Z_2$ and $R_3$ are hydrogen, an alkyl 3-[(1H-imidazol-4-yl)methyl]-2-hydroxybenzoate of formula :



(IV)

* C L M S *

in which $R_1$, $R_2$, $R_3$ and $R_4$ have the meanings given above and $R_9$ represents an alkyl radical containing 1 to 4 carbon atoms, is reduced; and

d) in that, optionally, the 1H-imidazoles of formula I thus obtained are converted into their pharmaceutically acceptable non-toxic acid addition salts.

* C L M S *