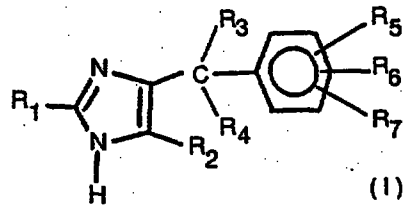
Description

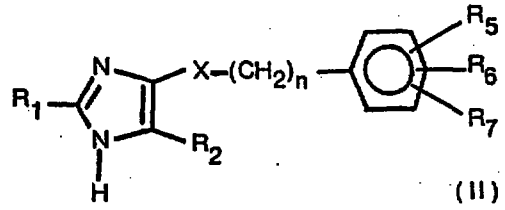
The present invention relates to substituted imidazole derivatives and their non-toxic, pharmaceutically acceptable acid addition salts, and their preparation, to pharmaceutical compositions containing the same, and to their use.

4-Benzyl- and 4-benzoylimidazole derivatives having valuable pharmaceutical activity are disclosed in EP—A—24 82 9. The imidazole derivatives of the present invention have the general formula:



(I)

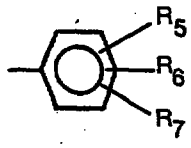
or



(II)

wherein R_1 is H, an alkyl of 1 to 4 carbon atoms or $—CH_2OH$; R_2 is H or CH_3; R_3 is

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_5$ ies, been

or  and R_4 is H or OH; or R_3 and R_4 together represent sent by ch a

$=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$, or $=CH-CH_2CH_2CH_3$; X is $-CH(R_8)-CH(R)-$

or $-C(R_{11})=C(R_{10})-$; R_5, R_6, and R_7,

which can be the same or different are H, $—CH_3$, $—CH_2CH_3$, halogen, OH or $—OCH_3$ or R_5 is hydrogen and R_6 and R_7 together form an $—O—CH_2—O$-bridge between two adjacent carbon atoms in the phenyl group;

$-CHR_8-$ is $-CH_2-$, $-CH(CH_3)-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$,

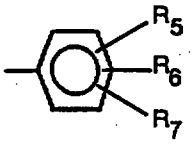
$-CH(-CH(CH_3)-CH_3)-$, $-CH(-CH_2CH_2CH_2CH_3)-$ or $>C=CH_2$, $>C=CH-CH_3$, $>C=CH-CH_2CH_3$,

$>C=C(CH_3)-CH_3$, $>C=CH-CH_2CH_2CH_3$; R_9 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$,

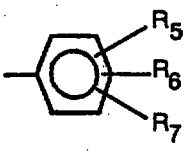
$-CH_2CH_2CH_2CH_3$ or OH; R_{10} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

or $-CH_2CH_2CH_2CH_3$; R_{11} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

or $-CH_2CH_2CH_2CH_3$; n is 0 to 4; provided that

— when R_4 is OH, R_1 is H or CH_3 and R_3 is  ;

then R_5, R_6 and R_7 are not all simultaneously hydrogen

— when R_1, R_2 and R_4 all are hydrogen and R_3 is  ;

then R_5, R_6, R_7 are not all simultaneously hydrogen;
— R_8 and R_9 are not simultaneously hydrogen; and
— R_{11} and R_{10} are not simultaneously hydrogen.

Because of the tautomerism in the imidazole ring the compounds of the general formula I and II are 4(5)-substituted imidazole derivatives.

The non-toxic pharmaceutically acceptable acid addition salts of these compounds are also within the scope of the invention.

The compounds of the formula (I) and (II) form acid addition salts with both organic and inorganic acids. They can thus form many pharmaceutically usable acid addition salts, as, for instance, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like.

The invention includes within its scope pharmaceutical compositions comprising at least one of the compounds of formula (I) or (II) or a non-toxic, pharmaceutically acceptable salt thereof, and a compatible pharmaceutically acceptable carrier therefor.

The invention provides, for example, the following specific compounds of formula (I):

4-[α,α-bis(2-methylphenyl)hydroxymethyl]imidazole
4-[[α-(2-methylphenyl)]-2-methylbenzyl]imidazole
4-(α-phenylbenzyl)-5-methylimidazole
4-[[α-(2,6-dimethylphenyl)]-α-methyl]hydroxymethyl]imidazole
4-[[α-(2,3-dimethylphenyl)]-α-methyl]hydroxymethyl]imidazole
4-[[α,α-bis(2-methylphenyl)hydroxymethyl]-5-methylimidazole
4-[[α-(2-methylphenyl)]-2-methylbenzyl]-5-methylimidazole
4-[(α-methyl)-2,6-dimethylbenzyl]imidazole
4-[(α-methyl)-2,3-dimethylbenzyl]imidazole
4-[(α-ethyl)-3-methylbenzyl]imidazole
4-[(α-butyl)-2,3-dimethylbenzyl]imidazole
4-[(α-methyl)-2,3-dimethylbenzyl]-2-methylimidazole
4-[(α-propyl)-2-methylbenzyl]imidazole
4-[(α-methyl)-2-methylbenzyl]imidazole
4-[(α-methyl)-2,5-dimethylbenzyl]imidazole
4-[α-ethyl-α-(3-methylphenyl)-hydroxymethyl]imidazole
4-[α-butyl-α-(2,3-dimethylphenyl)-hydroxymethyl]imidazole
4-[α-methyl-α-(2,3-dimethylphenyl)-hydroxymethyl]-2-methylimidazole
4-[α-propyl-α-(2-methylphenyl)-hydroxymethyl]imidazole
4-[α-methyl-α-(2-methylphenyl)-hydroxymethyl]imidazole
4-[α-methyl-α-(2,5-dimethylphenyl)-hydroxymethyl]imidazole
4-[α,α-bis-(2,3-dimethylphenyl)hydroxymethyl]imidazole
4-[α-(2,3-dimethylphenyl)-2,3-dimethylbenzyl]imidazole
4-[(α-ethyl)-2,6-dimethylbenzyl]imidazole
4-[(α-ethyl)-2,3-dimethylbenzyl]imidazole
1-(4-imidazolyl)-1-(2,3-dimethylphenyl)ethylene
1-(4-imidazolyl)-1-(2,6-dimethylphenyl)ethylene

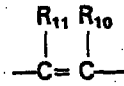
The following specific compounds of formula (II):

4-[2-(2,6-dimethylphenyl)-1-methylethyl]imidazole
4-[2-(2,6-dimethylphenyl)propyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-methylpropyl]imidazole
4-[2-(2,6-dimethylphenyl)-2-hydroxyethyl]imidazole
4-(2-phenylpropyl)imidazole
4-[2-(2,6-dimethylphenyl)-1-methylethenyl]imidazole

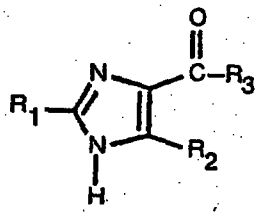
4-[2-(2,6-dimethylphenyl)-1-propenyl]imidazole
4-(2-methyl-4-phenyl-1-butenyl)imidazole
4-[2-(4-chlorophenyl)-1-methylpropyl]imidazole
4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]imidazole
4-[3-(2,6-dimethylphenyl)-2-methyl-1-propenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-ethylethenyl]imidazole
4-[2-(2,3-dimethylphenyl)-1-methylethenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-isopropylethenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-methylethenyl)]-2-methylimidazole
4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-5-methylimidazole
4-[2-(2,6-dichlorophenyl)-1-methylethenyl]imidazole
4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]imidazole
4-[3-(2,6-dimethylphenyl)-1-ethyl-1-propenyl]imidazole
4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]-5-methylimidazole
4-[5-(2,6-dimethylphenyl)-1-methylpentyl]imidazole
4-[4-(2,6-dichlorophenyl)-1-methyl-1-butenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-ethylethyl]imidazole
4-[2-(2,6-dimethylphenyl)-2-ethylethyl]imidazole
4-[2-(3,4-methylenedioxyphenyl)propyl]imidazole

The compounds of the present invention have been found to possess excellent antihypertensive activity. Preliminary tests have shown that they also possess other valuable pharmacological properties, for example, antithrombotic and diuretic effect. Antimycotic and antifungal properties have also been found.

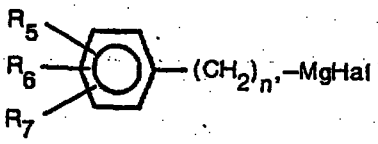
While all of the compounds of formula (I) and (II) essentially satisfy the objectives of the present invention, certain groups of compounds remain preferred. One such preferred group is represented by formula (I) wherein R_4 is hydrogen, R_3 is alkyl and R_5, R_6 and R_7, which can be the same or different, each are hydrogen, methyl, ethyl or halogen. Another preferred group of compounds is represented by formula (II), wherein R_5 R_6 and R_7, which can be the same or different, each are hydrogen, methyl, ethyl or halogen. Especially the compounds wherein n is greater than 0 possess valuable antimycotic properties. Especially good antihypertensive properties have been found in compounds of formula (II) wherein n is 0 and X is



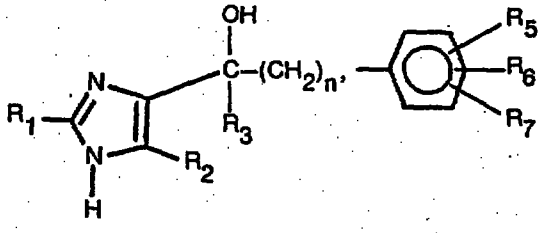
According to the feature of the invention, the compounds of formula (I) wherein R_4 is OH and the compounds of formula (II) are made by a Grignard reaction, in which an imidazolylketone of the formula



wherein R_1, R_2 and R_3 are as defined before, is reacted with an arylalkyl magnesium halide derivative or aryl magnesium halide derivative of the formula:



wherein R_5, R_6 and R_7 are as defined before, n' is 0 to 5 and Hal is a halogen atom to give compounds of the formula (III)

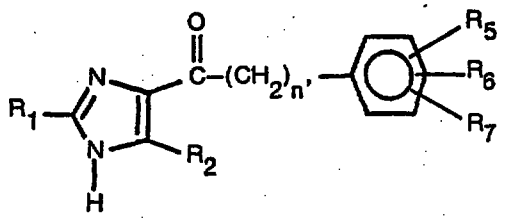


(III)

wherein R_1, R_2, R_3, R_5, R_6, R_7 and n' are as before.

The arylalkylmagnesium halide derivative can be, for example, an arylalkylmagnesiumbromide derivative, which is prepared by reacting the corresponding arylalkylbromide derivative with magnesium. Suitable solvents for the reaction include a variety of ethers, preferably tetrahydrofuran. The arylalkylmagnesiumhalide derivative is prepared in the usual way by adding the arylalkylmagnesiumhalide derivative in a suitable solvent, e.g. tetrahydrofuran, dropwise onto magnesium turnings covered by tetrahydrofuran, at the boiling point of the reaction mixture. When the magnesium turnings have reacted, the mixture is cooled slightly and the 4-imidazole derivative is added in solid form in small portions or in tetrahydrofurane solution. After the addition, the reaction mixture is refluxed until all of the 4-imidazole derivative has reacted. The reaction time varies between one and five hours.

Another process for the preparation of compounds of formula (III) is a Grignard reaction in which a compound of the formula (IV)



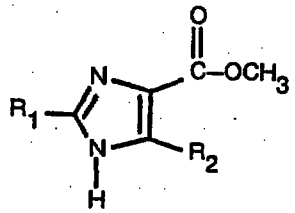
(IV)

wherein R_1—R_7 and n' are as before, is reacted with a compound of the formula

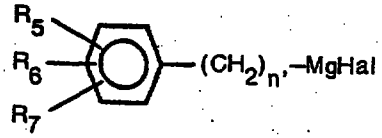
$$R_3MgHal$$

wherein R_3 is an alkyl or aryl as defined before and Hal is halogen.

Yet another process for the preparation of compounds of formula (III) is a Grignard reaction in which an imidazole carboxylic acid alkyl ester, preferably the methyl ester of the formula



wherein R_1 and R_2 are as before, is reacted in a first step with a Grignard reagent of the formula



wherein R_5, R_6, R_7 and n' are as before, to give a compound of formula (IV), which in a second step without isolation is reacted with a Grignard reagent of the formula

$$R_3MgHal$$

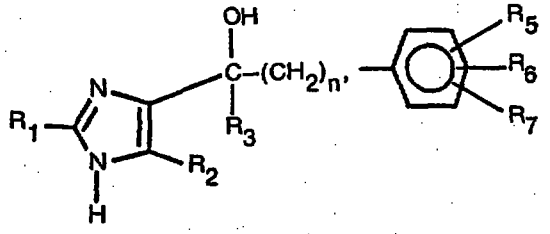
wherein R_3 is as defined before.

Compounds of formula (I) wherein R_4 is H can be prepared by reduction of compounds of formula (III) wherein n' is 0 with hydrogen. A suitable catalyst is e.g. palladium-on-carbon.

Unsaturated compounds of formula (I) wherein R_3 and R_4 are

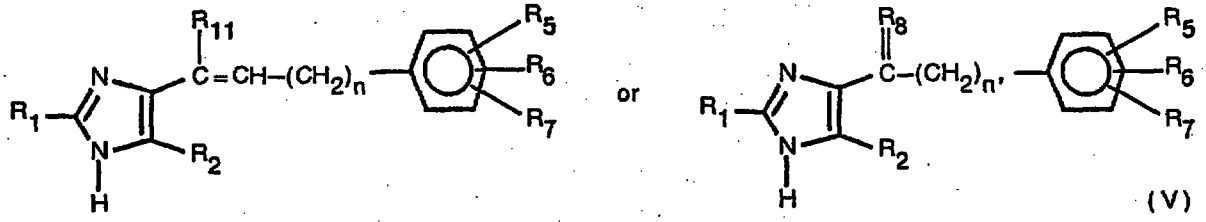
$=CH_2$, $=CH-CH_3$, $=CH-CH_2CH_3$, $=C(CH_3)-CH_3$ or $=CH-CH_2CH_2CH_3$

or formula (II) wherein R_{10} is hydrogen are prepared by dehydrating compounds of formula (III):



(III)

wherein R_1, R_2, R_5, R_6, R_7 are as defined before, R_3 is an alkyl or aryl as defined before and n' is 0 to 5, to give a compound of the formula (V)



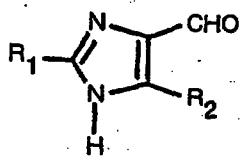
(V)

wherein R_1, R_2, R_5, R_6, R_7, and n and n' are as defined before; R_{11} is an alkyl as defined before and R_8 is an alkenyl as defined before.

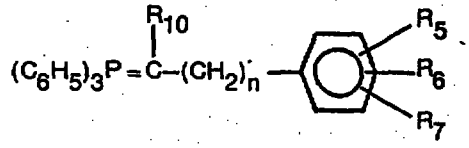
The dehydration is preferably performed by refluxing in an appropriate acidic solution, e.g. concentrated hydrochloric acid or heating for example with potassiumhydrogen sulfate.

The compounds of formula (V) can further be reduced with hydrogen in the presence of a palladium-on-carbon catalyst to the corresponding saturated compounds of formulae (I) and (II).

Compounds of formula (II) wherein R_{11} is hydrogen are prepared by a Wittig reaction which comprises reacting an imidazole aldehyde of the formula

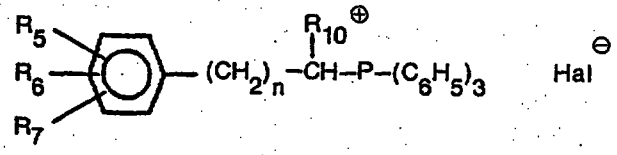


wherein R_1 and R_2 are as before, with an aralkylidenetriphenylphosphorane of the formula:



wherein R_5, R_6, R_7, R_{10} and n are as defined before, to give the unsaturated compounds of formula (II), which in a further step can be reduced to the corresponding saturated compounds of formula (II) as described above.

The aralkylidenetriphenylphosphoranes are preferably prepared by reacting the corresponding aralkyltriphenylphosphonium halide of the formula:

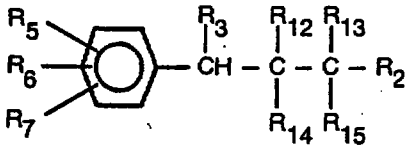


wherein R_5, R_6, R_7, R_{10} and n are as before and Hal is halogen, with a basic reagent, preferably butyllithium.

In the Grignard- and Wittig-syntheses described above, the free nitrogen atom in the imidazole starting material can be protected by different methods. Suitable protecting groups are for example benzyl, triphenylsilyl or dialkoxymethane. The removal of the protecting group can be performed in different ways,

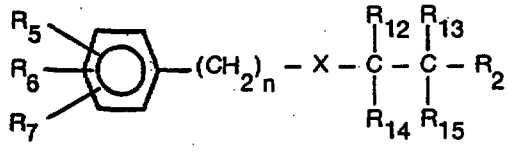
and depends on the kind of protecting group used. For example, a dialkoxymethane group is removed by acidic hydrolysis and a benzyl group by sodium in liquid ammonia.

The present invention further provides yet another method for preparing compounds of the invention. Thus, according to this embodiment of the invention, a starting material of the formula (VI) or (VII)



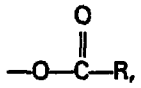
(VI)

or

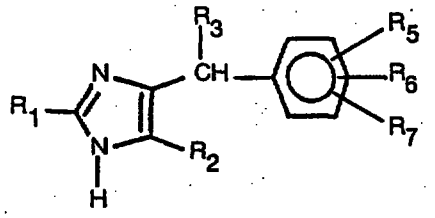


(VII)

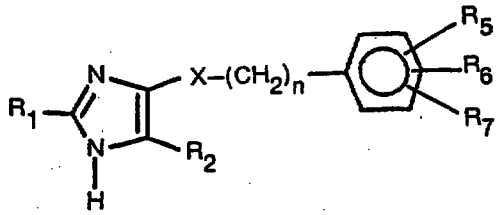
wherein R_2, R_3, R_5, R_6, R_7 and n are as hereinbefore defined; wherein R_{12}, R_{13}, R_{14} and R_{15}, which can be the same or different, are each hydrogen, hydroxy, mercapto, halogen, amino, —O— alkyl of 1 to 7 carbon atoms or



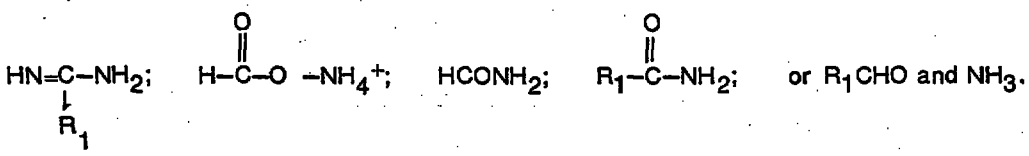
wherein R is an alkyl; or wherein R_{12} and R_{14} can be combined to form a keto group, or R_{13} and R_{15} can be combined to form a keto group, or both R_{12} and R_{14} and R_{13} and R_{15} can simultaneously form keto groups; is reacted with a reagent capable of converting said starting material to the corresponding imidazole of the formula:



or



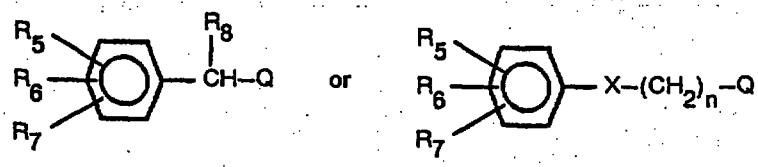
wherein R_1, R_2, R_3, R_5, R_6, R_7, X and n are defined as before. Reagents capable of converting the depicted starting material to the corresponding imidazole include $NH_3 + CH_2O$ (or a source of ammonia and formaldehyde



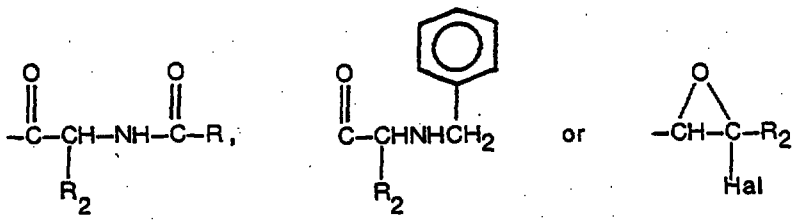
Choice of an appropriate reagent varies with the particular starting material employed.

When R_1 is hydrogen it is preferable to employ formamide at the reagent in cases where, in place of the bromine atom in the aforementioned starting materials, there is instead a hydroxyl, amino or acetyl group. In these instances, formamide is used in excess and acts in part as the solvent. Generally, the reaction is run at the boiling point of formamide for a period of time ranging from one to five hours.

Yet another process for the preparation of the compounds of formula (I) and (II) comprises reacting formamide with a benzene derivative of the formula:

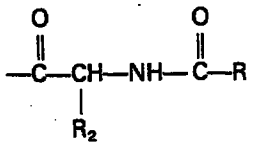


wherein R_5, R_6, R_7, R_8, n and X are as defined hereinabove, and Q is a radical of formula:

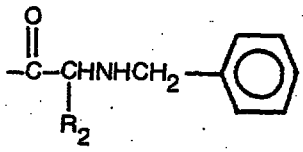


wherein R is a substituted and unsubstituted alkyl, arylalkyl or aryl group, and R_2, and Hal are as defined hereinabove. Preferably the reaction is performed by vigorously boiling the benzene derivative in formamide, the reaction time varying with the particular material employed.

Reaction times typically are from 30 minutes to 8 hours. Obviously, the formamide treatment will be followed by reaction with an appropriate acid (e.g. HCl) when Q is the starting material is

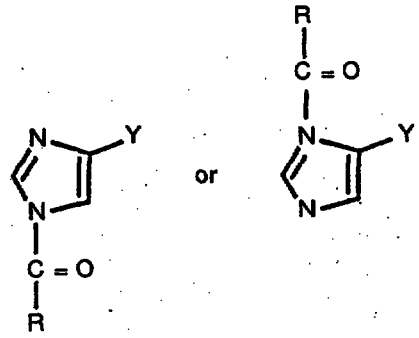


in order to obtain the corresponding compound of formula (I) and (II). Similarly, when a starting material wherein Q is



is employed, then the formamide treatment will be followed by hydrogenation, thus affording the desired compound of formula (I) and (II).

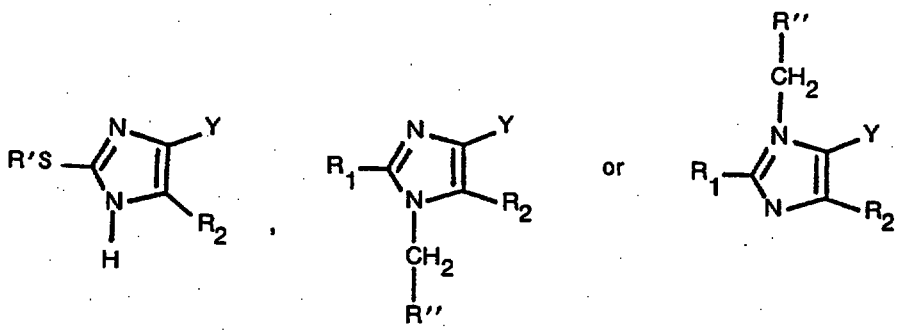
A further process for the preparation of the compounds of the formula (I) and (II) comprises hydrolysing a corresponding N-acetylated compound of the formula (I) and (II)



where Y is the arylalkylresidue determined by the formula (I) and (II), R is an alkyl group of 1 to 7 carbon atoms or an aryl radical of 6 to 10 carbon atoms.

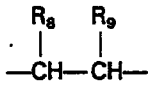
Preferably, the hydrolysis is carried out by boiling the starting material, an N-acylated imidazole derivative, in an aqueous solution of an inorganic acid until the reaction is completed.

Yet another process for the preparation of the compounds of formula (I) and (II) comprises hydrogenating a starting material of the formula:

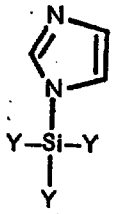


wherein Y is as defined before and R' is an aryl or alkyl and R'' is an aryl group. The hydrogenation is conveniently conducted in the presence of a suitable catalyst and under a hydrogen atmosphere, with stirring or using metallic sodium in liquid ammonia. Suitable catalysts include platinum oxide, palladium-on-carbon and Raney nickel. Reaction temperatures vary with the particular starting material employed, with typical temperatures being 25—70°C.

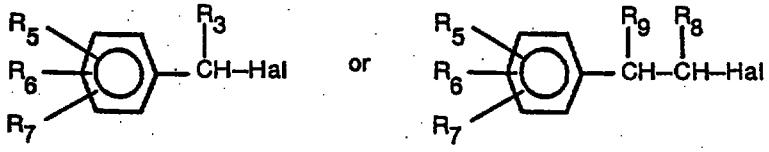
Yet another method for the preparation of the compounds of formula (I) or (II) wherein X is



comprises reacting a N-trialkylsilylimidazole of the formula



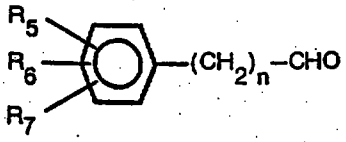
wherein Y is an alkyl group, preferably methyl, with an arylalkylhalogenide of the formulae



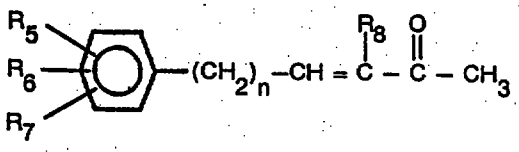
wherein R_3, R_5, R_6, R_7, R_8 and R_9 are as before and Hal is a halogen atom, in the presence of a Lewis acid, for example titanium tetrachloride, aluminium chloride or zinc chloride. As solvent can be used for example methylene chloride or chloroform. The reaction is preferably carried out at room temperature stirring the starting materials for 6—12 hours.

The intermediates of formula (VI) and (VII) can be prepared for example as follows:

An aldehyde of the formula



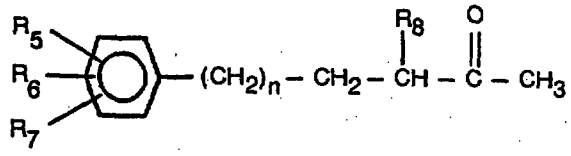
wherein R_5, R_6, R_7 and n are as before, is reacted in alkaline or acidic conditions with a ketone, preferably acetone, to give a compound of the formula (VIII) via direct aldol condensation:



(VIII)

wherein R_8 is an alkyl as defined before,

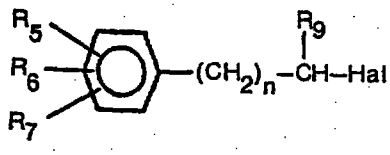
which compound in a second step is catalytically reduced to give the corresponding saturated compound of the formula:



(IX)

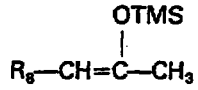
which compound in a third step is regioselectively brominated in methanol to give compounds of formula VII.

Another method for the preparation of the compounds of the general formula VII) is the regioselective alkylation process of ketones in which for example a halide compound of the formula (X)



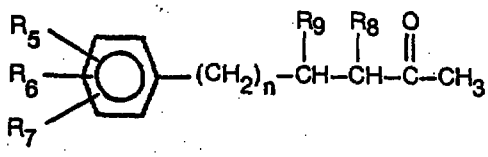
(X)

is reacted with a trimethylsilylenolether derivative of the general formula (XI)



(XI)

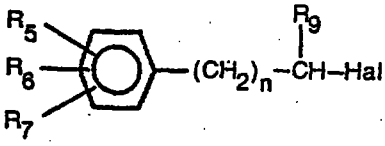
wherein R_8 is an alkyl as before,
in the presence of a Lewis acid, for example zinc (II) chloride, to give a compound of the formula (XII)



(XII)

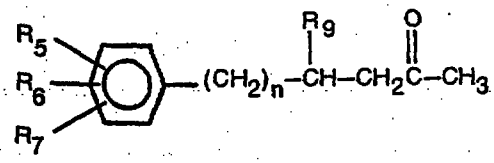
The compound of formula (XII) is further brominated as before to give compounds of the formula (VII).

When R_8 and R_2 are hydrogen yet another method for the preparation of compounds of the formula (VII) can be applied. In this method a halide of the general formula (XIII)



(XIII)

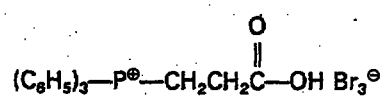
is reacted with lithiated N,N-dimethylhydrazone of acetone followed by hydrolysis to give a compound of the general formula (XIV)



(XIV)

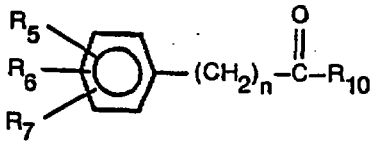
which compounds are brominated as before to give compounds of the formula (VII).

According to another method for the preparation of compounds of the formula (VII), compounds of the formula (VIII) are selectively brominated using as brominating agent for example 2-carboxyethyltriphenylphosphonium perbromide, which has the formula (XV)



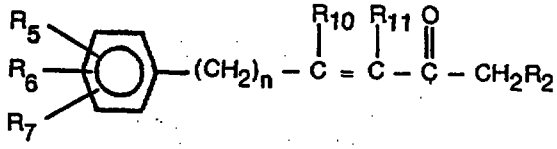
(XV)

Yet another method for the preparation of compounds of the formula (VII) is possible via a directed aldol condensation, in which for example a compound of the formula (XVI)



(XVI)

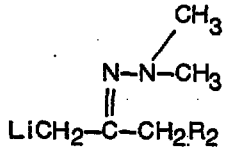
is reacted with the compound (XI) in the presence of a Lewis acid followed by dehydration to give a compound of the formula (XVII)



(XVII)

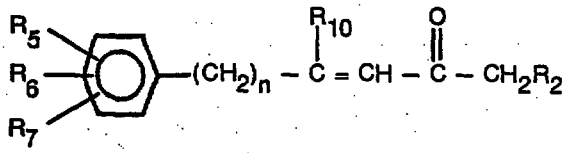
which compound is further brominated as before to give a compound of the formula (VII).

When R_{11} is hydrogen, compounds of the formula (VII) can be prepared from compounds of the formula (XVI), wherein these are reacted with 1-lithiated N,N-dimethylhydrazone of methylalkylketone of the formula (XVIII)



(XVIII)

Here in the first step compounds of the formula (XIX) are achieved,

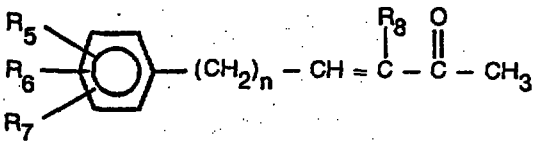


(XIX)

the bromination of which compounds are performed following the method above.

The preparation of compounds of the general formula (VII) can be accomplished from compounds of the general formula (XVII) by hydrogenation of the carbon-carbon double bond as well. The bromination in the second step leads to compounds of the formula (VII).

Alkylation of compounds of the general formula (XVII) when R_2 and R_{10} are hydrogen can be accomplished, too. In this method a compound of the formula (XX)



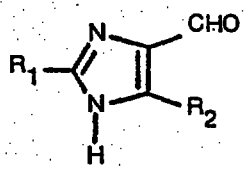
(XX)

is reacted with an alkylation reagent such as dialkyllithiocuprate (XXI) which undergoes 1,4-conjugate addition

$$(R)_2\,CuLi \qquad \text{(XXI)}$$

to form compounds of the formula (XII).

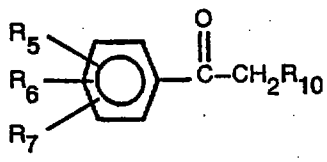
Condensation of an arylalkylketone or its vinylogue with 4-imidazole aldehydes of the formula (XXII)



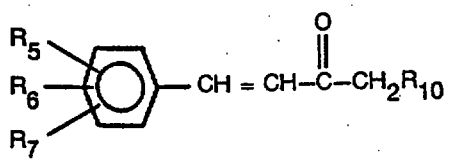
(XXII)

provides further another method for the preparation of compounds according to this invention. The

condensation is performed for example in aqueous alcohol catalysed by sodium hydroxide. Arylalkyl-ketones or their vinylogues have the general formulae (XXIII) and (XXIV)

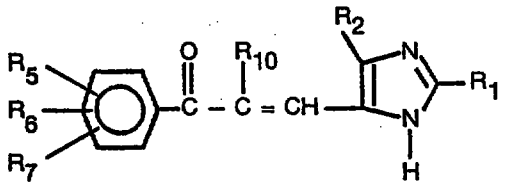


(XXIII)

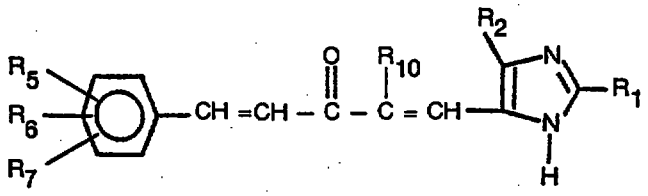


(XXIV)

In the first step this condensation gives unsaturated ketones of the formulae (XXV) and (XXVI)

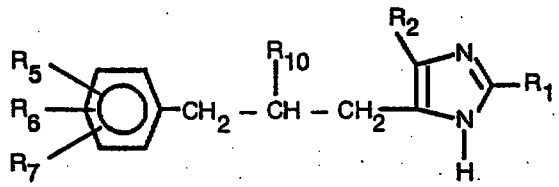


(XXV)

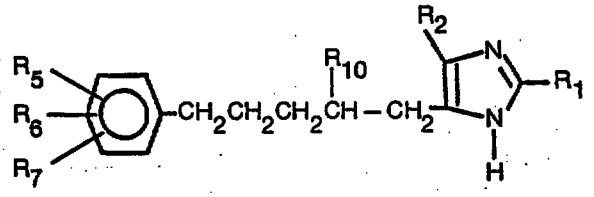


(XXVI)

which compounds are then hydrogenated to the end products according to the formulae (XXVII) and (XXVIII)

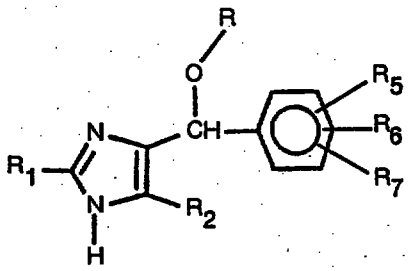


(XXVII)



(XXVIII)

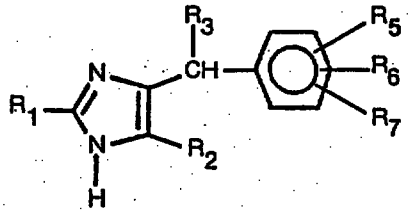
Yet another method for the preparation of compounds of formula (I) wherein R_4 is H comprises reacting a compound of the formula



wherein R_1, R_2, R_5, R_6 and R_7 are as before and R is an alkyl of 1 to 4 carbon atoms with a Grignard reagent of the formula

$$R_3—CH_2MgHal$$

in a mixture of tetrahydrofuran and toluene with refluxing to give a compound of the formula

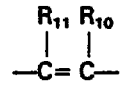


As stated herein above, the compounds of the general formula (I) and (II) and their non-toxic,

pharmaceutically acceptable acid addition salts have valuable pharmacological properties and have been found to possess excellent antihypertensive properties.

Tests have shown that they also possess other pharmacological properties as well, for example, anti-thrombotic activity. Furthermore, antimycotic and antifungal properties have been found, too.

The processes described above for the preparation of compounds of formula (II) wherein X is



result mainly in the trans isomer of the compound. The trans isomer can be converted to the cis isomer according to known methods, e.g. by heating it in the presence of an acid or by irradiating it with ultraviolet light.

Administration of isomeric compounds of formula (I) and (II), their non-toxic, pharmaceutically acceptable acid salts or mixtures thereof may be achieved parenterally, intravenously or orally. Typically, an effective amount of the derivative is combined with a suitable pharmaceutical carrier. As used herein, the term "effective amount" encompasses those amounts which yield the desired activity without causing adverse side-effects. The precise amount employed in a particular situation is dependent upon numerous factors such as method of administration, type of mammal, condition for which the derivative is administered, etc., and of course the structure of the derivative.

The pharmaceutical carriers which are typically employed with the derivatives of the present invention may be solid or liquid and are generally selected with the planned manner of administration in mind. Thus, for example, solid carriers include lactose, sucrose, gelatin and agar, while liquid carriers include water, syrup, peanut oil and olive oil. Other suitable carriers are well-known to those skilled in the art of pharmaceutical formulations. The combination of the derivative and the carrier may be fashioned into numerous acceptable forms, such as tablets, capsules, suppositories, solutions, emulsions, and powders.

The anti-hypertensive properties of the imidazole derivatives of the present invention have been determined by the following procedure. Sprague-Dawley rats of normal weight were first anesthetized with urethane. After this, the femoral artery was connected by way of a polyethylene tube with a blood pressure transducer. The test substance was then injected into the femoral vein or given intraperitoneally and the blood pressure and the pulse frequency were registered with a recorder.

In a further test for anti-hypertensive properties unanesthetized Wistar spontaneous hypertensive rats (SHR) were used. The test derivative was administered perorally by way of a tube into the stomach. The blood pressure was measured from the tail using an indirect bloodless method.

The diuretic activity was studied in rats by collecting the urine output during 0—5 hours after i.p. injection of the compounds. Before the test the animals were fasting overnight and got 10 ml water p.o. immediately before the injection.

The antithrombotic activity was investigated in vitro. The inhibiting activity of the compounds against ADP- and collagen-induced aggregation of thrombocytes was measured. In the test thrombocytes from a cow was used. To 1.2 ml of plasma containing 250000 thrombocytes/mm^3 were added 50 µl of a solution of the compound to be tested. After 10 min. incubation either ADP or collagen was added. The aggregation of the thrombocytes was turbidimetrically determined at $\lambda = 605$ nm.

The antimicrobial activity was determined *in vitro* according to a qualitative test for antibacterial and antifungal activity, using the agar diffusion method, against the following standard organisms: *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosus, Candida albicans* and *Aspergillus niger.*

The antifungal activity was determined *in vitro* against the following fungi: *Trichophyton rubrum, Trichophyton mentagrophytis, Microsporum canis, Epidermophyton floccosum, Chrysosporum, Candida albicans, Candida guilliermondi* and *Saccaromyces cerevisiae.* The fungi were cultured by plating on an agar nutrient medium. The compound to be tested was added before the incubation. A measure of the efficiency of the compound tested is the radius of the circle, within which the growth of the fungi has been inhibited.

Acute toxicity was determined by using female mice of NMRI-Strain with an age of about 7 months and weighing 30—40 g. The administration of the test compound was i.v.

Thus, the compound 4-[2-(2,6-dimethylphenyl)-1-methylethylenyl]imidazole, which has a LD_{50} value of 40 mg/kg i.v. in mice, was found in the blood pressure study with anesthetized rats of normal weight described above to cause a registrable lowering of the blood pressure at a dose of 3 µg/kg i.v. At a dose of 10 µg/kg i.v. the blood pressure lowering was quite clear and at a dose of 100—300 µg/kg i.v. the reduction of the blood pressure was on an average 38%. The duration of the effect was at least 30 minutes (after which time the determination was interrupted). A blood pressure lowering of more than 40% was obtained when 2 mg/kg of the compound was administered perorally. The duration of the effect was at least 5 h.

The compound 4-[2-(2,6-dimethylphenyl)-1-methylethyl]imidazole (LD_{50} = 40 mg/kg i.v. in mice) caused a blood pressure lowering of 20 per cent measured 30 minutes after the administration at a dose of 100 µg/kg i.v. When 10 mg/kg of the compound was given perorally, a blood pressure drop of 25% was obtained. Duration was at least 5 h.

The compound 4-[(α-methyl)-2,6-dimethylbenzyl]imidazole (LD_{50} = 150 mg/kg i.v. in mice) caused a blood pressure lowering of 30% at a dose of 1—10 mg/kg i.v. (30 min. after adminstration).

The compound 4-[(α-methyl)-2,3-dimethylbenzyl]imidazole (LD_{50} = 40 mg/kg i.v. in mice) caused a blood pressure drop of 55% at 10 µg/kg i.v. (after 30 min.). Given perorally (1 mg/kg) the compound gave a blood pressure drop of 20%. The duration was at least 5 h.

The compound 4-[2-(2,6-dimethylphenyl)propyl]imidazole, which has a LD_{50} value of 200 mg/kg i.v. in mice gave a blood pressure drop of 30% at a dose of 3 mg/kg i.v., measured 30 min. after administration.

The compound 4-[2-(2,6-dimethylphenyl)-2-ethylethyl]imidazole gave a blood pressure drop of about 25% at a dose of 3 mg/kg i.v., measured 30 min. after administration.

The compound 4-[2-(2,6-dimethylphenyl)-1-ethylethenyl]-imidazole which has a LD_{50} value of 110 mg/kg i.v. in mice, gave a blood pressure drop of 35% at a dose of 3 mg/kg intraperitoneally measured 30 min. after administration.

The compound 4-(α-methyl-2-methylbenzyl)imidazole, which has a LD_{50} value of 100 mg/kg i.v. in mice, gave a blood pressure drop of 20% at a dose of 0.3 mg/kg intraperitoneally measured 30 min. after adminstration.

The compound 4-[2-(2,6-dichlorophenyl)-1-methylethenyl]imidazole, which has a LD_{50} value of 50 mg/kg i.v. in mice gave a blood pressure drop of 25% at a dose of 0.3 mg/kg i.v. measured 30 min. after administration.

The compound 1-(4-imidazolyl)-1-(2,3-dimethylphenyl)ethylene, which has a LD_{50} value of 100 mg/kg i.v. in mice gave a blood pressure drop of about 40% at a dose of 3 mg/kg i.v. (after 30 min.). A blood pressure drop of 20% was obtained at a dose of 10 mg/kg perorally. The duration was at least 8 h.

The compound 4-(α-ethyl-2,3-dimethylbenzyl)-imidazole, which has a LD_{50} value of 40 mg/kg i.v. in mice gave a blood pressure drop of 40% at a dose of 1 mg/kg i.v. measured 30 min. after administration.

In the antithrombotic test, the compound 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]imidazole inhibited the collagen-induced and the ADP-induced aggregation of thrombocytes completely.

In the diuretic test, the compound 4-[2-(2,6-dimethylphenyl)-1-methylethyl]-imidazole caused an urine output increase of 227% measured 3 h after administration. The dose was 1 mg/kg i.p.

In the same test, the compound, 4-[2-(3,4-methylenedioxyphenyl)propyl]imidazole, which has a LD_{50} value of 170 mg/kg i.v. in mice, caused an urine output increase of 275% at a dose of 1 mg/kg p.o. measured 3 hours after administration. The corresponding value for a dose of 5 mg/kg p.o. was 452%.

The clinical dosage ranges for the compounds of the invention for oral administration of the antihypertensives have been estimated as 0.05 to 1 mg/kg per day.

In the Examples below, where ^{1}H—NMR spectrum shifts are presented, the NMR spectra were determined with a Perkin-Elmer R 24 or a Bruker WP80DS apparatus using an external tetramethylsilane standard, from which the presented chemical shifts (δ, ppm) are tabulated. The letters s, d, t and m are used to indicate a singlet, doublet, triplet or multiplet, respectively and coupling constants in hertz when given. In the same connection, the number of hydrogen atoms is also stated. The compounds which are indicated as bases are tested in deuterium methanol, deuterium acetone or deuterium chloroform, while the values for compounds which are indicated as hydrochlorides were determined in deuterium oxide. The presented ^{13}-NMR-spectrum were determined with a Bruker WP80DS apparatus.

The mass-spectra were determined with a Perkin-Elmer RMU—6E apparatus using direct inlet system. The temperature employed was the lowest temperature needed for the evaporation of the compound as base. In the examples the strongest and the most essential fragment-ions from a structural viewpoint are given as m/e values. In parenthesis is given the intensity of the fragment-ion in relation to the main peak.

Example 1

4-[α,α-bis(2-methylphenyl)hydroxymethyl]-5-methylimidazole

4,9 g (0,2 mol) of dry magnesium turnings are covered with 50 ml of dry tetrahydrofuran. The mixture is heated to boiling and a solution of 34 g (0.2 mol) of 2-bromotoluene in 50 ml dry tetrahydrofuran is added dropwise at such a rate that a smooth reaction is maintained. After the addition is complete, the reaction mixture is refluxed for about 30 minutes until the magnesium turnings no longer react. The reaction mixture is then cooled to about 50°C and 9,3 g of 5-methyl-4-imidazole carboxylic acid methyl ester are added in small portions. After the addition is complete, the mixture is refluxed for another 2 hours and the solvent is then distilled off to give about half of the original volume. The mixture is cooled and poured into 300 ml of cold water containing 15 ml of concentrated sulfuric acid, with agitation. The stirring is continued for an additional 15 minutes and the mixture is then filtered. The precipitate, filtered from the acidic water, which is the sulfate salt of the compound, is extracted to chloroform from basic water-ethanol solution. After evaporation, the crude product is recrystallized from acetone, m.p. 169—171°C.

^{1}H NMT (HCl-salt): 1.7 (s, 3H), 2.1 (s, 6H), 4.7 (s, 2H), 7.1 (m, 8H), 8.7 (s, 1H)

MS: 292 (55%), 274 (69%), 259 (100%), 232 (7%), 217 (9%), 201 (52%), 199 (72%), 167 (18%), 109 (63%)

Example 2

4-[α,α-bis(2-methylphenyl)hydroxymethyl]imidazole

A Grignard reagent is prepared from 68,4 g of o-bromotoluene and 9,6 g of Mg-turnings in 200 ml of THF. To this solution 12,6 g of 4-imidazole carboxylic acid methylester are added at 50°C and the reaction

mixture is refluxed for 5 hours. The mixture is then poured into cold water, which includes 60 ml of conc. HCl. The hydrochloride of the product is filtered off, washed with chloroform and recrystallized from isopropanol; yield 23 g (73%), m.p. 178—179°C. Liberation of hydrochloride is achieved in water-ethanol with sodiumhydroxide; m.p. 138—140°C.

^{1}H—NMR (HCl-salt): 1.9 (s, 6H), 4.6 (s, 3H), 6.7 (s, 1H), 7.0 (s, 8H), 8.7 (s, 1H)

Example 3

4-(α,α-diphenyl)hydroxymethyl-5-methylimidazole

The compound is prepared by the method described in Example 2 except that bromobenzene is used in place of o-bromotoluene and 5-methyl-4-imidazole carboxylic acid methyl ester in place of 4-imidazolecarboxylic acid methyl ester; yield 18,5 g (70%), m.p. 188—190°C (as base from ethanol).

^{1}H—HMR: 1.4 (s, 3H), 4.7 (s, 2H), 7.0 (s, 10H), 7.2 (s, 1H)

MS: 264 (80%), 246 (78%), 231 (28%), 218 (20%), 204 (9%), 187 (100%), 109 (64%), 105 (26%), 77 (34%)

Example 4

4-[[α-(2-methylphenyl)]-2-methylbenzyl]imidazole

The starting material, 4-[α,α-bis(2-methylphenyl)hydroxymethyl]imidazole is dissolved in 100 ml of acetic acid. 100 mg of Pd/C are added and the reaction mixture is stirred vigorously in a hydrogen atmosphere at about 60°C until the reaction is completed. The mixture is then filtered and distilled to a smaller volume. 70 ml of water are added and that mixture is then washed twice with 20 ml portions of chloroform. The aqueous phase is made alkaline with NaOH and extracted with chloroform (3 × 40 ml). The combined chloroform extracts are washed with water (1 × 10 ml) and dried over Na_2SO_4. The solution is evaporated to dryness. Yield 93%, m.p. 228—231°C (from ethanol). Hydrochloride in ethyl acetate-isopropanol: m.p. 245—254°C.

^{1}H—NMR: 2.1 (s, 6H), 4.7 (s, 2H), 5.8 (s, 1H), 6.6 (s, 1H), 6.9 (m, 8H), 8.7 (s, 1H)

Example 5

4-(α-phenylbenzyl)-5-methylimidazole

The compound is prepared from 4-(α,α-diphenyl)hydroxymethyl-5-methylimidazole according to the method in Example 4. Yield 69%, m.p. 198—204°C (from ethanol).

^{1}H—NMR: 1.6 (s, 3H), 4.5 (s, 1H), 5.3 (s, 1H), 6.8 (s, 10H), 7.3 (s, 1H)

Example 6

4-[α-(2-methylphenyl)-α-(2-methylbenzyl)]-5-methylimidazole

The compound is prepared according to the method in Example 4 using 4-[α,α-bis(2-methylphenyl)-hydroxymethyl]-5-methylimidazole as starting material. Yield 79%, m.p. 178—180°C (from water-ethanol).

^{1}H—NMR: 1.4 (s, 3H), 1.8 (s, 6H), 4.6 (s, 1H), 5.35 (s, 1H), 7.1 (m, 8H), 2.15 (s, 1H)

Example 7

4-[[α-(2,3-dimethylphenyl)-α-methyl]hydroxymethyl]imidazole, 1-(4-imidazolyl)-1-(2,3-dimethylphenyl)ethylene and 4-(α-methyl-2,3-dimethylbenzyl)imidazole

For the preparation of 2,3-dimethylmagnesiumbromide in the first step, 4,9 g of dry magnesium turnings are covered with 50 ml of dry tetrahydrofuran.

The mixture is heated to boiling and a solution of 37 g of 2,3-dimethylbromobenzene in 50 ml of tetrahydrofuran is added dropwise at such a rate that a smooth reaction is maintained. After the addition is complete the reaction mixture is refluxed from about 30 minutes until the magnesium turnings no longer react.

In the same way in another flask of methylmagnesiumbromide is prepared from 2,4 g of magnesium turnings and 9,5 g of methylbromide in tetrahydrofuran.

Yet another flask of 12,6 g of 4-imidazolecarboxylic acid methylester, is added to 100 ml of dry tetrahydrofuran and the mixture is stirred while heating to about 50°C. To this is then dropped the earlier prepared 2,3-dimethylmagnesiumbromide solution and immediately after that the methylmagnesiumbromide solution. To complete the reaction, the mixture is refluxed for several hours. The solvent is then distilled off to give about half of the original volume. The mixture is cooled and poured into 350 ml of cold water containing 50 ml of concentrated sulfuric acid, with agitation. The stirring is continued for an additional 15 minutes and the mixture is then filtered.

The pH of the filtrate is adjusted slightly basic and the mixture is extracted three times with 50 ml portions of methylene chloride. The combined methylene chloride extracts are washed with water and evaporated to dryness. The residue which contains crude 4-[[α-2,4-dimethylphenyl)-α-methyl]-hydroxymethyl]imidazole is further purified column chromatographically in silicagel using chloroform methanol as eluent. 1-(4-imidazolyl)-1-(2,3-dimethylphenyl)-ethylene is then obtained from the above product by heating it with potassiumhydrogen sulphate at 135°C.

^{1}H—NMR (HCl-salt): 2.104 (s, 3H), 2.313 (s, 3H), 5.187 (s, 2H), 5.358 (s, 1H), 6.106 (s, 1H), 7.03—7.22 (m, 4H), 8.98 (s, 1H)

^{13}C—NMR (HCl-salt: Signals at ppm: 18.073, 21.857, 118.789, 119.455, 127.961, 129.475, 132.230, 135.802, 136.498, 136.892, 137.921, 139.949, 140.070

Melting point at base: 137—140°C

4-(α-methyl-2,3-dimethylbenzyl)imidazole is obtained via hydrogenation with palladium-on-carbon catalyst in 2—N HCl according to the method described before.

^1H—NMR (HCl salt): 1.708 (d, 3H), 2.370 (broad s, 3H), 4.688 (q, 1H), 4.933 (s, 2H), 7.079—7.263 (m, 3H), 7.361 (s, 1H), 8.780 (s, 1H)

^{13}C—NMR (HCl-salt): Signals at ppm. 16.529, 21.917, 22.462, 34.662, 117.881, 126.660, 128.385, 131.079, 135.650, 136.952, 140.161, 140.163, 142.855

By the same method for example the following compounds were prepared:

4-(α-methyl-2,6-dimethylbenzyl)imidazole, M.p. (oxalate): 98.99°C

4-(α-ethyl-2,3-dimethylbenzyl)imidazole, M.p. (HCl-salt): 175—177°C

4-(α-butyl-2-methylbenzyl)imidazole

4-(α-methyl-2,3-dimethylbenzyl)-2-methylimidazole

Example 8

4-(2,6-dimethylphenyl)-3-buten-2-one

13,4 g (0,1 mol) of 2,6-dimethylbenzaldehyde, 100 ml of acetone, 100 ml of water and 2 g of calcium hydroxide are mixed together and refluxed for about 20—25 h with agitation. The precipitate is filtered off from the cold reaction mixture. 1 l of ice water is added to the filtrate with agitation. The product is crystallized at a yield of about 90%. M.p. of the recrystallized product: 34—35°C.

^1H—NMR: 7.55 (1Hd, 16.5), 7.00 (3Hs), 6.26 (1Hd, 16.5), 2.37 (3Hs), 2.31 (6Hs)

Example 9

4-(2,6-dimethylphenyl)-2-pentanone

To a mixture containing 20 g of CuI and 50 ml of tetrahydrofuran (THF) are added 105 ml of methyllithium dropwise during with agitation in a nitrogen atmosphere at a temperature of 0°C or lower until the yellow precipitate barely dissolves. Then 8.7 g of 4-(2,6-dimethylphenyl)-3-buten-2-one in 50 ml of THF are added slowly at 0°C. The stirring is continued for an additional 2 h with a gradual increase of the temperature to + 25°C. The reaction mixture obtained is hydrolysed with 300 ml of a solution of NH_4Cl. The ether layer is removed, dried and evaporated to give the crude product.

^1H—NMR: 6.85 (3Hs), 3.78 (1Hq + t, 7.5), 2.76 (2Hd, 7.5), 2.34 (6Hs), 1.99 (3Hs), 1.27 (3Hd, 7.5)

According to the same method, the compound 4-phenyl-2-pentanone was prepared.

^1H—NMR: 7.10 (5Hs), 3.26 (1Hq + t, 7.5), 2.62 (2 Hd, fine structur), 1.94 (3Hs), 1.20 (3Hd, 7)

Similarly 4-(3,4-dimethylenedioxyphenyl)-2-pentanone.

^1H—NMR: 6.62 (3H, s), 5.83 (2H, s), 3.20 (1Hq + t, 7), 2.67 (2H, d7), 2.04 (3Hs), 1.26 (3Hd7)

Example 10

1-bromo-4-(2,6-dimethylphenyl)-2-pentanone

To 3,8 g of 4-(2,6-dimethylphenyl)-2-pentanone in 25 ml of dry methanol 1.04 ml of bromine are added dropwise rapidly at a temperature not higher than + 5°C. Stirring is continued until the bromine colour disappears, while the temperature slowly rises to + 20°C. After evaporation the product is obtained at a yield of at least 70 %.

^1H—NMR: 6.98 (3Hs), 3.80 (1Hm), 3.67 (2Hs), 3.02 (2Hd), 2.35 (6Hs), 1.33 (3Hd,7)

According to the same method the compounds 1-bromo-4-phenyl-2-pentanone and 1-bromo-4-(2,6-dimethylphenyl)-3-methyl-2-butanone were prepared.

Similarly using two equivalents of bromine:

1-bromo-4-(2-bromo-4,5-methylenedioxyphenyl)-2-pentanone

^1H—NMR: 6.9 (1H, s) 6.67 (1H, s), 5.87 (2Hs), 3.80 (2Hs), 2.9 (3Hm), 1.19 (3Hd7)

Example 11

4-[2-(2,6-dimethylphenyl)propyl]imidazole

5,4 g of 1-bromo-4-(2,6-dimethylphenyl)-2-pentanone, 50 ml of formamide and 5 ml of water are refluxed with stirring for 3 h. The mixture is poured into 300 ml of water (pH 4—5), washed with ether, neutralized with $NaHCO_3$ and extracted with methylene chloride. After drying and evaporation 2,5 g of product are obtained. This is dissolved in ethyl acetate and HCl/ethylacetate is added. The product is evaporated to dryness, washed with ether, dissolved in water, neutralized with $NaHCO_3$ and extracted with methylene chloride. The evaporation residue is dissolved in ethyl acetate and the final product is precipitated as oxalate or hydrochloride. M.p. of the hydrochloride 194—198°C.

^1H—NMR (HCl-salt): 8.70 (1Hs), 6.9 (4Hs), 3.65 (1Hm), 3.21 (2H,d 8), 2.39 (6H broad s), 1.45 (3Hd 7)

According to the same method, the following compounds were prepared:

4-[2-(2,6-dimethylphenyl)-1-methylethyl]imidazole. M.p. of the oxalate 161—5°C.

^1H—NMR (oxalate): 8.75 (1H broad s), 7.05 (1Hs), 7.00 (3Hs), 3.0 (3Hm), 2.20 (6Hs), 1.31 (3Hd)

4-(2-phenylpropyl)imidazole (as oxalate)

^{1}H—NMR: 8.52 (1Hs), (7.22 (5Hs), 6.97 (1Hs), 3.05 (3Hm), 1.35 (3Hd)
M.p. of the oxalate: 166—168°C.
4-[2-(3,4-methylenedioxyphenyl)propyl]imidazole
^{1}H—NMR (as oxalate): 8.70 (1H, s), 7.11 (1H, s), 6.78 (3H, m), 5.95 (2H, s), 3.08 (3H, m), 1.40 (3H, d)
M.p. of oxalate: 154—156°C.
4-[2-(2,6-dimethylphenyl)butyl]imidazole
M.p. of oxalate 176—9°C.
^{1}H—NMR: 8.25 (1H, broad s), 6.95 (3H, s), 6.68 (1H, s), 3.2 (3H, m), 2.45 (3H, s), 2.6—2.0 (2H, m), 2.06 (3H, s), 1.87 (3H, t)

Example 12

4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one

A mixture of 13,4 g of 2,6-dimethylbenzaldehyde and 15 ml of 2-butanone is saturated with gaseous HCl with stirring. The starting temperature is 0°C, and it is raised to 20—25°C in 2 h. The reaction mixture is poured into 0,5 l of cold water, extracted with toluene and wahsed with a $NaHCO_3$-solution. The dried toluene extract is filtered, toluene and free 2-butanone are distilled off. The product is obtained by crystallization form di-isopropylether. M.p. 43—44°C.

^{1}H—NMR: 7.38 (1Hs), 6.98 (3Hs), 2.42 (3Hs), 2.11 (6Hs), 1.59 (3Hd, 1.4).

Example 13

1-bromo-4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one

To a mixture of 3,8 g of 4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one in 50 ml of THF a solution of 13 g of 2-carboxyethyltriphenylphosphoniumperbromide in 50 ml of THF is added dropwise at room temperature.

Stirring is continued for another 2 h. 200 ml of water and 100 ml of ligroin are added. The organic layer is washed with a Na_2CO_3-solution and water. After filtration and evaporation 5,5 g of crude product containing 85—90% of 1-bromo-4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one are obtained.

^{1}H—NMR: 7.51 (1H broad s), 7.05 (3Hs), 4.27 (2Hs), 2.18 (6Hs), 1.68 (3Hd, 1.3)

Example 14

4-[2-(2,6-dimethylphenyl)-1-methylethenyl]imidazole E-isomer

The compound is prepared according to the method described in Example 12, except that 1-bromo-4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one is used instead of 1-bromo-4-(2,6-dimethylphenyl)-2-pentanone. M.p. of the hydrochloride 260—262°C.

^{1}H—NMR: 8.82 (1H, d), 7.36 (1H, d), 7.20 (1H, broad s), 7.08 (3Hs), 2.20 (6Hs), 1.82 (3H, d, 1.2)

Using the same method the following compounds were prepared:

4-[2-(2,6-dichlorophenyl)-1-methylethenyl]imidazole. M.p. of the hydrochloride 210—212°C.
^{1}H—NMR (HCl-salt): 1.9 (s, 3H), 4.6 (broad signal, H_2O), 6.85 (s, 1H), 7.0—7.4 (m, 1 + 3H), 7.6 (s, 1H)

4-[2-(2,6-dimethylphenyl)-1-ethylethenyl]imidazole. M.p. of the hydrochloride 257—258°C.
^{1}H—NMR (HCl-salt): 1.1 (t, 3H), 2.35 (s, 6H), 2.4 (q, 2H), 4.8 (broad signal, H_2O), 7.1 (2 × s, 3 + 1H), 7.65 (s, 1H), 8.95 (s, 1H)

4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-5-methylimidazole. M.p. of the hydrochloride 250—252°C.

Example 15

4-(α-methyl-2,6-dimethylbenzyl)imidazole

To a mixture of N-(trimethylsilyl)imidazole (1,4 g) and titanium tetrachloride (1,6 ml) in dry chloroform (20 ml) a solution of 1-chloro-1-(2,6-dimethylphenyl)ethane (1,7 g) in dry chloroform (10 ml) was added. After stirring for 5 h at room temperature the product mixture was poured onto water, washed with ether and neutralized with sodium hydrogen carbonate. Filtration and extraction with methylene chloride gave 4-[(α-methyl)-2,6-dimethylbenzyl]imidazole, yeild 33%.

^{1}H—NMR: δ $CDCl_3$ 11.4 (1H, broad), 7.19 (1H, s), 6.83 (3H, s), 6.56 (1H, s), 4.52 (2H,q 6), 2.11 (6H, s), 1.63 (3H,d 6)

M.p. of the hydrochloride: 208—10°C.

^{13}C—NMR (as hydrochloride): δCD_3OD 139.8 (1C, s), 139.1 (1C, s), 137.6 (2C, s), 134.9 (1C, d), 130.8 (2C, d), 128.4 (1C, d), 116.6 (1C, d), 32.8 (1C, d), 20.6 (2C, q), 17.0 (1C, q)

Using the same method the following compounds were prepared:

4-(α-methyl-2-methylbenzyl)imidazole. M.p. of the hydrochloride 156—160°C.
^{1}H—NMR (HCl-salt): 1.63 (d, 3H), 2.40 (s, 3H), 4.52 (q, 1H), 5.10 (s, H_2O), 6.9—7.2 (m, 3H), 7.36 (s, 1H), 8.83 (d, 1H)

4-(α-methyl-2,3-dimethylbenzyl)imidazole
^{13}C—NMR (HCl-salt): 16.529, 21.917, 22.462, 34.662, 117.881, 126.660, 128.385, 131.079, 135.650, 136.952, 140.161, 140.161, 142.855

Example 16

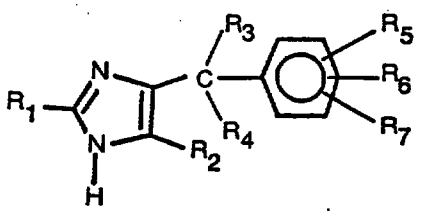
4-(α-ethyl-2,3-dimethylbenzyl)imidazole

6.0 g of 4-[α-(2,3-dimethylphenyl)ethoxymethyl]-imidazole is dissolved in toluene. To this solution is then added 22.8 g of ethylmagnesiumbromide in tetrahydrofurane and the mixture is refluxed for 20 hours. The mixture is then poured into cold hydrochloric acid and most of the organic solvents is evaporated. The mixture is extracted with methylene chloride. The extract is washed with water, dilute sodium hydroxide solution and water and evaporated to dryness.

The residue, which is crude product is further purified by liquid chromatography by using a column of silica gel and chloroform-methanol as eluent. After liquid chromatography purification the product melts at 173—176°C as hydrochloride.

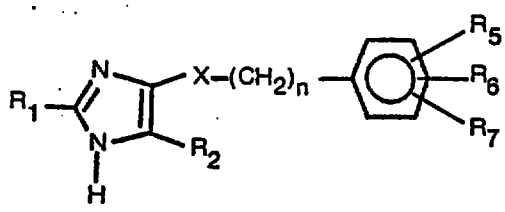
Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. Substituted imidazoles of the general formula



(I)

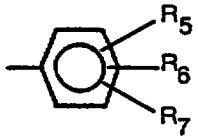
or



(II)

wherein R_1 is H, an alkyl of 1 to 4 carbon atoms or $-CH_2OH$; R_2 is H or CH_3; R_3 is

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,

or  and R_4 is H or OH;

or R_3 and R_4 together represent $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$,

or $=CH-CH_2CH_2CH_3$; X is $-CH(R_8)-CH(R_9)-$ or $-C(R_{11})=C(R_{10})-$; R_5, R_6 and R_7,

which can be the same or different are H, $-CH_3$, $-CH_2CH_3$, halogen, OH or $-OCH_3$ or R_5 is hydrogen and R_6 and R_7 together form an $-O-CH_2-O-$bridge between two adjacent carbon atoms in the phenyl group;

$-CHR_8-$ is $-CH_2-$, $-CHCH_3-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)-CH_3)-$,

$-CH(-CH_2CH_2CH_2CH_3)-$, or $>C=CH_2$, $>C=CH-CH_3$, $>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$,

or $>C=CH-CH_2CH_2CH_3$; R_9 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$,

$-CH_2CH_2CH_2CH_3$ or OH; R_{10} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,

Example 16

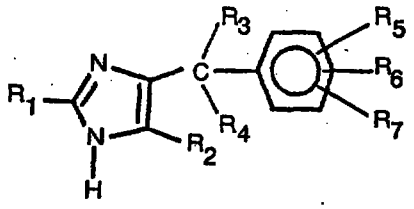
4-(α-ethyl-2,3-dimethylbenzyl)imidazole

6.0 g of 4-[α-(2,3-dimethylphenyl)ethoxymethyl]-imidazole is dissolved in toluene. To this solution is then added 22.8 g of ethylmagnesiumbromide in tetrahydrofurane and the mixture is refluxed for 20 hours. The mixture is then poured into cold hydrochloric acid and most of the organic solvents is evaporated. The mixture is extracted with methylene chloride. The extract is washed with water, dilute sodium hydroxide solution and water and evaporated to dryness.

The residue, which is crude product is further purified by liquid chromatography by using a column of silica gel and chloroform-methanol as eluent. After liquid chromatography purification the product melts at 173—176°C as hydrochloride.

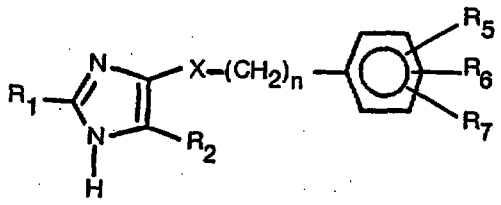
Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. Substituted imidazoles of the general formula



(I)

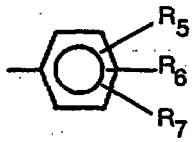
or



(II)

wherein R_1 is H, an alkyl of 1 to 4 carbon atoms or $-CH_2OH$; R_2 is H or CH_3; R_3 is

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,

or  and R_4 is H or OH;

or R_3 and R_4 together represent $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$,

or $=CH-CH_2CH_2CH_3$; X is $-CH(R_8)-CH(R_9)-$ or $-C(R_{11})=C(R_{10})-$; R_5, R_6 and R_7,

which can be the same or different are H, $-CH_3$, $-CH_2CH_3$, halogen, OH or $-OCH_3$ or R_5 is hydrogen and R_6 and R_7 together form an $-O-CH_2-O-$bridge between two adjacent carbon atoms in the phenyl group;

$-CHR_8-$ is $-CH_2-$, $-CHCH_3-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)-CH_3)-$,

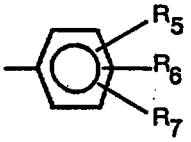
$-CH(-CH_2CH_2CH_2CH_3)-$, or $>C=CH_2$, $>C=CH-CH_3$, $>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$,

or $>C=CH-CH_2CH_2CH_3$; R_9 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$,

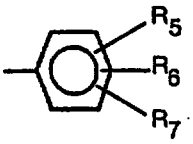
$-CH_2CH_2CH_2CH_3$ or OH; R_{10} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,

* C L M S *

$-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$; R_{11} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$; n is 0 to 4; provided that

— when R_4 is OH, R_1 is H or CH_3 and R_3 is  ;

then R_5, R_6 and R_7 are not all simultaneously hydrogen;

— when R_1, R_2 and R_4 all are hydrogen and R_3 is  ;

then R_5, R_6, R_7 are not all simultaneously hydrogen;
— R_8 and R_9 are not simultaneously hydrogen; and
— R_{11} and R_{10} are not simultaneously hydrogen;
and their non-toxic pharmaceutically acceptable acid addition salts.

2. A compound of formula (I) or (II) according to Claim 1 wherein each of R_5, R_6 and R_7, which can be the same or different, is hydrogen, methyl, ethyl or halogen.

3. A compound of formula (I) according to Claim 1 or 2 wherein R_4 is hydrogen and R_3 is methyl, ethyl, propyl, isopropyl or butyl.

4. A compound of formula (I) according to Claim 3 wherein R_1 is methyl.

5. A compound of formula (II) according to Claim 1 or 2 wherein X is $-C(R_{11})=C(R_{10})-$ and R_{10} is hydrogen.

6. A compound of formula (II) according to Claim 1 or 2 wherein X is $-C(R_{11})=C(R_{10})-$ and R_{11} is hydrogen.

7. A compound of formula (II) according to Claim 1 or 2 wherein X is $-CH(R_8)-CH(R_9)-$ and R_9 is hydrogen.

8. A compound of formula (II) according to Claim 1 or 2 wherein X is $-CH(R_8)-CH(R_9)-$ and R_8 is hydrogen.

9. A compound of formula (II) according to Claim 1, 2 or any of claims 5—8 wherein R_1 is hydrogen or methyl.

10. A compound of formula (II) according to Claim 1, 2 or any of claims 5—9 wherein n is 0 or 1.

11. A compound of formula (II) according to Claim 1 wherein each of R_5, R_6 and R_7, which can be the same or different, is hydrogen, methyl, ethyl or halogen; R_1 is hydrogen or methyl; R_2 is hydrogen or methyl, R_8 or R_{11} is methyl, ethyl or isopropyl, R_9 and R_{10} are hydrogen, and n is 0.

12. 4-[(α-Methyl)-2,6-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

13. 4-[(α-Methyl)-2,3-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

14. 4-[(α-Methyl)-2-methylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

15. 4-[2-(2,6-Dimethylphenyl)-1-methylethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

16. 4-[2-(2,6-Dimethylphenyl)propyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

17. 4-[2-(2,6-%Dimethylphenyl)-1-methylethenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

* C L M S *

18. 4-[2-(2,6-Dimethylphenyl)-1-ethylethenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

19. 4-[(α-Ethyl)-2,3-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

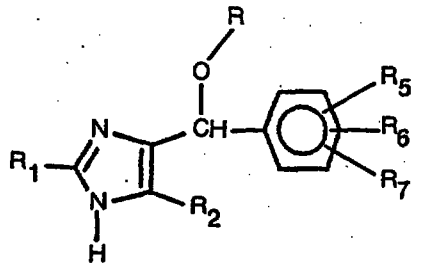
20. 4-[2-(2,6-Dichlorophenyl)-1-methylethenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

21. 4-[2-(2,6-Dimethylphenyl)-2-ethylethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

22. 4-[2-(3,4-Methylenedioxyphenyl)propyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

23. 1-(4-Imidazolyl)-1-(2,3-dimethylphenyl)-ethylene and its non-toxic pharmaceutically acceptable acid addition salts.

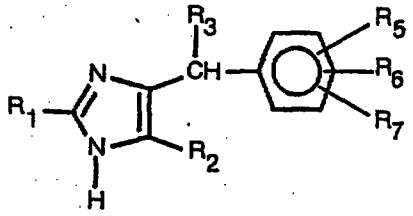
24. A process for the preparation of a compound of formula (I) as claimed in claim 1, wherein R_4 is H, which comprises reacting a compound of the formula



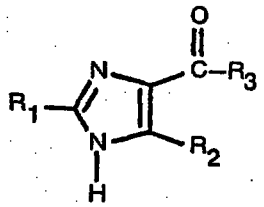
wherein R_1, R_2, R_5, R_6 and R_7 are as defined in claim 1 and R is an alkyl of 1 to 4 C-atoms, with a Grignard reagent of the formula

$$R_3—CH_2Mg\ Hal$$

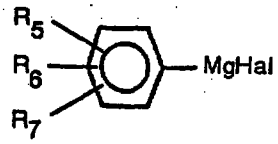
wherein R_3 is as defined in claim 1, to give a compound of the formula



25. A process for the preparation of a compound of formula (I) as claimed in Claim 1, wherein R_4 is OH, which comprises reacting an imidazolylketone of the formula



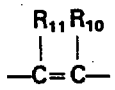
wherein R_1 and R_2 are as defined in Claim 1 and R_3 is as an alkyl or aryl as defined in Claim 1 with an aryl magnesium halide derivative of the formula



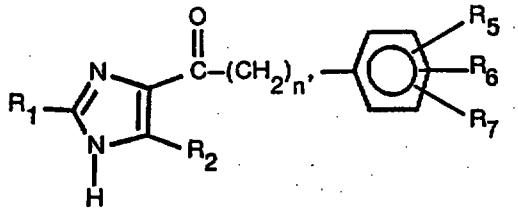
wherein R_5, R_6, R_7 are as in Claim 1 and Hal is halogen.

* C L M S *

26. A process for the preparation of a compound of formula (I) or (II) as claimed in Claim 1, wherein X is



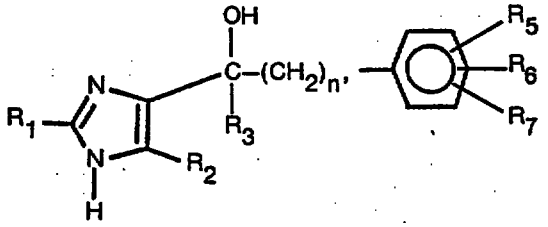
and R_{10} is hydrogen, which comprises reacting a compound of the formula:



wherein R_1—R_7 are as defined in Claim 1 and n' is 0 to 5 with a compound of the formula:

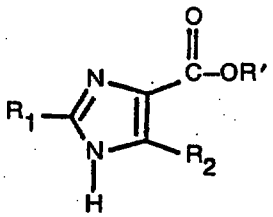
R_3MgHal

wherein R_3 is an alkyl or an aryl as defined in Claim 1 and Hal is halogen, to give a compound of the formula:

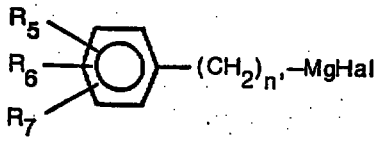


which finally is dehydrated to give a compound of formula (I) or (II).

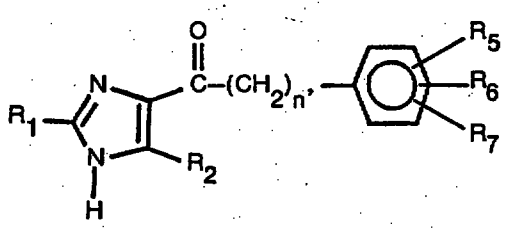
27. A process for the preparation of a compound of formula (I) or (II) as claimed in Claim 1, which comprises reacting an imidazole carboxylic acid alkyl ester of the formula:



wherein R_1 and R_2 are as defined in Claim 1 and R' is alkyl in a first step with a Grignard reagent of the formula:



wherein R_5, R_6, R_7 are as defined in Claim 1 and n' is 0 to 5, to give a compound of the formula



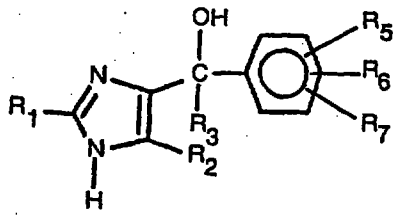
* C L M S *

which in a second step is reacted with a Grignard reagent of the formula

R_3MgHal

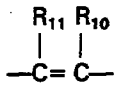
wherein R_3 is an alkyl or aryl as defined in Claim 1, to give a product, which in the final step is dehydrated to give a compound of formula (I) or (II).

28. A process for the preparation of a compound of formula (I) as claimed in Claim 1 wherein R_4 is hydrogen, which comprises catalytically reducing a compound of the formula

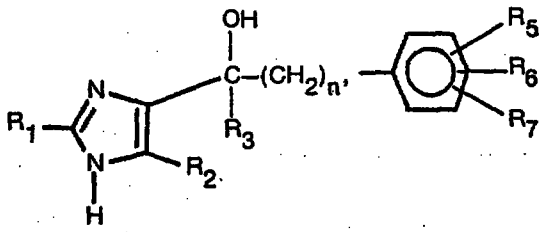


wherein R_1, R_2, R_5, R_6 and R_7 are as defined in Claim 1 and R_3 is an alkyl or aryl as defined in Claim 1.

29. A process for the preparation of a compound of formula (II) as claimed in Claim 1 wherein X is

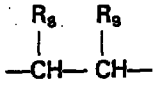


and R_{10} is hydrogen, which comprises dehydrating a compound of the formula

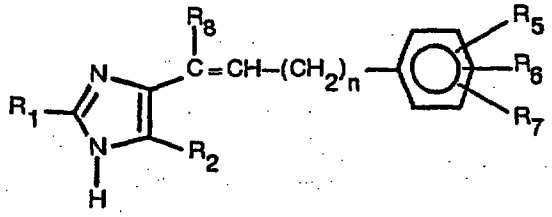


wherein R_1, R_2, R_5, R_6, R_7 are as defined in Claim 1, R_3 is an alkyl or aryl as defined in Claim 1 and n' is 1 to 5.

30. A process for the preparation of a compound of formula (II) as claimed in Claim 1 wherein X is

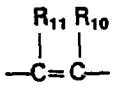


and R_9 is hydrogen, which comprises catalytically reducing a compound of the formula

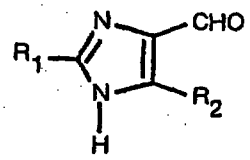


wherein R_1, R_2, R_5, R_6, R_7 and n are as defined in Claim 1 and R_8 is alkyl as in Claim 1.

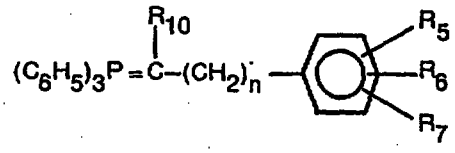
31. A process for the preparation of a compound of formula (II) as claimed in Claim 1 wherein X is



and R_{11} is hydrogen, which comprises reacting an imidazole aldehyde of the formula

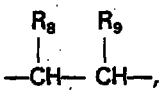


wherein R_1 and R_2 are as defined in Claim 1, with an aralkylidenetriphenylphosphorane of the formula:

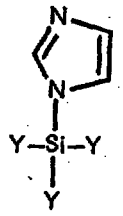


wherein R_5, R_6, R_7, R_{10} and n are as defined in Claim 1.

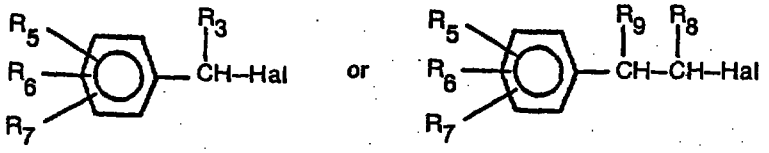
32. A process for the preparation of a compound of formula (I) or (II) as claimed in Claim 1 wherein X is



which comprises reacting a N-trialkylsilylimidazole of the formula

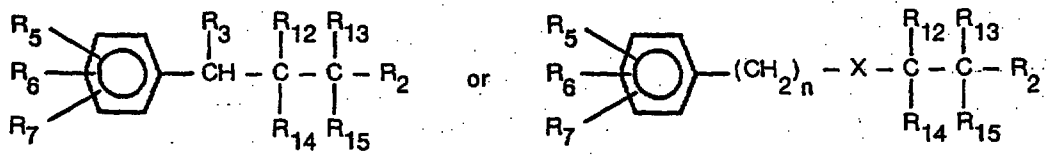


wherein Y is an alkyl group with an arylalkylhalogenide of the formula

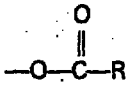


wherein R_3, R_5, R_6, R_7, R_8 and R_9 are as defined in Claim 1 and Hal is a halogen atom, in the presence of a Lewis acid.

33. A process for the preparation of a compound as claimed in Claim 1, which comprises reacting a starting material of the formula



wherein R_2, R_3, R_5, R_6, R_7 and n are as defined in claim 1, and R_{12}, R_{13}, R_{14} and R_{15}, which can be the same or different, are each hydrogen, hydroxy, mercapto, halogen, amino, —O— alkyl of 1 to 7 carbon atoms or

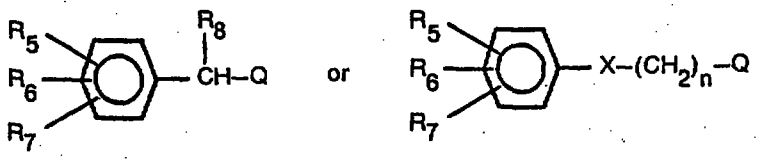


wherein R is an alkyl; or wherein R_{12} and R_{14} can be combined to form a keto group, or R_{13} and R_{15} can be combined to form a keto group, or both R_{12} and R_{14} and R_{13} and R_{15} can simultaneously form keto groups, with a reagent capable of converting said starting material to the corresponding imidazole.

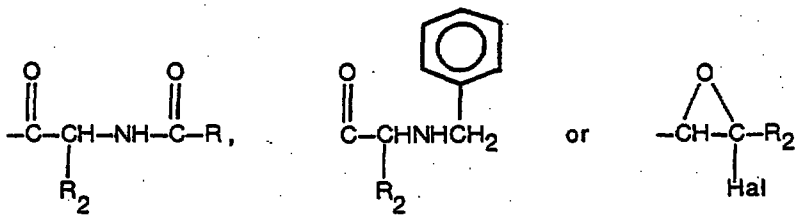
* C L M S *

34

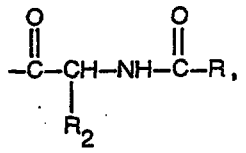
34. A process for the preparation of a compound as claimed in Claim 1 which compriss reacting formamide with a compound of the formula



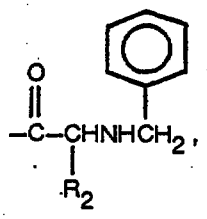
wherein R_5, R_6, R_7, R_8 and n are as defined in Claim 1 and Q is



(wherein Hal is a halogen atom, R is a substituted or unsubstituted alkyl, aralkyl or aryl group), provided that:

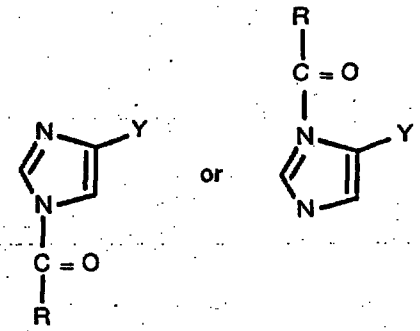
a) when Q is 

the reaction with formamide is followed by treatment of the intermediate product with acid; and

b) when Q is 

the reaction with formamide is followed by hydrogenation of the intermediate product.

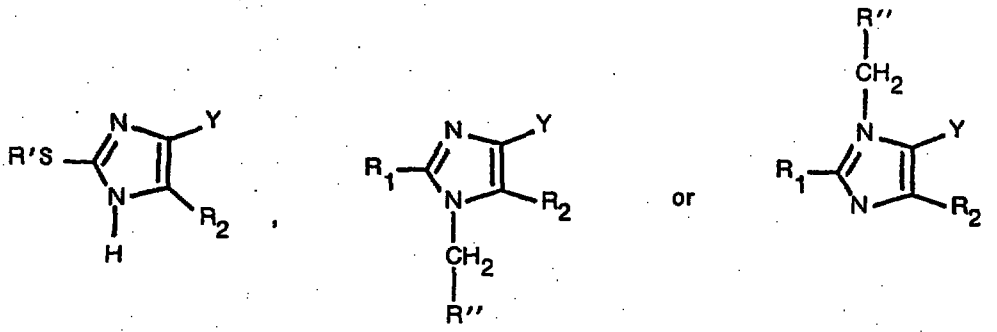
35. A process for the preparation of a compound as claimed in Claim 1 which comprises hydrolysing a compound of the formula



where Y is the arylalkylresidue determined by the formula (I) and (II), R is an alkyl group of 1 to 7 carbon atoms or an aryl radical of 6 to 10 carbon atoms.

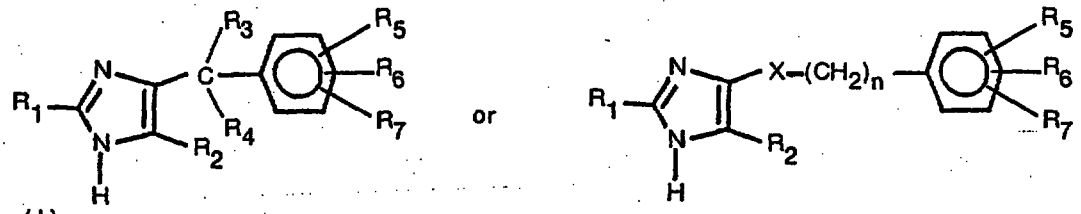
* C L M S *

36. A process for the preparation of a compound as claimed in Claim 1 which comprises hydrogenating a compound of the formula



wherein Y is as defined in Claim 36, R' is an aryl or alkyl and R'' is an aryl group.

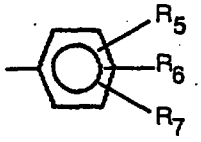
37. A substituted imidazole of the general formula



(I) (II)

wherein R_1 is H, an alkyl of 1 to 4 carbon atoms or $-CH_2OH$; R_2 is H or CH_3; R_3 is

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,

or  and R_4 is H or OH;

or R_3 and R_4 together represent $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$,

or $=CH-CH_2CH_2CH_3$; X is $-CH(R_8)-CH(R_9)-$ or $-C(R_{11})=C(R_{10})-$; R_5, R_6 and R_7,

which can be the same or different are H, $-CH_3$, $-CH_2CH_3$, halogen, OH or $-OCH_3$ or R_5 is hydrogen and R_6 and R_7 together form an $-O-CH_2-O-$ bridge between two adjacent carbon atoms in the phenyl group;

$-CHR_8-$ is $-CH_2-$, $-CH(CH_3)-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$,

$-CH(-CH(CH_3)-CH_3)-$, $-CH(-CH_2CH_2CH_2CH_3)-$ or $C=CH_2$, $C=CH-CH_3$,

$>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$, or $>C=CH-CH_2CH_2CH_3$; R_9 is H, $-CH_3$, $-CH_2CH_3$,

* C L M S *

$-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$ or OH; R_{10} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$; R_{11} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$; n is 0 to 4;

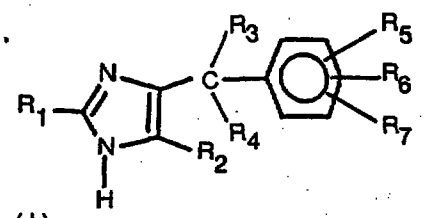
provided that R_{11} and R_9 or R_8 and R_{10} are not simultaneously hydrogen, and its non-toxic pharmaceutically acceptable acid addition salts, for use in therapy as an antihypertensive agent, antithrombotic agent, diuretic agent, antimycotic or antifungal agent.

38. A pharmaceutical composition comprising an imidazole derivative as defined in Claim 37 or a non-toxic pharmaceutically acceptable acid addition salt thereof and a compatible pharmaceutically acceptable carrier therefor.

39. A pharmaceutical composition comprising an imidazole derivative as claimed in anyone of one of the Claims 1 to 23 or a non-toxic pharmaceutically acceptable salt thereof and a compatible pharmaceutically acceptable carrier therefor.

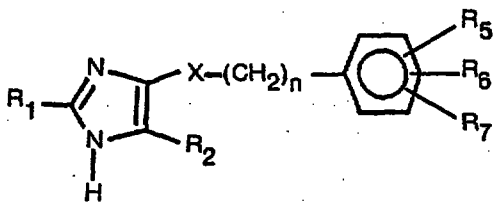
Claim for the Contracting State: AT

1. A process for the preparation of a compound of the formula:



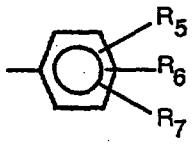
(I)

or



(II)

wherein R_1 is H, an alkyl of 1 to 4 carbon atoms or $-CH_2OH$; R_2 is H or CH_3; R_3 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,



and R_4 is H or OH;

or R_3 and R_4 together represent $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$, or $=CH-CH_2CH_2CH_3$; X is $-CH(R_8)-CH(R_9)-$ or $-C(R_{11})=C(R_{10})-$; R_5, R_6 and R_7, which can be the same or different are H, $-CH_3$, $-CH_2CH_3$, halogen, OH or $-OCH_3$ or R_5 is hydrogen and R_6 and R_7 together form an $-O-CH_2-O-$bridge between two adjacent carbon atoms in the phenyl group;

$-CHR_8-$ is $-CH_2-$, $-CHCH_3-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)-CH_3)-$,

* C L M S *

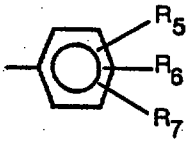
$-CH(-CH_2CH_2CH_2CH_3)-$, or $>C=CH_2$, $>O=CH-CH_3$, $>O=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$,

or $C=CH-CH_2CH_2CH_3$; R_9 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$,

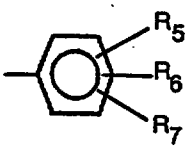
$-CH_2CH_2CH_2CH_3$ or OH; R_{10} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,

$-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$; R_{11} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

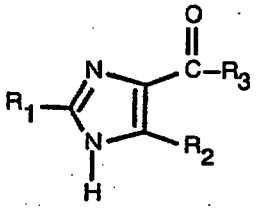
or $-CH_2CH_2CH_2CH_3$; n is 0 to 4; provided that

— when R_4 is OH, R_1 is H or CH_3 and R_3 is  ;

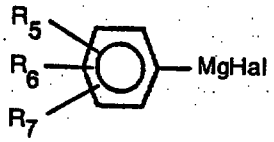
then R_5, R_6 and R_7 are not all simultaneously hydrogen

— when R_1, R_2 and R_4 all are hydrogen and R_3 is  ;

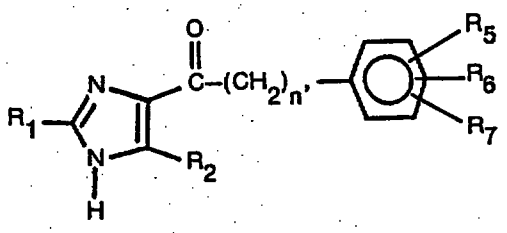
then R_5, R_6, R_7 are not all simultaneously hydrogen
— R_8 and R_9 are not simultaneously hydrogen
— R_{11} and R_{10} are not simultaneously hydrogen
and their non-toxic pharmaceutically acceptable acid addition salts, which comprises
a) reacting an imidazolylketone of the formula:



wherein R_1 and R_2 are as defined above and R_3 is an alkyl or aryl as defined above with an aryl magnesium halide derivative of the formula:



wherein R_5, R_6, R_7 are as above and Hal is halogen to give a compound of formula (I) wherein R_4 is OH;
b) reacting a compound of the formula:

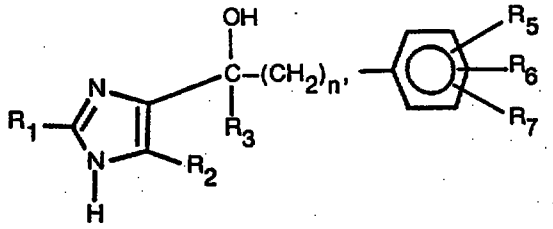


* C L M S *

wherein R_1—R_7 are as defined above and n' is 0 to 5 with a compound of the formula:

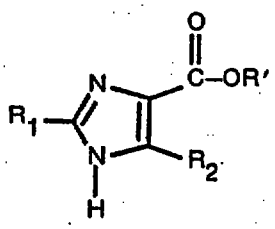
R_3MgHal

wherein R_3 is an alkyl or an aryl as defined above and Hal is halogen, to give a compound of the formula:

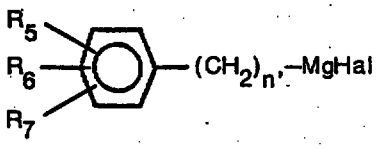


which finally is dehydrated, to give a compound of formula (I) or (II) wherein X is  and R_{10} is hydrogen;

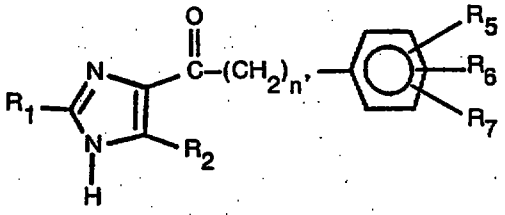
c) reacting an imidazole carboxylic acid alkyl ester of the formula:



wherein R_1 and R_2 are as defined above and R' is alkyl in a first step with a Grignard reagent of the formula:



wherein R_5, R_6, R_7 are as defined in above and n' is 0 to 5, to give a compound of the formula:

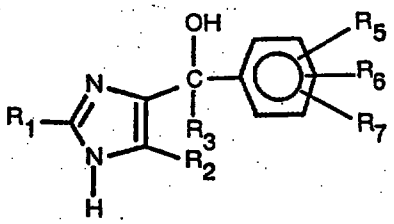


which in a second step is reacted with a Grignard reagent of the formula:

R_3MgHal

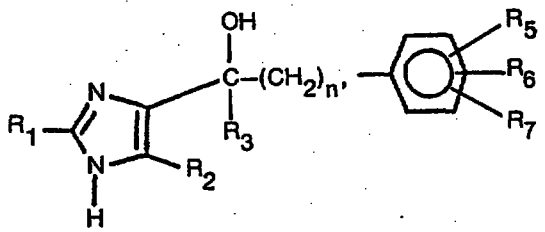
wherein R_3 is an alkyl or aryl as defined above to give a product, which in the final step is dehydrated, to give a compound of formula (I) or (II);

d) catalytically reducing a compound of the formula:



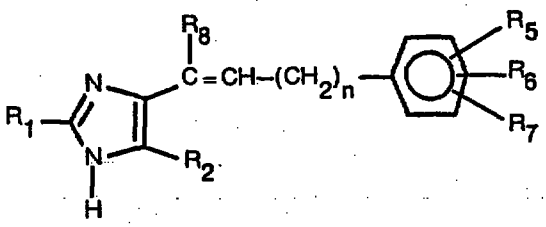
wherein R_1, R_2, R_5, R_6 and R_7 are as defined above and R_3 is an alkyl or aryl as defined above;

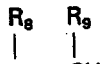
e) dehydrating a compound of the formula:



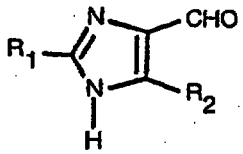
wherein R_1, R_2, R_5, R_6, R_7 are as defined above, R_3 is an alkyl or aryl as defined above and n' is 1 to 5 to give a compound of formula (II) wherein X is  and R_{10} is hydrogen;

f) catalytically reducing a compound of the formula

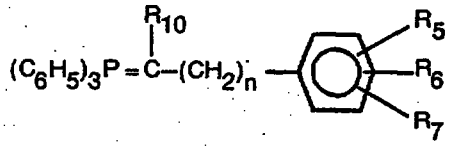


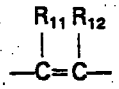
wherein R_1, R_2, R_5, R_6, R_7 and n are as defined above and R_8 is alkyl as above to give a compound of formula (II) wherein X is  and R_9 is hydrogen;

g) reacting an imidazole aldehyde of the formula:

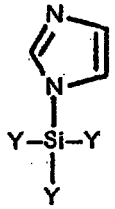


wherein R_1 and R_2 are as defined above, with an aralkylidenetriphenylphosphorane of the formula:

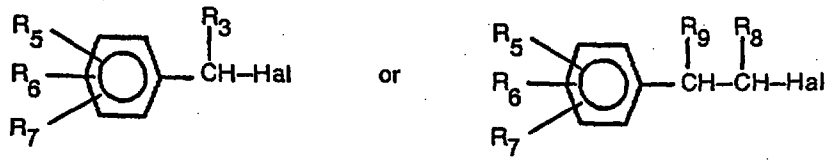


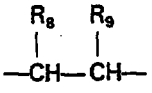
wherein R_5, R_6, R_7, R_{10} and n are as defined above to give a compound of formula (II) wherein X is  and R_{11} is hydrogen;

h) reacting a N-trialkylsilylimidazole of the formula:

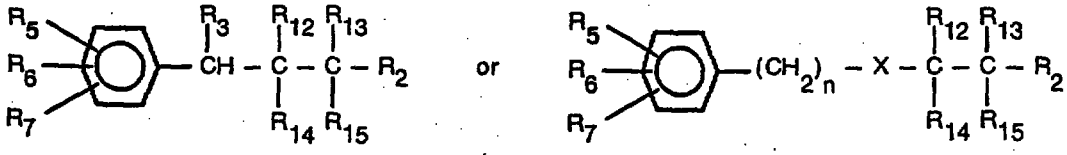


wherein Y is an alkyl group, with an arylalkylhalogenide of the formula

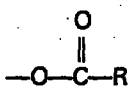


wherein R_3, R_5, R_6, R_7, R_8 and R_9 are as defined above and Hal is a halogen atom, in the presence of a Lewis acid to give a compound of formula (I) or formula (II) wherein X is 

i) reacting a starting material of the formula:

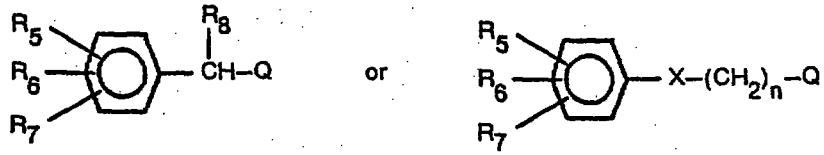


wherein R_2, R_3, R_5, R_6, R_7 and n are as hereinbefore defined, and R_{12}, R_{13}, R_{14} and R_{15}, which can be the same or different, are each hydrogen, hydroxy, mercapto, halogen, amino, —O— alkyl of 1 to 7 carbon atoms or

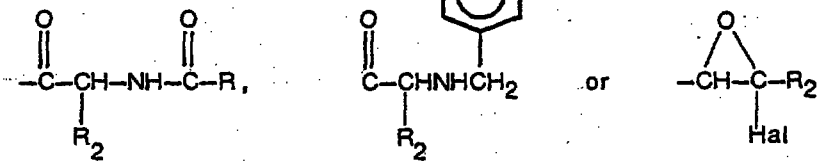


wherein R is an alkyl; or wherein R_{12} and R_{14} can be combined to form a keto group, or R_{13} and R_{15} can be combined to form a keto group, or both R_{12} and R_{14} and R_{13} and R_{15} can simultaneously form keto groups, with a reagent capable of converting said starting material to the corresponding imidazole;

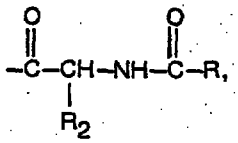
j) reacting formamide with a compound of the formula:



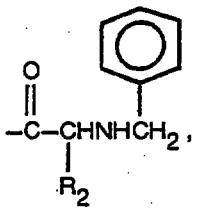
wherein R_5, R_6, R_7, R_8 and n are as defined above and Q is



(wherein Hal is a halogen atom, R is a substituted or unsubstituted alkyl, aralkyl or aryl group), provided that:

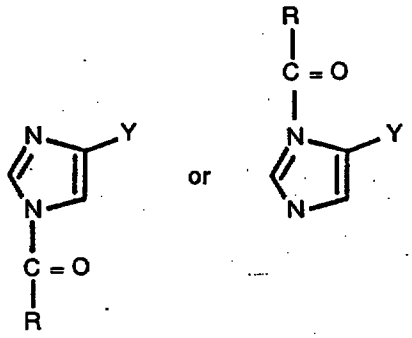
a) when Q is 

the reaction with formamide is followed by treatment of the intermediate product with acid; and

b) when Q is 

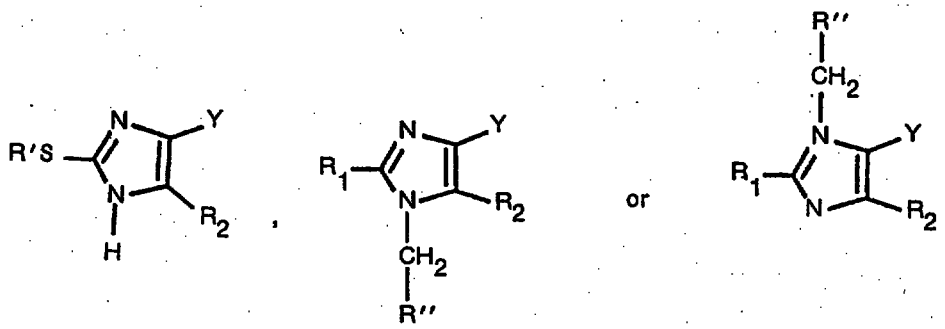
the reaction with formamide is followed by hydrogenation of the intermediate product;

k) hydrolysing a compound of the formula:



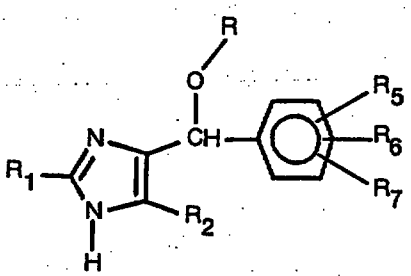
wherein Y is the arylalkyl residue determined by the formula (I) and (II), R is an alkyl group of 1 to 7 carbon atoms or an aryl radical of 6 to 10 carbon atoms;

l) hydrogenating a compound of the formula:



wherein R_1 and R_2 are as hereinbefore defined, Y is as defined under (k), R' is an aryl or alkyl and R'' is an aryl group; or

m) reacting a compound of the formula:

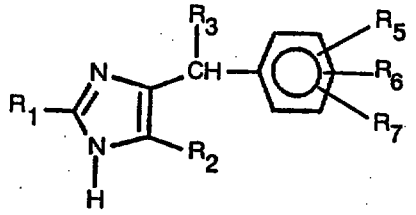


wherein R_1, R_2, R_5, R_6 and R_7 are as defined above and R is an alkyl of 1 to 4 C-atoms, with a Grignard reagent of the formula:

$$R_3—CH_2Mg\,Hal$$

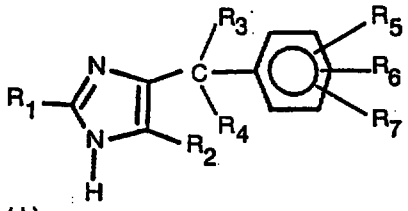
* C L M S *

wherein R_3 is as defined above to give a compound of the formula:



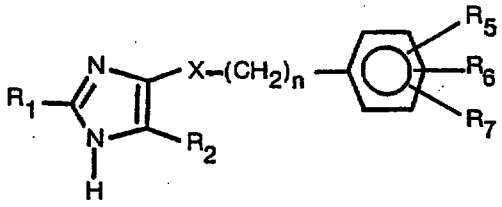
Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Substituierte Imidazole der allgemeinen Formel



(I)

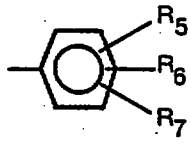
oder



(II)

worin bedeuten: R1 H, ein Alkyl mit 1 bis 4 Kohlenstoffatomen oder $-CH_2OH$; R_2 H oder CH_3; R_3

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,

oder  und R_4 H oder OH;

oder R_3 und R_4 zusammen: $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$

oder $=CH-CH_2CH_2CH_3$; X $-CH(R_8)-CH(R_9)-$ oder $-C(R_{11})=C(R_{10})-$; R_5, R_6 und R_7,

die gleich oder verschieden sein können, H, $-CH_3$, $-CH_2CH_3$, Halogen, OH oder $-OCH_3$ oder R_5 Wasserstoff und R_6 und R_7 bilden zusammen eine $-O-CH_2-O-$Brücke zwischen zwei anliegenden Kohlenstoffatom in der Phenylgruppe;

$-CHR_8-$ bedeutet $-CH_2-$; $-CHCH_3-$,

$-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)-CH_3)-$,

$-CH(-CH_2CH_2CH_2CH_3)-$ oder $>C=CH_2$, $>C=CH-CH_3$, $>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$,

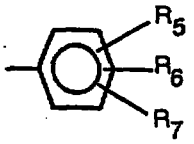
oder $>C=CH-CH_2CH_2CH_3$; R_9 ist H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$,

* C L M S *

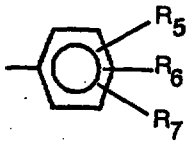
$-CH_2CH_2CH_2CH_3$ oder OH, R_{10} ist H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

oder $-CH_2CH_2CH_2CH_3$; R_{11} ist H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

oder $-CH_2CH_2CH_2CH_3$; n 0 bis 4, mit dem Proviso, daß dann,

wenn R_4 OH, R_1, H oder CH_3 und R_3 

bedeutet, dann R_5, R_6 und R_7 nicht alle gleichzeitig Wasserstoff sind; wenn R_1, R_2 und R_4 alle Wasserstoff sind und R_3



bedeutet, dann R_5, R_6 und R_7 nicht alle gleichzeitig Wasserstoff sind, R_8 und R_9 nicht gleichzeitig Wasserstoff sind und R_{11} und R_{10} nicht gleichzeitig Wasserstoff sind, und deren nichttoxischen pharmazeutisch annehmbaren Säureadditionssalze.

2. Verbindung der Formel (I) oder (II) gemäß Anspruch 1, worin jeder der Reste R_5, R_6 und R_7, die gleich oder verschieden sein können, Wasserstoff, Methyl, Ethyl oder Halogen bedeuten.

3. Eine Verbindung der Formel (I) gemäß Ansprüchen 1 oder 2, worin R_4 Wasserstoff und R_3 Methyl, Ethyl, Propyl, Isopropyl oder Butyl bedeutet.

4. Eine Verbindung der Formel (I) gemäß Anspruch 3, gemäß R_1 Methyl bedeutet.

5. Eine Verbindung der Formel (II) gemäß Ansprüchen 1 oder 2, worin X $-C(R_{11})=C(R_{10})-$ und R_{10} Wasserstoff bedeuten.

6. Eine Verbindung der Formel (II) gemäß Ansprüchen 1 oder 2, worin X $-C(R_{11})=C(R_{10})-$ und R_{11} Wasserstoff bedeuten.

7. Eine Verbindung der Formel (II) gemäß Ansprüchen 1 oder 2, worin X $-CH(R_8)-CH(R_9)-$ und R_9 Wasserstoff bedeuten.

8. Eine Verbindung der Formel (II) gemäß Ansprüchen 1 oder 2, worin X $-CH(R_8)-CH(R_9)-$ und R_8 Wasserstoff bedeuten.

9. Eine Verbindung der Formel (II) gemäß Ansprüchen 1 oder 2, oder einem der Ansprüche 5—8, worin R_1 Wasserstoff oder Methyl bedeutet.

10. Eine Verbindung der Formel (II) gemäß Ansprüchen 1, 2 oder einem der Ansprüche 5—9, worin n 0 oder 1 bedeutet.

11. Eine Verbindung der Formel (II) gemäß Anspruch 1, worin jeder der Reste R_5, R_6 und R_7, die gleich oder verschieden sein können, Wasserstoff, Methyl, Ethyl oder Halogen; R_1 Wasserstoff oder Methyl; R_2 Wasserstoff oder Methyl, R_8 oder R_{11} Methyl, Ethyl oder Isopropyl, R_9 und R_{10} Wasserstoff und n gleich 0 bedeuten.

12. 4-[(α-Methyl)-2,6-dimethylbenzyl]imidazol und dessen nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

13. 4-[(α-Methyl)-2,3-dimethylbenzyl]imidazol und dessen nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

14. 4-[(α-Methyl)-2-methylbenzyl]imidazol und dessen nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

* C L M S *

15. 4-[2(2,6-Dimethylphenyl)-1-methylethyl]imidazol und dessen nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

16. 4-[2(2,6-Dimethylphenyl)propyl]imidazol und dessen nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

17. 4-[2(2,6-Dimethylphenyl)-1-methylethenyl]imidazol und dessen nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

18. 4-[2(2,6-Dimethylphenyl)-1-ethylethenyl]imidazol und dessen nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

19. 4-[(α-Ethyl)-2,3-dimethylbenzyl]imidazol und dessen nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

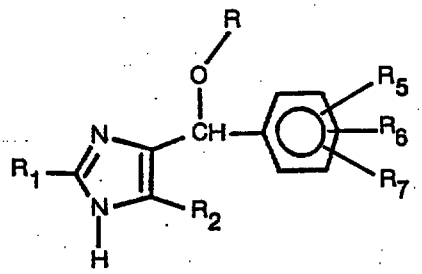
20. 4-[2-(2,6-Dichlorphenyl)-1-methylethenyl]imidazol und dessen nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

21. 4-[2-(2,6-Dimethylphenyl)-2-ethylethyl]imidazol und deren nichttoxischen pharmazeutisch annehmbaren Säureadditionssalze.

22. 4-[2-(3,4-Methylendioxyphenyl)propyl]imidazol und deren nichttoxische pharmazeutisch annehmbare Säureadditionssalze.

23. 1-(4-Imidazolyl)-1-(2,3-dimethylphenyl)-ethylen und deren nichttoxischen pharmazeutisch annehmbaren Säureadditionssalze.

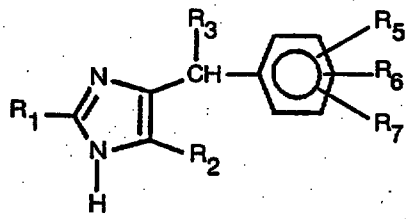
24. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, worin R_4 H bedeutet, dadurch gekennzeichnet, daß man eine Verbindung der Formel



worin R_1, R_2, R_5, R_6 und R_7 die in Anspruch 1 angegebene Bedeutung haben und R Alkyl mit 1 bis 4 C—Atomen bedeutet, mit einem Grignard-Reagens der Formel

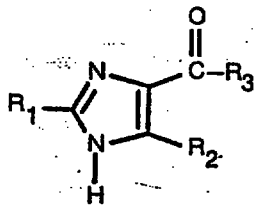
$$R_3—CH_2Mg\ Hal,$$

worin R_3 die in Anspruch 1 angegebene Bedeutung hat unter Erhalt einer Verbindung der Formel

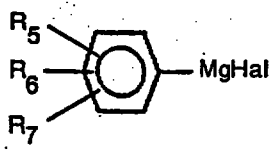


umsetzt.

25. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, worin R_4 OH bedeutet, dadurch gekennzeichnet, daß man ein Imidazolylketon der Formel

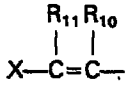


worin R_1 und R_2 die in Anspruch 1 angegebene Bedeutung haben und R_3 ein Alkyl oder Aryl gemäß Anspruch 1 ist mit einem Arylmagnesiumhalogenidderivat der Formel

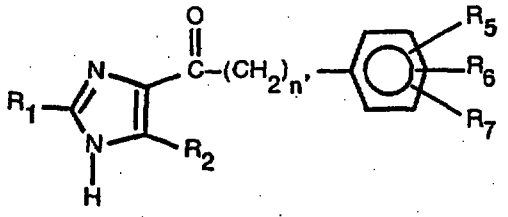


worin R_5, R_6, R_7 die in Anspruch 1 angegebene Bedeutung haben und Hal Halogen bedeutet, umsetzt.

26. Verfahren zur Herstellung einer Verbindung der Formeln (I) oder (II) gemäß Anspruch 1, worin X



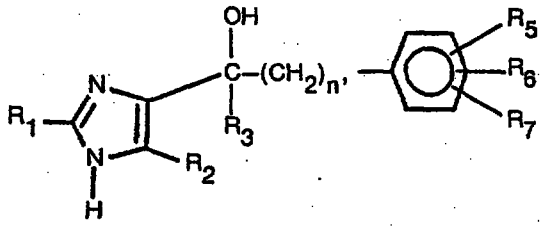
bedeutet und R_{10} Wasserstoff ist, dadurch gekennzeichnet, daß man eine Verbindung der Formel



worin R_1—R_7 die in Anspruch 1 angegebene Bedeutung haben und n' 0 bis 5 bedeutet mit einer Verbindung der Formel

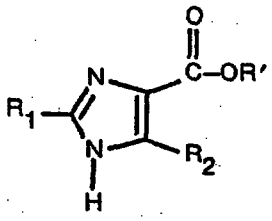
R_3MgHal,

worin R_3 ein Alkyl oder ein Aryl gemäß Anspruch 1 ist und Hal Halogen bedeutet, umsetzt, unter Erhalt einer Verbindung der Formel

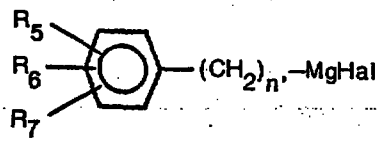


welche dann schließlich dehydratisiert wird unter Erhalt einer Verbindung der Formel (I) oder (II).

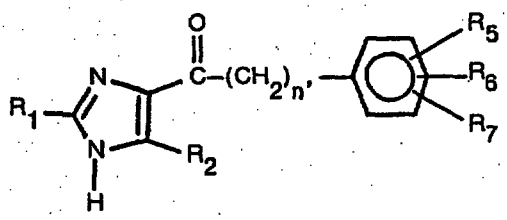
27. Verfahren zur Herstellung einer Verbindung der Formel (I) oder (II) gemäß Anspruch 1, dadurch gekennzeichnet, daß man einen Imidazolcarboxylsäurealkylester der Formel:



worin R_1 und R_2 die in Anspruch 1 angegebene Bedeutung haben und R' Alkyl bedeutet in einer ersten Stufe mit einem Grignard-Ragens der Formel



worin R_5, R_6 und R_7 die in Anspruch 1 angegebene Bedeutung haben und n' 0 bis 5 bedeutet, umsetzt unter Erhalt einer Verbindung der Formel

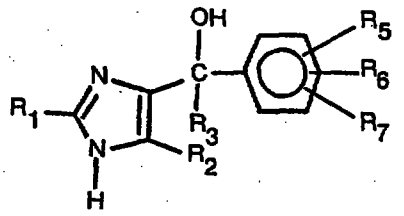


die dann in einer zweiten Stufe mit einem Grignard-Reagens der Formel

R_3MgHal,

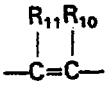
worin R_3 Alkyl oder Aryl gemäß Anspruch 1 ist, umgesetzt wird unter Erhalt eines Produktes, welches in der letzten Stufe dann dehydratisiert wird unter Erhalt einer Verbindung der Formeln (I) oder (II).

28. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, worin R_4 Wasserstoff bedeutet, dadurch gekennzeichnet, daß man katalytisch eine Verbindung der Formel

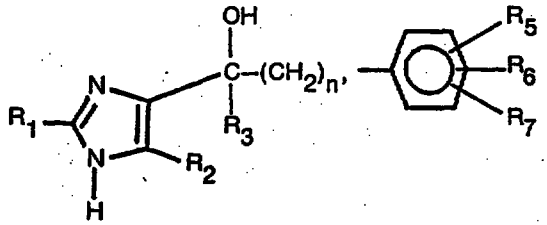


worin R_1, R_2, R_5, R_6 und R_7 die in Anspruch 1 angegebene Bedeutung haben und R_3 ein Alkyl oder Aryl gemäß Anspruch 1 ist, reduziert.

29. Verfahren zur Herstellung einer Verbindung der Formel (II) gemäß Anspruch 1, worin X

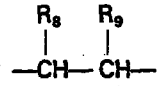


und R_{10} Wasserstoff bedeutet, dadurch gekennzeichnet, daß man eine Verbindung der Formel

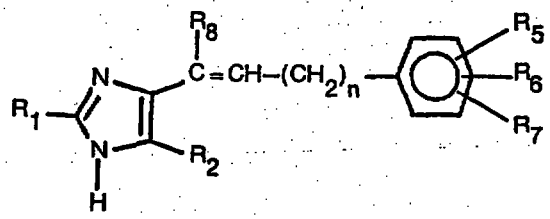


worin R_1, R_2, R_5, R_6, R_7 die in Anspruch 1 angegebene Bedeutung haben, und R_3 Alkyl oder Aryl gemäß Anspruch 1 und N' 1 oder 5 bedeuten, umsetzt.

30. Verfahren zur Herstellung einer Verbindung der Formel (II) gemäß Anspruch 1, worin X

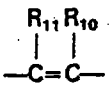


und R_9 Wasserstoff bedeuten, dadurch gekennzeichnet, daß man katalytisch eine Verbindung der Formel



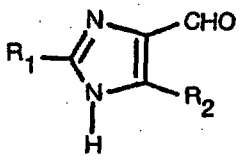
worin R_1, R_2, R_5, R_6, R_7 und n die in Anspruch 1 angegebene Bedeutung haben und R_8 Alkyl wie in Anspruch 1 bedeutet, reduziert.

31. Verfahren zur Herstellung einer Verbindung der Formel (II) gemäß Anspruch 1, worin X

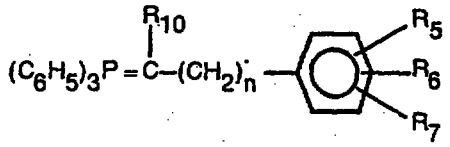


* C L M S *

und R_{11} Wasserstoff bedeuten, dadurch gekennzeichnet, daß man ein Imidazolaldehyd der Formel

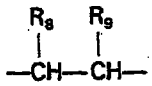


worin R_1 und R_2 die in Anspruch 1 angegebene Bedeutung haben mit einem Aralkylidentriphenylphosphoran der Formel

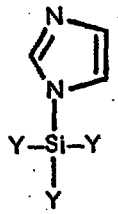


worin R_5, R_6, R_7, R_{10} und n die in Anspruch 1 angegebene Bedeutung haben, umsetzt.

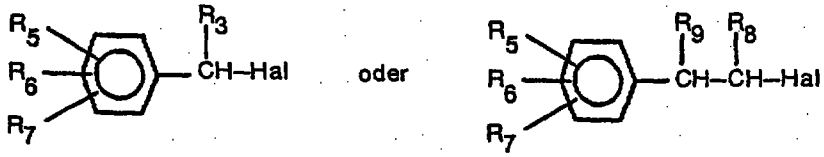
32. Verfahren zur Herstellung einer Verbindung der Formel (I) oder (II) gemäß Anspruch 1, worin X



bedeutet, dadurch gekennzeichnet, daß man ein N-Trialkylsilylimidazol der Formel

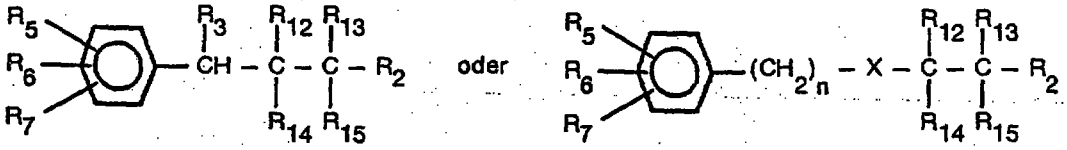


worin Y eine Alkylgruppe ist mit einem Arylalkylhalogenid der Formel

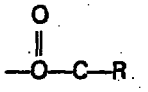


worin R_3, R_5, R_6, R_7, R_8 und R_9 die in Anspruch 1 angegebene Bedeutung haben und Hal ein Halogenatom bedeutet in Gegenwart einer Lewis-Säure umsetzt.

33. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, dadurch gekennzeichnet, daß man ein Ausgangsmaterial der Formeln



worin R_2, R_3, R_5, R_6, R_7 und n die in Anspruch 1 angegebene Bedeutung haben und R_{12}, R_{13}, R_{14} und R_{15}, die gleich oder verschieden sein können, jeweils Wasserstoff, Hydroxy, Mercapto, Halogen, Amino, —O—Alkyl mit 1 bis 7 Kohlenstoffatomen oder

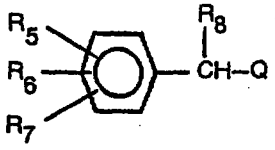


bedeutet, worin R Alkyl bedeutet; oder worin R_{12} und R_{14} zusammen eine Ketogruppe bilden oder R_{13} und R_{15} zusammen eine Ketogruppe bilden oder sowohl R_{12} und R_{14} und R_{13} und R_{15} gleichzeitig Ketogruppen

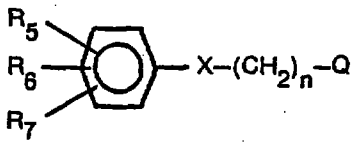
* C L M S *

bilden mit einem Reagens, das in der Lage ist, das genannte Ausgangsmaterial in das entsprechend Imidazol umzuwandeln, umsetzt.

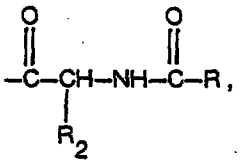
34. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, dadurch gekennzeichnet, daß man Formamid mit einer Verbindung der Formel

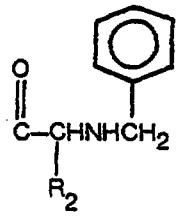


oder

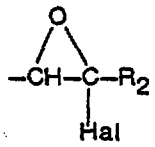


umsetzt, worin R_5, R_6, R_7, R_8 und n die in Anspruch 1 angegebene Bedeutung haben und Q



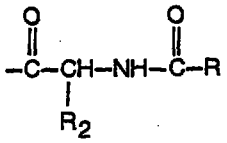


oder



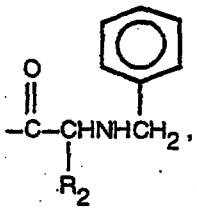
(worin Hal ein Halogenatom, R substituierte oder unsubstituierte Alkyl-, Aralkyl- oder Arylgruppen bedeuten), mit dem Proviso, daß

a) wenn Q



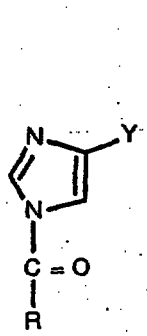
bedeutet, anschließend an die Umsetzung mit Formamid eine Behandlung des Zwischenproduktes mit Säure erfolgt und

b) wenn Q

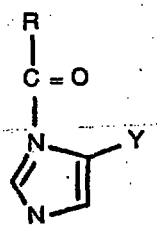


bedeutet, anschließend an die Umsetzung mit Formamid eine Hydrierung des Zwischenproduktes erfolgt.

35. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung der Formeln



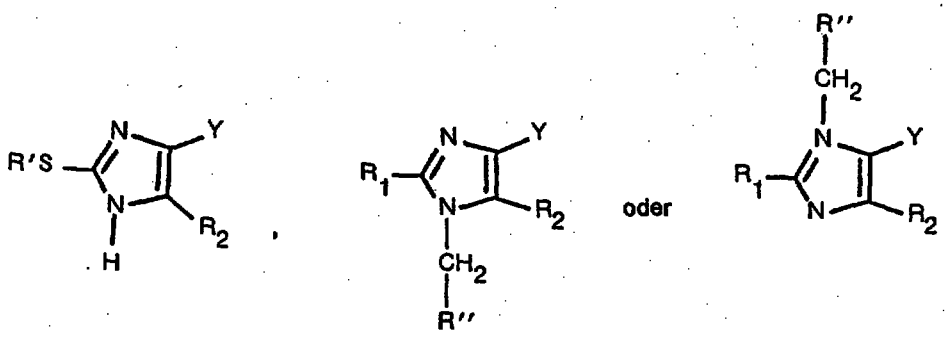
oder



worin Y ein Arylalkylrest der durch die Formeln (I) und (II) bestimmt ist und R eine Alkylgruppe mit 1 bis 7 Kohlenstoffatomen oder ein Arylrest mit 6 bis 10 Kohlenstoffatomen bedeutet, hydrolysiert.

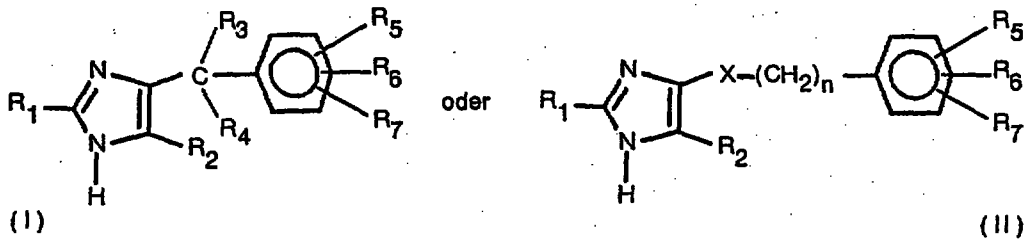
* C L M S *

36. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung der Formeln



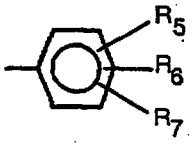
worin Y die in Anspruch 36 angegebene Bedeutung hat und R' eine Aryl- oder Alkyl- und R'' eine Arylgruppe bedeutet, hydriert.

37. Ein substituiertes Imidazol der allgemeinen Formeln (I) oder (II)



worin bedeuten: R_1 H, Alkyl mit 1 bis 4 Kohlenstoffatomen oder $-CH_2OH$; R_2 H oder CH_3; R_3

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,

oder  und R_4 H oder OH;

oder R_3 und R_4 zusammen: $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$,

oder $=CH-CH_2CH_2CH_3$;

X $-CH(R_8)-CH(R_9)-$ oder $-C(R_{11})=C(R_{10})-$; R_5, R_6 und R_7,

die gleich oder verschieden sein können, H, $-CH_3$— CH_2CH_3, Halogen, OH oder $-CH_3$ oder R_5 Wasserstoff und R_6 und R_7 zusammen eine —O—CH_2—O—Brücke zwischen zwei anliegenden Kohlenstoffatomen in der Phenylgruppe bedeuten;

$-CHR_8-$ bedeutet $-CH_2-$; $-CH(CH_3)-$, $-CH(-CH_2CH)-$, $-CH(-CH_2CH_2CH_3)-$,

$-CH(-CH(CH_3)-CH_3)-$, $-CH(-CH_2CH_2CH_2CH_3)-$ oder $C=CH_2$, $C=CH-CH_3$,

$>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$ oder $>C=CH-CH_2CH_2CH_3$;

R_9 bedeutet H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$ oder OH;

R_{10} bedeutet H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ oder $-CH_2CH_2CH_2CH_3$;

R_{11} bedeutet H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ oder $-CH_2CH_2CH_2CH_3$,

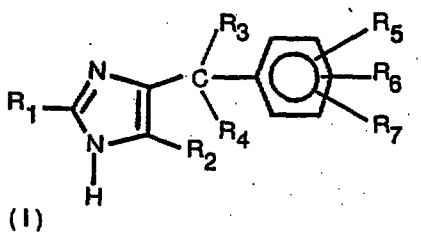
n 0 bis 4, mit dem Proviso, daß R_{11} und R_9 oder R_8 und R_{10} nicht gleichzeitig Wasserstoff bedeuten, und die nichttoxischen pharmazeutisch annehmbaren Säureadditionssalze für die Verwendung bei der Therapie als antihypertensive Mittel, antithrombotische Mittel, diuretische Mittel, antimycotische oder Antifungimittel.

38. Pharmazeutische Zusammensetzung umfassend ein Imidazolderivat gemäß Anspruch 37 oder ein nichttoxisches pharmazeutisch annehmbares Säureadditionssalz davon und einen verträglichen pharmazeutisch annehmbaren Träger dafür.

39. *Eine pharmazeutische Zusammensetzung umfassend ein Imidazolderivat gemäß einem der* Ansprüche 1 bis 23 oder ein nichttoxisches pharmazeutisch annehmbares Säureadditionssalz davon und einen verträgliches pharmazeutisch annehmbarer Träger dafür.

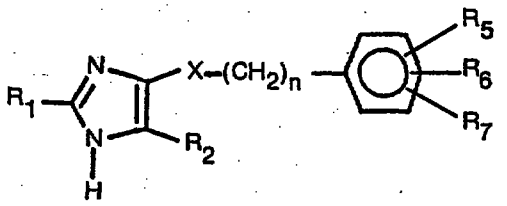
Patentanspruch für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formeln



(I)

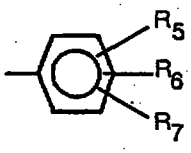
oder



(II)

worin bedeuten: R_1 H, ein Alkyl mit 1 bis 4 Kohlenstoffatomen oder $-CH_2OH$; R_2 H oder CH_3; R_3

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,

oder  und R_4 H oder OH;

oder R_3 und R_4 zusammen: $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$,

oder $=CH-CH_2CH_2CH_3$;

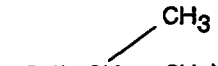
X $-CH(R_8)-CH(R_9)-$ oder $-C(R_{11})=C(R_{10})-$; R_5, R_6 und R_7,

die gleich oder verschieden sein können, H, $-CH_3$, $-CH_2CH_3$, Halogen, OH oder $-OCH_3$ oder R_5

* C L M S *

Wasserstoff und R_6 und R_7 bilden zusammen eine —O—CH_2—O-Brücke zwischen zwei anliegenden Kohlenstoffatomen in der Phenylgruppe;

$-CHR_8-$ bedeutet $-CH_2-$, $-CHCH_3-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$,



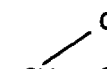
$-CH(-CH(CH_3)-CH_3)-$, $-CH(-CH_2CH_2CH_2CH_3)-$ oder $>C=CH_2$, $>C=CH-CH_3$, $>C=CH-CH_2CH_3$,



$>C=C(CH_3)-CH_3$, oder $C=CH-CH_2CH_2CH_3$; R_9 ist H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,



$-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$ oder OH; R_{10} ist H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,

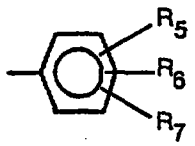




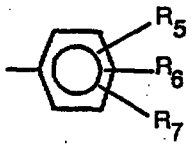
$-CH(CH_3)-CH_3$ oder $-CH_2CH_2CH_2CH_3$; R_{11} ist H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

oder $-CH_2CH_2CH_2CH_3$; n 0 bis 4, mit dem Proviso,

daß dann, wenn R_4 OH, R_1, H oder CH_3 und R_3

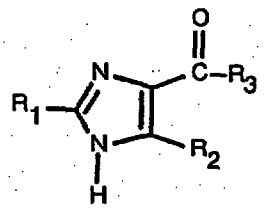


bedeutet, dann R_5, R_6 und R_7 nicht alle gleichzeitig Wasserstoff sind; wenn R_1, R_2 und R_4 alle Wasserstoff sind und R_3

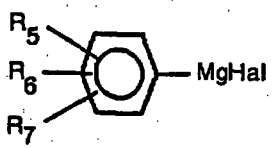


bedeutet, dann R_5, R_6 und R_7 nicht alle gleichzeitig Wasserstoff sind; R_8 und R_9 nicht gleichzeitig Wasserstoff sind und R_{11} und R_{10} nicht gleichzeitig Wasserstoff sind, und deren nichttoxischen pharmazeutisch annehmbaren Säureadditionssalze, dadurch gekennzeichnet, daß man

a) ein Imidazolylketon der Formel



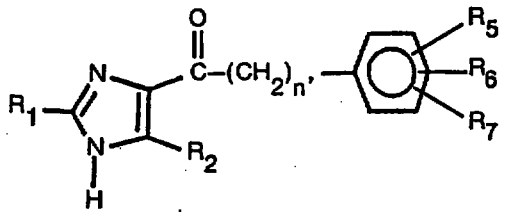
worin R_1 und R_2 die oben angegebene Bedeutung haben und R_3 Alkyl oder Aryl der oben genannten Bedeutung haben mit einem Arylmagnesiumhalogenidderivat der Formel



worin R_5, R_6, R_7 die vorhergehende Bedeutung haben und Hal Halogen ist unter Erhalt einer Verbindung der Formel (I), worin R_4 OH ist, umsetzt;

* C L M S *

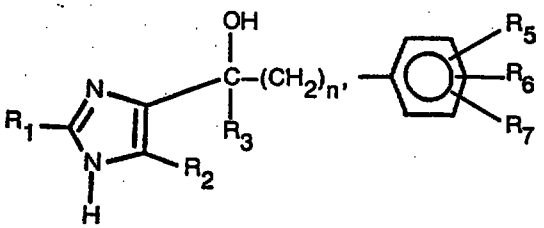
b) eine Verbindung der Formel



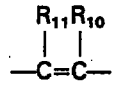
worin R_1—R_7 die vorher angegebene Bedeutung haben und n' 0 bis 5 bedeutet mit einer Verbindung der Formel:

$$R_3MgHal,$$

worin R_3 Alkyl oder Aryl wie vorher angegeben ist und Hal Halogen bedeutet, umsetzt, unter Erhalt einer Verbindung der Formel:

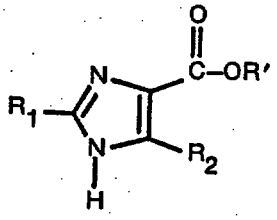


die dann anschließend dehydratisiert wird unter Erhalt einer Verbindung der Formel (I) oder (II), worin X

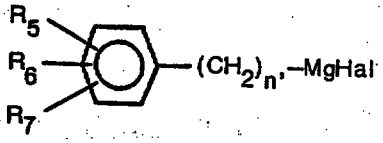


und R_{10} Wasserstoff bedeuten;

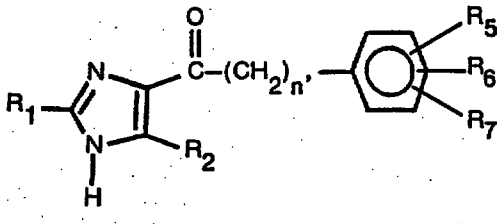
c) einen Imidazolcarboxylsäureester der Formel:



worin R_1 und R_2 die vorher angegebene Bedeutung haben und R' Alkyl bedeutet in einer ersten Stufe mit einem Grignard-Reagens der Formel



worin R_5, R_6 und R_7 die vorher angegebene Bedeutung haben und n' 0 bis 5 ist, umsetzt, unter Erhalt einer Verbindung der Formel:



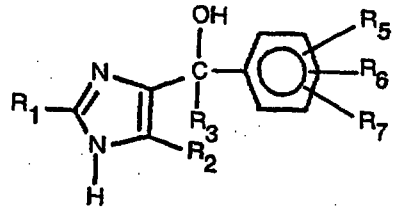
* C L M S *

welche in einer zweiten Stufe mit einem Grignard-Reagens der Formel:

R_3MgHal,

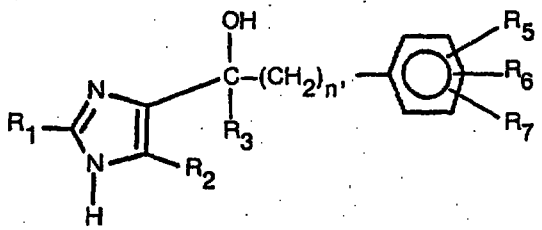
worin R_3 Alkyl oder Aryl wie vorher angegeben ist, umsetzt, unter Erhalt eines Produktes, welches in der letzten Stufe dehydratisiert wird unter Erhalt einer Verbindung der Formeln (I) oder (II);

d) daß man katalytisch eine Verbindung der Formel:

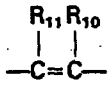


worin R_1, R_2, R_5, R_6 und R_7 die vorher angegebene Bedeutung haben und R_3 Alkyl oder Aryl wie vorher angegeben ist, reduziert;

e) daß man eine Verbindung der Formel

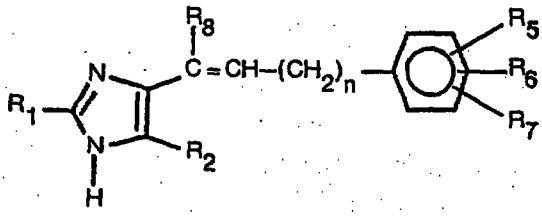


worin R_1, R_2, R_5, R_6, R_7 die vorher angegebene Bedeutung haben und R_3 Alkyl oder Aryl wie vorher angegeben ist und n' 1 bis 5 bedeutet, unter Erhalt einer Verbindung der Formel (II), worin X



und R_{10} Wasserstoff bedeuten, dehydratisiert;

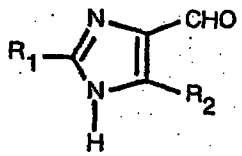
f) daß man eine Verbindung der Formel:



worin R_1, R_2, R_5, R_6, R_7 und n die vorher angegebene Bedeutung haben und R_8 Alkyl wie vorher angegeben

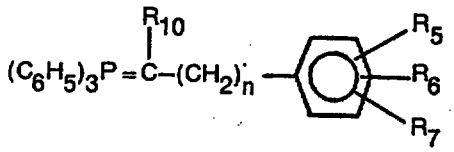
ist, unter Erhaltung einer Formel (II), worin X  ist und R_9 Wasserstoff bedeutet, reduziert;

g) daß man einen Imidazolaldehyd der Formel:



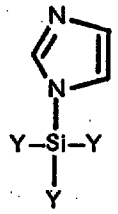
* C L M S *

worin R_1 und R_2 die vorher angegebene Bedeutung haben, mit einem Aralkylidentriphenylphosphoran der Formel:

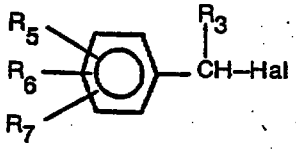
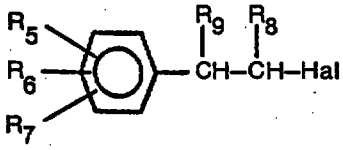


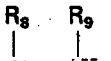
worin R_5, R_6, R_7, R_{10} und n die vorher angegebene Bedeutung haben, unter Erhalt einer Verbindung der Formel (II), worin X  und R_{11} Wasserstoff bedeuten, umsetzt;

h) daß man ein N-Trialkylsilylimidazol der Formel:

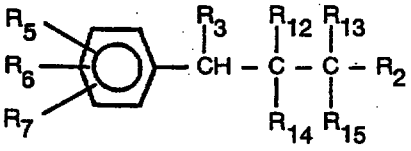
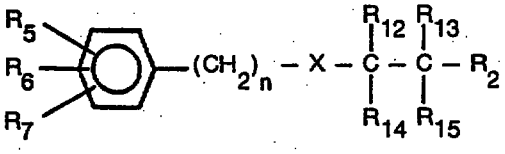


worin Y eine Alkylgruppe ist mit einem Aralkylhalogenid der Formeln;

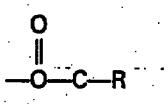
 oder 

worin R_3, R_5, R_6, R_7, R_8 und R_9 die vorher angegebene Bedeutung haben und Hal eine Halogenatom bedeutet, in Gegenwart einer Lewis-Säure umsetzt unter Erhalt einer Verbindung der Formel (I) oder Formel (II), worin X  ist;

i) daß man ein Ausgangsmaterial der Formeln

 oder 

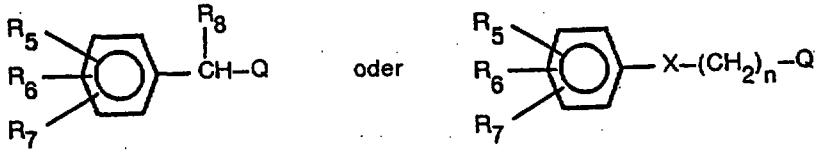
worin R_2, R_3, R_5, R_6, R_7 und n die vorher angegebene Bedeutung haben und R_{12}, R_{13}, R_{14} und R_{15}, die gleich oder verschieden sein können, jeweils Wasserstoff, Hydroxy, Mercapto, Halogen, Amino, —O— Alkyl mit 1 bis 7 Kohlenstoffatomen oder



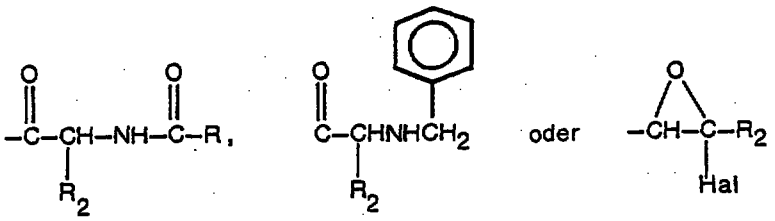
bedeuten, worin R Alkyl ist, oder worin R_{12} und R_{14} zusammen eine Ketogruppe bilden oder R_{13} und R_{15} zusammen eine Ketogruppe bilden oder sowohl R_{12} und R_{14} und R_{13} und R_{15} gleichzeitig Ketogruppen bilden können mit einem Reagens, das in der Lage ist, das Ausgangsmaterial in das entsprechende Imidazol zu überführen, umsetzt;

* C L M S *

j) daß man Formamid mit einer Verbindung der Formel:

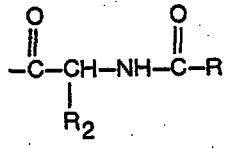


worin R_5, R_6, R_7, R_8 und n die vorher angegebene Bedeutung haben und Q



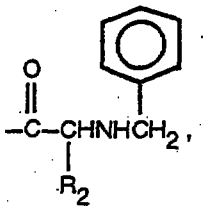
(worin Hal ein Halogenatom, R eine substituierte oder unsubstituierte Alkyl-, Aralkyl- oder Arylgruppe bedeuten), umsetzt mit dem Proviso, daß,

a) wenn Q



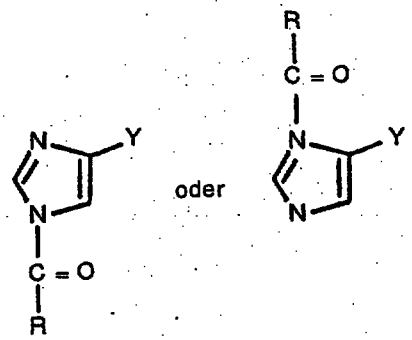
bedeutet, im Anschluß an die Umsetzung mit Formamid eine Behandlung des Zwischenproduktes mit Säure erfolgt und

b) wenn Q



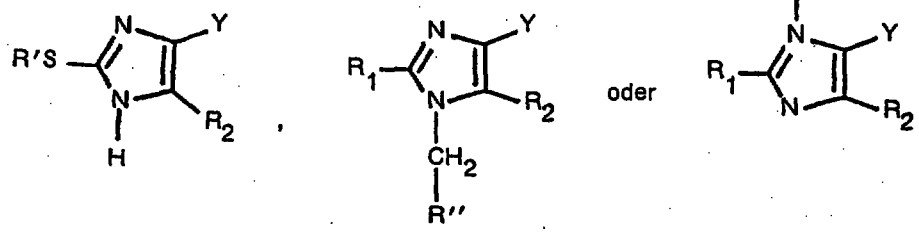
bedeutet, im Anschluß an die Umsetzung mit Formamid eine Hydrierung des Zwischenproduktes folgt;

k) daß man eine Verbindung der Formeln:



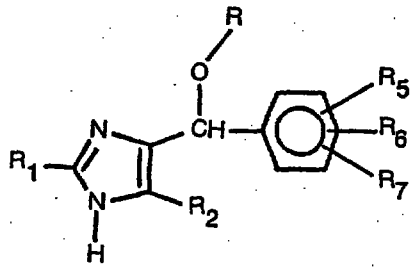
worin Y der Arylalkylrest ist, der durch die Formeln (I) und (II) bestimmt wird, R eine Alkylgruppe mit 1 bis 7 Kohlenstoffatomen oder einen Arylrest mit 6 bis 10 Kohlenstoffatomen bedeutet, hydrolysiert;

l) daß man eine Verbindung der Formeln



worin R_1 und R_2 die vorher angegebene Bedeutung haben und Y die unter (k) angegebene Bedeutung hat und R' eine Aryl- oder Alkylgruppe und R'' eine Arylgruppe bedeutet, hydriert oder

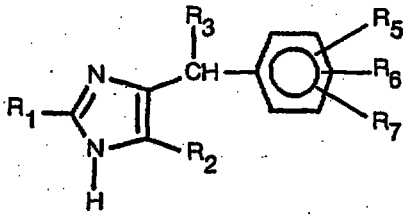
m) eine Verbindung der Formel:



worin R_1, R_2, R_5, R_6 und R_7 die vorher angegebene Bedeutung haben und R Alkyl mit 1 bis 4 Kohlenstoffatomen mit einem Grignard-Reagens der Formel:

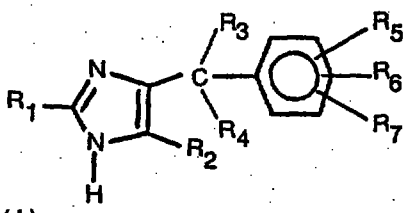
$$R_3—CH_2MgHal$$

worin R_3 die vorher angegebene Bedeutung hat, umsetzt unter Erhalt einer Verbindung der Formel:



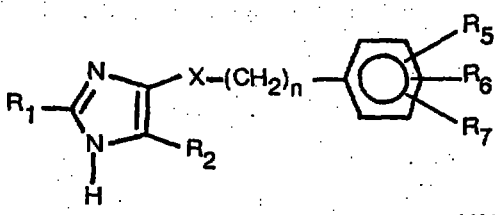
Revendications pour les Etats contactants: BE CH DE FR GB IT LI LU NL SE

1. Imidazoles substitués répondant à la formule générale:



(I)

ou



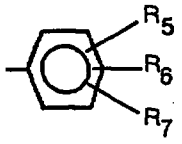
(II)

dans laquelle R_1 est H, un radical alkyle de 1 à 4 atomes de carbone ou $—CH_2OH$; R_2 est H ou CH_3; R_3 est

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,

* C L M S *

57

ou  et R_4 est H ou OH;

ou R_3 et R_4 représentent ensemble $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$,

ou $=CH-CH_2CH_2CH_3$; X est $-CH(R_8)-CH(R_9)-$ ou $-C(R_{11})=C(R_{10})-$; R_5, R_6, et R_7,

qui peuvent être identiques ou différents, représentent chacun H, $-CH_3$, $-CH_2CH_3$, un halogène, OH ou $-OCH_3$ ou bien R_5 est un atome d'hydrogène et R_6 et R_7 forment conjointement un pont $-O-CH_2-O-$ entre deux atomes de carbone adjacents dans le radical phényle;

$-CHR_8-$ est $-CH_2-$, $-CH(CH_3)-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)-CH_3)-$,

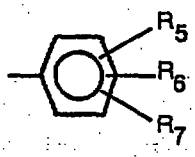
$-CH(-CH_2CH_2CH_2CH_3)-$ ou $>C=CH_2$, $>C=CH-CH_3$, $>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$,

ou $>C=CH-CH_2CH_2CH_3$; R_9 est H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$,

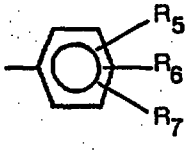
$-CH_2CH_2CH_2CH_3$ ou OH; R_{10} est H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

ou $-CH_2CH_2CH_2CH_3$; R_{11} est H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

ou $-CH_2CH_2CH_2CH_3$; *n* est 0 à 4; à la condition que

quand R_4 est OH, R_1 est H ou CH_3 et R_3 est  ;

alors R_5, R_6 et R_7 ne soient pas tous simultanément l'hydrogène

quand R_1, R_2 et R_4 sont tous l'hydrogène et R_3 est  ;

alors R_5, R_6, R_7 ne soient pas tous simultanément l'hydrogène; R_8 et R_9 ne soient pas simultanément l'hydrogène; et R_{11} et R_{10} ne soient pas simultanément l'hydrogène; et leurs sels d'addition avec des acides, non toxiques pharmaceutiquement acceptables.

2. Composés de la formule I ou II selon la revendication 1, dans lequel R_5, R_6 et R_7, qui peuvent être identiques ou différents, représentent un atome d'hydrogène, ou un radical méthyle, éthyle ou un halogène.

* C L M S *

3. Composé de formule I selon la revendication 1 ou 2, dans lequel R_4 est l'hydrogène et R_3 est le radical méthyle, éthyle, propyle, isopropyle ou butyle.

4. Composé de formule I selon la revendication 3, dans lequel R_1 est méthyle.

5. Composé de formule II selon la revendication 1 ou 2, dans lequel X est $-\overset{R_{11}}{\underset{}{C}}=\overset{R_{10}}{\underset{}{C}}-$ et R_{10} est l'hydrogène.

6. Composé de formule II selon la revendication 1 ou 2, dans lequel X est $-\overset{R_{11}}{\underset{}{C}}=\overset{R_{10}}{\underset{}{C}}-$ et R_{11} est l'hydrogène.

7. Composé de formule II selon la revendication 1 ou 2, dans lequel X est $-\overset{R_8}{\underset{}{CH}}-\overset{R_9}{\underset{}{CH}}-$ et R_9 est l'hydrogène.

8. Composé de formule II selon la revendication 1 ou 2, dans lequel X est $-\overset{R_8}{\underset{}{CH}}-\overset{R_9}{\underset{}{CH}}-$ et R_8 est l'hydrogène.

9. Composé de formule II selon la revendication 1, 2 ou l'une quelconque des revendications 5 à 8, dans lequel R_1 est l'hydrogène ou un radical méthyle.

10. Composé de formule II selon la revendication 1 ou 2 ou selon l'une quelconque des revendications 5 à 9, dans lequel *n* est 0 ou 1.

11. Composé de formule II, selon la revendication 1, dans lequel R_5, R_6 et R_7, qui peuvent être identiques ou différents, représentent un atome d'hydrogène ou un radical méthyle, éthyle ou un halogène; R_1 est un atome d'hydrogène ou le radical méthyle; R_2 est un atome d'hydrogène ou un radical méthyle, R_8 ou R_{11} est le radical méthyle, éthyle ou isopropyle, R_9 et R_{10} sont des atomes d'hydrogène et *n* est 0.

12. 4-[(α-méthyl)-2,6-diméthylbenzyl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

13. 4[(α-méthyl)-2,3-diméthylbenzyl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

14. 4[(α-méthyl)-2-méthylbenzyl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

15. 4-[2-(2,6-diméthylphényl)-1-méthyléthyl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

16. 4-[2-(2,6-diméthylphényl)propyl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

17. 4-[2-(2,6-diméthylphényl)-1-méthyléthényl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

18. 4-[2-(2,6-diméthylphényl)-1-éthyléthényl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

19. 4-[(α-éthyl)-2,3-diméthylbenzyl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

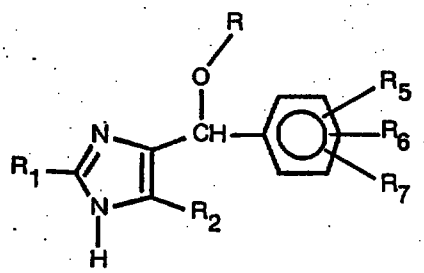
20. 4-[2-(2,6-dichlorophényl)-1-méthyléthényl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

21. 4-[2-(2,6-diméthylphényl)-2-éthyléthyl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

22. 4-[2-(3,4-méthylènedioxyphényl)propyl]imidazole et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

23. 1-(4-imidazolyl)-1-(2,3-diméthylphényl)-éthylène et ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables.

24. Procédé de préparation d'un composé de formule I selon la revendication 1, où R_4 est H, qui consiste à faire réagir un composé de formule:

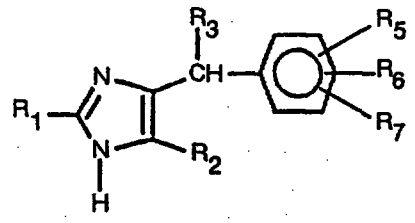


* C L M S *

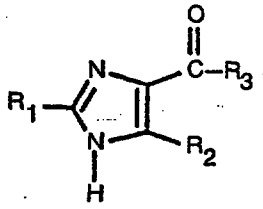
dans laquelle R_1, R_2, R_5, R_6 et R_7 sont tels que définis dans la revendication 1, et R est un radical alkyle de 1 à 4 atomes de carbone, avec un réactif de Grignard de formule:

$$R_3—CH_2—Mg\ Hal$$

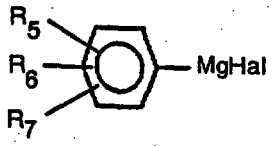
où R_3 est tel que défini dans la revendication 1, pour donner un composé de formule:



25. Procédé pour la préparation d'un composé de formule I selon la revendication 1, où R_4 est OH, qui consiste à faire réagir une imidazolyl-cétone de formule:

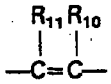


où R_1 et R_2 sont tels que définis dans la revendication 1 et R_3 est un radical alkyle ou aryle tel que défini dans la revendication 1, avec un dérivé d'halogénure d'arylmagnésium de formule:

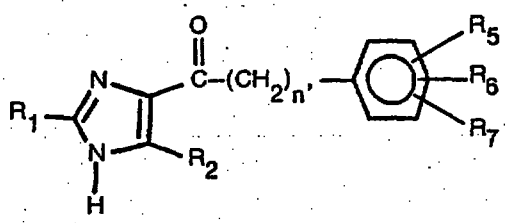


où R_5, R_6, R_7 sont comme dans la revendication 1 et Hal est un halogène.

26. Procédé de préparation d'un composé de formule I ou II selon la revendication 1, où X est



et R_{10} est un atome d'hydrogène, qui consiste à faire réagir un composé de formule:

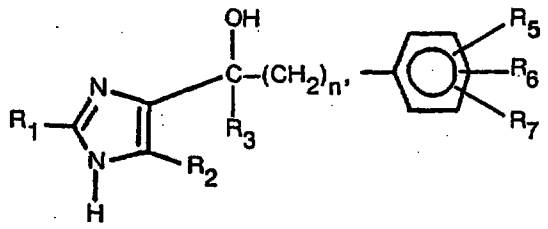


où R_1—R_7 sont tels que définis dans la revendication 1 et n' est 0 à 5 avec un composé de formule:

$$R_3Mg\ Hal$$

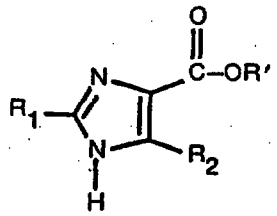
* C L M S *

où R_3 est un radical alkyle ou aryle tel que défini dans la revendication 1 et Hal est un atome d'halogène, pour obtenir un composé de formule:

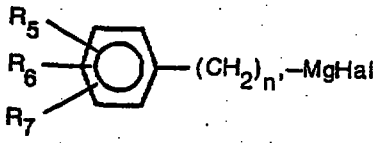


qu'on déshydrate finalement pour obtenir un composé de formule I ou II.

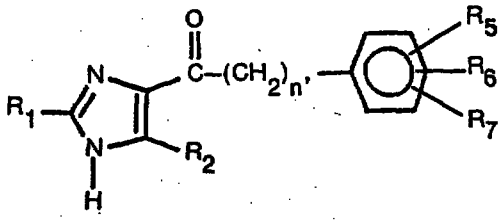
27. Procédé depréparation d'un composé de formule I ou II selon la revendication 1, qui consiste à faire réagir, en un premier stade, un ester alkylique d'acide imidazolecarboxylique de formule:



où R_1 et R_2 sont tels que définis dans la revendication 1 et R' est un radical alkyle, avec un réactif de Grignard de formule:



où R_5, R_6 et R_7 sont tels que définis dans la revendication 1 et *n'* est 0 à 5, pour obtenir un composé de formule:

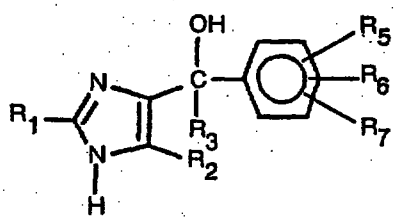


qu'on fait réagir en un second stade avec un réactif de Grignard de formule:

R_3MgHal

où R_3 est un radical alkyle ou aryle tel que définis dans la revendication 1, pour obtenir un produit qu'on déshydrate ou un stade final pour obtenir un composé de formule I ou II.

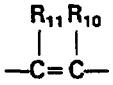
28. Procédé de préparation d'un composé de formule I selon la revendication 1, où R_4 est un atome d'hydrogène, qui consiste à réduire par voie catalytique un composé de formule:



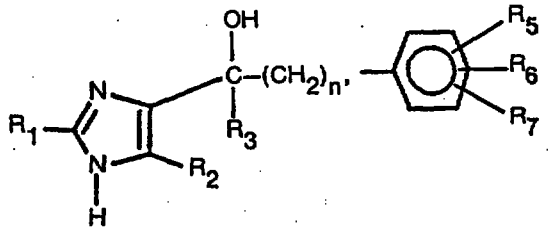
où R_1, R_2, R_5, R_6 et R_7 sont tels que définis dans la revendication 1, et R_3 est un radical alkyle ou aryle tel que définis dans la revendication 1.

* C L M S *

29. Procédé de préparation d'un composé de formule II selon la revendication 1, où X représente

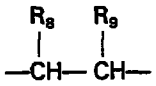


et R_{10} est un atome d'hydrogène, qui consiste à déshydrater un composé de formule:

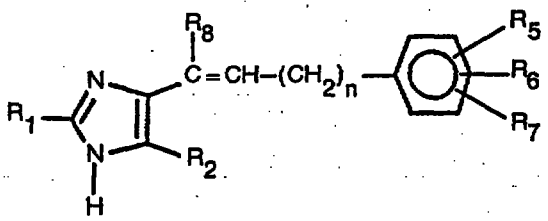


où R_1, R_2, R_3, R_6 et R_7 sont tels que définis dans la revendication 1, R_3 est un radical alkyle ou aryle tels que définis dans la revendication 1 et n' est de 1 à 5.

30. Procédé de préparation d'un composé de formule II selon la revendication 1, où X re-résente

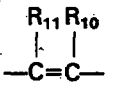


et R_9 est un atome d'hydrogène, qui consiste à réduire catalytiquement un composé de formule:

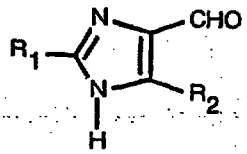


où R_1, R_2, R_5, R_6, R_7 et n sont tels que définis dans la revendication 1, et R_8 est un radical alkyle selon la revendication 1.

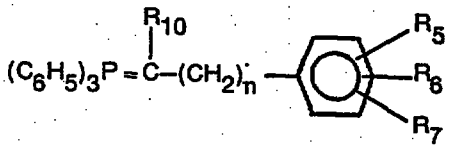
31. Procédé de préparation d'un composé de formule II, selon la revendication 1, où X est



et R_{11} est un atome d'hydrogène qui consiste à faire réagir un imidazole-aldéhyde de formule:



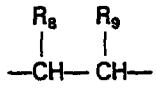
dans laquelle R_1 et R_2 sont tels que définis dans la revendication 1, avec un aralkylidènetriphényl-phosphorane de formule:



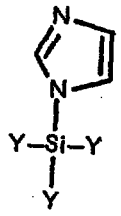
dans laquelle R_5, R_6, R_7, R_{10} et n sont tels que dans la revendication 1.

* C L M S *

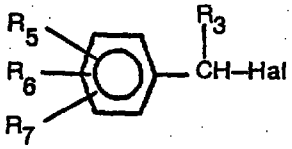
32. Procédé de préparation d'un composé de formule I ou II selon la revendication 1, où X est



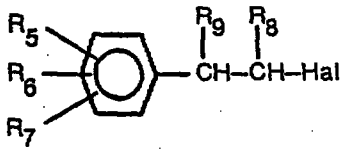
qui consiste à faire réagir un N-trialkylsilyl-imidazole de formule:



dans laquelle Y est un radical alkyle avec un halogénure d'arylalkyle de formule:

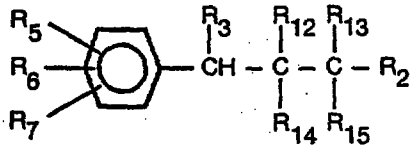


ou

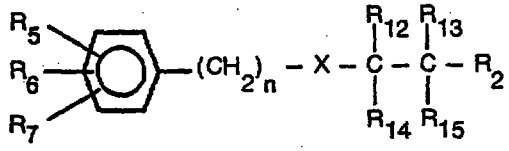


dans laquelle R_3, R_5, R_6, R_7, R_8 et R_9 sont tels que définis dans la revendication 1, et Hal est un atome d'halogène, en présence d'un acide de Lewis.

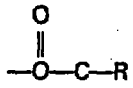
33. Procédé de préparation d'un composé selon la revendication 1 qui consiste à faire réagir une matière de départ de formule:



ou

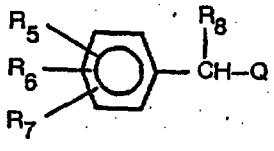


dans laquelle R_2, R_3, R_5, R_6, R_7 et n sont tels que définis dans la revendication 1 et R_{12}, R_{13}, R_{14} et R_{15}, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un radical hydroxy, mercapto, un halogène, amino, —O—alkye de 1 à 7 atomes de carbone ou

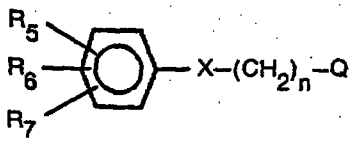


où R est un radical alkyle; ou dans laquelle R_{12} et R_{14} peuvent être combinés pour former un groupe céto, ou bien R_{13} et R_{15} peuvent être combinés pour former un groupe céto, ou bien R_{12}et R_{14} ainsi que R_{13} et R_{15} peuvent former simultanément des groupes céto, avec un réactif capable de convertir ladite matière de départ en imidazole correspondant.

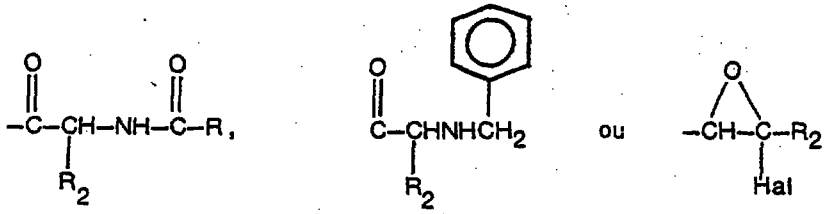
34. Procédé de préparation d'un composé selon la revendication 1, qui consiste à faire réagir le formamide avec un composé de formule:



ou

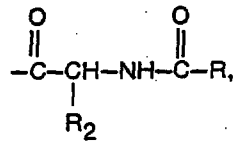


où R_5, R_6, R_7, R_8 et n sont tels que dans la revendication 1 et Q est



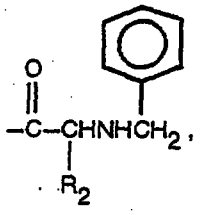
(où Hal est un atome d'halogène, R est un radical alkyle, aralkyle, ou aryle substitués ou non substitués, à la condition que:

a) quand Q est



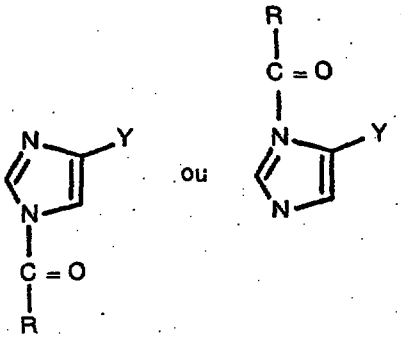
la réaction avec le formamide est suivie d'un traitement du produit intermédiaire avec un acide; et

b) quand Q est



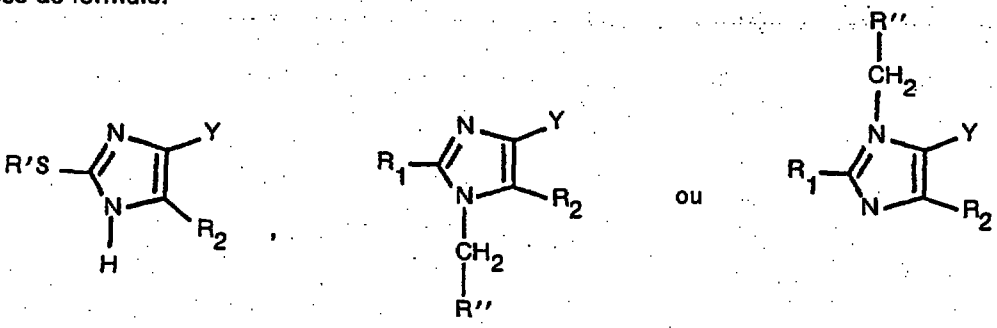
la réaction avec le formamide est suivie de l'hydrogénation du produit intermédiaire.

35. Procédé de préparation d'un composé selon la revendication 1, qui consiste à hydrolyser un composé de formule



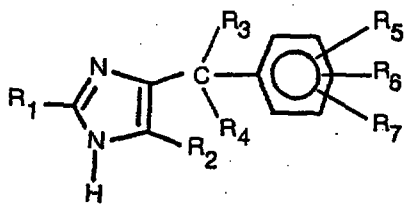
dans laquelle Y est un reste d'arylalkyle déterminé par la formule I et II, R est un radical alkyle de 1 à 7 atomes de carbone ou un radical aryle de 6 à 10 atomes de carbone.

36. Procédé de préparation d'un composé selon la revendication 1, qui consiste à hydrogéner un composé de formule:



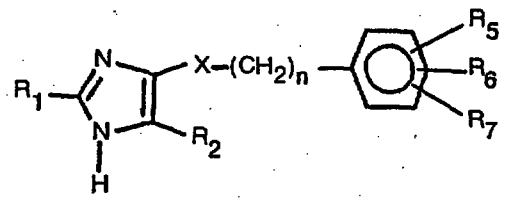
dans laquelle Y est tel que définis dans la revendication 36, R' est un radical aryle ou alkyle et R'' est un radical aryle.

37. Imidazole substitué de formule générale:



(I)

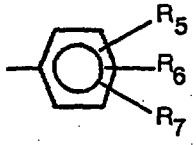
ou



(II)

dans laquelle R_1 est H, un radical alkyle de 1 à 4 atomes de carbone ou $-CH_2OH$; R_2 est H ou CH_3; R_3 est

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,

ou  et R_4 est H ou OH;

ou R_3 et R_4 représentent ensemble $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$,

ou $=CH-CH_2CH_2CH_3$; X est $-CH(R_8)-CH(R_9)-$ ou $-C(R_{11})=C(R_{10})-$; R_5, R_6, et R_7,

qui peuvent être identiques ou différents sont H, $-CH_3$, $-CH_2CH_3$, halogène, OH ou OCH_3 ou R_5 est l'hydrogène et R_6 et R_7 forment ensemble un pont $-O-CH_2O-$ entre deux atomes de carbone dans le groupe phényle;

$-CHR_8-$ est $-CH_2-$, $-CH(CH_3)-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)-CH_3)-$,

$-CH(-CH_2CH_2CH_2CH_3)-$ ou $C=CH_2$, $C=CH-CH_3$, $>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$,

ou $>C=CH-CH_2CH_2CH_3$; R_9 est H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$,

$-CH_2CH_2CH_2CH_3$ ou OH; R_{10} est H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

ou $-CH_2CH_2CH_2CH_3$; R_{11} est H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$

ou $-CH_2CH_2CH_2CH_3$;

n est 0 à 4; à la condition que R_{11} et R_9 ou R_8 et R_{10} ne soient pas simultanément des atomes d'hydrogène et ses sels d'addition avec des acides, non toxiques, pharmaceutiquement acceptables, pour emploi en

* C L M S *

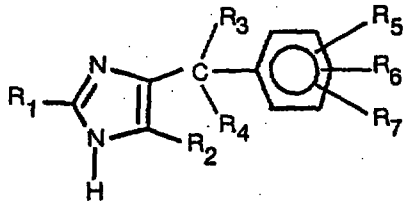
thérapie comme agent anti-hypertenbseur, agent anti-thrombose, agent diurétique, agent anti-mycose ou anti-fongique.

38. Composition pharmaceutique comprenant un dérivé d'imidazole selon la revendication 37 ou son sel d'addition avec un acide, non toxique, pharmaceutiquement acceptable et un véhicule compatible, pharmaceutiquement acceptable pour celui-ci.

39. Composition pharmaceutique comprenant un dérivé d'imidazole selon l'une quelconque des revendications 1 à 23 ou son sel d'addition avec un acide, non toxique, pharmaceutiquement acceptable et un véhicule compatible pharmaceutiquement acceptable pour celui-ci.

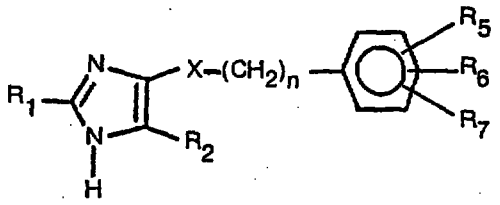
Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule:



(I)

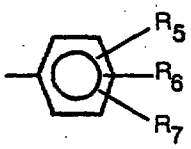
ou



(II)

dans laquelle R_1 est H, un radical alkyle de 1 à 4 atomes de carbone ou $-CH_2OH$; R_2 est H ou CH_3; R_3 est

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$,

ou  et R_4 est H ou OH; ou R_3 et R_4 représentent ensemble

$=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$, ou $=CH-CH_2CH_2CH_3$;

X est $-CH(R_8)-CH(R_9)-$ ou $-C(R_{11})=C(R_{10})-$; R_5, R_6, et R_7,

qui peuvent être identiques ou différents, représentent chacun H, $-CH_3$, $-CH_2CH_3$, un halogène, OH ou $-OCH_3$ ou bien R_5 est un atomd d'hydrogène et R_6 et R_7 forment conjointement un pont $-O-CH_2-O-$ entre deux atomes de carbone adjacents dans le radical phényle;

CHR_8- est $-CH_2-$, $-CH(CH_3)-$, $-CH(-CH_3CH_3)-$, $-CH(-CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)-CH_3)-$,

$-CH(-CH_2CH_2CH_2CH_3)-$ ou $>C=CH_2$, $>C=CH-CH_3$, $>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$, ou

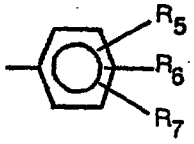
$>C=CH-CH_2CH_2CH_3$; R_9 est H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$,

* C L M S *

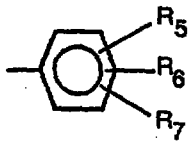
$-CH_2CH_2CH_2CH_3$ ou OH; R_{10} est H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$

ou $-CH_2CH_2CH_2CH_3$; R_{11} est H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$

ou $-CH_2CH_2CH_2CH_3$; *n* est 0 à 4; à la condition que;

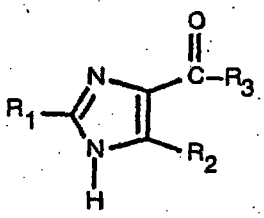
quand R_4 est OH, R_1 est H ou CH_3 et R_3 est  ;

alors R_5, R_6 et R_7 ne soient pas tous simultanément l'hydrogène

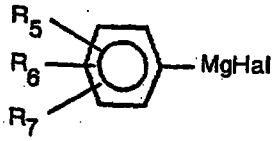
quand R_1, R_2 et R_4 sont tous l'hydrogène et R_3 est  ;

alors R_5, R_6, R_7 ne soient pas tous simultanément l'hydrogène; R_8 et R_9 ne soient pas simultanément l'hydrogène; et R_{11} et R_{10} ne soient pas simultanément l'hydrogène; et des ses sels d'addition avec des acides non toxiques, pharmaceutiquement acceptables, qui consiste:

a) à faire réagir une imidaolylcétone de formule:

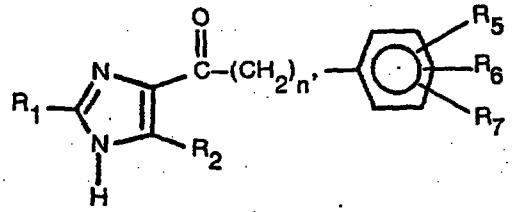


dans laquelle R_1 et R_2 sont tels que définis plus haut et R_3 est un radical alkyle ou aryle tel que défini plus haut, avec un dérivé d'halogénure d'aryl-magnésium de formule:



dans laquelle R_5, R_6, R_7 sont tels qu'indiqué ci-dessus et Hal est un atome d'halogène, pour obtenir un composé de formule I dans lequel R_4 est OH;

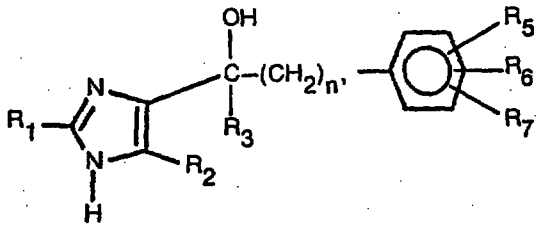
b) à faire réagir un composé de formule:



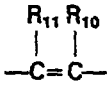
dans laquelle R_1 à R_7 sont tels que définis ci-dessus et n' est de 0 à 5, avec un composé de formule:

R_3MgHal

dans laquelle R_3 est un radical alkyle ou aryle tel que défini plus haut et Hal est un atome d'halogène, pour obtenir un composé de formule:

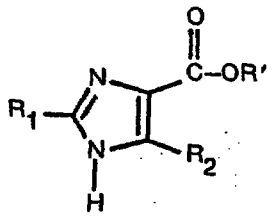


qu'on déshydrate finalement pour obtenir un composé de formule I ou II dans laquelle X est

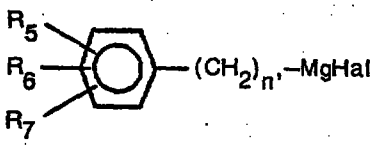


et R_{10} est un atome d'hydrogène;

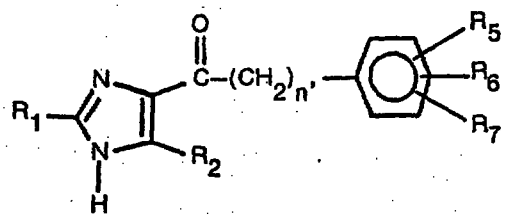
c) à faire réagir un ester alkylique d'acide imidazolecarboxylique de formule:



dans laquelle R_1 et R_2 sont comme ci-dessus et R' est un radical alkyle, dans un premier stade avec un réactif de Grignard de formule:



dans laquelle R_5, R_6, R_7 sont tels que définis plus haut et n' est de 0 à 5, pour obtenir un composé de formule:

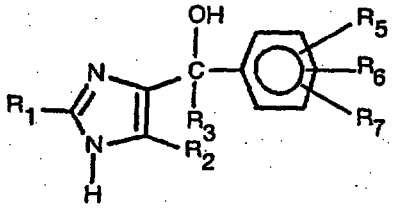


qu'on fait réagir, en un second stade, avec un réactif de Grignard de formule:

$$R_3—MgHal$$

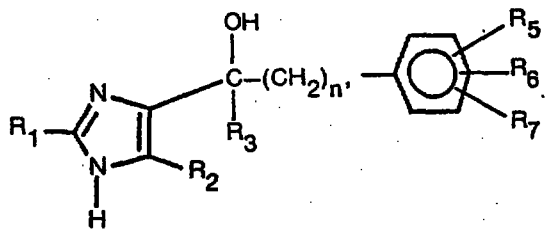
dans laquelle R_3 est un radical alkyle ou aryle tel que défini plus haut, pour obtenir un produit qu'on déshydrate au stade final afin d'obtenir un composé de formule I ou II;

d) à réduire catalytiquement un composé de formule:

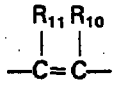


dans laquelle R_1, R_2, R_5, R_6 et R_7 sont tels que définis plus haut et R_3 est un radical alkyle ou aryle tel que défini plus haut;

e) à déshydrater un composé de formule:

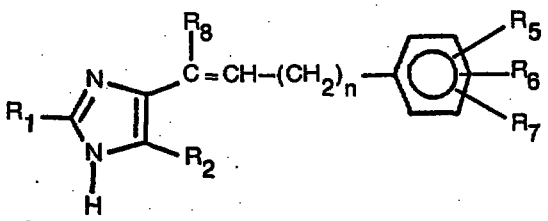


dans laquelle R_1, R_2, R_5, R_6, R_7 sont tels que définis plus haut, R_3 est un radical alkyle ou aryle tel que défini plus haut et n' est de 1 à 5, pous donner un composé de formule II dans lequel X est

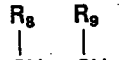


et R_{10} est un atome d'hydrogène;

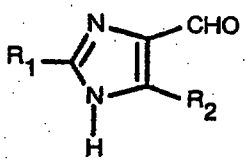
f) à réduire catalytiquement un composé de formule:



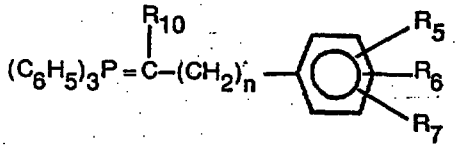
dans laquelle R_1, R_2, R_5, R_6, R_7 et n sont comme ci-dessus et R_8 est un radical alkyle comme ci-dessus, pour

obtenir un composé de formule II dans lequel X est  et R_9 est un atome d'hydrogène;

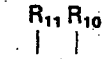
g) à faire réagir un imidazole-aldéhyde de formule:



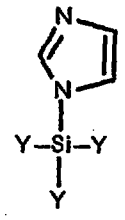
dans laquelle R_1 et R_2 sont tels que définis plus haut, avec un aralkylidènetriphénylphosphorane de formule:



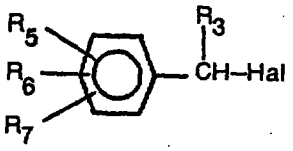
dans laquelle R_5, R_6, R_7, R_{10} et n sont domme définis ci-dessus, pour donner un composé de formule II dans

lequel X est  et R_{11} est un atome d'hydrogène;

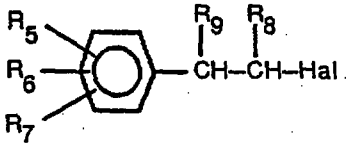
h) à faire réagir un N-trialkylsilylimidazole de formule:



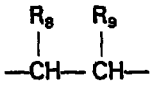
dans laquelle Y est un radical alkyle, avec un halogénure d'arylalkyl de formule:



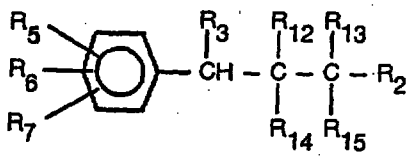
ou



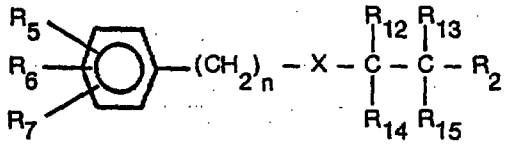
dans laquelle R_3, R_5, R_6, R_7, R_8 et R_9 sont comme définis ci-dessus et Hal est un atome d'halogène, en présence d'un acide de Lewis, pour donner un composé de formule I ou II dans laquelle X est



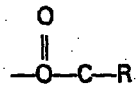
i) à faire réagir une matière de départ de formule:



ou

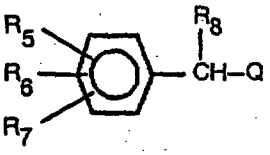


dans laquelle R_2, R_3, R_5, R_6, R_7 et n sont tels que définis ci-dessus et R_{12}, R_{13}, R_{14} et R_{15}, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un radical hydroxy, mercapto, halogène, amino, —O—alkyle de 1 à 7 atomes de carbone ou

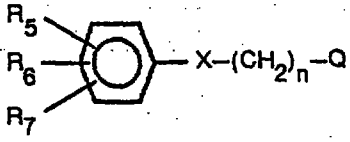


où R est un radical alkyle; ou bien R_{12} et R_{14} peuvent être combinés pour former un groupe céto, ou R_{13} et R_{15} peuvent être combinés pour former un groupe céto ou à la fois R_{12} et R_{14} et R_{13} et R_{15} peuvent former simultanément des groupes céto, avec un réactif capable de convertir ladite matière de départ en imidazole correspondant;

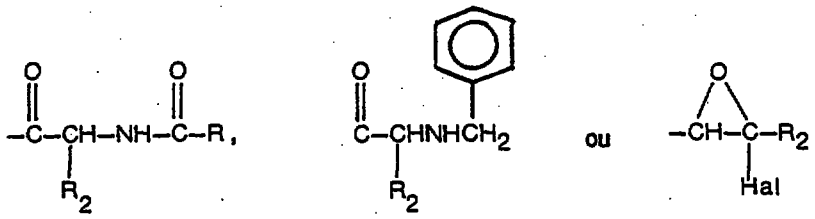
j) à faire réagir un formamide avec un composé de formule:



ou

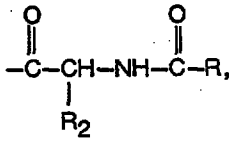


dans laquelle R_5, R_6, R_7, R_8 et *n* sont tels que définis plus haut et Q représente



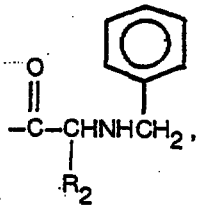
(où Hal est un atome d'halogène, R est un radical alkyle, aralkyle ou aryle) substitués ou non su non substitués, a la condition que

a) quand Q est



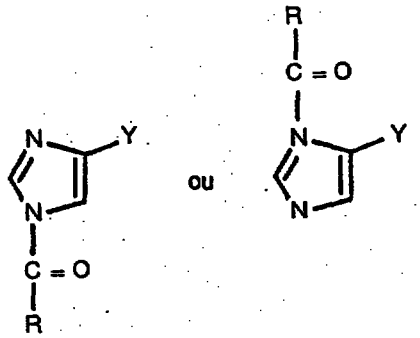
la réaction avec le formamide soit suivie d'un traitement du produit intermédiaire avec un acide; et

b) quand Q est



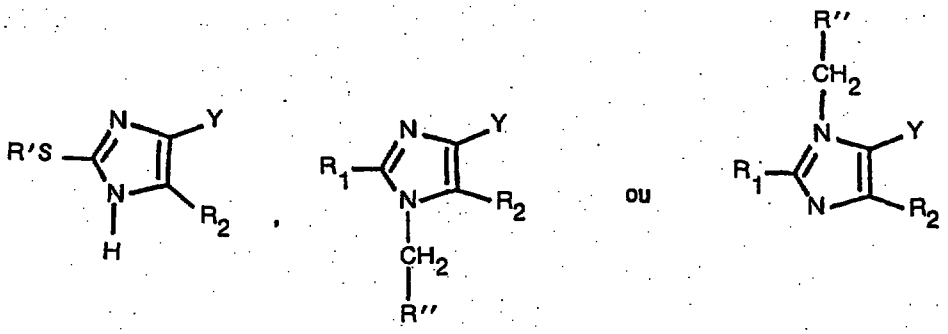
la réaction avec le formamide soit suivie de l'hydrogénation du produit intermédiaire;

k) à hydrolyser un composé de formule:



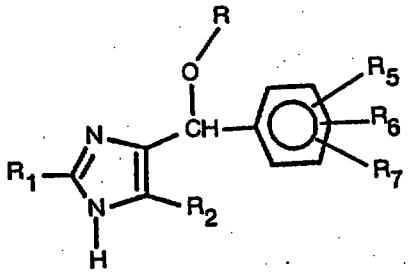
dans laquelle Y est un reste d'arylalkyle déterminé par la formule I et II, R est un radical alkyle de 1 à 7 atomes de carbone ou aryle de 6 à 10 atomes de carbone;

l) à hydrogéner un composé de formule:



dans lesquelles R_1 et R_2 sont tels que définis plus haut, Y est tel que défini dans (k), R' est un radical aryle ou alkyle et R'' est un radical aryle; ou

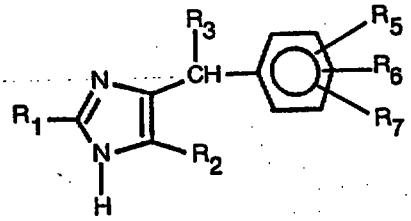
m) à faire réagir un composé de formule:



dans laquelle R_1, R_2, R_5, R_6 et R_7 sont comme définis ci-dessus et R est un radical alkyle de 1 à 4 atomes de carbone avec un réactif de Grignard de formule

$$R_3—CH_2—Mg\ Hal$$

dans laquelle R_3 est comme indiqué ci-dessus pour obtenir un composé de formule:



* C L M S *