(11)

4-Benzyl- and 4-benzoylimidazole derivatives, processes for their preparation and pharmaceutical compositions comprising the same.

The present invention relates to substituted imidazole derivatives, pharmaceutical compositions containing the same, their preparation, and their use.

A wide variety of compounds possessing antihypertensive properties are known. According to their pharmacological mechanism, these compounds can be grouped as follows:

1. Diuretics, e.g. tienilic acid (U.S. Patent 3,758,606), metolazone (U.S. Patent 3,360,518) and bumetadine (U.S. Patent 3,634,583);

2. Stimulants of central α-adrenergic receptors, e.g., clonidine (U.S. Patent 3,202,660), imidazole derivatives [Jen et al, *J. Med. Chem. 18* (1975), 90], guanabenz (German OLS 1,802,364), BS 100—141 (French Patent 1,584,670), tiamenidine (German OLS 1,941,761), guanazodine (British Patent 1,216,096) and guanethidine (U.S. Patent 2,928,829);

3. α-Adrenergic blocking agents, e.g., prazosin (U.S. Patent 3,511,836);

4. β-Adrenergic blocking agents, e.g. propanolol (U.S. Patent 3,337,628) and metoprolol (British Patent No. 1,308,106 and German Patent 2,106,209);

5. Dopamine-β-hydroxylase inhibitors, e.g. bupicomide (U.S. Patent No. 3,519,717 and German OLS 2,217,084);

6. Norepinephrine-depleting drugs, e.g., MJ 10459—2 [Mathier et al, *J. Med. Chem. 16* (1973) 901];

7. Inhibitors of the renin-angiotensin system, e.g. saralasine (U.S. Patent No. 3,751,404 and German Patent 2,127,393); and

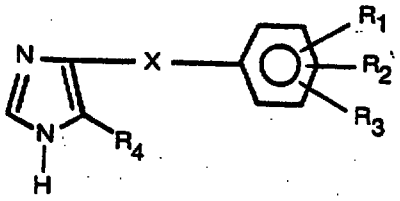
8. Peripheral vasodilators, e.g. minoxidil (U.S. Patent 3,644,364).

Anti-ulcer agents are also known, for example, the H_2-antihistamine cimetidine (U.S. Patent 3,876,647), timoprazole (U.S. patent 4,045,563) and CP—26154 anticholinergic compounds and prostaglandin derivatives (Langman, Drugs, *141* (1977), 105—115).

4-(5)-Benzyl-5(4)-methylimidazole and 5(4)-ethyl-4(5)-benzylimidazole are described in French Patent 2,122,395, but according to our experiments they have no antihypertensive activity. For example the compound 4 - benzyl - 5 - methyl - imdazole has in our tests no effect on the blood pressure of rats at any dosage; on the contrary the blood pressure rises with a dosage of 1 mg/kg i.v. in rats.

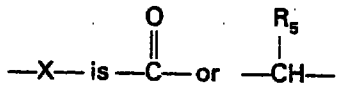
4-Benzyl-imidazole and 4-benzoyl-imidazole are disclosed in Chemical Abstracts *86* 106471, 4 - (α - phenyl)methoxymethyl - 5 - methyl - imidazole is disclosed in Chemical Abstracts *88* 164250 and 4 - (2',5'-dimethyl benzyl) - 5 - methyl - imidazole is disclosed in Chemical Abstracts *58* 13935g.

The present invention provides the compounds of the formula:



(I)

wherein R_1, R_2 and R_3, which can be the same or different, are each selected from hydrogen, chloro, bromo, fluoro, methyl, ethyl, methoxy, amino, hydroxy and nitro but are not all hydrogen; R_4 is hydrogen or alkyl of 1 to 7 carbon atoms:



wherein R_5 is hydrogen, hydroxy or —OR_6 and R_6 is alkyl of 1 to 7 carbon atoms or phenyl; and their non-toxic pharmaceutically acceptable acid addition salts and mixtures thereof.

Examples of pharmaceutically usable acid addition salts are, for instance, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, and ascorbates.

The compounds of formula I are novel provided that (a) when R_1 is 2-methyl, R_2 is 5-methyl, R_3 is hydrogen and R_4 is methyl, then —X— is other than —CH_2—.

The present invention provides, for example, the following specific compounds of formula (I) wherein X is —CH_2—:—

4-(2'-methylbenzyl)imidazole
4-(3'-methylbenzyl)imidazole
4-(4'-methylbenzyl)imidazole

4-(2'-methoxybenzyl)imidazole
4-(3'-methoxybenzyl)imidazole
4-(4'-methoxybenzyl)imidazole
4-(2'-ethylbenzyl)imidazole
4-(4'-ethylbenzyl)imidazole
4-(2'-chlorobenzyl)imidazole
4-(4'-chlorobenzyl)imidazole
4-(2',6'-dibromobenzyl)imidazole
4-(2'-bromobenzyl)imidazole
4-(2'-fluorobenzyl)imidazole
4-(2',6'-dichlorobenzyl)imidazole
4-(2',6'-difluorobenzyl)imidazole
4-(2',6'-dimethylbenzyl)imidazole
4-(2',3'-dimethylbenzyl)imidazole
4-(2',4'-dimethylbenzyl)imidazole
4-(3',4'-dimethylbenzyl)imidazole
4-(3',5'-dimethylbenzyl)imidazole
4-(2',6'-diethylbenzyl)imidazole
4-(2',4',6'-trimethylbenzyl)imidazole
4-(4'-amino-3',5'-dichlorobenzyl)imidazole
4-(3'-amino-2',6'-dimethylbenzyl)imidazole
5-methyl-4-(2'-methylbenzyl)imidazole
5-methyl-4-(2',3'-dimethylbenzyl)imidazole
4-(2',6'-dimethylbenzyl)-5-methylimidazole
4-(4'-amino-3',5'-dimethylbenzyl)-5-methylimidazole

The present invention further provides the following specific compounds as examples of compounds of formula (I) wherein X is —CHOH—:—

5-methyl-4-(α-2'-methylphenyl)hydroxymethylimidazole
5-methyl-4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole
5-methyl-4-[α-(2',3'-dimethylphenyl)]hydroxymethylimidazole
4-[α-(2'-methylphenyl)]hydroxymethylimidazole
4-[α-(3'-methylphenyl)]hydroxymethylimidazole
4-[α-(4'-methylphenyl)]hydroxymethylimidazole
4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole
4-[α-(3'-methoxyphenyl)]hydroxymethylimidazole
4-[α-(4'-methoxyphenyl)]hydroxymethylimidazole
4-[α-(2'-ethylphenyl)]hydroxymethylimidazole
4-[α-(4'-ethylphenyl)]hydroxymethylimidazole
4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole
4-[α-(2',3'-dimethylphenyl)]hydroxymethylimidazole
4-[α-(2',4'-dimethylphenyl)]hydroxymethylimidazole
4-[α-(3',4'-dimethylphenyl)]hydroxymethylimidazole
4-[α-(3',5'-dimethylphenyl)]hydroxymethylimidazole
4-[α-(2',6'-diethylphenyl)]hydroxymethylimidazole
4-[α-(3'-amino-2',6'-dimethylphenyl)]hydroxymethylimidazole
4-[α-(4'-chlorophenyl)]hydroxymethylimidazole
4-[α-(2',4',6'-trimethylphenyl)]hydroxymethylimidazole

The following compounds can be mentioned as specific examples of the compounds of formula (I) wherein X is —$CHOR_6$—:—

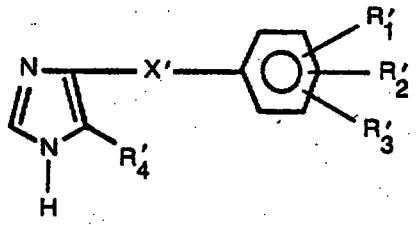
4-[α-(2'-methylphenyl)]methoxymethylimidazole
4-[α-(2'-methylphenyl)]ethoxymethylimidazole
4-[α-(3'-methylphenyl)]ethoxymethylimidazole
4-[α-(4'-methylphenyl)]ethoxymethylimidazole
4-[α-(2'-methoxyphenyl)]ethoxymethylimidazole
4-[α-(3'-methoxyphenyl)]ethoxymethylimidazole
4-[α-(4'-methoxyphenyl)]ethoxymethylimidazole
4-[α-(2',4',6'-trimethylphenyl)]ethoxymethylimidazole
4-[α-(2',6'-dimethylphenyl)]methoxymethylimidazole
4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole
5-methyl-4-[α-(2',6'-dimethylphenyl)]methoxymethylimidazole
5-methyl-4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole

The following compounds are illustrative of the 4-benzoylimidazoles of the invention, i.e. the compounds of formula (I) wherein X is —CO—:—

4-(2′-methylbenzoyl)imidazole
4-(3′-methylbenzoyl)imidazole
4-(4′-methylbenzoyl)imidazole
4-(2′-methoxybenzoyl)imidazole
4-(3′-methoxybenzoyl)imidazole
4-(4′-methoxybenzoyl)imidazole
4-(2′-ethylbenzoyl)imidazole
4-(4′-chlorobenzoyl)imidazole
4-(2′,6′-dimethylbenzoyl)imidazole
4-(2′,3′-dimethylbenzoyl)imidazole
4-(2′,4′-dimethylbenzoyl)imidazole
4-(3′,4′-dimethylbenzoyl)imidazole
4-(3′,5′-dimethylbenzoyl)imidazole
4-(2′,4′,6′-trimethylbenzoyl)imidazole
5-methyl-4-(2′-methylbenzoyl)imidazole
4-(2′,6′-dimethylbenzoyl)-5-methylimidazole
4-(2′,6′-dimethyl-3′-nitrobenzoyl)imidazole

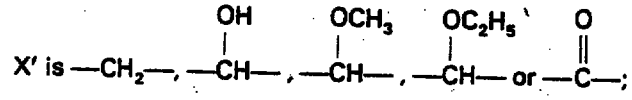
The compounds of formula (I) (as free bases and as pharmaceutically acceptable salts thereof) have been found to possess excellent anti-hypertensive, anti-ulcer, diuretic, sedative, analgesic, anti-inflammatory and tranquilizing properties. The positions and nature of the substituents affect the relative strength of these pharmacological properties.

While all of the compounds of formula (I) essentially satisfy the objectives of the present invention, certain groups of compounds are preferred. One such preferred group, valuable inter alia for their anti-hypertensive activity, can be represented by the structural formula:



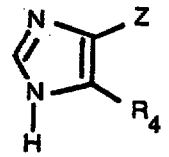
(II)

wherein

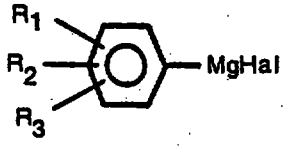


R'_1, R'_2 and R'_3, which can be the same or different, are each hydrogen, chloro, bromo, fluoro, hydroxy, methyl, ethyl or methoxy but are not all hydrogen; and R'_4 is hydrogen or methyl. It is desirable for the substituent or substituents in the benzene ring to be in the 2-, 3-, or 4-position, the 2, 3-, 2,4- or 2,6-positions or in the 2,4,6,-positions.

According to a feature of the invention, compounds of formula (I) are made by a Grignard reaction in which an imidazole of the formula:

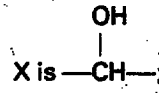


wherein R_4 is defined as before and Z is —CHO or —COOR, is reacted with a phenylmagnesium halide derivative of the formula:

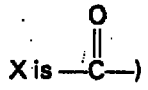


wherein R_1, R_2 and R_3 are defined as before and Hal is a halogen atom. In the imidazole starting

material, the —COOR radical can represent any ester grouping, for example, R can be selected from a wide variety of substituted and unsubstituted alkyl, aralkyl and aryl groups. When Z in the starting material is —CHO, the product is the corresponding compound of formula (I) wherein



when Z in the starting material is —COOR, the corresponding benzoyl derivative (i.e. the compound of formula (I) wherein

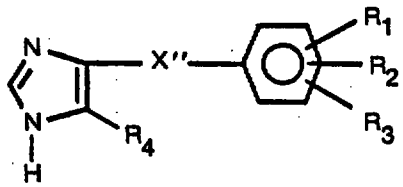


is obtained.

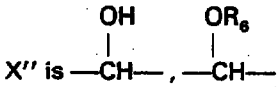
The phenylmagnesiumhalide derivative can be, for example, a phenylmagnesiumbromide derivative, which is prepared by reacting the corresponding bromobenzene derivative with magnesium. Suitable solvents for the reaction include a variety of ethers, preferably tetrahydrofuran. The phenylmagnesiumhalide derivative is prepared in the usual way by adding the bromobenzene 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. After the addition, the reaction is refluxed until all of the 4-imidazole has reacted. The reaction time varies between one and five hours. In the reaction, at least two equivalents of phenylmagnesiumhalide are used per one equivalent of 4-imidazolealdehyde, because the last mentioned compound contains active hydrogen which binds a part of the Grignard reagent.

The above-described Grignard reaction utilizing a 4-imidazolealdehyde as starting material is a surprising and new method for the synthesis of imidazole derivatives. The process is surprising in view of the teachings of the prior art. Thus, for example Deulofeu et al, *J. Org. Chem. 14,* (1949), 915 states that 4-imidazolealdehyde does not react with methylmagnesiumiodide, i.e., in the Grignard reaction.

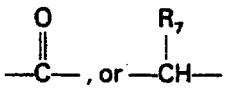
Another process for the preparation of compounds of the present invention comprises reduction of a compound of the formula:



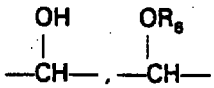
wherein R_1, R_2, R_3 and R_4 are defined as hereinabove and



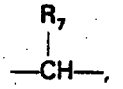
wherein R_6 is defined as before.



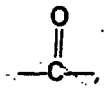
wherein R_7 is a hydrogenolysable group such as a halogen atom or a sulfonate radical. When X'' in the depicted starting material is



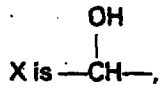
or



then X in the resultant product of formula (I) is $—CH_2—$. When the starting material is a benzoyl derivative, i.e., when X'' in the starting material is

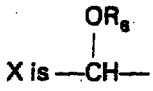


then it is possible to obtain either the corresponding compound of formula (I) wherein

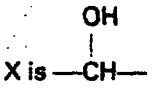


or the corresponding compound of formula (I) wherein X is $—CH_2—$. The reduction is preferably performed under acid conditions, in the presence of a catalyst and under a hydrogen atmosphere. Suitable solvents include water, alcohols (such as ethanol) and acetic acid. The solution is acidified by adding an appropriate acid, e.g., hydrochloric acid. Suitable catalysts are, for example, platinum oxide, palladium-on-carbon or Raney-nickel. The reaction is conveniently carried out at a temperature of 25—70°C with good stirring, although reaction conditions will of course vary depending on the nature of the desired derivative.

The compounds of formula (I) wherein

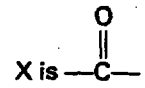


can be conveniently prepared by treatment of a corresponding compound of formula (I) wherein

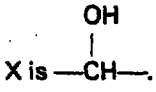


with a compound of the formula R_8OH in the presence of acid. Preferably, the imidazole starting material is simply refluxed in a suitable alcohol in the presence of an acid, suitable acids for this purpose being inorganic and organic acids, e.g., hydrochloric acid.

The compounds of formula (I) wherein

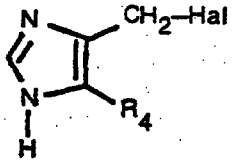


can also be prepared by oxidation of the corresponding compounds of formula (I) wherein

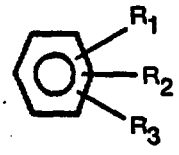


The oxidation is conveniently performed using nitric acid as the oxidizing agent, although other common oxidants can also be used. Typically, the imidazole starting material is dissolved in nitric acid and the reaction mixture is maintained at elevated temperature until the reaction is completed. If the treatment with nitric acid is of long duration and a large excess of acid is employed, nitration of the aromatic ring can occur at the same time.

An alternative route to the compounds of formula (I) wherein X is $—CH_2—$ comprises reacting a 4-halomethylimidazole of the formula:

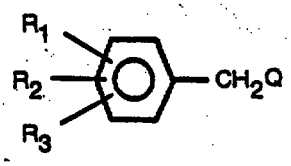


wherein R_4 is defined as before and Hal is a halogen atom, with a benzene derivative of the formula:

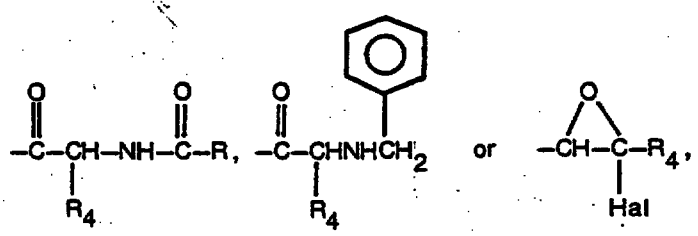


wherein R_1, R_2 and R_3 are defined as before. Typically, the alkylation proceeds by contacting the imidazole, e.g., 4-chloromethylimidazole, with the benzene derivative, with stirring at an elevated temperature. Suitable solvents for use in this process include alcohols and aromatic hydrocarbons (e.g. xylene). The imidazole derivative can be employed in the form of an acid addition salt (e.g., the hydrochloride), in which case an equivalent amount of an appropriate base such as sodium carbonate is added. If the benzene is a base, e.g., 2,6-dichloroaniline, then two equivalents thereof are employed per one equivalent of imidazole derivative.

Yet another process for the preparation of the compounds of formula (I) wherein X is $-CH_2-$ comprises reacting a benzene derivative of the formula:

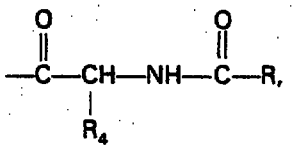


wherein R_1, R_2 and R_3 are defined as hereinabove and Q is



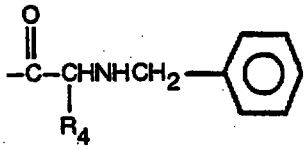
wherein R, R_4 and Hal are defined as hereinabove, with formamide.

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. The formamide treatment is followed by reaction with an appropriate acid (e.g. HCl) when Q in the starting material is



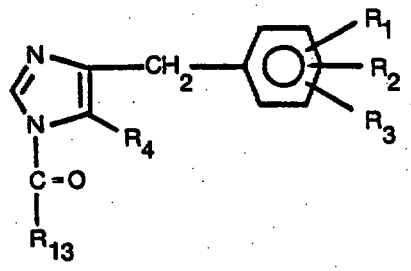
in order to obtain the corresponding compound of formula (I) wherein X is $-CH_2-$.

Similarly, when a starting material wherein Q is



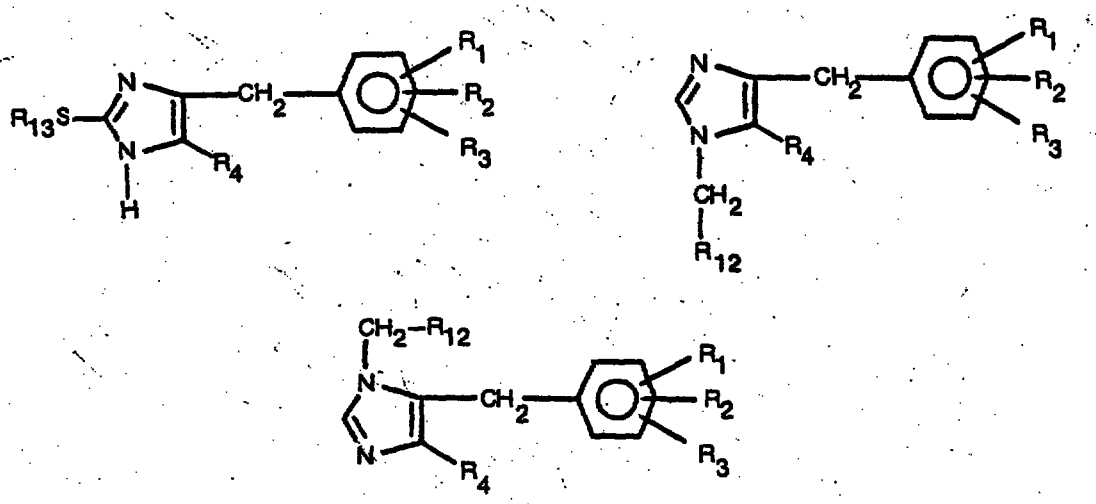
is employed, then the formamide treatment is followed by hydrogenation, thus affording the desired compound of formula (I).

A further process for the preparation of the subject compounds wherein X is $-CH_2-$ comprises hydrolysis of the corresponding compounds of the formula:



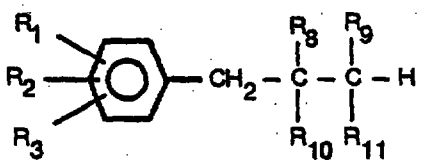
wherein R_1, R_2, R_3 and R_4 are defined as before and R_{13} is alkyl of 1 to 7 carbon atoms or aryl of 6 to 10 carbon atoms. Preferably, the hydrolysis is carried out by boiling the starting material, an N-acetylated imidazole derivative, in an aqueous solution of an inorganic acid until the reaction is completed.

Yet another process for the preparation of the compounds of formula (I) wherein X is —CH_2— comprises hydrogenation of a starting material of formula:

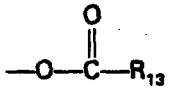


wherein R_1, R_2, R_3, R_4 and R_{13} are defined as before and R_{12} is an aryl group. The hydrogenation is conveniently conducted in the presence of a suitable catalyst and under a hydrogen atmosphere, with stirring. Suitable catalysts include platinum oxide, palladium-on-carbon and Raney nickel. Reaction temperatures vary with the particular starting material employed, with typical temperatures being 25—70°C.

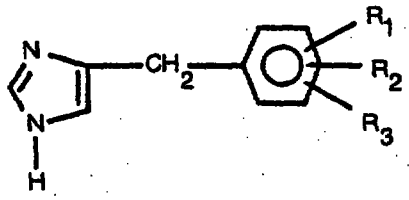
The present invention further provides yet another process for preparing certain select compounds of the invention. Thus, according to this embodiment of the invention, a starting material of the formula:



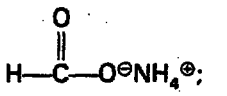
wherein R_1, R_2 and R_3 are as hereinbefore defined, R_8, R_9, R_{10} and R_{11}, which can be the same or different, are each hydrogen, hydroxy, halogen, amino- —O— alkyl or



wherein R_{13} is defined as before, or wherein R_8 and R_{10} can be combined to form a keto group, or R_9 and R_{11} can be combined to form a keto group, or both R_8 and R_{10} and R_9 and R_{11} can simultaneously form keto groups, is reacted with a reagent capable of converting said starting material into an imidazole of the formula:

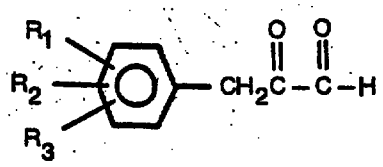


wherein R_1, R_2 and R_3 are defined as before. Reagents capable of converting the depicted starting material into the corresponding imidazole include $NH_3 + CH_2O$ (or a source of ammonia and formaldehyde); HN=CH—NH_2;



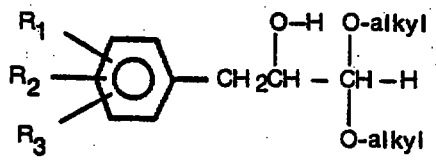
and $HCONH_2$ (formamide). The choice of an appropriate reagent varies with the particular starting material employed. For instance, when the starting material is a haloketone or a haloaldehyde, for

example, when R_8 and R_{10} together form a keto group, R_9 is bromine and R_{11} is hydrogen, or when R_9 and R_{11} form a keto group, R_8 is bromine and R_{10} is hydrogen, then it is preferable to react the starting material with formamide in order to obtain the 4-benzylimidazole derivative. It is likewise preferable to employ formamide as 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. If the starting material is a glyoxal derivative, e.g., benzyl glyoxal or other compound of the type:



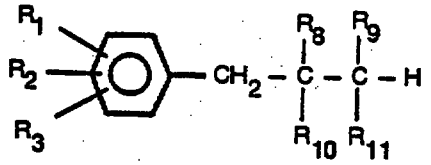
then the ammonia needed for the synthesis of the imidazole ring is suitably taken from ammonium acetate, while the needed formalin is taken from hexamethylenetetramine. Two equivalents of these reagents are used per equivalent of glyoxal derivative. Suitable solvents are, for example, dimethylformamide and formamide. Typically, the reaction temperature is the boiling point of the reaction mixture, and the reaction time is usually from one to three hours. Alternatively, the glyoxal derivative can be reacted directly with ammonia and formaldehyde, or with formamide, but the yields of desired product are generally lower.

A surprising aspect of the abovementioned reaction is the fact that the hydroxyacetal starting materials, e.g. compounds of the formula:

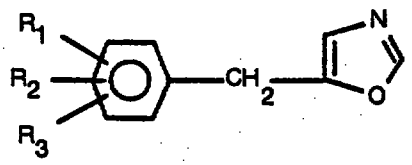


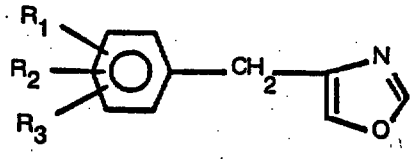
very readily react with formamide to form the corresponding imidazoles.

As a variation of the above-described process, the starting material of formula:



can be treated with an appropriate reagent, particularly formamide, under milder conditions than those discussed above, allowing isolation of the intermediate oxazole, which can then be further reacted with formamide to afford the corresponding compound of formula (I). In this variation, the first formamide treatment is carried out at a low temperature (80—120°C, depending on the particular starting material employed), to afford an oxazole of the formula:





which can then be easily reacted with formamide, typically at about 180°C, for about 4 hours, to afford the desired compound of the present invention. The starting material used in this process can be prepared by known methods. Reference is made to Examples 49(a), (b) and (c) and 50(a) below for a description of methods which, it being understood are illustrative of procedures which can be utilized to prepare the desired starting materials.

As stated above, the compounds of the general formula (I) and their non-toxic, pharmaceutically acceptable acid addition salts have valuable pharmacological properties and have been found to possess excellent anti-hypertensive, anti-ulcer, diuretic, sedative, analgesic, anti-inflammatory and tranquilizing activity in mammals.

The compounds of formula (I) and their non-toxic, pharmaceutically acceptable acid addition salts or mixtures thereof may be administered parenterally, intravenously or orally. Typically, an effective amount of the compound 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, and condition for which the derivative is administered, as well as the structure of the derivative. One of the most potent anti-hypertensive derivatives of the invention is 4-(2',6'-dimethylbenzyl)imidazole, the daily dose of which generally ranges from about 0.01—0.05 milligrams per kilogram of mammal.

The pharmaceutical carriers which are typically employed with the imidazole derivatives of the present invention may be solid or liquid and are generally selected dependent on the planned manner of administration. 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 and the blood pressure and the pulse frequency were registered with a recorder. The minimum doses producing a significant change were found, i.e. ± at least 20% in the case of blood pressure, and ± at least 3% in the case of pulse frequency.

In a further test for anti-hypertensive properties unanesthetized Okamoto-Aoki 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 preventive effect on the formation of ulcers of the compounds of formula (I) has been tested in the following manner. Female Sprague-Dawley rats, approximately ten weeks old and weighing 200—250 g. each, were fasted overnight. The rats were divided into two groups. The rats in one group were given only 20 mg/kg p.o. of indomethacin, while the rats in the other group were given the test compound by i.p. administration simultaneously with the indomethacin administration. The rats were killed after 4 hours and the anti-ulcer effect was estimated by counting the ulcers and comparing the number of them in the rats receiving test compound to the number of ulcers found by induction with indomethacin.

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 sedative potency of the compounds was evaluated by following tests:

1) The sleeping time of male chickens (1—5 days old) was studied after administration of the test substances i.m. into two animals per dose level (Delbarre & Schmitt, Eur. J. Pharmacol, 22:355, 1973).

2) Potentiation of barbiturate sleeping time was studied in mice. The compound examined was given i.p. 30 minutes before the pentobarbitone (60 mg/kg i.p.).

3) Spontaneous motility of mice and rats was measured using the Animex-activity meter. The test compounds were administered i.p. 30 minutes before the measuring periods of two minutes.

The analgesic activity was tested in the following manner:

Writhing test

The compounds studied and saline were administered p.o. to rats and 45 min later 1 ml of 1% acetic acid was administered i.p. The number of writhes was recorded in the following 25 min. period (Koster et al: Fed. Proc. 18:412, 1959).

Hot plate test

Test compounds or saline were given i.p. to male mice and 30 min thereafter the time on 55°C plate was recorded. The results are expressed as compared to saline.

The anti-inflammatory activity was determined by inhibition of the carrageenan induced oedema in rats by the compounds examined (Winter C.A. et al., Proc. Soc. Exp. Biol. Med. 111:544, 1962).

The tranquilizing activity was determined by the following methods:

Irwin screen in rats (Irwin S., Psychopharmacologia 13:222, 1968)

Especially sedatory and cataleptic activity and effects on muscle tone are observed.

— Tranquilizing — taming — effect on cattle:

The test compounds were administered i.m. to cattle, mostly to heifers (150—200 kg). The animals were observed for 3 hours: especially the vital functions, reaction to pain and handling, muscle tone, possible sleep etc.

The most suitable tranquilized state of an animal includes the ability to retain the upright position and coordination with minimal avoidance reactions to painful stimuli and handling.

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.

Some examples of the pharmacological properties of the compounds of the invention are as follows:

4-(2',6'-Dimethylbenzyl)imidazole, which has a LD_{50} value of 40 mg/kg i.v., was found in the blood pressure study with anesthetized rats of normal weight described above to cause a detectable lowering of the blood pressure even with a dose of 1 μg/kg i.v.

With a dose of 3 μg/kg i.v. the blood pressure lowering was quite clear and with a dose of 10 μg/kg i.v. the reduction of blood pressure was on an average 30%, the decrease of pulse frequency being 12% on an average. The duration of the effect was at least 50 minutes (after which time the determination was interrupted). As the LD_{50} is 40 mg/kg i.v. in mice, it can be concluded that the therapeutic range is very broad. When the anti-hypertensive effect of the compound was determined with awake SHR-rats, it was found that the decrease of blood pressure was about 20% with a dose of 100 μg/kg p.o. and 25% with a dose of 300 μg/kg p.o. four hours after the administration. When the anti-ulcer effect of the compound was determined in the manner described above, it was found that a dose of 5 μg/kg i.p. completely prevented the formation of ulcers.

For the compound 4-(2'-methylbenzyl)imidazole, having a LD_{50} of 25 mg/kg i.v. in mice, the following results in the above-mentioned tests were obtained: lowering of blood pressure with a dose of 0.5 mg/kg i.v. of 10%, 30 minutes after administration; complete prevention of the formation of ulcers at a dose of 5 μg/kg i.p.

The compound 4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole, having a LD_{50} of 125 mg/kg i.v. in mice, gave the following results in the above-mentioned tests: A lowering of blood pressure with a dose of 300 μg/kg i.v. was noticeable; with a dose of 3 mg/kg p.o. with awake SHR rats, the decrease was 20% 3 hours after administration. With a dose of 5 mg/kg, the compound completely prevented the formation of ulcers, while with a dose of 0.5 mg/kg, the prevention was partial.

When 4-[α-(2'-methylphenyl)]hydroxymethylimidazole, having a LD_{50} of 160 mg/kg i.v. in mice was tested as above, no anti-hypertensive effect was found. On the other hand, a dose of 5 mg/kg completely prevented the formation of ulcers and a dose of 0.5 mg/kg prevented them partly.

When 5-methyl-4-(2',6'-dimethylbenzyl)imidazole having a LD_{50} of 27 mg/kg i.v. in mice, was tested as above, no anti-hypertensive effect was found. A dose of 0.5 mg/kg partly prevented the formation of ulcers and the dose 5 mg/kg prevented them completely.

When 4-(2',6'-dimethylbenzoyl)imidazole, having LD_{50} of over 100 mg/kg i.v. in mice, was tested as above, only a very slight anti-hypertensive effect was found. A dose of 20 mg/kg prevented completely the formation of ulcers, while 10 mg/kg prevented them partially.

When 4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole, having a LD_{50} of 45 mg/kg i.v. in mice, was tested, it possessed only a very slight anti-hypertensive effect. However, a dose of 5 mg/kg completely prevented the formation of ulcers, while 0.5 mg/kg prevented them partly.

A summary of the pharmacological properties of the compounds of the invention is given in the following Tables. In the Tables, + means having a moderate effect and ++ means a marked effect.

Examples of Compounds with Anti-Hypertensive Effects

	Blood pressure Minimum Dose (mg/kg i.v.) having a significant lowering effect
4-(2',6'-dimethylbenzyl)imidazole	0.003—0.1
4-(2',3'-dimethylbenzyl)imidazole	0.01—0.1
4-(2'-methylbenzyl)imidazole	0.01—0.1
4-(2',6'-dichlorobenzyl)imidazole	0.03—0.1
4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole	0.1—3
4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole	0.3—1

	Pulse frequency Minimum Dose (mg/kg i.v.) having a significant lowering effect	increasing effect
4-(2',6'-dimethylbenzyl)imidazole	0.003	—
4-(2',3'-dimethylbenzyl)imidazole	0.01—1	3—10
4-(2'-methylbenzyl)imidazole	0.1—1	—
4-(2',6'-dichlorobenzyl)imidazole	0.03—0.1	—
4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole	0.1	—
4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole	1	—

Examples of Compounds with a high Therapeutic Index for Treatment of Ulcerous Conditions

	Dosage mg/kg		Therapeutic Index
	LD_{50} (mouse, i.v.)	ED_{50}	
4-(2',6'-dimethylbenzyl)imidazole	40	0.005	8000
4-(2',3'-dimethylbenzyl)imidazole	35	0.005	7000
4-(2',4'-dimethylbenzyl)imidazole	65	0.03	2167
4-(2'-ethylbenzyl)imidazole	34	0.005	6800
4-(2'-methylbenzyl)imidazole	25	0.005	5000
4-(3'-methylbenzyl)imidazole	38	0.02	1900
4-(2',4',6'-trimethylbenzyl)imidazole	63	0.03	2100
4-(2'-chlorobenzyl)imidazole	65	0.03	2167
4-(2',6'-dichlorobenzyl)imidazole	48	0.03	1600

Examples of Compounds with Diuretic Effect

	Dosage mg/kg	Diuretic 2.5h	effect % 5h
4-[α-(2',3'-dimethylphenyl)]hydroxymethylimidazole	10.0	411	280
	0.6	160	
	0.15	145	
4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole	30.0	121	66
	0.5	150	
4-[α-(2'-ethylphenyl)]hydroxymethylimidazole	30.0	234	211
4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole	30.0	158	68
4-(2',4'-dimethylbenzyl)imidazole	30.0	228	181
4-(2',3'-dimethylbenzyl)imidazole	0.05	150	
4-(2',6'-dimethylbenzyl)imidazole	0.05	150	
4-(2'-methylbenzyl)imidazole	30.0	128	49
	0.05	100	
4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole	30.0	60	16

Examples of Compounds with Sedative Effect

	Dosage, mg		
	0,3—1,0	3—10	30—60
4-(2',4'-dimethylbenzyl)imidazole	++		
4-(2',3'-dimethylbenzyl)imidazole	++		
4-(3'-methylbenzyl)imidazole		+	
4-(2',4',6'-trimethylbenzyl)imidazole	++		
4-(2'-ethylbenzyl)imidazole	++		
4-(3'-methoxybenzyl)imidazole		+	
4-(2'-chlorobenzyl)imidazole	++		
4-[α-(2',3'-dimethylphenyl)]hydroxymethylimidazole	++		
4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole			++
5-methyl-4-(2',6'-dimethylbenzyl)imidazole			+

Examples of Compounds with Analgesic Effect

	Analgesic activity		
	method dosage mg/kg	increase in HP-time (%) W-number x)	activity
4-(3'-methylbenzyl)imidazole	W 30	0	++
4-(2',3'-dimethylbenzyl)imidazole	HP 0.6	200	+
4-(2',4'-dimethylbenzyl)imidazole	W 100	0	++
	HP 1.5	200	+
4-(2'-methylbenzyl)imidazole	HP 1.5	200	+
4-(2'-chlorobenzyl)imidazole	HP 1.5	200	+
4-[α-(2',4'-dimethylphenyl)]hydroxymethylimidazole	W 100	1.3	+
	HP 1.5	—	
4-[α-(2',3'-dimethylphenyl)]hydroxymethylimidazole	W 100	0	++
	HP 1.5	400	++
4-[α-(2'-methylphenyl)]hydroxymethylimidazole	W 100	0	++
4-[α-(3'-methylphenyl)]hydroxymethylimidazole	W 100	0	++
4-[α-(4'-methylphenyl)]hydroxymethylimidazole	W 100	0.6	++
4-[α-(2'-ethylphenyl)]hydroxymethylimidazole	W 100	0	++
	HP 1.5	300	+
4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole	W 100	2.5	+
4-[α-(3'-methoxyphenyl)]hydroxymethylimidazole	W 100	0	++
4-[α-(4'-methoxyphenyl)]hydroxymethylimidazole	W 100	1.9	+
	HP 1.5	—	
4-[α-(2',6'-dimethylphenyl)]methoxymethylimidazole	W 100	13	+
4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole	W 100	0.6	++
5-Methyl-4-(2'-methylbenzyl)imidazole	W 30	43	+
5-Methyl-4-[α-(2',6'-dimethylphenyl)]hydroxy-methylimidazole	W 100	13	+

x) HP = hot plate test
W = writhing test

Examples of Compounds with Anti-Inflammatory Effects

	Anti-inflammatory activity at 100 mg/kg. p.o. in the rat	
	inhibition of carrageenan-induced oedema (%)	activity
4-(2',4'-dimethylbenzyl)imidazole	76	++
4-(3'-methylbenzyl)imidazole	61	+
4-[α-(2',3'-dimethylphenyl)]hydroxymethylimidazole	52	+
4-[α-(2'-methylphenyl)]hydroxymethylimidazole	41	+
4-[α-(3'-methylphenyl)]hydroxymethylimidazole	34	+
4-[α-(4'-methylphenyl)]hydroxymethylimidazole	38	+
4-[α-(2-ethylphenyl)]hydroxymethylimidazole	73	++
4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole	69	++
4-[α-(3'-methoxyphenyl)]hydroxymethylimidazole	71	++
4-[α-(2',6'-dimethylphenyl)]methoxymethylimidazole	40	+
4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole	35	+
4-(4'-methylbenzoyl)imidazole	40	+
5-Methyl-4-(2'-methylbenzyl)imidazole	44	+
5-Methyl-4-[α-(2',6'-dimethylphenyl)]hydroxy-methylimidazole	52	+
5-Methyl-4-[α-(2'-methylphenyl)]hydroxymethyl-imidazole	67	+
5-Methyl-4-(2'-methylbenzoyl)imidazole	44	+

Examples of Compounds with Tranquilizing Effects

	Activity in rats			
	dose mg/kg	decrease of motility	loss of muscle tone	catalepsia
4-(2',3'-dimethylbenzyl)imidazole	1.0	+	+	—
4-(2'-chlorobenzyl)imidazole	0.25	+	—	+
4-(2',4',6'-trimethylbenzyl)imidazole	1.0	++	—	+
4-(2',6'-dimethylbenzyl)imidazole	1.0	++	+	—
4-(3'-methylbenzyl)imidazole	1.0	+	—	—

	Activity in cattle		
	dose mg/kg	loss of avoidance	loss of muscle tone
4-(2',3'-dimethylbenzyl)imidazole	0.1	++	—
4-(2'-chlorobenzyl)imidazole	0.1	+	—
4-(2',4',6'-trimethylbenzyl)imidazole	0.1	+	+
4-(2',6'-dimethylbenzyl)imidazole	0.05	++	+
4-(3'-methylbenzyl)imidazole	0.1	+	—

The invention is illustrated by the following Examples.

In these Examples, where ^1H—NMR spectrum shifts are presented, the NMR spectra were determined with a Perkin Elmer R 24 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. 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 mass-spectra were determined with a Perkin Elmer RMU 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 fragmentations from a structural viewpoint are given as m/e values. In parenthesis is given the intensity of the fragmentation in relation to the main peak.

Example 1

4-[α-(2'-Methylphenyl) hydroxymethylimidazole

4.8 g of dry magnesium turnings are covered with 100 ml of dry tetrahydrofuran (THF). The mixture is heated to boiling and a solution of 2-bromotoluene in 50 ml of dry tetrahydrofuran is added dropwise at such a rate that gentle refluxing is maintained. After the addition is complete, the reaction mixture is refluxed for an additional 30 minutes. The reaction mixture is cooled to 50°C and 9.6 g of 4-imidazolealdehyde are added slowly in small portions. After the addition is complete, the mixture is refluxed for 4 hours. Then, the reaction mixture is cooled and poured into 100 ml of cold water containing 20 ml of concentrated hydrochloric acid. Part of the tetrahydrofuran is distilled off to give a smaller volume and the tetrahydrofuran is replaced with water. The mixture is washed twice with 50 ml portions of chloroform. The aqueous layer is made alkaline with sodium hydroxide solution (pH about 8). The precipitate which forms is washed with water and dried. The crude product is recrystallized from a mixture of water and ethanol to give a product melting at 163—164°C.

NMR: 1.9 (s, 3H), 4.85 (s, 2H), 5.7 (s, 1H), 6.35 (s, 1H), 6.85 (m, 3H), 7.3 (m, 2H).

MS: 188 (37%), 171 (14%), 170 (98%), 169 (100%), 155 (12%), 143 (28%), 142 (19%), 116 (19%), 115 (29%), 97 (21%), 95 (27%), 91 (21%), 69 (26%).

Example 2

4-[α-(2',6'-Dimethylphenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated except that 1-bromo-2,6-dimethylbenzene is used in place of 2-bromotoluene. The product, after recrystallization from ethanol, melts at 166—167°C.

NMR: 2.0 (s, 6H), 4.7 (s, 2H), 5.95 (s, 1H), 6.3 (s, 1H), 6.7 (s, 3H), 7.25 (s, 1H).

MS: 202 (60%), 187 (14%), 184 (100%), 183 (96%), 169 (38%), 157 (18%), 156 (25%), 134 (16%), 133 (20%), 115 (18%), 105 (18%), 97 (32%), 95 (40%), 91 (24%), 77 (16%), 69 (50%).

Example 3

4-[α-(3'-Methylphenyl)-hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 3-bromotoluene is used. The product melts at 120—122°C.

NMR: 1.85 (s, 3H), 4.15 (s, 2H), 5.3 (s, 1H), 6.35 (s, 1H), 6.75 (m, 4H), 7.2 (s, 1H).

MS: 188 (100%), 187 (29%), 171 (21%), 170 (30%), 144 (17%), 143 (40%), 115 (16%), 97 (63%), 96 (67%), 95 (73%), 91 (33%), 69 (49%), 68 (51%).

Example 4

4-[α-(4'-Methylphenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 4-bromotoluene is used. The product, after recrystallization from a water-ethanol mixture, melts at 116—119°C.

NMR: 2.25 (s, 3H), 5.6 (s, 2H), 5.75 (s, 1H), 6.75 (s, 1H), 7.2 (m, 5H).

MS: 188 (100%), 171 (36%), 170 (50%), 155 (14%), 143 (48%), 97 (49%), 96 (88%), 95 (98%), 91 (43%), 69 (56%), 68 (68%).

Example 5

4-[α-(2',4'-Dimethylphenyl]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 1-bromo-2,4-dimethylbenzene is used. The crude product thus obtained is recrystallized from a water-ethanol mixture to give a product melting at 115—120°C.

NMR: 2.0 (s, 3H), 2.1 (s, 3H), 4.95 (s, 2H), 5.8 (s, 1H), 6.95 (s, 1H), 6.8 (m, 2H), 7.2 (m, 1H), 7.4 (s, 1H).

MS: 202 (62%), 185 (25%), 184 (100%), 183 (73%), 169 (39%), 157 (23%), 156 (24%), 133 (13%), 130 (13%), 115 (15%), 105 (11%), 97 (12%), 95 (44%), 91 (26%), 77 (14%), 69 (33%).

Example 6

4-[α-(2',3'-Dimethylphenyl]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 1-bromo-2,3-dimethylbenzene is used. The melting point of the product, after recrystallization from water-ethanol, is 140—142°C.

NMR: 1.75 (s, 3H), 1.85 (s, 3H), 4.75 (s, 2H), 5.65 (s, 1H), 6.25 (s, 1H), 6.85 (m, 3H), 7.2 (s, 1H).

Example 7

4-[α-(3',4'-Dimethylphenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 1-bromo-3,4-dimethylbenzene is used.

NMR: 1.85 (s, 6H), 4.8 (s, 2H), 5.4 (s, 1H), 6.6 (m, 4H), 7.2 (s, 1H).

Example 8

4-[α-(2'-Methoxyphenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 1-bromo-2-methoxybenzene is used. The product is transformed to the hydrochloride in isopropanol. The melting point of the hydrochloride is 166—168°C.

NMR (HCl salt): 3.65 (s, 3H), 4.7 (s, 3H), 6.1 (1H), 7.1 (m, 5H), 8.5 (s, 1H).

Example 9

4-[α-(3'-Methoxyphenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 1-bromo-3-methoxybenzene is used. After recrystallization from a water-ethanol mixture, the product melts at 96—97°C.

NMR: 3.75 (s, 3H), 5.1 (s, 2H), 5.75 (s, 1H), 7.0 (m, 5H), 7.55 (s, 1H).

Example 10

4-[α-(4'-Methoxyphenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 1-bromo-4-methoxybenzene is used. The product melts at 127—129°C.

NMR: 3.7 (s, 3H), 5.25 (s, 2H), 5.75 (s, 1H), 7.1 (m, 5H), 7.55 (s, 1H).

Example 11

4-[α-(4'-Chlorophenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 1-bromo-4-chlorobenzene is used. After recrystallization from water-ethanol, the products melts at 159—160°C.

NMR: 4.75 (s, 2H), 5.45 (s, 1H), 6.5 (s, 1H), 7.0 (s, 4H), 7.25 (s, 1H).

Example 12

4-[α-(2'-Ethylphenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 1-bromo-2-ethylbenzene is used. After recrystallization from water-ethanol, the product melts at 139—142°C.

NMR: 1.1 (t, 3H), 2.65 (q, 2H), 5.05 (s, 2H), 6.05 (s, 1H), 6.65 (s, 1H), 17.3 (m, 4H), 7.55 (s, 1H).

Example 13

4-[α-(2',4',6'-Trimethylphenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that bromomesitylene is used. After recrystallization from water-ethanol, the product melts at 186—188°C.

NMR: 1.95 (s, 9H), 4.6 (s, 2H), 5.95 (s, 1H), 6.3 (s, 1H), 6.5 (s, 2H), 7.25 (s, 1H).

Example 14

5-Methyl-4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole

The procedure of Example 1 is repeated, except that 1-bromo-2,6-dimethylbenzene is used in place of 2-bromotoluene and 5-methyl-4-imidazolealdehyde is used in place of 4-imidazolealdehyde. The melting point of the free base, after recrystallization from H_2O-ethanol, is 277—278°C. The melting point of the hydrochloride is >300°C.

NMR (HCl salt): 1.7 (s, 3H), 2.2 (s, 6H), 4.75 (s, 3H), 6.4 (s, 1H), 7.1 (s, 3H), 8.65 (s, 1H).

Example 15

4-(2'-Methylbenzyl)imidazole

5.9 g of 4-[α-(2'-methylphenyl)]hydroxymethylimidazole are dissolved in 40 ml of 4 *N* HCl solution. About 60 mg of 10% palladium-on-carbon (Pd/C) are added and themixture is stirred vigorously under a hydrogen atmosphere at about 60°C until no more hydrogen is consumed (about 4 hours). The reaction mixture is then filtered and washed twice with 10 ml portions of chloroform. The aqueous phase is then made alkaline (pH about 9) with sodium hydroxide solution and extracted with chloroform (3×10 ml). The combined chloroform extracts are washed with water (1×10 ml), dried over Na_2SO_4 and evaporated to dryness. The crude product is purified by converting it into the hydrochloride in acetone. The melting point of the hydrochloride is 133—135°C.

NMR (HCl salt): 2.1 (s, 3H), 3.85 (s, 2H), 4.75 (s, 2H), 6.9 (s, 1H), 7.1 (s, 4H), 8.5 (s, 1H).

MS: 172 (100%), 171 (40%), 157 (30%), 144 (21%), 130 (17%), 128 (14%), 115 (13%), 104 (33%), 81 (17%).

Example 16

4-(2',6'-Dimethylbenzyl)imidazole

10 g of 4-[α-(2',6'-dimethylphenyl)]hydroxymethyl-*1H*-imidazole are dissolved in 100 ml of acetic acid. 100 mg of 10% 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 sodium hydroxide solution 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. The crude product is crystallized from ethyl acetate to give a product melting at 126—128°C. The corresponding hydrochloride, prepared in ethyl acetate, melts at 207—210°C.

NMR (HCl salt): 1.95 (s, 6H), 3.8 (s, 2H), 4.65 (s, 2H), 6.55 (s, 1H), 6.8 (s, 3H), 8.55 (s, 1H).

MS: 186 (100%), 185 (37%), 171 (41%), 158 (12%), 144 (15%), 143 (11%), 142 (18%), 118 (42%), 91 (11%), 81 (21%).

Example 17

4-(3'-Methylbenzyl)imidazole

The procedure of Example 15 is repeated, except that 4-[α-(3'-methylphenyl)]hydroxymethylimidazole is used in place of 4-[α-(2'-methylphenyl)]hydroxymethylimidazole. The corresponding hydrochloride is then prepared in ethyl acetate, m.p. 127—130°C.

NMR (HCl salt): 2.25 (s, 3H), 3.95 (s, 2H), 4.65 (s, 2H), 7.15 (m, 5H), 8.55 (s, 1H).

Example 18

4-(4'-Methylbenzyl)imidazole

The procedure of Example 16 is repeated, except that 4-[α-(4'-methylphenyl)]hydroxymethylimidazole is used in place of 4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole. The hydrochloride salt melts at 161—164°C.

NMR (HCl salt): 2.1 (s, 3H), 3.8 (s, 2H), 4.8 (s, 2H), 7.0 (s, 5H), 8.45 (s, 1H).

Example 19

4-(2',4'-Dimethylbenzyl)imidazole

The procedure of Example 15 is repeated, except that 4-[α-(2',4'-dimethylphenyl)]hydroxymethylimidazole is used. After recrystallization from ethylacetate-isopropanol, the corresponding hydrochloride is prepared in ethylacetate. It melts at 151—153°C.

NMR (HCl salt): 2.25 (s, 6H), 4.05 (s, 2H), 4.9 (s, 2H), 7.0 (s, 3H), 7.15 (s, 1H), 8.85 (s, 1H).

Example 20

4-(2',3'-Dimethylbenzyl)imidazole

The procedure of Example 15 is repeated, except that 4-[α-(2',3'-dimethylphenyl)]hydroxymethylimidazole is used. The product, after recrystallization from acetone, melts at 114—116°C.

NMR: 1.6 (s, 3H), 1.65 (s, 3H), 3.35 (s, 2H), 4.1 (s, 1H), 6.0 (s, 1H), 6.4 (m, 3H), 7.0 (s, 1H).

Example 21

4-(3',4'-Dimethylbenzyl)imidazole

The procedure of Example 15 is repeated, except that 4-[α-(3',4'-dimethylphenyl)]hydroxymethylimidazole is used. The melting point of the hydrochloride is 158—163°C.

NMR (HCl salt): 1.95 (s, 6H), 3.75 (s, 2H), 4.65 (s, 2H), 6.85 (s, 3H), 6.95 (s, 1H), 8.45 (s, 1H).

Example 22

4-(2'-Ethylbenzyl)imidazole

The procedure of Example 15 is repeated, except that 4-[α-(2'-ethylphenyl)]hydroxymethylimidazole is used. The product, after recrystallization from n-butylacetate, melts at 104—106°C.

NMR (HCl salt): 1.3 (t, 3H), 2.83 (q, 2H), 4.3 (s, 2H), 5.5 (s, 2H), 7.35 (s, 5H), 9.05 (s, 1H).

Example 23

4-(2',4',6'-Trimethylbenzyl)imidazole

The procedure of Example 15 is repeated, except that 4-(2',4',6'-trimethylphenyl)]hydroxymethylimidazole is used. The melting point of the hydrochloride is 167—170°C.

NMR (HCl salt): 1.95 (s, 9H), 3.85 (s, 2H), 4.85 (s, 2H), 6.45 (s, 1H), 6.65 (s, 2H), 8.6 (s, 1H).

Example 24

4-(2'-Methoxybenzyl)imidazole

The procedure of Example 15 is repeated, except that 4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole is used.

NMR (HCl salt): 3.55 (s, 3H), 3.65 (s, 2H), 4.65 (s, 1H), 6.8 (s, 5H), 8.3 (s, 1H).

Example 25

4-(3'-Methoxybenzyl)imidazole

The procedure of Example 15 is repeated, except that 4-[α-(3'-methoxyphenyl)]hydroxymethylimidazole is used. The melting point of the hydrochloride is 151—153°C.

NMR (HCl salt): 3.55 (s, 3H), 3.75 (s, 2H), 4.6 (m, 2H), 6.65 (m, 3H), 6.95 (s, 1H), 7.1 (s, 1H), 8.4 (s, 1H).

Example 26

4-(4'-Methoxybenzyl)imidazole

The procedure of Example 15 is repeated, except that 4-[α-(4'-methoxyphenyl)]hydroxymethylimidazole is used.

NMR: 3.5 (2, 3H), 3.75 (s, 2H), 6.85 (m, 5H), 7.3 (s, 1H), 12.2 (2, 1H).

Example 27

4-[α-(2'-Methylphenyl)]ethoxymethylimidazole

10 g of 4-[α-(2'-methylphenyl)]hydroxymethylimidazole are dissolved in 60 ml of absolute ethanol. Hydrogen chloride gas is passed into the solution for 1 hour, during which time the reaction mixture is maintained at reflux, with stirring. The mixture is then evaporated to dryness. 60 ml of water are added to dissolve the distillation residue, then the solution is made alkaline with sodium carbonate and extracted three times with 50 ml portions of chloroform. The combined chloroform extracts are washed with water and dried over sodium sulfate. The filtrate is evaporated to dryness to give a crude product, after which recrystallization from ethyl acetate melts at 129—131°C.

NMR: 1.0 (t, 3H), 2.1 (s, 2H), 3.45 (q, 2H), 4.4 (s, 2H), 5.65 (s, 1H), 7.1 (m, 5H), 9.15 (s, 1H).

Example 28

4-[α-(2',6'-Dimethylphenyl)]ethoxymethyl-5-methylimidazole

The procedure of Example 27 is repeated, except that 4-[α-(2',6'-dimethylphenyl)]hydroxymethyl-5-methylimidazole is used.

NMR (HCl salt): 1.05 (1, 3H), 1.65 (s, 3H), 2.1 (s, 6H), 3.4 (q, 2H), 4.65 (s, 2H), 5.95 (s, 1H), 6.95 (s, 3H), 8.5 (s, 1H).

MS: 244 (38%), 229 (9%), 215 (15%), 199 (39%), 183 (100%), 162 (39%), 139 (29%), 133 (35%), 111 (25%), 109 (17%), 105 (13%).

Example 29

4-[α-(2',6'-Dimethylphenyl)]ethoxymethylimidazole

The procedure of Example 27 is repeated, except that 4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole is used. The product melts at 142—147°C. The corresponding hydrochloride, prepared in a mixture of ethyl acetate and isopropanol, melts at 136—139°C.

NMR (HCl salt): 1.1 (t, 3H), 2.15 (s, 6H), 3.4 (q, 2H), 4.6 (s, 2H), 6.0 (s, 1H), 6.85 (s, 1H), 7.05 (m, 3H), 8.65 (s, 1H).

Example 30

4-[α-(3'-Methylphenyl)-ethoxymethylimidazole

The procedure of Example 27 is repeated, except that 4-[α-(3'-methylphenyl)]hydroxymethylimidazole is used. The hydrochloride, prepared in isopropanolethylacetate, melts at 135—140°C.

NMR (HCl salt): 1.2 (t, 3H), 2.25 (s, 3H), 3.55 (q, 2H), 4.75 (s, 2H), 5.55 (s, 1H), 7.1 (s, 1H), 8.7 (s, 1H).

MS: 216 (23%), 187 (6%), 172 (53%), 171 (100%), 170 (20%), 155 (7%), 144 (15%), 143 (27%), 97 (20%), 95 (23%), 91 (15%).

Example 31

4-[α-(3'-Methoxyphenyl)]ethoxymethylimidazole

The procedure of Example 27 is repeated, except that 4-[α-(3'-methoxyphenyl)]hydroxymethylimidazole is used.

NMR (HCl salt): 1.05 (t, 3H), 3.4 (q, 2H), 3.6 (s, 3H), 4.75 (s, 2H), 5.45 (s, 1H), 6.9 (m, 5H), 8.65 (s, 1H).

Example 32

4-[α-(4'-Methoxyphenyl)]ethoxymethylimidazole

The procedure of Example 27 is repeated, except that 4-[α-(4'-methoxyphenyl)]hydroxymethylimidazole is used.

NMR (HCl salt): 1.0 (t, 3H), 3.3 (q, 2H), 3.55 (s, 3H), 4.7 (s, 2H), 5.4 (s, 1H), 6.95 (m, 5H), 8.6 (s, 1H).

Example 33

4-[α-(2',6'-Dimethylphenyl)]methoxymethylimidazole

10 g of 4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole is dissolved in 60 ml of methanol. Hydrogen chloride gas is passed into the solution for 1 hour, during which time the mixture is maintained at reflux. The mixture is then evaporated to dryness. 100 ml of water are added and the solution is made alkaline with sodium carbonate. The solution is then extracted three times with 50 ml portions of chloroform. The combined chloroform extracts are washed with water, dried over sodium sulfate and filtered, and the filtrate is evaporated to dryness. The corresponding hydrochloride, prepared in ethyl acetate isopropanol, melts at 176—179°C.

NMR (HCl salt): 2.2 (s, 6H), 3.3 (s, 3H), 4.7 (s, 2H), 6.0 (s, 1H), 6.9 (s, 1H), 7.15 (s, 3H), 8.7 (s, 1H).

Example 34

5-Methyl-4-(2',6'-dimethylbenzyl)imidazole

6 g of 5-methyl-4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole are dissolved in 50 ml of acetic acid. About 60 mg of 10% palladium-on-carbon are added and the mixture is stirred vigorously in hydrogen atmosphere at about 60°C for as long as hydrogen is consumed (about 6 hours). The mixture is then cooled and filtered. The filtrate is distilled to a smaller volume and 50 ml of water is added. The resultant solution is made alkaline with sodium hydroxide solution, with cooling. The precipitate which forms is filtered and washed with water. The product melts at 142—145°C.

NMR: 1.5 (s, 3H), 1.85 (s, 6H), 3.6 (s, 2H), 4.1 (s, 1H), 6.7 (s, 3H), 7.0 (s, 1H).

MS: 200 (99%), 199 (12%), 185 (44%), 172 (6%), 118 (100%), 95 (19%).

Example 35

5-Methyl-4-(2'-methylbenzoyl)imidazole

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 34 g 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 20 g of 5-methyl-4-imidazolecarboxylic 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 pH of the filtrate is adjusted to 7—11 and the solution is extracted three times with 30 ml portions of chloroform. The combined chloroform extracts are washed with water and evaporated to dryness. The residue, which contains the crude product, is converted to the hydrochloride in ethanol. After recrystallization from ethanol, the hydrochloride melts at 289—291°C. The 5-methyl-4-(2'-methylbenzoyl)-*1H*-imidazole is liberated from the hydrochloride in water with sodium hydroxide. It melts at 165—166°C.

NMR (HCl salt): 2.0 (s, 3H), 2.15 (s, 3H), 4.75 (s, 2H), 7.3 (s, 4H), 8.8 (s, 1H).

MS: 200 (33%), 185 (100%), 172 (15%), 171 (14%), 119 (14%), 110 (11%), 91 (25%).

Example 36

5-Methyl-4-(2',6'-dimethylbenzoyl)imidazole

The procedure of Example 35 is repeated, except that 1-bromo-2,6-dimethylbenzene is used in place of 2-bromotoluene. The melting point of the hydrochloride is 268—271°C. The base, which is liberated from the hydrochloride in water, has a melting point of 179—181°C.

NMR (HCl salt): 1.9 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 4.7 (s, 2H), 7.15 (m, 3H), 8.9 (s, 1H).

Example 37

5-Methyl-4-[α-(2'-methylphenyl)]hydroxymethylimidazole

5.1 g of 5-methyl-4-(2'-methylbenzoyl)imidazole are dissolved in 25 ml of ethanol. 0.9 g of sodium borohydride is added while stirring at room temperature. After the addition is complete, the mixture is stirred for 4 hours at room temperature, then evaporated to dryness. 30 ml of water are added to the residue and the resultant mixture is stirred and cooled. The precipitate is removed by filtration and washed with water. After recrystallization from water-ethanol, the product melts at 148—150°C.

NMR: 1.65 (s, 3H), 1.8 (s, 3H), 4.7 (s, 2H), 5.65 (s, 1H), 7.0 (m, 4H), 7.1 (s, 1H).

MS: 202 (75%), 185 (24%), 184 (68%), 183 (35%), 168 (100%), 157 (16%), 156 (13%), 120 (11%), 119 (15%), 115 (19%), 111 (48%), 109 (27%), 91 (26%), 89 (55%).

Example 38

5-Methyl-4-(2'-methylbenzyl)imidazole

2.1 g of 5-methyl-4-(2'-methylbenzoyl)imidazole are dissolved in 10 ml of acetic acid. 0.2 g of 10% palladium-on-carbon is added and the reaction mixture is agitated vigorously at about 60°C in a hydrogen atmosphere until the uptake of hydrogen ceases. The mixture is then cooled and filtered and the filtrate is evaporated to dryness. The residue is dissolved in 20 ml of water and the resultant solution is made alkaline (pH about 10) with sodium hydroxide. The precipitate which forms is removed by filtration, washed with water and dried. The product is transformed to the hydrochloride in isopropanol, its melting point after recrystallization from water-ethanol being 266—268°C. The free base, 5-methyl-4-(2'-methylbenzyl)imidazole, which is liberated from the hydrochloride in water with sodium hydroxide, has a melting point of 138—140°C.

NMR (HCl salt): 1.95 (s, 3H), 2.05 (s, 3H), 3.7 (s, 2H), 4.6 (s, 2H), 7.05 (s, 4H), 8.35 (d, 1H).

MS: 186 (100%), 185 (26%), 158 (7%), 144 (9%), 115 (8%), 104 (53%), 95 (18%).

Example 39

4-(2'-Methylbenzoyl)imidazole

5.0 g of 4-[α-(2'-methylphenyl)]hydroxymethylimidazole are added in small portions to 12.5 ml of 65% nitric acid heated to 60°C. The mixture is stirred at about 80°C for 5 hours, then is distilled to a smaller volume. 50 ml of water are added and the resultant solution is made alkaline with sodium hydroxide (pH about 12) with cooling. The alkaline solution is filtered and the filtrate is neutralized with diluted hydrochloric acid (pH=7), cooled and filtered. The precipitate is washed with water and dried to yield crude 4-(2'-methylbenzoyl)imidazole.

Example 40

4-(2',6'-Dimethylbenzoyl)imidazole

The procedure of Example 39 is repeated, except that the imidazole starting material is 4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole. The product melts at 131—133°C.

NMR: 1.75 (s, 6H), 4.8 (s, 1H), 6.7 (m, 3H), 7.0 (s, 1H), 7.55 (s, 1H).

Example 41

4-(4'-Methylbenzoyl)imidazole

The procedure of Example 39 is repeated, except that the imidazole starting material is 4-[α-(4-methylphenyl)]hydroxymethylimidazole. The hydrochloride, which is prepared in isopropanol, melts at 205—210°C.

NMR: 2.55 (s, 3H), 4.85 (s, 2H), 7.85 (m, 4H), 8.35 (s, 1H), 9.20 (s, 1H).

MS: 186 (100%), 171 (37%), 159 (33%), 119 (87%), 95 (48%), 91 (52%).

Example 42

4-(2',6'-Dimethyl-3'-nitrobenzoyl)imidazole

10 g of 4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole are dissolved in 30 ml of concentrated nitric acid and the solution is heated with stirring at 100°C for 10 hours. 150 ml of water are then added and the solution is evaporated to a smaller volume in order to remove the excess of nitric acid. Water is added and the reaction mixture is neutralized with sodium hydroxide, with cooling. The precipitate which forms is filtered and worked with water and ethanol. The prodcut melts at 210—215°C. The corresponding hydrochloride, prepared in isopropanol, melts at 245—249°C.

NMR: 2.4 (s, 6H), 5.15 (s, 2H), 7.85 (m, 2H), 8.25 (s, 1H), 9.45 (s, 1H).
MS: 245 (100%), 244 (7%), 230 (8%), 228 (18%), 217 (65%), 200 (15%), 199 (11%), 198 (18%), 171 (19%), 95 (71%).

Example 43

4-(4'-Amino-3',5'-dichlorobenzyl)-5-methylimidazole

A mixture of 6.0 g of 4-chloromethyl-5-methylimidazole hydrochloride, 9.0 g of 2,6-dichloroaniline and 40 ml of xylene is refluxed with stirring for 3 hours. The mixture is then filtered and the precipitate is washed with xylene. The precipitate is dissolved in 50 ml of water and the pH is adjusted to 8. The solution is extracted with toluene (3x30 ml). The combined toluene extracts are washed with 10 ml of water and evaporated to dryness. The residue, which is crude 4-(4'-amino-3',5'-dichlorobenzyl)-5-methylimidazole, is converted to the hydrochloride in isopropanol with HCl-ethyl-acetate. The free base is liberated from the hydrochloride in water with sodium hydroxide. The melting point of the base is 172—175°C.

NMR (HCl salt): 2.0 (s, 3H), 4.5 (s, 2H), 4.8 (s, 4H), 7.25 (s, 2H), 8.55 (s, 1H).
MS: 254 (2%), 220 (15%), 189 (6%), 164 (8%), 163 (43%), 162 (5%), 161 (67%), 95 (100%).

Example 44

4-(4'-Amino-3',5'-dichlorobenzyl)imidazole

The procedure of Example 43 is repeated, except that 4-chloromethylimidazole is used in place of 4-chloromethyl-5-methylimidazole. The product melts at 178—181°C.

Example 45

4-(2',4',6'-Trimethylbenzyl)imidazole

3.0 g of 4-chloromethylimidazole hydrochloride are suspended in 20 ml of mesitylene. 5 ml of dimethylformamide are added and the reaction mixture is refluxed for 12 hours, then cooled. 30 ml of water are added, the layers are separated, and the aqueous phase is washed with chloroform. The aqueous solution is then made alkaline with sodium carbonate solution and extracted with chloroform. The combined chloroform extracts are washed with water and evaporated to dryness. The residue, which is crude 4-(2',4',6'-trimethylbenzyl)imidazole, is converted to the hydrochloride by treatment with concentrated hydrochloric acid. The hydrochloride salt melts at 166—169°C.

Example 46

(a) 2,6-Dichlorobenzylglyoxal diethyl acetal

2.5 g of magnesium turnings are covered with 100 ml of dry diethyl ether. To that mixture is then added dropwise a solution of 24 g of 2,6-dichlorobenzylbromide in 50 ml of dry diethyl ether at such a rate that a smooth reaction is maintained. After the addition is complete the reaction mixture is refluxed for one additional hour, then cooled to room temperature. The reaction mixture is then added dropwise, over a period of 2 hours, to a cooled (0—5°C) solution of diethoxyacetic acid piperidinyl amide (21.5 g) in 100 ml of diethyl ether. After the addition is complete, the reaction mixture is stirred for an additional hour at 5°C. The mixture is then poured into cold sulfuric acid (400 ml water containing 30 ml of concentrated sulfuric acid). The ether layer is separated and evaporated to dryness. The residue, which consists of crude 2,6-dichlorobenzylglyoxal diethylacetal, is distilled under reduced pressure (130—140°C/1mmHg) and used in Example 46(b) and 47(a) set forth below.

(b) 1,1-Diethoxy-2-hydroxy-3-(2',6'-dichlorophenyl)propane

29.1 g of 2,6-dichlorobenzylglyoxal diethyl acetal are dissolved in 200 ml of ethanol and to the solution is then added, in small portions at room temperature, 1.9 g of sodium borohydride. After the addition is complete, the mixture is stirred at room temperature for another 4 hours. 200 ml of water are added and the solution is extracted with ethyl acetate. The combined ethyl acetate extracts are washed with water and evaporated to dryness. The residue, which consists of crude 1,1-diethoxy-2-hydroxy-3-(2',6'-dichlorophenyl)propane, is used in steps (c) and (e) of this Example as set forth below.

(c) 1-(2',6'-Dichlorophenyl)-3-hydroxy-2-propanone

10 g of 1,1-diethoxy-2-hydroxy-3-(2',6'-dichlorophenyl)propane are dissolved in 40 ml of ethanol, 20 ml of concentrated hydrochloric acid are added, and the mixture refluxed for 4 hours, then evaporated to dryness. 10 ml of toluene are added and the solution is again evaporated to dryness in order to remove the water. The residue, crude 1-(2',6'-dichlorophenyl)-3-hydroxy-2-propanone, is used in Example 46(d) below. After recrystallization from diisopropyl ether, the product melts at 111—114°C.

(d) 4-(2',6'-Dichlorobenzyl)imidazole

9.0 g of 1-(2',6'-dichlorophenyl)-3-hydroxy-2-propanone and 20 ml of formamide are combined. The mixture is heated at 180°C for 4 hours, then is cooled and diluted with 50 ml water. The pH is adjusted with hydrochloric acid to 3—4 and the reaction mixture is washed three times with 50 ml

portions of chloroform. The aqueous layer is then made alkaline with sodium hydroxide (pH=8—9) and the mixture is extracted three times with 50 ml portions of chloroform. The combined chloroform extracts are washed with water, and evaporated to dryness. The residue, which consists of the crude product, is converted to the hydrochloride in ethyl acetate-isopropanol. The hydrochloride melts at 244—248°C. The base, which is liberated from the hydrochloride in water with sodium hydroxide, melts at 142—145°C.

NMR (HCl salt): 4.15 (s, 2H), 4.65 (s, 2H), 7.0 (s, 1H), 7.2 (m, 3H), 8.55 (s, 1H).

MS: 228 (10%), 226 (16%), 193 (30%), 192 (13%), 191 (100%), 166 (12%), 164 (37%), 156 (15%), 81 (15%).

(e) 4-(2',6'-Dichlorobenzyl)imidazole

5.0 g of 1,1-diethoxy-2-hydroxy-3-(2',6'-dichlorophenyl)propane and 15 ml of formamide are combined and the mixture is heated with stirring at 180°C for 4 hours. Excess formamide is removed by distillation and the reaction mixture is diluted with water. The pH is adjusted with hydrochloric acid to 3—4. Subsequent treatment is as described in (d) above. The hydrochloride melts at 244—248°C.

Example 47

(a) 2,6-Dichlorobenzylglyoxal

A mixture of 10 g of 2,6-dichlorobenzylglyoxal diethyl acetal, 40 ml of ethanol and 20 ml of concentrated hydrochloric acid is refluxed for 4 hours and then evaporated to dryness. The residue, which is a yellowish oil, consists of crude 2,6-dichlorobenzylglyoxal and is used in step (b) of this Example as set forth below.

(b) 4-(2',6'-Dichlorobenzyl)oxazole

21.7 g of crude, 2,6-dichlorobenzylglyoxal are dissolved in 50 ml of formamide. 7.0 g of hexamethylenetetramine and 30.8 g of ammonium acetate are added and the reaction mixture is stirred at 100°C for 2 hours, then is evaporated to dryness *in vacuo*. 200 ml of water are added and the pH of the aqueous phase is adjusted, while stirring, to 2—3 with concentrated hydrochloric acid. The solution is washed with toluene (3×50 ml). The aqueous solution is made alkaline with sodium hydroxide (pH=8—9) and then extracted three times with chloroform (1×100 ml and 2×50 ml). The combined chloroform extracts are washed with water, dried with sodium sulfate and evaporated to dryness. The residue, which consisted of crude product, is used in step (c) below.

(c) 4-(2',6'-Dichlorobenzyl)imidazole

A mixture of 10 g of 4-(2',6'-dichlorobenzyl)oxazole and 30 ml of formamide is stirred at 180°C for 4 hours. The mixture is cooled and diluted with water. The reaction product is thereafter isolated in the same manner as described in Example 46(d).

Example 48

4-(2'-Chlorobenzyl)imidazole

The procedure of Example 46(e) is repeated, except that 1,1-diethoxy-2-hydroxy-3-(2'-chlorophenyl)propane is used in place of the 1,1-diethoxy-2-hydroxy-3-(2',6'-dichlorophenyl)propane. The product melts at 168—171°C.

NMR (HCl salt): 4.05 (s, 2H), 4.65 (s, 2H), 7.05 (s, 1H), 7.25 (s, 4H), 8.55 (s, 1H).

Example 49

4-(2'-Methylbenzyl)imidazole

A mixture of 1.7 g of 1-(2'-methylphenyl)-3-chloro-2,3-epoxypropane and 10 ml of formamide is refluxed for 22 hours. Excess formamide is distilled off and 20 ml of water are added. The mixture is extracted with chloroform (3×10 ml) and the aqueous phase is made alkaline with sodium hydroxide. The alkaline solution is then extracted three times with 10 ml portions of chloroform and the combined chloroform extracts are washed with water, dried with sodium sulfate and evaporated to dryness. The residue, which is crude 4-(2'-methylbenzyl)imidazole, is transformed to the hydrochloride in acetone by adding an ethyl acetate solution containing dry hydrogen chloride. The melting point of the hydrochloride is 131—134°C.

NMR (HCl salt): 2.1 (s, 3H), 3.85 (s, 2H), 4.75 (s, 2H), 6.9 (s, 1H), 7.1 (s, 4H), 8.5 (s, 1H).

Example 50

4-(2',3'-Dimethylbenzyl)imidazole

A mixture of 7.6 g of 4-(2',3'-dimethylbenzyl)-N-acetylimidazole and 30 ml of 6*N* hydrochloric acid is refluxed with stirring for 4 hours. The mixture is distilled to a smaller volume and 50 ml of water are added. The pH is adjusted with sodium hydroxide to 8—9. The mixture is then cooled and filtered and the filter cake is washed with water and dried. The product melts at 110—115°C.

NMR: 1.6 (s, 3H), 1.65 (s, 3H), 3.35 (s, 2H), 4.1 (s, 1H), 6.0 (s, 1H), 6.4 (m, 3H), 7.0 (s, 1H).

Example 51

4-(2'-Methylbenzyl)imidazole

10 g of 4-[α-(2'-methylphenyl)]chloromethylimidazole is dissolved in 50 ml of ethanol. 0.1 g of 10% palladium-on-carbon is added and the reaction mixture is stirred at room temperature in a hydrogen atmosphere until no more hydrogen is consumed. The mixture is then filtered and the filtrate is evaporated to dryness. 50 ml of water are added to the residue and the resulting solution is made alkaline (pH=8—9) with sodium hydroxide. The solution is extracted with chloroform, and the chloroform extracts are washed with water and evaporated to dryness. The residue is dissolved in acetone. HCl and ethyl acetate are added, thus affording the hydrochloride, melting at 132—133°C.

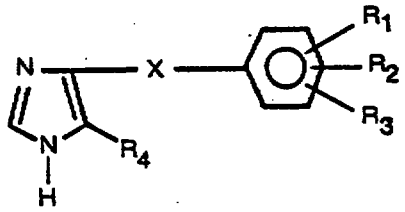
Example 52

4-(2'-Methylbenzyl)imidazole

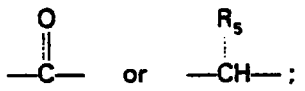
12.3 g of N-benzyl-4-(2'-methylbenzyl)imidazole are dissolved in 100 ml of ethanol. 0.3 g of 10% palladium-on-carbon is added and the reaction mixture is stirred vigorously at 70°C in a hydrogen atmosphere until the uptake of hydrogen ceases. The mixture is cooled and filtered. Subsequent treatment as described in Example 54 above affords the desired product.

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

1. A compound of formula:



wherein R_1, R_2 and R_3, which can be the same or different, are each selected from hydrogen, chloro, bromo, fluoro, methyl, ethyl, methoxy, amino, hydroxy and nitro but are not all hydrogen; R_4 is hydrogen or alkyl of 1 to 7 carbon atoms; X is



wherein R_5 is hydrogen, hydroxy or OR_6 and R_6 is alkyl or 1 to 7 carbon atoms or phenyl; and their non-toxic pharmaceutically acceptable acid addition salts and mixtures thereof; with the proviso that when R_1 is 2-methyl, R_2 is 5-methyl, R_3 is hydrogen and R_4 is methyl, then —X— is other than $—CH_2—$.

2. A compound according to claim 1 in which X is $—CH_2—$, —CHOH—, $—CH(OCH_3)—$, $—CH(OC_2H_5)—$, or —CO—, R_1, R_2 and R_3 are each hydrogen, chloro, bromo, fluoro, methyl, ethyl, hydroxy or methoxy but are not all hydrogen and R_4 is hydrogen or methyl.

3. A compound according to claim 1, 2 or 3 in which R_1 is a substituent in the 2-, 3-, or 4-position and R_2 and R_3 is hydrogen, or R_1 and R_2 are substituents in the 2,3-, 2,4- or 2,6-positions and R_3 is hydrogen, or R_1, R_2 and R_3 are substituents in the 2,4,6-positions.

4. 4-[α-(2'-Methylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

5. 4-[α-(2',6'-Dimethylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

6. 4-[α-(3'-Methylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

7. 4-[α-(4'-Methylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

8. 4-[α-(2',3'-Dimethylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

9. 4-[α-(2'-Ethylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

10. 4-[α-(2'-Methoxyphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

11. 4-[α-(3'-Methoxyphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

12. 4-(2'-Methylbenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

Example 51

4-(2'-Methylbenzyl)imidazole

10 g of 4-[α-(2'-methylphenyl)]chloromethylimidazole is dissolved in 50 ml of ethanol. 0.1 g of 10% palladium-on-carbon is added and the reaction mixture is stirred at room temperature in a hydrogen atmosphere until no more hydrogen is consumed. The mixture is then filtered and the filtrate is evaporated to dryness. 50 ml of water are added to the residue and the resulting solution is made alkaline (pH=8—9) with sodium hydroxide. The solution is extracted with chloroform, and the chloroform extracts are washed with water and evaporated to dryness. The residue is dissolved in acetone. HCl and ethyl acetate are added, thus affording the hydrochloride, melting at 132—133°C.

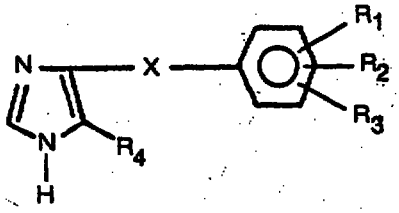
Example 52

4-(2'-Methylbenzyl)imidazole

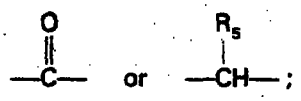
12.3 g of N-benzyl-4-(2'-methylbenzyl)imidazole are dissolved in 100 ml of ethanol. 0.3 g of 10% palladium-on-carbon is added and the reaction mixture is stirred vigorously at 70°C in a hydrogen atmosphere until the uptake of hydrogen ceases. The mixture is cooled and filtered. Subsequent treatment as described in Example 54 above affords the desired product.

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

1. A compound of formula:



wherein R_1, R_2 and R_3, which can be the same or different, are each selected from hydrogen, chloro, bromo, fluoro, methyl, ethyl, methoxy, amino, hydroxy and nitro but are not all hydrogen; R_4 is hydrogen or alkyl of 1 to 7 carbon atoms; X is



wherein R_5 is hydrogen, hydroxy or OR_6 and R_6 is alkyl or 1 to 7 carbon atoms or phenyl; and their non-toxic pharmaceutically acceptable acid addition salts and mixtures thereof; with the proviso that when R_1 is 2-methyl, R_2 is 5-methyl, R_3 is hydrogen and R_4 is methyl, then —X— is other than $—CH_2—$.

2. A compound according to claim 1 in which X is $—CH_2—$, —CHOH—, $—CH(OCH_3)—$, $—CH(OC_2H_5)—$, or —CO—, R_1, R_2 and R_3 are each hydrogen, chloro, bromo, fluoro, methyl, ethyl, hydroxy or methoxy but are not all hydrogen and R_4 is hydrogen or methyl.

3. A compound according to claim 1, 2 or 3 in which R_1 is a substituent in the 2-, 3-, or 4-position and R_2 and R_3 is hydrogen, or R_1 and R_2 are substituents in the 2,3-, 2,4- or 2,6-positions and R_3 is hydrogen, or R_1, R_2 and R_3 are substituents in the 2,4,6-positions.

4. 4-[α-(2'-Methylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

5. 4-[α-(2',6'-Dimethylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

6. 4-[α-(3'-Methylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

7. 4-[α-(4'-Methylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

8. 4-[α-(2',3'-Dimethylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

9. 4-[α-(2'-Ethylphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

10. 4-[α-(2'-Methoxyphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

11. 4-[α-(3'-Methoxyphenyl)]hydroxymethylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

12. 4-(2'-Methylbenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

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13. 4-(2',6'-Dimethylbenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

14. 4-(3'-Methylbenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

15. 4-(2',4'-Dimethylbenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

16. 4-(2',3'-Dimethylbenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

17. 4-(2'-Ethylbenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

18. 4-(2',4',6'-Trimethylbenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

19. 4-(2',6'-Dichlorobenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

20. 4-(2'-Chlorobenzyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

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

22. 4-(2',6'-Dimethylbenzoyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

23. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 22 as the free base or a non-toxic pharmaceutically acceptable acid addition salt thereof, in combination with a pharmaceutically acceptable inert carrier.

24. A compound as claimed in any one of claims 1 to 22 as the free base or as a non-toxic pharmaceutically acceptable acid addition salt thereof for use in therapy as an anti-hypertensive, anti-ulcer, diuretic, sedative, analgesic, anti-inflammatory or tranquilizing agent.

25. 4-(2',6'-Dimethylbenzyl)imidazole, 4-(2',3'-dimethylbenzyl)imidazole, 4-(2'-methylbenzyl)-imidazole, 4-(2',6'-dichlorobenzyl)imidazole, 4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole or 4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole, as free base or a non-toxic pharmaceutically acceptable acid addition salt thereof for use in therapy for treating hypertension.

26. 4-(2',6'-Dimethylbenzyl)imidazole, 4-(2',3'-dimethylbenzyl)imidazole, 4-(2',4'-dimethylbenzyl)imidazole, 4-(2'-ethylbenzyl)imidazole, 4-(2'-methylbenzyl)imidazole, 4-(3'-methylbenzyl)-imidazole, 4-(2',4',6'-trimethylbenzyl)imidazole, 4-(2'-chlorobenzyl)imidazole or 4-(2',6'-dichlorobenzyl)imidazole, as free base or a non-toxic pharmaceutically acceptable acid addition salt thereof for use in therapy for trating ulcerous conditions.

27. 4-[α-(2',3'-Dimethylphenyl)]hydroxymethylimidazole, 4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole, 4-[α-(2'-ethylphenyl)]hydroxymethylimidazole, 4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole, 4-(2',3'-dimethylbenzyl)imidazole, 4-(2',4'-dimethylbenzyl)imidazole, 4-(2',6'-dimethylbenzyl)imidazole, 4-(2'-methylbenzyl)imidazole, or 4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole, as free base or a non-toxic pharmaceutically acceptable acid addition salt thereof for use in therapy as a diuretic.

28. 4-(2',4'-Dimethylbenzyl)imidazole, 4-(2',3'-dimethylbenzyl)imidazole, 4-(3'-methylbenzyl)-imidazole, 4-(2',4',6'-trimethylbenzyl)imidazole, 4-(2'-ethylbenzyl)imidazole, 4-(3'-methoxybenzyl)-imidazole, 4-(2'-chlorobenzyl)imidazole, 4-[α-(2',3'-dimethylphenyl)]hydroxymethylimidazole, 4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole, or 5-methyl-4-(2',6'-dimethylbenzyl)imidazole as free base or a non-toxic pharmaceutically acceptable acid addition salt thereof for use in therapy as a sedative agent.

29. 4-(2',3'-Dimethylbenzyl)imidazole, 4-(2',4'-dimethylbenzyl)imidazole, 4-(2'-methylbenzyl)-imidazole, 4-(3'-methylbenzyl)imidazole, 4-(2'-chlorobenzyl)imidazole, 4-[α-(2',4'-dimethylphenyl)]-hydroxymethylimidazole, 4-[α-(2',3'-dimethylphenyl)]hydroxymethylimidazole, 4-[α-(2'-methylphenyl)]hydroxymethylimidazole, 4-[α-(3'-methylphenyl)]hydroxymethylimidazole, 4-[α-(4'-methylphenyl)]hydroxymethylimidazole, 4-[α-(2'-ethylphenyl)]hydroxymethylimidazole, 4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole, 4-[α-(3'-methoxyphenyl)]hydroxymethylimidazole, 4-[α-(4'-methoxyphenyl)]hydroxymethylimidazole, 4-[α-(2',6'-dimethylphenyl)]methoxymethylimidazole, 4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole, 5-methyl-4-(2'-methylbenzyl)imidazole or 5-methyl-4-[α-(2',6'-dimethylphenyl)hydroxymethylimidazole, as free base or a non-toxic pharmaceutically acceptable acid addition salt thereof, for use in therapy as an analgesic agent.

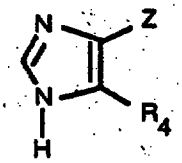
30. 4-(2',4'-Dimethylbenzyl)imidazole, 4-(3'-methylbenzyl)imidazole, 4-[α-(2',3-dimethylphenyl)]hydroxymethylimidazole, 4-[α-(2'-methylphenyl)]hydroxymethylimidazole, 4-[α-(3'-methylphenyl)]hydroxymethylimidazole, 4-[α-(4'-methylphenyl)]hydroxymethylimidazole, 4-[α-(2'-ethylphenyl)]hydroxymethylimidazole, 4-[α-(2'-methoxyphenyl)]hydroxymethylimidazole, 4-[α-(3'-methoxyphenyl)]hydroxymethylimidazole, 4-[α-(2',6'-dimethylphenyl)]methoxymethylimidazole, 4-[α-(2',6'-dimethylphenyl)]ethoxymethylimidazole, 4-(4'-methylbenzoyl)imidazole, 5-methyl-4-(2'-methylbenzyl)imidazole, 5-methyl-4-[α-(2',6'-dimethylphenyl)]hydroxymethylimidazole, 5-methyl-4-[α-(2'-methylphenyl)hydroxymethylimidazole or 5-methyl-4-(2'-methylbenzoyl)imidazole, as free base or a

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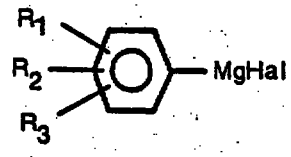
non-toxic pharmaceutically acceptable acid addition salt thereof for use in therapy as an anti-inflammatory agent.

31. 4-(2',3'-Dimethylbenzyl)imidazole, 4-(2'-chlorobenzyl)imidazole, 4-(2',4',6'-trimethylbenzyl)-imidazole, 4-(2',6'-dimethylbenzyl)-imidazole, or 4-(3'-methylbenzyl)imidazole, as free base or a non-toxic pharmaceutically acceptable acid addition salt thereof for use in therapy as a tranquilizing agent.

32. A process for the preparation of a compound as claimed in claim 1 in which —X— is —CO— or —CHOH—, which comprises reacting an imidazole derivative of the formula:

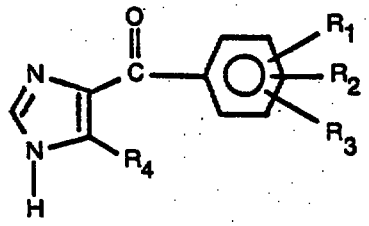


wherein R_4 is as defined in claim 1 and Z is —CHO or —COOR (COOR being an ester grouping) with a phenylmagnesium halide of the formula:



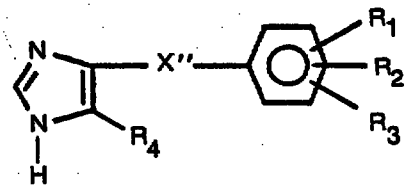
wherein R_1, R_2 and R_3 are as defined in claim 1 and Hal is a halogen atom.

33. A process for the preparation of a compound as claimed in claim 1 in which X is —CHOH— which comprises reducing a compound of the formula:

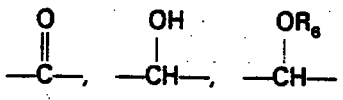


wherein R_1, R_2, R_3 and R_4 are as defined in claim 1.

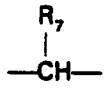
34. A process for the preparation of a compound as claimed in claim 1 wherein X is —CH_2— which comprises reducing a compound of the formula:



wherein R_1, R_2, R_3 and R_4 are as defined in claim 1 and —X''— is



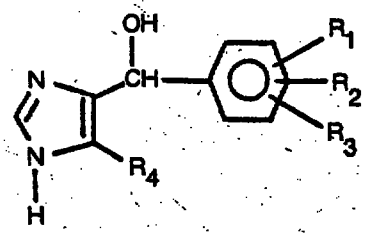
(wherein R_6 is as defined in claim 1), or



wherein R_7 is a hydrogenolysable group.

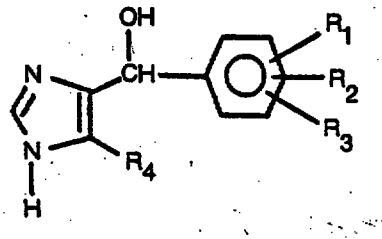
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35. A process for the preparation of a compound as claimed in claim 1 wherein X is —CH_2OR_6—, which comprises reacting a compound of the formula:



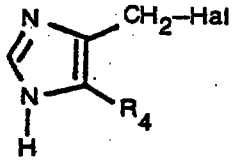
wherein R_1, R_2, R_3 and R_4 are as defined in claim 1 with a compound of the formula R_6OH wherein R_6 is as defined in claim 1, in the presence of acid.

36. A process for the preparation of a compound as claimed in claim 1 wherein X is —CO— which comprises oxidizing a compound of the formula:

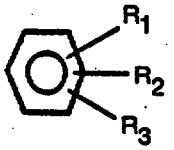


wherein R_1, R_2, R_3 and R_4 are as defined in claim 1.

37. A process for the preparation of a compound as claimed in claim 1 wherein X is —CH_2—, which comprises reacting a 4-halomethylimidazole of the formula:

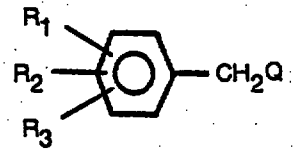


wherein R_4 is as defined in claim 1 and Hal is a halogen atom, with a benzene derivative of the formula:

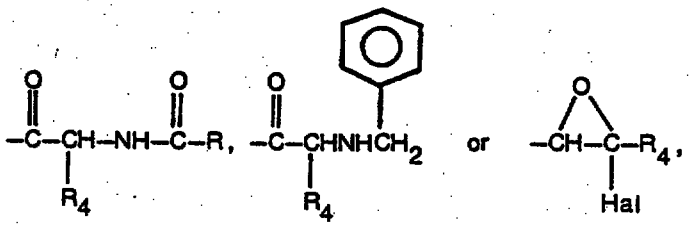


wherein R_1, R_2 and R_3 are as defined in claim 1.

38. A process for the preparation of a compound as claimed in claim 1 wherein X is —CH_2— which comprises reacting formamide with a compound of the formula:

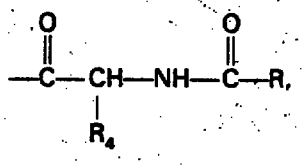


wherein R_1, R_2 and R_3 are as defined in claim 1 and Q is a radical of the formula:



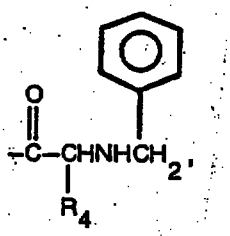
where Hal is a halogen atom, R_4 is as defined in claim 1, and R is a substituted or unsubstituted alkyl, aralkyl or aryl group, provided that:

(a) when Q is



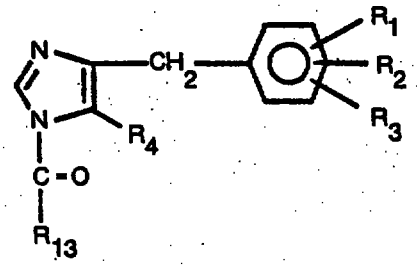
the reaction with formamide is followed by treatment of the intermediate product with acid; and

(b) when Q is



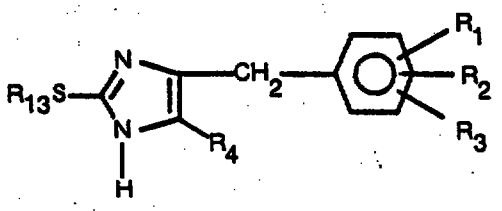
the reaction with formamide is followed by hydrogenation of the intermediate product.

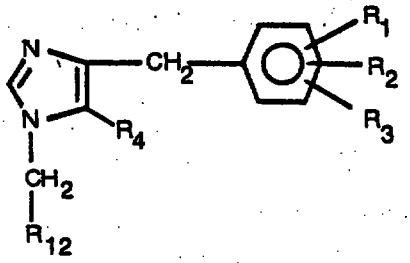
39. A process for the preparation of a compound as claimed in claim 1 wherein X is —CH_2—, which comprises hydrolysing a compound of the formula:



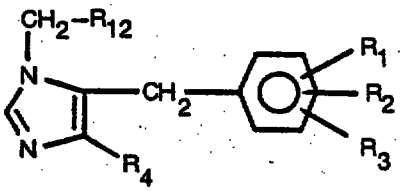
wherein R_1, R_2, R_3 and R_4 are as defined in claim 1 and R_{13} is alkyl of 1 to 7 carbon atoms or aryl of 6 to 10 carbon atoms.

40. A process for the preparation of a compound as claimed in claim 1 wherein X is —CH_2—, which comprises hydrogenolysis of a compound of the formula:



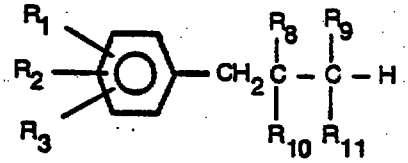


or

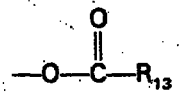


wherein R_1, R_2, R_3 and R_4 are as defined in claim 1, R_{13} is alkyl of 1 to 7 carbon atoms or aryl of 6 to 10 carbon atoms, and R_{12} is aryl.

41. A process for the preparation of a compound as claimed in claim 1 wherein X is —CH_2—, which comprises reacting a starting material of the formula:

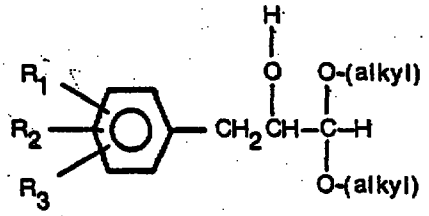


wherein R_1, R_2 and R_3 are as defined in claim 1 and R_8, R_9, R_{10} and R_{11}, which are the same or different, are each hydrogen, hydroxy, halogen, amino, —O-alkyl containing 1 to 7 carbon atoms, or



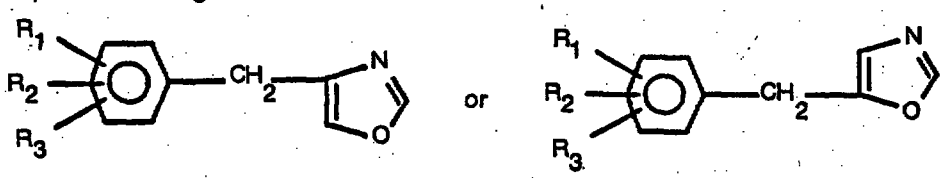
(wherein R_{13} is alkyl or 1 to 7 carbon atoms or aryl of 6 to 10 carbon atoms), or wherein R_8 and R_{10} can be combined to form a keto group, or R_9 and R_{11} can be combined to form a keto group, or both R_8 and R_{10} and R_9 and R_{11} can simultaneously form keto groups; with $NH_3 + CH_2O$ (or a source of ammonia and formaldehyde), HN=CH—NH_2, ammonium formate, or formamide to give the corresponding imidazole.

42. A process for the preparation of a compound as claimed in claim 1 wherein X is —CH_2—, which comprises reacting a starting material of the formula:



wherein the alkyl groups contain 1 to 7 carbon atoms and R_1, R_2 and R_3 are as defined in claim 1, with formamide to give the corresponding imidazole.

43. A process for the preparation of a compound as claimed in claim 1 wherein X is —CH_2— which comprises reacting formamide with an oxazole of the formula:

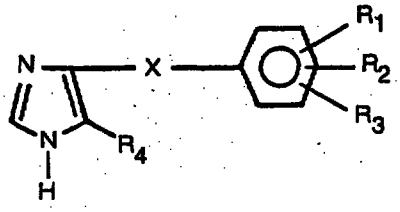


wherein R_1, R_2 and R_3 are as defined in claim 1.

44. A compound as claimed in claim 1 when prepared by a process as claimed in any of claims 32 to 43.

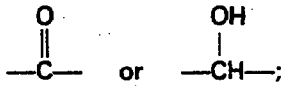
Claims for Contracting State: AT

1. A process for the preparation of a therapeutically active imidazole derivative of the formula:

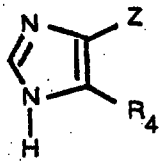


(I)

wherein R_1, R_2 and R_3, which can be the same or different, are each selected from hydrogen, chloro, bromo, fluoro, methyl, ethyl, methoxy, amino, hydroxy and nitro but are not all hydrogen; R_4 is hydrogen or alkyl of 1 to 7 carbon atoms; X is

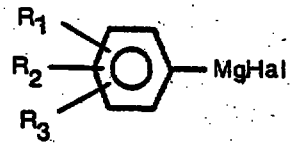


or a non-toxic pharmaceutically acceptable acid addition salt thereof; which comprises reacting an imidazole derivative of the formula:



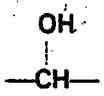
* C L M S *

wherein R_4 is as defined above and Z is —CHO or —COOR (—COOR being an ester grouping), with a phenylmagnesiumhalide of the formula:

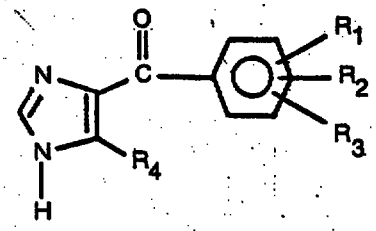


wherein R_1, R_2 and R_3 are as defined above and Hal is a halogen atom.

2. Process for the preparation of a compound as defined in claim 1 except that X is

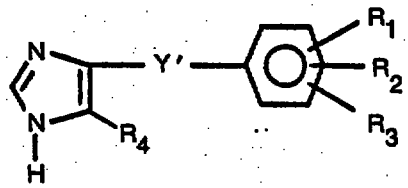


which comprises reducing a compound of the formula:

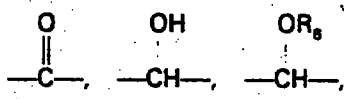


wherein R_1, R_2, R_3 and R_4 are as defined in claim 1.

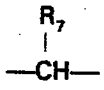
3. Process for the preparation of a compound as defined in claim 1 except that —X— is $—CH_2$ and when R_1 is 2-methyl, R_2 is 5-methyl and R_3 is hydrogen, R_4 is not methyl, which comprises reducing a compound of the formula:



wherein R_1, R_2, R_3 and R_4 are as defined in claim 1 and —Y'— is

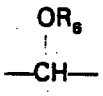


(wherein R_6 is alkyl of 1 to 7 carbon atoms or phenyl) or

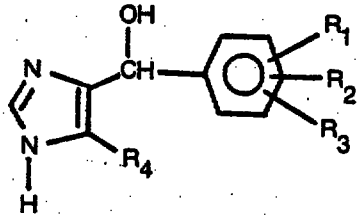


(wherein R_7 is a hydrogenolysable group.

4. Process for the preparation of a compound as defined in claim 1 except that X is



wherein R_6 is alkyl of 1 to 7 carbon atoms, or phenyl, which comprises reacting a compound of the formula:

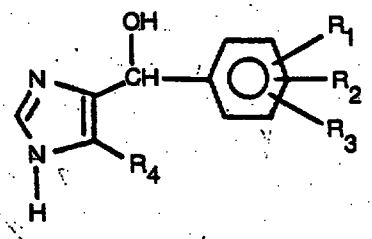


wherein R_1, R_2, R_3 and R_4 are as defined in claim 1 with a compound of the formula R_6OH wherein R_6 is as hereinbefore defined, in the presence of acid.

5. Process for the preparation of a compound as defined in claim 1 except that —X— is

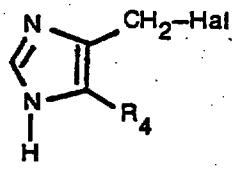


which comprises oxidizing a compound of the formula:

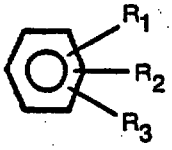


wherein R_1, R_2, R_3 and R_4 are as defined in claim 1.

6. Process for the preparation of a compound as defined in claim 1 except that X is $—CH_2—$ and when R_1 is 2-methyl, R_2 is 5-methyl and R_3 is hydrogen, R_4 is not methyl which comprises reacting a 4-halomethylimidazole of the formula:

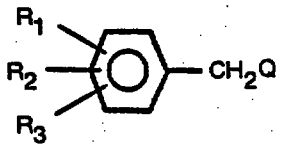


wherein R_4 is as defined in claim 1 and Hal is a halogen atom, with a benzene derivative of the formula:

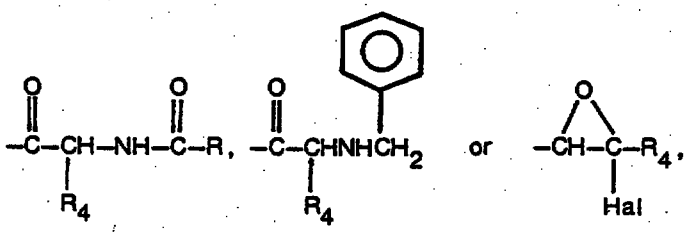


wherein R_1, R_2 and R_3 are as defined in claim 1.

7. Process for the preparation of a compound as defined in claim 1 except that X is $—CH_2—$ and when R_1 is 2-methyl, R_2 is 5-methyl, and R_3 is hydrogen, R_4 is not methyl, which comprises reacting formamide with a compound of the formula:

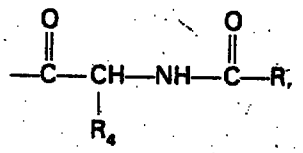


wherein R_1, R_2 and R_3 are as defined in claim 1 and Q is



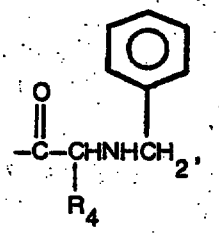
(wherein Hal is a halogen atom), R_4 is as defined in claim 1, and R is a substituted or unsubstituted alkyl, aralkyl or aryl group, provided that:

a) when Q is



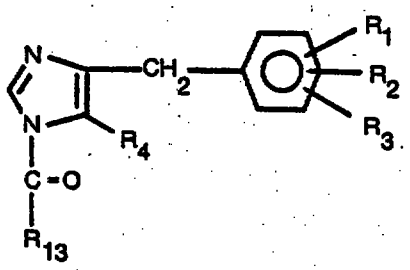
the reaction with formamide is followed by treatment of the intermediate product with acid; and

b) when Q is



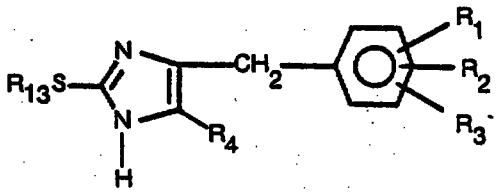
the reaction with formamide is followed by hydrogenation of the intermediate product.

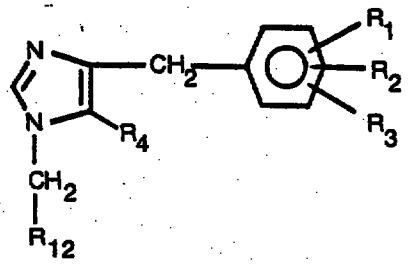
8. Process for the preparation of a compound as defined in claim 1 except that X is —CH_2— and when R_1 is 2-methyl, R_2 is 5-methyl, and R_3 is hydrogen, R_4 is not methyl, which comprises hydrolyzing a compound of the formula:



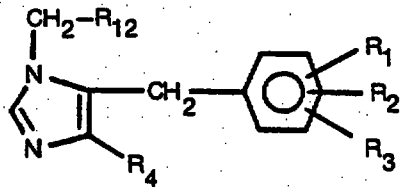
wherein R_1, R_2, R_3 and R_4 are as defined in claim 1 and R_{13} is an alkyl radical of 1 to 7 carbon atoms, or aryl of 6 to 10 carbon atoms.

9. Process for the preparation of a compound as defined in claim 1 except that X is —CH_2— and when R_1 is 2-methyl, R_2 is 5-methyl, and R_3 is hydrogen, R_4 is not methyl, which comprises hydrogenolysing a compound of the formula:



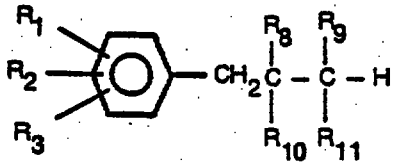


or

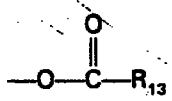


wherein R_1, R_2, R_3 and R_4 are as defined in claim 1, R_{13} is alkyl of 1 to 7 carbon atoms, or aryl of 6 to 10 carbon atoms, and R_{12} is aryl.

10. Process for the preparation of a compound as defined in claim 1, except that R_4 is hydrogen and X is CH_2, which comprises reacting a starting material of the formula:

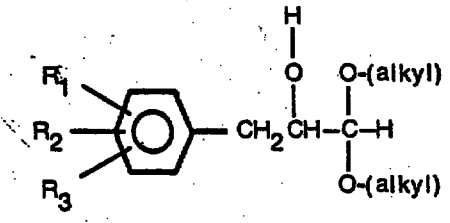


wherein R_1, R_2 and R_3 are as defined above and R_8, R_9, R_{10} and R_{11}, which can be the same or different, are each hydrogen, hydroxy, halogen, amino, —O-alkyl of 1 to 7 carbon atoms, or



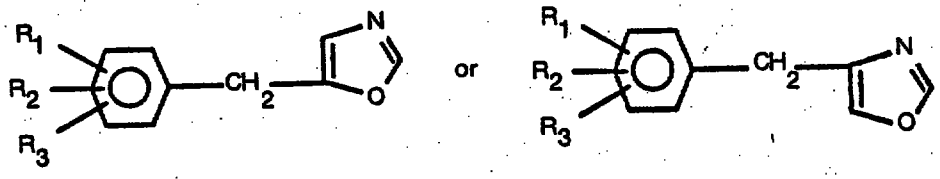
(wherein R_{13} is alkyl of 1 to 7 carbon atoms, or aryl of 6 to 10 carbon atoms); or R_8 and R_{10} are combined to form a keto group, or R_9 and R_{11} can be combined to form a keto group, or both R_8 and R_{10} and R_9 and R_{11} can simultaneously form keto groups); with NH_3+CH_2O (or a source of ammonia and formaldehyde), HN=CH—NH_2, ammonium formate or formamide.

11. Process for the preparation of a compound as defined in claim 1, except that R_4 is hydrogen and X is CH_2, which comprises reacting a compound of the formula:



wherein the alkyl groups contain 1 to 7 carbon atoms each and R_1, R_2 and R_3 are as defined in claim 1, with formamide.

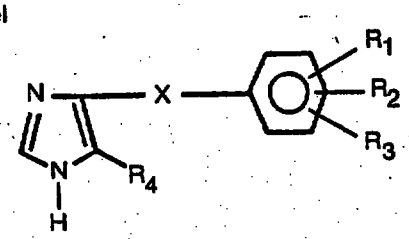
12. Process for the preparation of a compound as claimed in claim 1, except that R_4 is hydrogen and X is —CH_2—, which comprises reacting formamide with an oxazole of the formula:



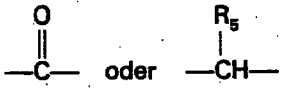
wherein R_1, R_2 and R_3 are as defined in claim 1.

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

1. Verbindung der Formel



wobei R_1, R_2 und R_3, die gleich oder verschieden sein können, jeweils unter Wasserstoff, Chloro, Bromo, Fluoro, Methyl, Äthyl, Methoxy, Amino, Hydroxy und Nitro ausgewählt werden aber nicht alle Wasserstoff sind, R_4 Wasserstoff oder Alkyl mit 1 bis 7 Kohlenstoffatomen ist, X



ist, wobei R_5 Wasserstoff, Hydroxy oder OR_6 ist und R_6 Alkyl mit 1 bis 7 Kohlenstoffatomen oder Phenyl ist, und ihre nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze und Mischungen davon, unter der Voraussetzung, daß, wenn R_1 2-Methyl, R_2 5-Methyl, R_3 Wasserstoff und R_4 Methyl ist, dann —X— etwas anderes als —CH_2— ist.

2. Verbindung nach Anspruch 1, bei der X —CH_2—, —CHOH—, —$CH(OCH_3)$—, —$CH(OC_2H_5)$— oder —CO— ist, R_1, R_2 und R_3 jeweils Wasserstoff, Chloro, Bromo, Fluoro, Methyl, Äthyl, Hydroxy oder Methoxy sind aber nicht alle Wasserstoff und R_4 ist Wasserstoff oder Methyl.

3. Verbindung nach Anspruch 1, 2 oder 3, bei der R_1 ein Substituent in der 2-, 3- oder 4-Position ist und R_2 und R_3 Wasserstoff ist, oder R_1 und R_2 Substituenten in den 2,3-, 2,4- oder 2,6-Positionen sind und R_3 Wasserstoff ist, oder R_1, R_2 und R_3 Substituenten in den 2,4,6-Positionen sind.

4. 4-[α-(2'-Methylphenyl)]Hydroxymethyl-Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

5. 4-[α-(2',6'-Dimethylphenyl)]Hydroxymethyl-Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

6. 4-[α-(3'-Methylphenyl)]Hydroxymethyl-Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

7. 4-[α-(4'-Methylphenyl)]Hydroxymethyl-Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

8. 4-[α-(2', 3'-Dimethylphenyl)]Hydroxymethyl-Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

9. 4-[α-(2'-Äthylphenyl)]Hydroxymethyl-Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

10. 4-[α-(2'-Methoxyphenyl)]Hydroxymethyl-Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

11. 4-[α-(3'-Methoxyphenyl)]Hydroxymethyl-Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

12. 4-(2'-Methylbenzyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

13. 4-(2', 6'-Dimethylbenzyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

14. 4-(3'-Methylbenzyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

15. 4-(2', 4'-Dimethylbenzyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

16. 4-(2', 3'-Dimethylbenzyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

17. 4-(2'-Äthylbenzyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

18. 4-(2', 4', 6'-Trimethylbenzyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

19. 4-(2', 6'-Dichlorobenzyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

20. 4-(2'-Chlorobenzyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

21. 4-[α-(2', 6'-Dimethylphenyl)]Äthoxymethyl-Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

22. 4-(2', 6'-Dimethylbenzoyl)Imidazol und seine nicht-toxischen pharmazeutisch akzeptablen sauren Anlagerungssalze.

23. Pharmazeutische Zusammensetzung mit einer Verbindung nach einem der Ansprüche 1 bis 22 als freie Base oder ein nicht-toxisches pharmazeutisch akzeptables sauers Anlagerungssalz davon, in Verbindung mit einem pharmazeutisch akzeptablen inertes Trägerstoff.

24. Verbindung nach einem der Ansprüche 1 bis 22 als freie Base oder als nicht-toxisches pharmazeutisch akzeptables saures Anlagerungssalz davon zum Gebruach in der Therapie als antihypertensives, geschwürhemmendes, diuretisches, sedatives, analgetisches, entzündungshemmendes oder ruhigstellendes Mittel.

25. 4-(2', 6'-Dimethylbenzyl)Imidazol, 4-(2', 3'-Dimethylbenzyl)Imidazol, 4-(2'-Methylbenzyl)-Imidazol, 4-(2', 6'-Dichlorobenzyl)Imidazol, 4-[α-(2',6'-Dimethylphenyl)]Hydroxymethyl-Imidazol oder 4-[α-(2'-Methoxyphenyl)]Hydroxymethyl-Imidazol als freie Base oder nicht-toxisches pharmazeutisch akzeptables saures Anlagerungssalz davon für den Gebrauch in der Therapie zur Behandlung von erhöhtem Blutdruck.

26. 4-(2', 6'-Dimethylbenzyl)Imidazol, 4-(2', 3'-Dimethylbenzyl)Imidazol, 4-(2', 4'-Dimethylbenzyl)Imidzol, 4-(2'-Äthylbenzyl)Imidazol, 4-(2'-Methylbenzyl)Imidazol, 4-(3'-Methylbenzyl)-Imidazol, 4-(2', 4', 6'-Trimethylbenzyl)Imidazol, 4-(2'-Chlorobenzyl)Imidazol oder 4-(2', 6'-Dichlorobenzyl)Imidazol als freie Base oder nicht-toxisches pharmazeutisch akzeptables saures Anlagerungssalz davon zum Gebrauch in der Therapie für die Behandlung von geschwürigen Zuständen.

27. 4-[α-(2', 3'-Dimethylphenyl)]Hydroxymethyl-Imidazol, 4-[α-(2', 6'-Dimethylphenyl)]-Hydroxymethyl-Imidazol, 4-[α-(2-Äthylphenyl)]Hydroxy-Imidazol, 4-[α-(2'-Methoxyphenyl)]Hydroxymethyl-Imidazol, 4-(2', 3'-Dimethylbenzyl)Imidazol, 4-(2', 4'-Dimethylbenzyl)Imidazol, 4-(2', 6'-Dimethylbenzyl)Imidazol, 4-(2'-Methylbenzyl)Imidazol oder 4-[α-(2', 6'-Dimethylphenyl)]Äthoxymethyl-Imidazol als freie Base oder als nicht-toxisches pharmazeutisch akzeptables saures Anlagerungssalz davon für den Gebrauch in der Therapie als Diuretikum.

28. 4-(2',4'-Dimethylbenzyl)Imidazol, 4-(2',3'-Dimethylbenzyl)Imidazol, 4-(3'-Methylbenzyl)-Imidazol, 4-(2', 4', 6'-Trimethylbenzyl)Imidazol, 4-(2'-Äthylbenzyl)Imidazol, 4-(3'-Methoxybenzyl)-Imidazol, 4-(2'-Chlorobenzyl)Imidazol, 4-[α-(2', 3'-Dimethylphenyl)]Hydroxymethyl-Imidazol, 4-[α-(2'-

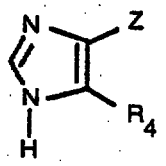
Methoxyphenyl)Hydroxymethyl-Imidazol oder 5-Methyl-4-(2', 6'-Dimethylbenzyl)Imidazol als freie Base oder nicht-toxisches pharmazeutisch akzeptables saures Anlagerungssalz davon zum Gebrauch in der Therapie als sedativer Wirkstoff.

29. 4-(2', 3'-Dimethylbenzyl)Imidazol, 4-(2', 4'-Dimethylbenzyl)Imidazol, 4-(2'-Methylbenzyl)-Imidazol, 4-(3'-Methylbenzyl)Imidazol, 4-(2'-Chlorobenzyl)Imidazol,
4-[α-(2', 4'-Dimethylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(2', 3'-Dimethylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(2'-Methylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(3'-Methylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(4'-Methylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(2'-Äthylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(2'-Methoxyphenyl)]Hydroxymethyl-Imidazol,
4-[α-(3'-Methoxyphenyl)]Hydroxymethyl-Imidazol,
4-[α-(4'-Methoxyphenyl)]Hydroxymethyl-Imidazol,
4-[α-(2', 6'-Dimethylphenyl)]Methoxymethyl-Imidazol,
4-[α-(2', 6'-Dimethylphenyl)]Äthoxymethyl-Imidazol,
5-Methyl-4-(2'-Methylbenzyl)Imidazol oder 5-Methyl-4-[α-(2', 6'-Dimethylphenyl)]Hydroxymethyl-Imidazol als freie Base oder nicht-toxisches pharmazeutisch akzeptables saures Anlagerungssalz davon, zum Gebrauch in der Therapie als analgetischer Wirkstoff.

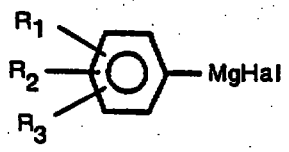
30. 4-(2', 4'-Dimethylbenzyl)Imidazol 4-(3'-Methylbenzyl)Imidazol, 4-[α-(2', 3'-Dimethylphenyl)]-Hydroxymethyl-Imidazol,
4-[α-(2'-Methylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(3'-Methylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(4'-Methylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(2'-Äthylphenyl)]Hydroxymethyl-Imidazol,
4-[α-(2'-Methoxyphenyl)]Hydroxymethyl-Imidazol,
4-[α-(3'-Methoxyphenyl)]Hydroxymethyl-Imidazol,
4-[α-(2', 6'-Dimethylphenyl)]Methoxymethyl-Imidazol,
4-[α-(2', 6'-Dimethylphenyl)]Äthoxymethyl-Imidazol,
4-(4'-Methylbenzoyl)Imidazol,
5-Methyl-4-(2'-Methylbenzyl)Imidazol
5-Methyl-4-[α-(2', 6'-Dimethylphenyl)]Hydroxymethyl-Imidazol,
5-Methyl-4-[α-(2'-Methylphenyl)]Hydroxymethyl-Imidazol oder
5-Methyl-4-(2'-Methylbenzoyl)Imidazol als freie Base oder als nicht-toxisches pharmazeutisch akzeptables saures Anlagerungssalz davon zum Gebrauch in der Therapie als entzündungshemmender Wirkstoff.

31. 4-(2', 3'-Dimethylbenzyl)Imidazol,
4-(2'-Chlorobenzyl)Imidazol,
4-(2', 4', 6'-Trimethylbenzyl)Imidazol,
4-(2', 6'-Dimethylbenzyl)Imidazol, oder
4-(3'-Methylbenzyl)Imidazol als freie Base oder als nicht-toxisches pharmazeutisch akzeptables saures Anlagerungssalz davon zum Gebrauch in der Therapie als ruhigstellender Wirkstoff.

32. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, in der —X— —CO— oder —CHOH— ist, welches die Reaktion eines Imidazol-Derivats der Formel

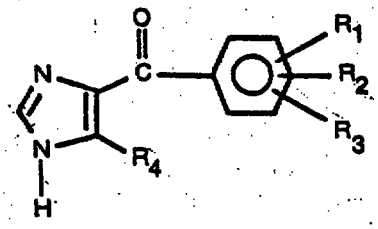


wobei R_4 wie in Anspruch 1 definiert ist und Z —CHO oder —COOR (COOR ist eine Ester-Gruppe) ist, mit einem Phenylmagnesiumhalid der Formel



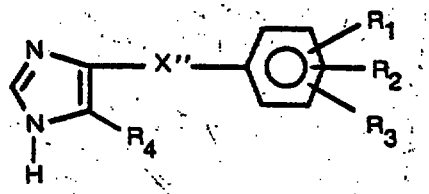
wobei R_1, R_2 und R_3 wie in Anspruch 1 definiert sind und Hal ein Halogenatom ist, aufweist.

33. Verfahren für die Herstellung einer Verbindung nach Anspruch 1, bei der X —CHOH— ist, welches die Reduzierung einer Verbindung der Formel

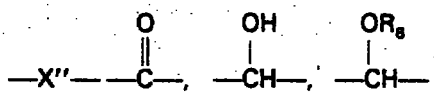


wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind, aufweist.

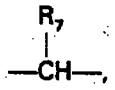
34. Verfahren für die Herstellung einer Verbindung nach Anspruch 1, bei der X —CH_2— ist, welches die Reduzierung einer Verbindung der Formel



wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind und

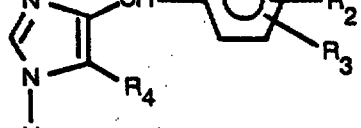


(wobei R_6 wie in Anspruch 1 definiert ist) oder



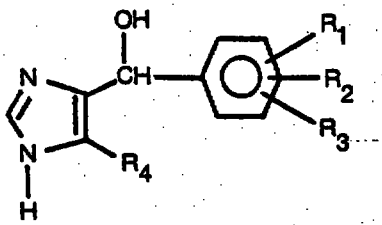
wobei R_7 eine hydrogenolysierbare Gruppe ist, ist, aufweist.

35. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, bei der X —CH_2OR_6— ist, welches die Reaktion einer Verbindung der Formel



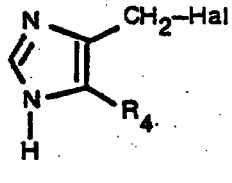
wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind mit einer Verbindung der Formel R_6OH, wobei R_6 wie in Anspruch 1 definiert ist in Gegenwart von Säure aufweist.

36. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, bei der X —CO— ist, welches Oxidierung einer Verbindung der Formel

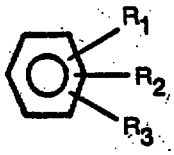


wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind, aufweist.

37. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei X —CH_2— ist, welches die Reaktion eines 4-Halomethyl-Imidazols der Formel

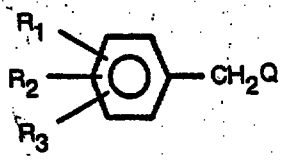


wobei R_4 wie in Anspruch 1 definiert ist und Hal ein Halogenatom, ist, mit einem Benzol-Derivat der Formel

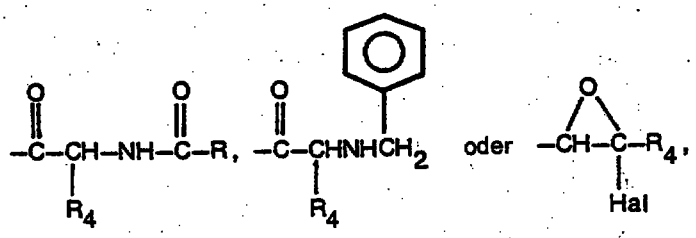


wobei R_1, R_2 und R_3 wie in Anspruch 1 definiert sind, aufweist.

38. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei X —CH_2— ist, welches die Reaktion von Formamid mit einer Verbindung der Formel

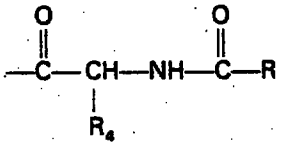


wobei R_1, R_2 und R_3 wie in Anspruch 1 definiert sind und Q ein Radikal der Formel



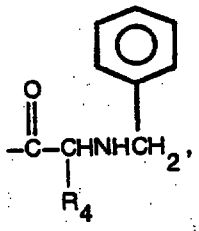
wobei Hal ein Halogenatom ist, R_4 wie in Anspruch 1 definiert ist und R eine substituierte oder nichtsubstituierte Alkyl-, Aralkyl- oder Aryl-Gruppe ist, unter der Voraussetzung, daß

(a) wenn Q



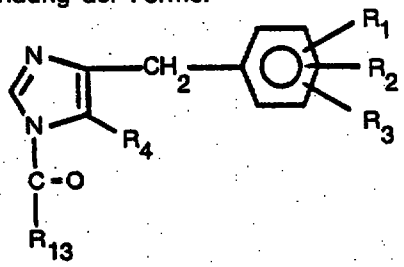
ist, die Reaktion mit Formamid von einer Behandlung des Zwischenproduktes mit Säure gefolgt wird und

(b) wenn Q



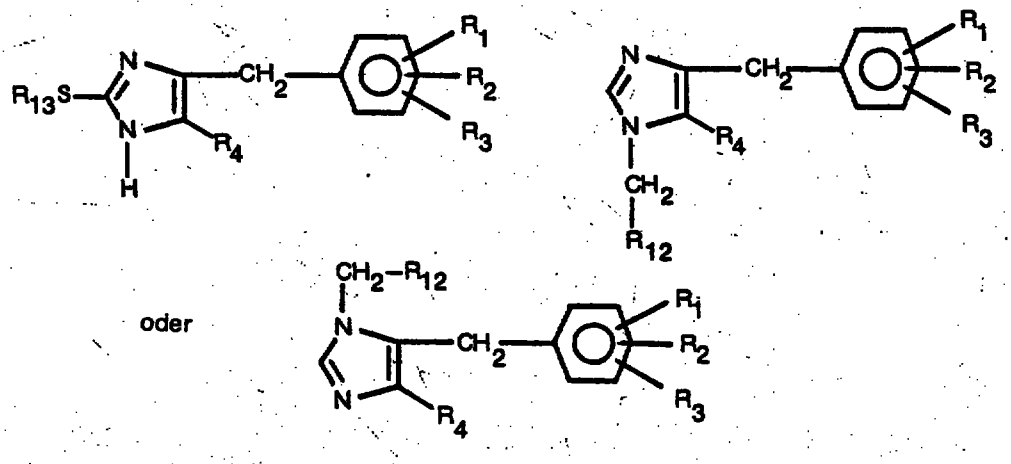
ist, die Reaktion mit Formamid von einer Hydrogenisierung des Zwischenproduktes gefolgt wird, aufweist.

39. Verfahren für die Herstellung einer Verbindung nach Anspruch 1, wobei X —CH_2— ist, welches Hydrolyse einer Verbindung der Formel



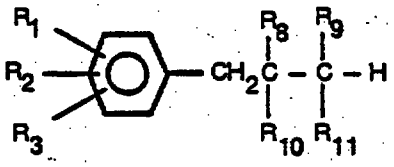
wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind und R_{13} ein Alkyl mit 1 bis 7 Kohlenstoffatomen oder Aryl mit 6 bis 10 Kohlenstoffatomen ist, aufweist.

40. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei X —CH_2— ist, welches Hydrogenolyse einer Verbindung der Formel

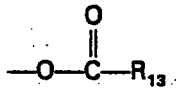


wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind, R_{13} eine Alkyl mit 1 bis 7 Kohlenstoffatomen oder Aryl mit 6 bis 10 Kohlenstoffatomen ist und R_{12} ein Aryl ist, aufweist.

41. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei X —CH_2— ist, welches die Reaktion eines Ausgangsmaterials der Formel

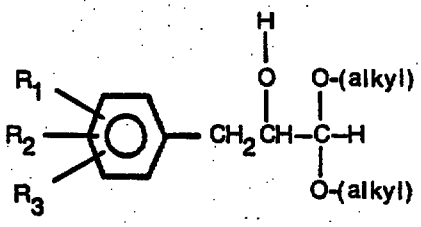


wobei R_1, R_2 und R_3 wie in Anspruch 1 definiert sind und R_8, R_9, R_{10} und R_{11} welche gleich oder verschiedenartig sind, jeweils Wasserstoff, Hydroxy, Halogen, Amino, —O-Alkyl mit 1 bis 7 Kohlenstoffatomen oder



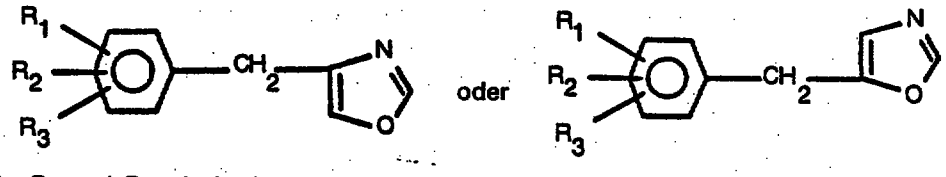
(wobei R_{13} ein Alkyl mit 1 bis 7 Kohlenstoffatomen oder Aryl mit 6 bis 10 Kohlenstoffatomen ist) sind, oder wobei R_8 und R_{10} kombiniert werden können zur Bildung einer Keto-Gruppe oder R_9 und R_{11} kombiniert werden können zur Bildung einer Keto-Gruppe, oder sowohl R_8 und R_{10} und R_9 und R_{11} gleichzeitig Keto-Gruppen bilden können, mit NH_3 + CH_2O (oder eine Quelle für Ammoniak und Formaldehyd), HN=CH—NH_2, Ammoniumformat oder Formamid zur Bildung des entsprechenden Imidazols, aufweist.

42. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei X —CH_2— ist, welches die Reaktion eines Ausgangsmaterials der Formel



wobei die Alkyl-Gruppen 1 bis 7 Kohlenstoffatome enthalten und R_1, R_2 und R_3 wie in Anspruch 1 definiert sind, mit Formamid zur Bildung des entsprechenden Imidazols aufweist.

43. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei X —CH_2— ist, welches die Reaktion von Formamid mit einem Oxazol der Formel

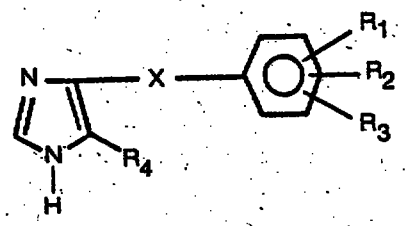


wobei R_1, R_2 und R_3 wie in Anspruch 1 definiert sind, einschließt.

44. Verbindung nach Anspruch 1, hergestellt nach einem Verfahren nach einem der Ansprüche 32 bis 43.

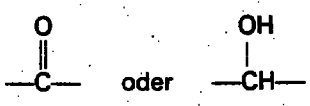
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines therapeutisch wirksamen Imidazol-Derivats der Formel:

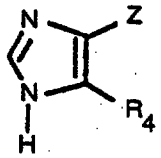


(I)

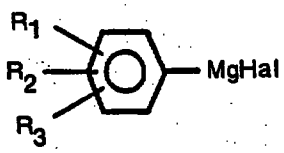
wobei R_1, R_2 und R_3, die gleich oder verschieden sein können, jeweils aus Wasserstoff, Chlor, Brom, Fluor, Methyl, Äthyl, Methoxy, Amino, Hydroxy und Nitro gewählt werden aber nicht alle Wasserstoff sind, R_4 Wasserstoff oder Alkyl mit 1 bis 7 Kohlenstoffatomen, X



ist; oder ein nichttoxisches pharmazeutisch akzeptables saures Anlagerungssalz davon, welches die Reaktion eines Imidazol-Derivats der folgenden Formel einschließt:

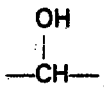


wobei R_4 wie oben definiert ist und Z —CHO oder —COOR (—COOR ist ein Ester-Gruppe) ist, mit einem Phenylmagnesiumhalid der Formel:

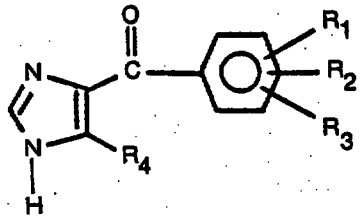


wobei R_1, R_2 und R_3 wie oben definiert sind und Hal ein Halogenatom ist.

2. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß X

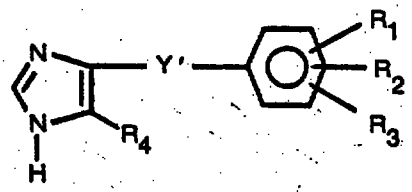


ist, welches das Reduzieren einer Verbindung der Formel

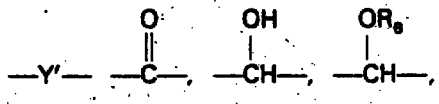


einschließt, wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind.

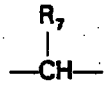
3. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß —X— —CH_2 ist und, wenn R_1 2-Methyl ist, R_2 5-Methyl ist und wenn R_3 Wasserstoff ist, R_4 nicht Methyl ist, das das Reduzieren einer Verbindung der Formel



einschließt, wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind und

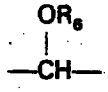


(wobei R_8 Alkyl mit 1 bis 7 Kohlenstoffatomen oder Phenyl ist) oder

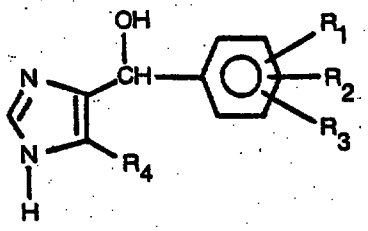


(wobei R_7 eine hydrogenolysierbare Gruppe ist) ist.

4. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß X



ist, wobei R_8 ein Alkyl mit 1 bis 7 Kohlenstoffatomen oder Phenyl ist, welches die Reaktion einer Verbindung der Formel

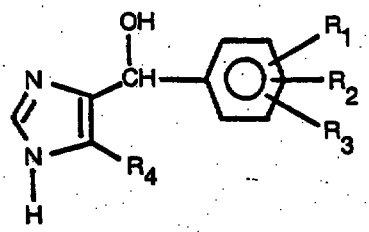


wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel R_8OH, wobei R_8 wie oben definiert in Anwesenheit von Säure einschließt.

5. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß —X—

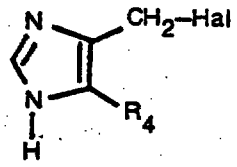


ist, das das Oxidieren einer Verbindung der Formel

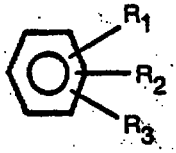


wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind, einschließt.

6. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß X —CH_2— ist und wenn R_1 2-Methyl ist, R_2 5-Methyl ist und wenn R_3 Wasserstoff ist, R_4 nicht Methyl ist, welches die Reaktion eines 4-Halomethyl-Imidazols der Formel

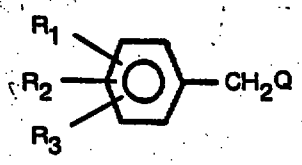


wobei R_4 wie in Anspruch 1 definiert ist und Hal ein Halogenatom ist, mit einem Benzol-Derivat der Formel

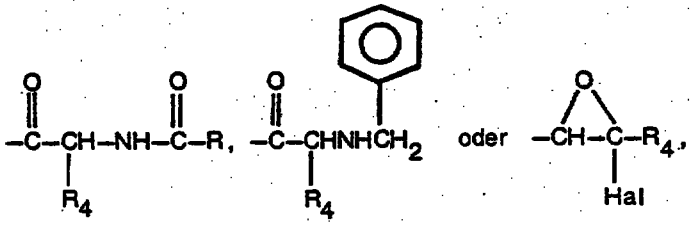


wobei R_1 R_2 und R_3 wie in Anspruch 1 definiert sind, einschließt.

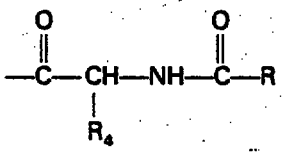
7. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß X —CH_2— ist und wenn R_1 2-Methyl ist, R_2 5-Methyl ist und wenn R_3 Wasserstoff ist, R_4 nicht Methyl ist, welches Reaktion von Formamid mit einer Verbindung der Formel



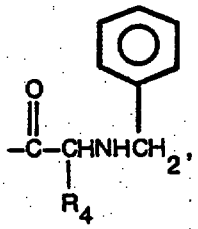
wobei R_1, R_2 und R_3 wie in Anspruch 1 definiert sind und Q



sind, (wobei Hal ein Halogenatom ist)
R_4 wie in Anspruch 1 definiert ist, und R eine substituierte oder nichtsubstituierte Alkyl-, Aralkyl- oder Aryl-Gruppe ist, vorausgesetzt, daß
a) wenn Q

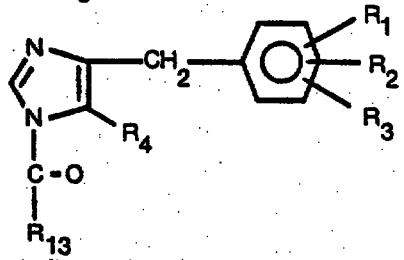


ist, die Reaktion mit Formamid von einer Behandlung des Zwischenproduktes mit Säure gefolgt wird und
b) wenn Q



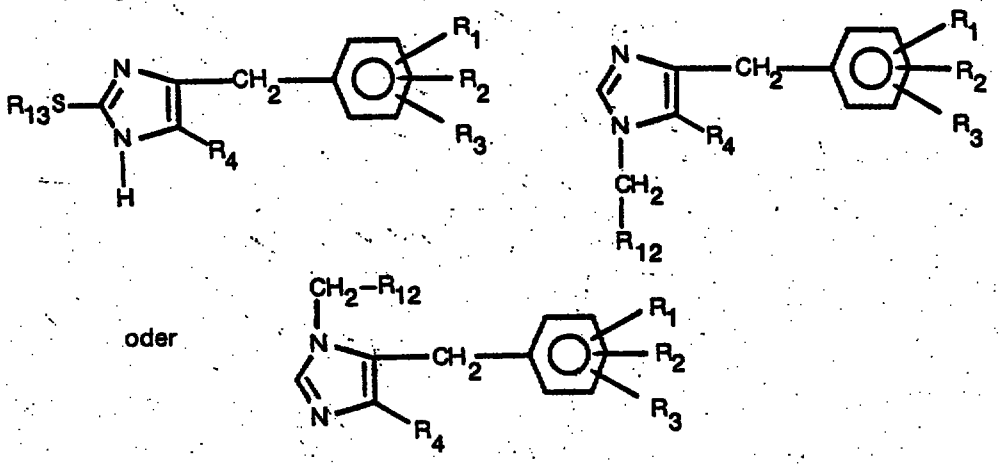
ist, die Reaktion mit Formamid von einer Hydrierung des Zwischenproduktes gefolgt wird, einschließt.

8. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß X —CH_2— ist und wenn R_1 2-Methyl ist, R_2 5-Methyl ist und wenn R_3 Wasserstoff ist, R_4 nicht Methyl ist, welches die Hydrolyse einer Verbindung der Formel



wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind und R_6 ein Alkylradikal mit 1 bis 7 Kohlenstoffatomen oder Aryl mit 6 bis 10 Kohlenstoffatomen ist, einschließt.

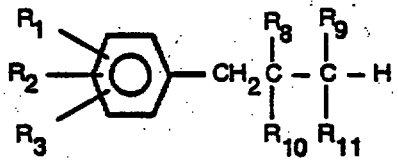
9. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß X —CH_2— ist und wenn R_1 2-Methyl ist, R_2 5-Methyl ist und wenn R_3 Wasserstoff ist, R_4 nicht Methyl ist, welcher die Hydrogenolyse einer Verbindung der Formel



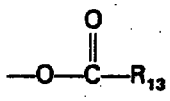
oder

wobei R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind, R_{13} ein Alkyl mit 1 bis 7 Kohlenstoffatomen oder Aryl mit 6 bis 10 Kohlenstoffatomen und R_{12} ein Aryl ist, einschließt.

10. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß R_4 Wasserstoff und X CH_2 ist, welches die Reaktion eines Ausgangsmateriales der Formel

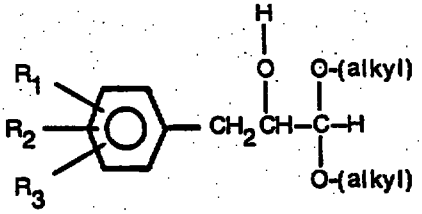


wobei R_1, R_2 und R_3 wie oben definiert und R_8, R_9, R_{10} und R_{11}, die gleich oder verschieden sein können, jeweils Wasserstoff, Hydroxy, Halogen, Amino, —O-Alkyl mit 1 bis 7 Kohlenstoffatomen oder



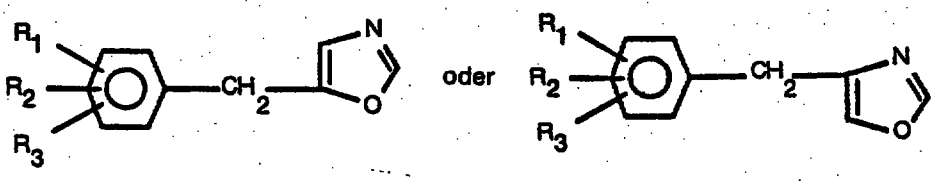
(wobei R_{13} ein Alkyl mit 1 bis 7 Kohlenstoffatomen oder Aryl mit 6 bis 10 Kohlenstoffatomen ist) oder R_8 und R_{10} kombiniert werden zur Bildung einer Keto-Gruppe oder R_9 und R_{11} zur Bildung einer Keto-Gruppe kombiniert werden oder sowohl R_8 und R_{10} und R_9 und R_{11} gleichzeitig Keto-Gruppen bilden) mit NH_3+CH_2O (oder eine Quelle für Ammoniak und Formaldehyd), HN=CH—NH_2, Ammoniumformat oder Formamid, einschließt.

11. Verfahren für die Herstellung einer wie in Anspruch 1 definierten Verbindung, außer daß R_4 Wasserstoff ist und X CH_2 ist, welches die Reaktion einer Verbindung der Formel



wobei die Alkyl-Gruppen 1 bis 7 Kohlenstoffatome jeweils enthalten und R_1, R_2 und R_3 wie in Anspruch 1 definiert sind, mit Formamid einschließt.

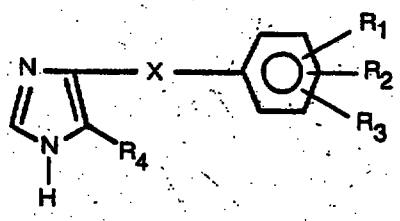
12. Verfahren für die Herstellung einer wie in Anspruch 1 beanspruchten Verbindung, außer daß R_4 Wasserstoff ist und X —CH_2— ist, welches die Reaktion von Formamid mit einem Oxazol der formel



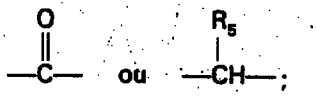
wobei R_1, R_2 und R_3 wie in Anspruch 1 definiert sind, einschließt.

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

1. Composé de formule:



dans laquelle R_1, R_2 et R_3, qui peuvent être identiques ou différents, sont choisis chacun parmi l'hydrogène et les groupes chloro, bromo, fluoro, méthyle, éthyle, méthoxy, amino, hydroxyl et nitro mais ne sont pas tous des atomes d'hydrogène; R_4 est un atome d'hydrogène ou un radical alkyle de 1 à 7 atomes de carbone; X représente le groupe



dans lequel R_5 est un atome d'hydrogène, un radical hydroxyle ou OR_6 et R_6 est un radical alkyle de 1 à 7 atomes de carbone ou phényle; et leurs sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables, et leurs mélanges; à la condition que lorsque R_1 est le radical 2-méthyle, R_2 est le radical 5-méthyle, R_3 est l'hydrogène et R_4 est le radical méthyle, alors —X— soit autre que $—CH_2—$.

2. Composé selon la revendication 1, dans lequel X est $—CH_2—$, —CHOH—, $—CH(OCH_3)—$, $—CH(OC_2H_5)—$, ou —CO—; R_1, R_2 et R_3 représentent chacun un atome d'hydrogène ou un radical chloro, bromo, fluoro, méthyle, éthyle, hydroxyle ou méthoxy mais ne sont pas tous des atomes d'hydrogène et R_4 est un atome d'hydrogène ou le radical méthyle.

3. Composé selon les revendications 1 ou 2, dans laquelle R_1 est unsubstituant sur la position 2, 3 ou 4, et R_2 et R_3 sont des atomes d'hydrogène, ou bien R_1 et R_2 sont des substituants sur les positions 2, 3, 2,4 ou 2,6 et R_3 est un atome d'hydrogène, ou bien R_1, R_2 et R_3 sont des substituants sur les positions 2, 4, 6.

4. 4-[α-(2′-méthylphényl)]hydroxyméthylimidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

5. 4-[α-(2′,6′-diméthylphényl)]hydroxyméthylimidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

6. 4-[α-(3′-méthylphényl)]hydroxyméthylimidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

7. 4-[α-(4′-méthylphényl)]hydroxyméthylimidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

8. 4-[α-(2′,3′-diméthylphényl)]hydroxyméthylimidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

9. 4-[α-(2′-éthylphényl)]hydroxyméthylimidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

10. 4-[α-(2′-méthoxyphényl)]hydroxyméthylimidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

11. 4-[α-(3′-méthoxyphényl)]hydroxyméthylimidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

12. 4-(2′-méthylbenzyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

13. 4-(2′,6′-diméthylbenzyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

14. 4-(3′-méthylbenzyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

15. 4-(2′,4′-diméthylbenzyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

16. 4-(2′,3′-diméthylbenzyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

17. 4-(2′-éthylbenzyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

18. 4-(2′,4′,6′-triméthylbenzyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

19. 4-(2',6'-dichlorobenzyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

20. 4-(2'-chlorobenzyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

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

22. 4-(2',6'-diméthylbenzoyl)imidazole et ses sels d'addition avec des acides, non-toxiques, pharmaceutiquement acceptables.

23. Composition pharmaceutique comprenant un composé tel que revendiqué dans l'une quelconque des revendications 1 à 22 sous forme d'une base libre ou d'un de ses sels d'addition avec des acides, non-toxique, pharmaceutiquement acceptable, en combinaison avec un véhicule inerte pharmaceutiquement acceptable.

24. Composé tel que revendiqué dans l'une quelconque des revendications 1 à 22 sous forme d'une base libre ou d'un de ses sels d'addition avec des acides, non-toxique, pharmaceutiquement acceptable pour utilisation en thérapie comme agent antihypertensif, anti-ulcéreux, diurétique, sédatif, analgésique, anti-inflammatoire ou tranquillisant.

25. 4-(2',6'-diméthylbenzyl)imidazole, 4-(2',3'-diméthylbenzyl)imidazole, 4-(2'-méthylbenzyl)-imidazole, 4-(2',6'-dichlorobenzyl)imidazole, 4-[α-(2',6'-diméthylphényl)]hydroxyméthylimidazole ou 4-[α-(2'-méthoxyphényl)]hydroxyméthylimidazole, sous forme de base libre ou d'un de leurs sels d'addition avec des acides, non-toxique, pharmaceutiquement acceptable, pour utilisation en thérapie de traitement de l'hypertension.

26. 4-(2',6'-diméthylbenzyl)imidazole, 4-(2',3'-diméthylbenzyl)imidazole, 4-(2',4'-diméthylbenzyl)imidazole, 4-(2'-éthylbenzyl)imidazole, 4-(2'-méthylbenzyl)-imidazole, 4-(3'-méthylbenzyl)-imidazole, 4-(2',4',6'-triméthylbenzyl)imidazole, 4-(2'-chlorobenzyl)imidazole ou 4-(2',6'-dichlorobenzyl)imidazole, sous forme de base libre ou d'un de leurs sels d'addition avec des acides, non-toxique, pharmaceutiquement acceptable, pour utilisation en thérapie de traitement d'états ulcéreux.

27. 4-[α-(2',3'-diméthylphényl)]hydroxyméthylimidazole, 4-[α-(2',6'-diméthylphényl)]hydroxyméthylimidazole, 4-[α-(2'-éthylphényl)]hydroxyméthylimidazole, 4-[α-(2'-méthoxyphényl)]hydroxyméthylimidazole, 4-(2',3'-diméthylbenzyl)imidazole, 4-(2',4'-diméthylbenzyl)imidazole, 4-(2',6'-diméthylbenzyl)imidazole, 4-(2'-méthylbenzyl)imidazole, ou 4-[α-(2',6'-diméthylphényl)]éthoxyméthylimidazole, sous forme de base libre ou d'un de leurs sels d'addition avec des acides, non-toxique, pharmaceutiquement acceptable, pour utilisation en thérapie comme un diurétique.

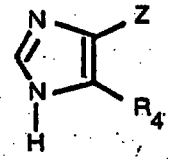
28. 4-(2',4'-diméthylbenzyl)imidazole, 4-(2',3'-diméthylbenzyl)imidazole, 4-(3'-méthylbenzyl)-imidazole, 4-(2',4',6'-triméthylbenzyl)imidazole, 4-(2'-éthylbenzyl)imidazole, 4-(3'-méthoxybenzyl)-imidazole, 4-(2'-chlorobenzyl)imidazole, 4-[α-(2',3'-diméthylphényl)]hydroxyméthylimidazole, 4-[α-(2'-méthoxyphényl)]hydroxyméthylimidazole, ou 5-méthyl-4-(2',6'-diméthylbenzyl)imidazole, sous forme des base libre ou d'un de leurs sels d'addition avec des acides, non-toxique, pharmaceutiquement acceptable, pour utilisation en thérapie comme agent sédatif.

29. 4-(2',3'-diméthylbenzyl)imidazole, 4-(2',4'-diméthylbenzyl)imidazole, 4-(2'-méthylbenzyl)-imidazole, 4-(3'-méthylbenzyl)imidazole, 4-(2'-chlorobenzyl)imidazole, 4-[α-(2',4'-diméthylphényl)]-hydroxyméthylimidazole, 4-[α-(2',3'-diméthylphényl)]hydroxyméthylimidazole, 4-[α-(2'-méthylphényl)]hydroxyméthylimidazole, 4-[α-(3'-méthylphényl)]hydroxyméthylimidazole, 4-[α-(4'-méthylphényl)]hydroxyméthylimidazole, 4-[α-(2'-éthylphényl)]hydroxyméthylimidazole, 4-[α-(2'-méthoxyphényl)]hydroxyméthylimidazole, 4-[α-(3'-méthoxyphényl)]hydroxyméthylimidazole, 4-[α-(4'-méthoxyphényl)]hydroxyméthylimidazole, 4-[α-(2',6'-diméthylphényl)]méthoxyméthylimidazole, 4-[α-(2',6'-diméthylphényl)]éthoxyméthylimidazole, 5-méthyl-4-(2'-méthylbenzyl)imidazole ou 5-méthyl-4-[α-(2'-6'-diméthylphényl)]hydroxyméthylimidazole, sous forme de base libre ou d'un de leurs sels d'addition avec des acides, non-toxique, pharmaceutiquement acceptable, pour utilisation en thérapie comme un agent analgésique.

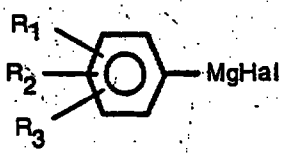
30. 4-(2',4'-diméthylbenzyl)imidazole, 4-(3'-méthylbenzyl)imidazole, 4-[α-(2',3'-diméthylphényl)]hydroxyméthylimidazole, 4-[α-(2'-méthylphényl)]hydroxyméthylimidazole, 4-[α-(3'-méthylphényl)]hydroxyméthylimidazole, 4-[α-(4'-méthylphényl)]hydroxyméthylimidazole, 4-[α-(2'-éthylphényl)]hydroxyméthylimidazole, 4-[α-(2'-méthoxyphényl)]hydroxyméthylimidazole, 4-[α-(3'-méthoxyphényl)]hydroxyméthylimidazole, 4-[α-(2',6'-diméthylphényl)]méthoxyméthylimidazole, 4-[α-(2',6'-diméthylphényl)]éthoxyméthylimidazole, 4-(4'-méthylbenzyl)imidazole, 5-méthyl-4-(2'-méthylbenzyl)-imidazole, 5-méthyl-4-[α-(2',6'-diméthylphényl)]hydroxyméthylimidazole ou 5-méthyl-4-(2'-méthylbenzoyl)imidazole, sous forme de base libre ou d'un de leurs sels d'addition avec des acides, non-toxique, pharmaceutiquement acceptable, pour utilisation en thérapie comme agent anti-inflammatoire.

31. 4-(2',3'-diméthylbenzyl)imidazole, 4-(2'-chlorobenzyl)imidazole, 4-(2',4',6'-triméthylbenzyl)-imidazole, 4-(2',6'-diméthylbenzyl)imidazole, ou 4-(3'-méthylbenzyl)imidazole, sous forme de base libre ou d'un de leurs sels d'addition avec des acides, non-toxique, pharmaceutiquement acceptable, pour utilisation en thérapie comme agent tranquilisant.

32. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel —X— est —CO— ou —CHOH—, qui consiste à faire réagir un dérivé d'imidazole de formule:

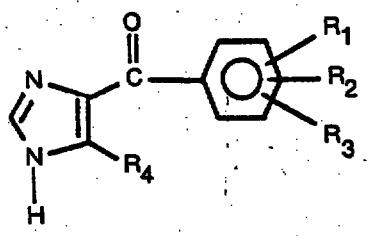


dans laquelle R_4 est tel que défini dans la revendication 1, et Z est —CHO ou —COOR (COOR étant un groupement ester) avec un halogénure de phénylmagnésium de formule:



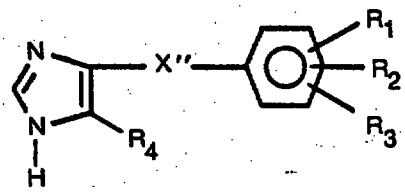
dans laquelle R_1, R_2 et R_3 sont tels que définis dans la revendication 1, et Hal est un atome d'halogène.

33. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est —CHOH—, qui consiste à réduire un composé de formule: le:

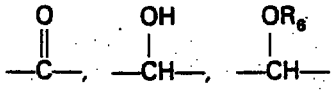


dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1.

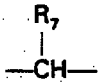
34. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est —CH_2—, qui consiste à réduire un composé de formule:



dans laquelle R_1, R_2, R_3, et R_4 sont tels que définis dans la revendication 1, et —X''— représente un groupe

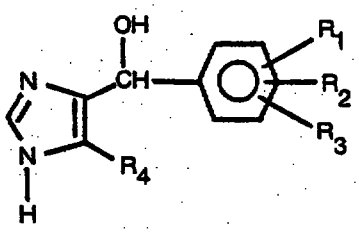


(dans lequel R_6 est tel que défini dans la revendication 1), ou



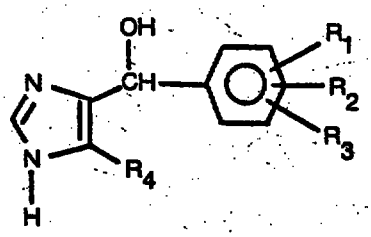
dans lequel R_7 est un groupe hydrogénolysable.

35. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est —CH_2OR_6— qui, consiste à faire réagir un composé de formule:



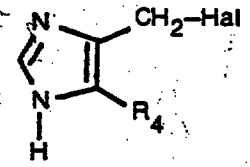
dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1, avec un composé de formule R_6OH dans laquelle R_6 est tel que défini dans la revendication 1, en présence d'un acide.

36. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est —CO—, qui consiste à oxyder un composé de formule:

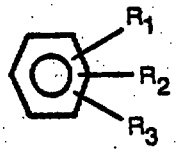


dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1.

37. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est —CH_2—, qui consiste à faire réagir un 4-halogénométhylimidazole de formule:

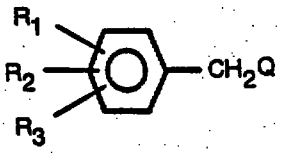


dans laquelle R_4 est tel que défini dans la revendication 1, et Hal est un atome d'halogène, avec un dérivé benzènique de formule:

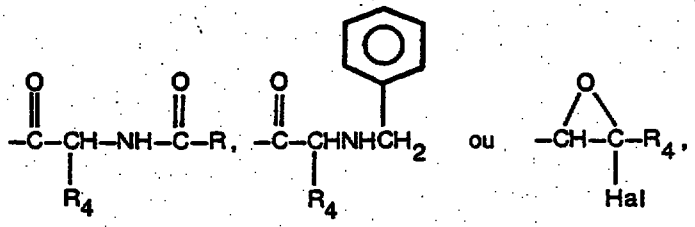


dans laquelle R_1, R_2 et R_3 sont tels que définis dans la revendication 1.

38. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est —CH_2—, qui consiste à faire réagir du formamide avec un composé de formule:

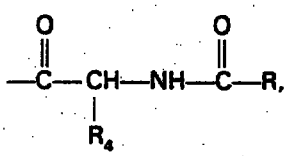


dans laquelle R_1, R_2 et R_3 sont tels que définis dans la revendication 1, et Q est un radical de formule:



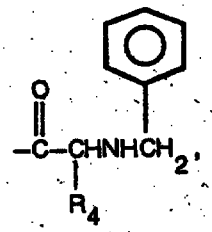
dans laquelle Hal est un atome d'halogène; R_4 est tel que défini dans la revendication 1, et R est un radical alkyle, aralkyle ou aryle substitué ou non-substitué, à la condition que:

(a) quand Q représente



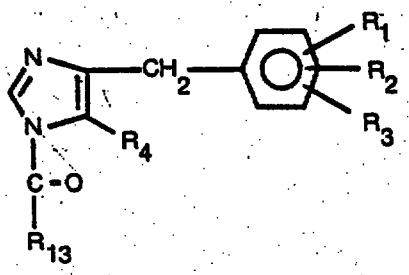
la réaction avec le formamide soit suivie d'un traitement du produit intermédiaire par un acide; et

(b) quand Q représente



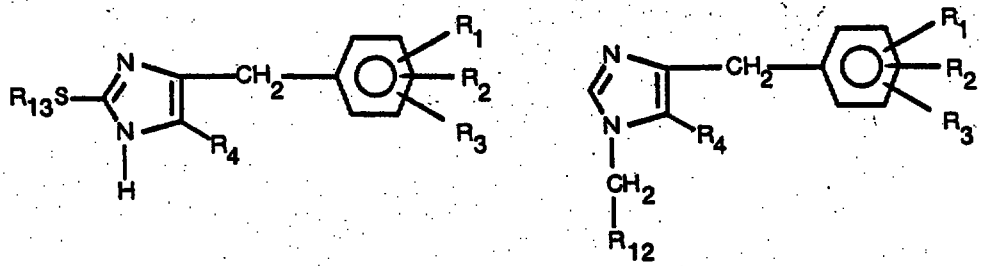
la réaction avec le formamide soit suivie d'une hydrogénation du produit intermédiaire.

39. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est —CH_2—, qui consiste à hydrolyser un composé de formule:

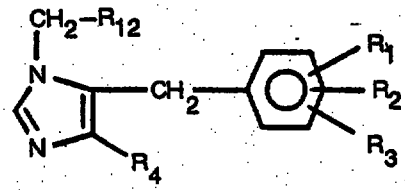


dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1, et R_{13} est un radical alkyle de 1 à 7 atomes de carbone ou aryle de 6 à 10 atomes de carbone.

40. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est —CH_2—, qui consiste à soumettre à l'hydrogénolyse un composé de formule:

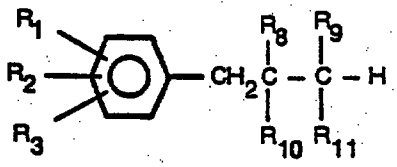


ou

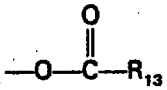


dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1; R_{13} est un radical alkyle de 1 à 7 atomes de carbone ou aryle de 6 à 10 atomes de carbone, et R_{12} est un radical aryle.

41. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est —CH_2—, qui consiste à faire réagir une matière de départ de formule:



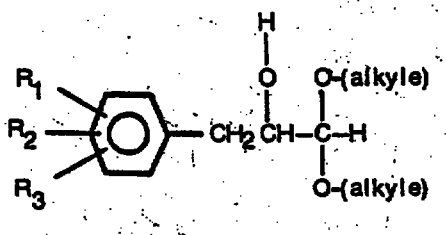
dans laquelle R_1, R_2 et R_3 sont tels que définis dans la revendication 1, et R_8, R_9, R_{10} et R_{11}, qui sont identiques ou différents, représentent chacun un atome d'hydrogène ou d'halogène ou un radical hydroxyle, amino, —O-alkyle contenant 1 à 7 atomes de carbone ou



(dans lequel R_{13} est un radical alkyle de 1 à 7 atomes de carbone ou aryle de 6 à 10 atomes de

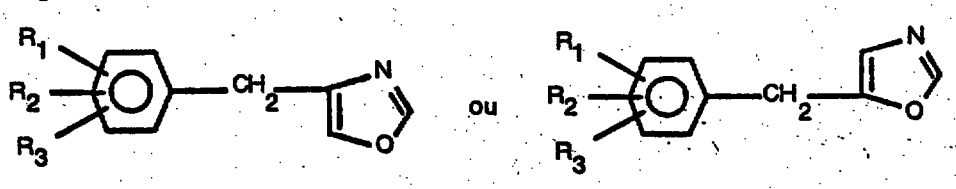
carbone), ou dans laquelle R_8 et R_{10} peuvent être combinés pour former un groupe céto, ou bien R_9 et R_{11} peuvent être combinés pour former un groupe céto, ou bien à la fois R_8 et R_{10} et R_9 et R_{11} peuvent former simultanément des groupes céto; avec NH_3+CH_2O (ou une source d'ammoniac et de formaldéhyde), $HN{=}CH{-}NH_2$, le formiate d'ammonium ou le formamide pour donner l'imidazole correspondant.

42. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est $-CH_2-$, qui consiste à faire réagir une matière de départ de formule:



dans laquelle les radicaux alkyle contiennent 1 à 7 atomes de carbone, et R_1, R_2 et R_3 sont tels que définis dans la revendication 1, avec le formamide pour obtenir l'imidazole correspondant.

43. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, dans lequel X est $-CH_2-$, qui consiste à faire réagir le formamide avec un oxazole de formule:

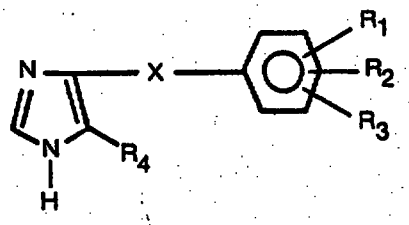


dans laquelle R_1, R_2 et R_3 sont tels que définis dans la revendication 1.

44. Composé tel que revendiqué dans la revendication 1 quand il est préparé par un procédé tel que revendiqué dans l'une quelconque des revendications 32 à 43.

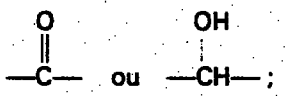
Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un dérivé d'imidazole thérapeutiquement actif de formule:

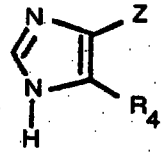


(I)

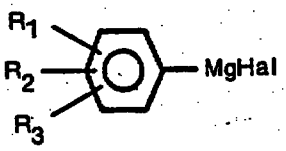
dans laquelle R_1, R_2 et R_3, qui peuvent être identiques ou différents, sont choisis chacun parmi l'hydrogène et les groupes chloro, bromo, fluoro, méthyle, éthyle, méthoxy, amino, hydroxyle et nitro mais ne sont pas tous des atomes d'hydrogène; R_4 est un atome d'hydrogène ou un radical alkyle de 1 à 7 atomes de carbone; X représente le groupe



ou un sel d'addition avec un acide, non-toxique, pharmaceutiquement acceptable de celui-ci; qui consiste à faire réagir un dérivé d'imidazole de formule:

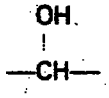


dans laquelle R_4 est tel que défini plus haut, et Z représente —CHO ou —COOR (—COOR étant un groupement ester), avec un halogénure de phénylmagnésium de formule:

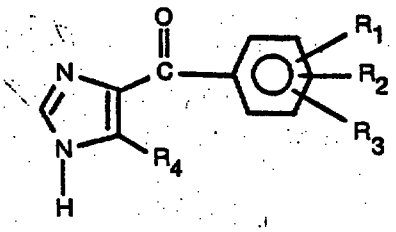


dans laquelle R_1, R_2 et R_3 sont tels que définis plus haut et Hal est un atome d'halogène.

2. Procédé de préparation d'un composé tel que défini dans la revendication 1, sauf que X est

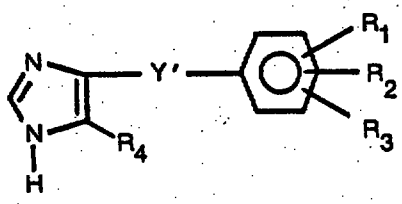


qui consiste à réduire un composé de formule:

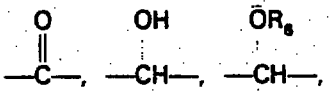


dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1.

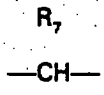
3. Procédé de préparation d'un composé tel que défini dans la revendication 1, sauf que —X— est $—CH_2$ et lorsque R_1 est le radical 2-méthyle, R_2 est le radical 5-méthyle et R_3 est l'hydrogène, R_4 n'est pas un radical méthyle, qui consiste à réduire un composé de formule:



dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dan la revendication 1 et —Y'— est

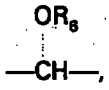


(dans lequel R_6 est un radical alkyle de 1 à 7 atomes de carbone ou phényle) ou

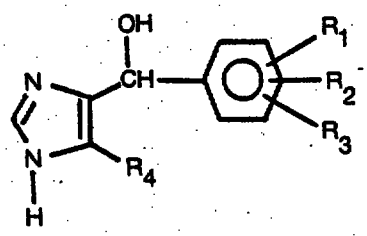


(dans lequel R_7 est un groupe hydrogénolysable).

4. Procédé de préparation d'un composé tel que défini dans la revendication 1, sauf que X est



dans lequel R_6 représente un radical alkyle de 1 à 7 atomes de carbone, ou phényle, qui consiste à faire réagir un composé de formule:

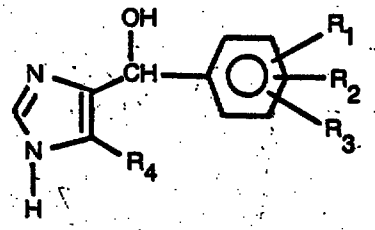


dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1, avec un composé de formule R_6OH dans laquelle R_6 est tel que défini plus haut, en présence d'un acide.

5. Procédé de préparation d'un composé tel que défini dans la revendication 1, sauf que —X— est

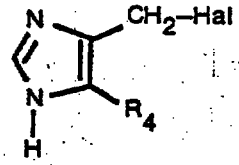


qui consiste à oxyder un composé de formule:

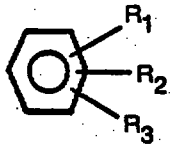


dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1.

6. Procédé de préparation d'un composé tel que défini dans la revendication 1, sauf que X est —CH_2— et lorsque R_1 est le radical 2-méthyle, R_2 est le radical 5-méthyle et R_3 est l'hydrogène, R_4 n'est pas le radical méthyle, qui consiste à faire réagir un 4-halogénométhylimidazole de formule:

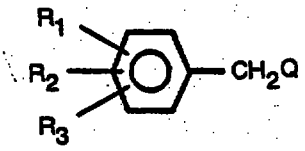


dans laquelle R_4 est tel que défini dans la revendication 1, et Hal est un atome d'halogène, avec un dérivé benzènique de formule:

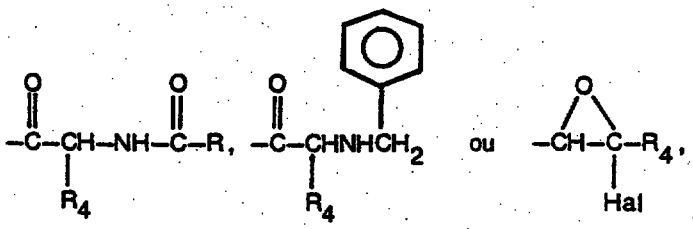


dans laquelle R_1, R_2 et R_3 sont tels que définis dans la revendication 1.

7. Procédé de préparation d'un composé tel que défini dans la revendication 1, sauf que X est —CH_2— et lorsque R_1 est le radical 2-méthyle, R_2 est le radical 5-méthyle, et R_3 est l'hydrogène, R_4 n'est pas la radical méthyle, qui consiste à faire réagir le formamide avec un composé de formule:

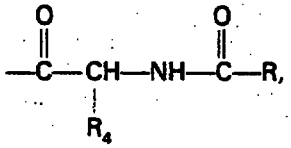


dans laquelle R_1, R_2 et R_3 sont tels que définis dans la revendication 1, et Q représente le groupe

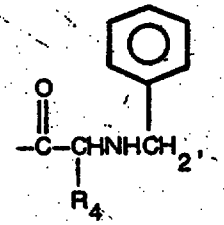


(dans lequel Hal est un atome d'halogène), R_4 est tel que défini dans la revendication 1, et R est un radical alkyle, aralkyle ou aryle substitué ou non substitué, à la condition que:

a) quand Q est

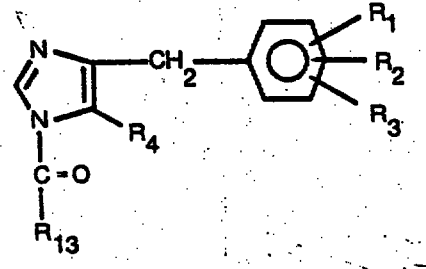


la réaction avec le formamide soit suivie d'un traitement du produit intermédiaire par un acide; et
b) quand Q est



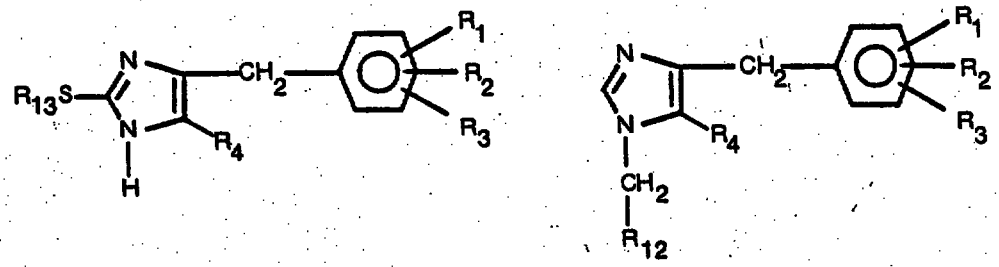
la réaction avec la formamide soit suivie d'une hydrogénation du produit intermédiaire.

8. Procédé de préparation d'un composé tel que défini dans la revendication 1, sauf que X est —CH_2— et lorsque R_1 est le radical 2-méthyle, R_2 est le radical 5-méthyle et R_3 est l'hydrogène, R_4 n'est pas le radical méthyle, qui consiste à hydrolyser un composé de formule:

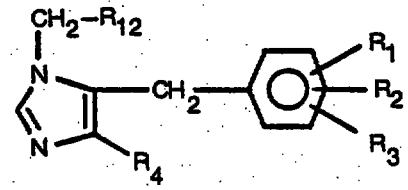


dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1, et R_6 est un radical alkyle de 1 à 7 atomes de carbone, ou aryle de 6 à 10 atomes de carbone.

9. Procédé de préparation d'un composé tel que défini dans la revendication 1, sauf que X est —CH_2— et lorsque R_1 est le radical 2-méthyle, R_2 est le radical 5-méthyle et R_3 est l'hydrogène, R_4 n'est pas le radical méthyle, qui consiste à soumettre à l'hydrogénolyse un composé de formule:

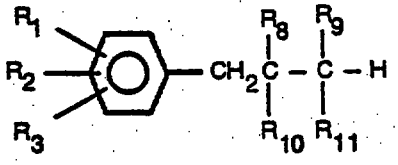


ou

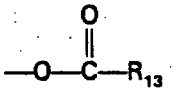


dans laquelle R_1, R_2, R_3 et R_4 sont tels que définis dans la revendication 1, R_{13} est un radical alkyle de 1 à 7 atomes de carbone, ou aryle de 6 à 10 atomes de carbone, et R_{12} est un radical aryle.

10. Procédé de préparation d'un composé tel que défini dans la revendication 1, sauf que R_4 est un atome d'hydrogène, et X est CH_2, qui consiste à faire réagir une matière de départ de formule:

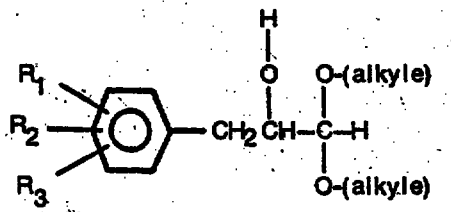


dans laquelle R_1, R_2 et R_3 sont tels que définis ci-dessus, et R_8, R_9, R_{10} et R_{11} qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou d'halogène ou un groupe hydroxyle, amino, —O-alkyle de 1 à 7 atomes de carbone, ou



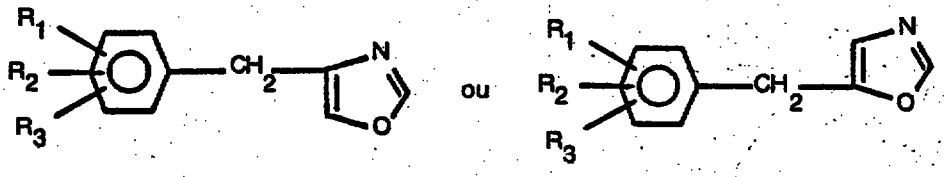
(dans lequel R_{13} est un radical alkyle de 1 à 7 atomes de carbone ou aryle de 6 à 10 atomes de carbone), ou bien R_8 et R_{10} sont combinés pour former un groupe céto, ou bien R_9 et R_{11} peuvent être combinés pour former un groupe céto, ou bien à la fois R_8 et R_{10}, et R_9 et R_{11} peuvent former simultanément des groupes céto; avec NH_3+CH_2O (ou une source d'ammoniac ou de formaldéhyde), $HN{=}CH{-}NH_2$, le formiate d'ammonium ou le formamide.

11. Procédé de préparation d'un composé tel que défini dans la revendication 1, excepté que R_4 est un atome d'hydrogène et X est CH_2, qui consiste à faire réagir un composé de formule:



dans laquelle les radicaux alkyle contiennent chacun 1 à 7 atomes de carbone et R_1, R_2 et R_3 sont tels que définis dans la revendication 1, avec du formamide.

12. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, sauf que R_4 est un atome d'hydrogène et X est $-CH_2-$, qui consiste à faire réagir le formamide avec un oxazole de formule:



dans laquelle R_1, R_2 et R_3 sont tels que définis dans la revendication 1.