

[54] ANTIHYPERTENSIVE SUBSTITUTED  
IMIDAZOLE DERIVATIVES

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[\*] Notice: The portion of the term of this patent subsequent to Jun. 8, 1999 has been disclaimed.

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[30] Foreign Application Priority Data

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[52] U.S. Cl. .... 514/396; 514/397; 514/400; 548/335; 548/336; 548/342

[58] Field of Search ..... 548/335, 336, 341, 342, 548/345; 542/458, 400, 468; 424/273 R; 514/397, 400, 396

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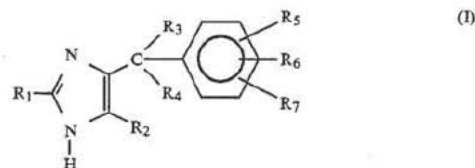
Kelley, J., et al., *J. Pharm. Sci.*, 70(3), 341-343, (1981).

Primary Examiner—Richard A. Schwartz

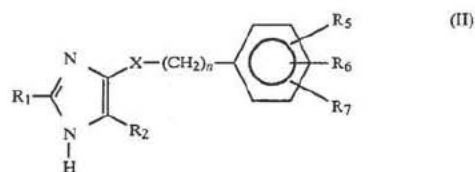
Attorney, Agent, or Firm—Armstrong, Nikaido, Marmelstein & Kubovcik

[57] ABSTRACT

The invention provides novel compounds of the formula:



or



wherein the various substituents are defined herein below. Processes for the preparation of these compounds are described, as are novel pharmaceutical compositions comprising at least one of the compounds or their salts. The compounds and their non-toxic salts exhibit valuable pharmacological activity and are useful in the treatment of mammals, especially as antihypertensive agents. Furthermore, some of the compounds have proved to possess antithrombotic and diuretic activity. Antimycotic and antifungal properties have also been found.

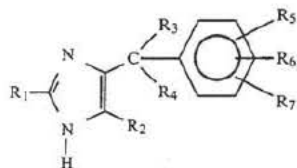
12 Claims, No Drawings

## ANTIHYPERTENSIVE SUBSTITUTED IMIDAZOLE DERIVATIVES

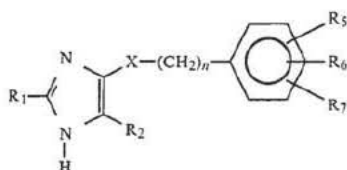
### DESCRIPTION

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

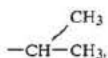
The imidazole derivatives of the present invention have the general formula:



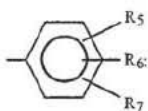
or



wherein R<sub>1</sub> is H, an alkyl of 1 to 4 carbon atoms, e.g. methyl or —CH<sub>2</sub>OH; R<sub>2</sub> is H or CH<sub>3</sub>; R<sub>3</sub> is —CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,



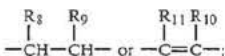
—CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH=CH<sub>2</sub>, or



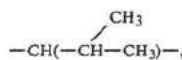
and R<sub>4</sub> is H or OH; or R<sub>3</sub> and R<sub>4</sub> together represent



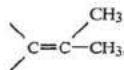
or =CH—CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; X is



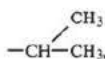
R<sub>5</sub>, R<sub>6</sub>, and R<sub>7</sub>, which can be the same or different are H, —CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>3</sub>, halogen, OH or —OCH<sub>3</sub> or R<sub>5</sub> is hydrogen and R<sub>6</sub> and R<sub>7</sub> together form an —O—CH<sub>2</sub>—O—bridge between two adjacent carbon atoms in the phenyl group; —CHR<sub>8</sub>— is —CH<sub>2</sub>—, —CH(CH<sub>3</sub>)—, —CH(—CH<sub>2</sub>CH<sub>3</sub>)—, —CH(—CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)—,



5 —CH(—CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)— or >C=CH<sub>2</sub>,  
>C=CH—CH<sub>3</sub>, >C=CH—CH<sub>2</sub>CH<sub>3</sub>,



15 >C=CH—CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; R<sub>9</sub> is H, —CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>3</sub>,  
(I) —CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,



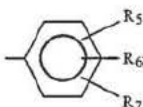
20 —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> or OH; R<sub>10</sub> is H, —CH<sub>3</sub>,  
—CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,

(II) 25 —CH(—CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)—

or —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; R<sub>11</sub> is H, —CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>3</sub>,  
—CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,

30 —CH(—CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)—

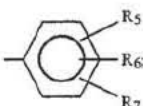
or —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; n is 0 to 4; provided that  
when R<sub>4</sub> is OH, R<sub>1</sub> is H or CH<sub>3</sub> and R<sub>3</sub> is



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then R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are not all simultaneously hydro-

45 gen; when R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> all are hydrogen and R<sub>3</sub> is



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then R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> are not all simultaneously hydrogen;  
R<sub>8</sub> and R<sub>9</sub> are not simultaneously hydrogen; and  
R<sub>11</sub> and R<sub>10</sub> are not simultaneously hydrogen.

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

60 stituted imidazole derivatives.  
The non-toxic pharmaceutically acceptable acid addi-

65 tion salts of these compounds are also within the scope  
of the invention.  
The compounds of the formula (I) and (II) form acid  
addition salts with both organic and inorganic acids.  
They can thus form many pharmaceutically usable acid  
addition salts, as, for instance, chlorides, bromides, sul-

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

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

- 4-[ $\alpha$ , $\alpha$ -bis(2-methylphenyl)hydroxymethyl]imidazole  
 4-[[ $\alpha$ -(2-methylphenyl)]-2-methylbenzyl]imidazole  
 4-( $\alpha$ -phenylbenzyl)-5-methylimidazole  
 4-[[ $\alpha$ -(2,6-dimethylphenyl)]- $\alpha$ -methyl]hydroxymethylimidazole  
 4-[[ $\alpha$ -(2,3-dimethylphenyl)]- $\alpha$ -methyl]hydroxymethylimidazole  
 4-[ $\alpha$ , $\alpha$ -bis(2-methylphenyl)hydroxymethyl]-5-methylimidazole  
 4-[[ $\alpha$ -(2-methylphenyl)]-2-methylbenzyl]-5-methylimidazole  
 4-[( $\alpha$ -methyl)-2,6-dimethylbenzyl]imidazole  
 4-[( $\alpha$ -methyl)-2,3-dimethylbenzyl]imidazole  
 4-[( $\alpha$ -ethyl)-3-methylbenzyl]imidazole  
 4-[( $\alpha$ -butyl)-2,3-dimethylbenzyl]imidazole  
 4-[( $\alpha$ -methyl)-2,3-dimethylbenzyl]-2-methylimidazole  
 4-[( $\alpha$ -propyl)-2-methylbenzyl]imidazole  
 4-[( $\alpha$ -methyl)-2-methylbenzyl]imidazole  
 4-[( $\alpha$ -methyl)-2,5-dimethylbenzyl]imidazole  
 4-[ $\alpha$ -ethyl- $\alpha$ -(3-methylphenyl)-hydroxymethyl]imidazole  
 4-[ $\alpha$ -butyl- $\alpha$ -(2,3-dimethylphenyl)-hydroxymethyl]imidazole  
 4-[ $\alpha$ -methyl- $\alpha$ -(2,3-dimethylphenyl)-hydroxymethyl]-2-methylimidazole  
 4-[ $\alpha$ -propyl- $\alpha$ -(2-methylphenyl)-hydroxymethyl]imidazole  
 4-( $\alpha$ -methyl-2-chlorobenzyl)imidazole  
 4-[ $\alpha$ -methyl- $\alpha$ -(2-methylphenyl)-hydroxymethyl]imidazole  
 4-[ $\alpha$ -methyl- $\alpha$ -(2,5-dimethylphenyl)-hydroxymethyl]imidazole  
 4-[ $\alpha$ , $\alpha$ -bis-(2,3-dimethylphenyl)hydroxymethyl]imidazole  
 4-[ $\alpha$ -(2,3-dimethylphenyl)-2,3-dimethylbenzyl]imidazole  
 4-[( $\alpha$ -ethyl)-2,6-dimethylbenzyl]imidazole  
 4-[( $\alpha$ -ethyl)-2,3-dimethylbenzyl]imidazole  
 1-(4-imidazolyl)-1-(2,3-dimethylphenyl)ethylene  
 1-(4-imidazolyl)-1-(2,6-dimethylphenyl)ethylene  
 1-(4-imidazolyl)-1-(2,3-dimethylphenyl)propene  
 1-(4-imidazolyl)-1-(2,3-dimethylphenyl)pentene

The following specific compounds of formula (II):

- 4-[2-(2,6-dimethylphenyl)-1-methylethyl]imidazole  
 4-[2-(2,6-dimethylphenyl)propyl]imidazole  
 4-[2-(2,3-dimethylphenyl)propyl]imidazole  
 4-[2-(2,6-dimethylphenyl)-1-methylpropyl]imidazole  
 4-[2-(2,6-dimethylphenyl)-2-hydroxyethyl]imidazole  
 4-(2-phenylpropyl)imidazole  
 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]imidazole  
 4-[2-(2,6-dimethylphenyl)-1-propenyl]imidazole  
 4-(2-methyl-4-phenyl-1-butenyl)imidazole  
 4-[2-(4-chlorophenyl)-1-methylpropyl]imidazole  
 4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]imidazole  
 4-[3-(2,6-dimethylphenyl)-2-methyl-1-propenyl]imidazole  
 4-[2-(2,6-dimethylphenyl)-1-ethylethenyl]imidazole  
 4-[2-(2,3-dimethylphenyl)-1-methylethenyl]imidazole  
 4-[2-(2,6-dimethylphenyl)-1-isopropylethenyl]imidazole

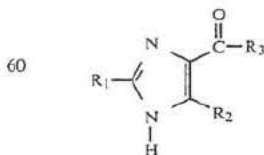
- 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-2-methylimidazole  
 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-5-methylimidazole  
 4-[2-(2,6-dichlorophenyl)-1-methylethenyl]imidazole  
 4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]imidazole  
 4-[3-(2,6-dimethylphenyl)-1-ethyl-1-propenyl]imidazole  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

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

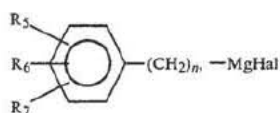
While all of the compounds of formula (I) and (II) essentially satisfy the objectives of the present invention, certain groups of compounds remain preferred. One such preferred group is represented by formula (I) wherein  $R_4$  is hydrogen,  $R_3$  is alkyl and  $R_5$ ,  $R_6$  and  $R_7$ , which can be the same or different, each are hydrogen, methyl, ethyl or halogen. Another preferred group of compounds is represented by formula (II), wherein  $R_5$ ,  $R_6$  and  $R_7$ , which can be the same or different, each are hydrogen, methyl, ethyl or halogen. In such compounds, those in which  $R_1$  is hydrogen or methyl,  $R_2$  is hydrogen or methyl,  $R_8$  or  $R_{11}$  is methyl, ethyl or isopropyl,  $R_9$  and  $R_{10}$  are hydrogen and  $n$  is 0 may be mentioned. Especially the compounds wherein  $n$  is greater than 0 possess valuable antimycotic properties. Especially good antihypertensive properties have been found in compounds of formula (II) wherein  $n$  is 0 and  $X$  is



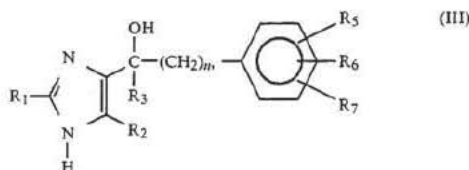
According to the feature of the invention, the compounds of formula (I) wherein  $R_4$  is OH and the compounds of formula (II) are made by a Grignard reaction, in which an imidazolylketone of the formula



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



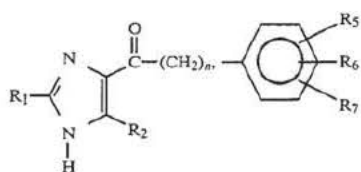
wherein  $R_5$ ,  $R_6$  and  $R_7$  are as defined before,  $n'$  is 0 to 5 and Hal is a halogen atom to give compounds of the formula (III)



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

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

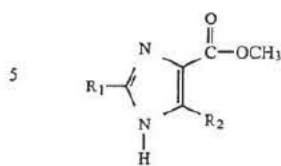
Another process for the preparation of compounds of formula (III) is a Grignard reaction in which a compound of the formula (IV)



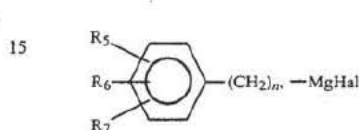
wherein  $R_1$ - $R_7$  and  $n'$  are as before, is reacted with a compound of the formula



wherein  $R_3$  is an alkyl or aryl as defined before and Hal is halogen. Yet another process for the preparation of compounds of formula (III) is a Grignard reaction in which an imidazole carboxylic acid alkyl ester, preferably the methyl ester of the formula



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



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



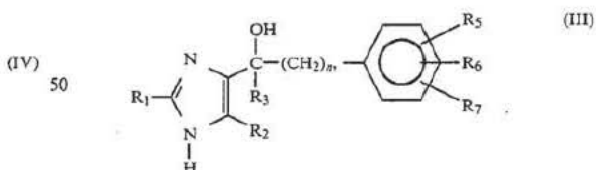
wherein  $R_3$  is as defined before.

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

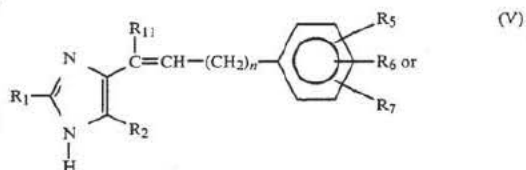
Unsaturated compounds of formula (I) wherein  $R_3$  and  $R_4$  are  $=CH_2$ ,  $=CH-CH_3$ ,  $=CH-CH_2CH_3$ ,



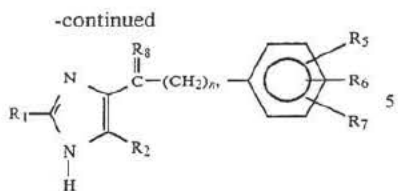
or  $=CH-CH_2CH_2CH_3$  or formula (II) wherein  $R_{10}$  is hydrogen are prepared by dehydrating compounds of formula (III):



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



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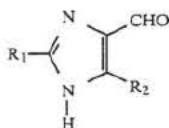


wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, and n and n' are as defined before; R<sub>11</sub> is an alkyl as defined before and R<sub>8</sub> is an alkenyl as defined before.

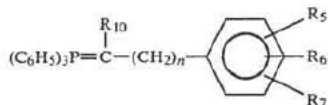
The dehydration is preferably performed by refluxing in an appropriate acidic solution, e.g. concentrated hydrochloric acid or heating for example with potassium-hydrogen sulfate.

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

Compounds of formula (II) wherein R<sub>11</sub> is hydrogen are prepared by a Wittig reaction which comprises reacting an imidazole aldehyde of the formula

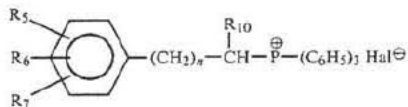


wherein R<sub>1</sub> and R<sub>2</sub> are as before, with an aralkylidene-triphenylphosphorane of the formula:



wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>10</sub> and n are as defined before, to give the unsaturated compounds of formula (II), which in a further step can be reduced to the corresponding saturated compounds of formula (II) as described above.

The aralkylidene-triphenylphosphoranes are preferably prepared by reacting the corresponding aralkyl-triphenylphosphonium halide of the formula:



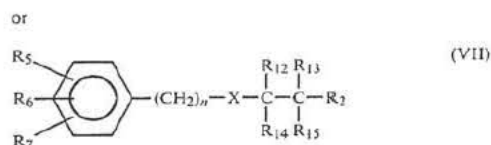
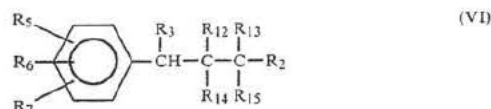
wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>10</sub> and n are as before and Hal is halogen, with a basic reagent, preferably butyllithium.

In the Grignard- and Wittig-syntheses described above, the free nitrogen atom in the imidazole starting material can be protected by different methods. Suitable protecting groups are for example benzyl, triphenylsilyl or dialkoxymethane. The removal of the protecting group can be performed in different ways, and depends on the kind of protecting group used. For example, a dialkoxymethane group is removed by acidic hydrolysis and a benzyl group by sodium in liquid ammonia.

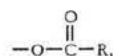
The present invention further provides yet another method for preparing compounds of the invention.

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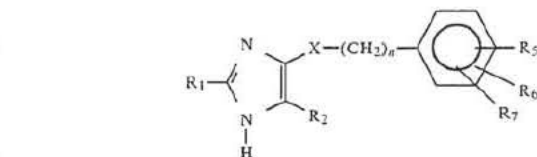
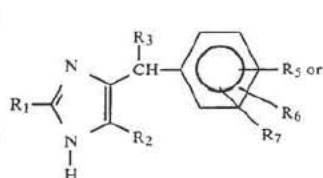
Thus, according to this embodiment of the invention, a starting material of the formula (VI) or (VII)



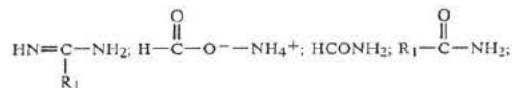
wherein R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and n are as hereinbefore defined; wherein R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub> and R<sub>15</sub>, which can be the same or different, are each hydrogen, hydroxy, mercapto, halogen, amino, -O- alkyl of 1 to 7 carbon atoms or



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



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, X and n are defined as before. Reagents capable of converting the depicted starting material to the corresponding imidazole include NH<sub>3</sub>+CH<sub>2</sub>O (or a source of ammonia and formaldehyde);



or R<sub>1</sub>CHO and NH<sub>3</sub>. Choice of an appropriate reagent varies with the particular starting material employed.

When R<sub>1</sub> is hydrogen it is 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

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