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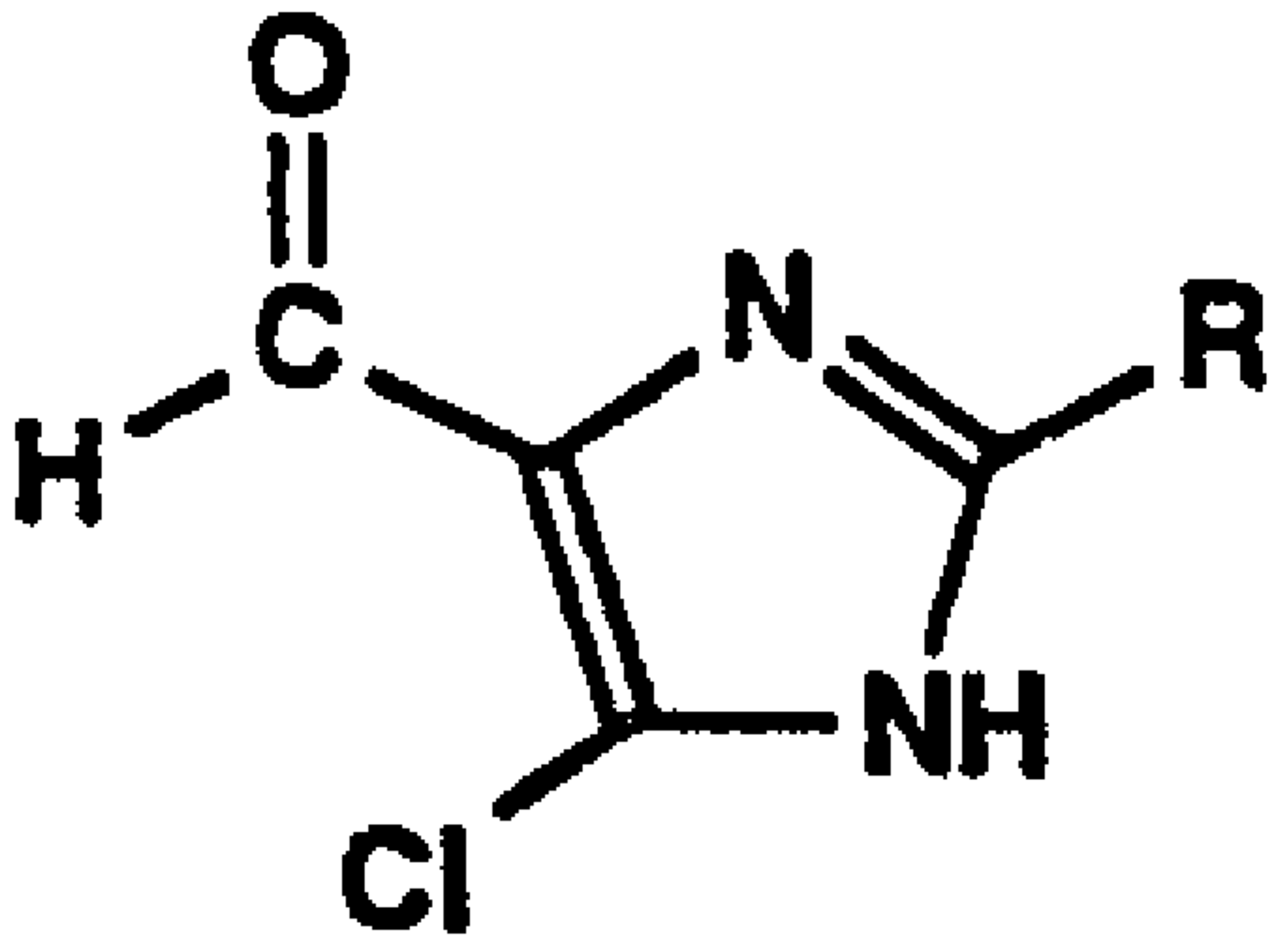
(54) **Titre :** METHODE POUR LA PREPARATION DE 5-CHLOROIMIDAZOLE-4-CARBALDEHYDES SUBSTITUES EN 2
(54) **Title:** PROCESS FOR THE PREPARATION OF 2-SUBSTITUTED 5-CHLOROIMIDAZOLE-4-CARBALDEHYDES



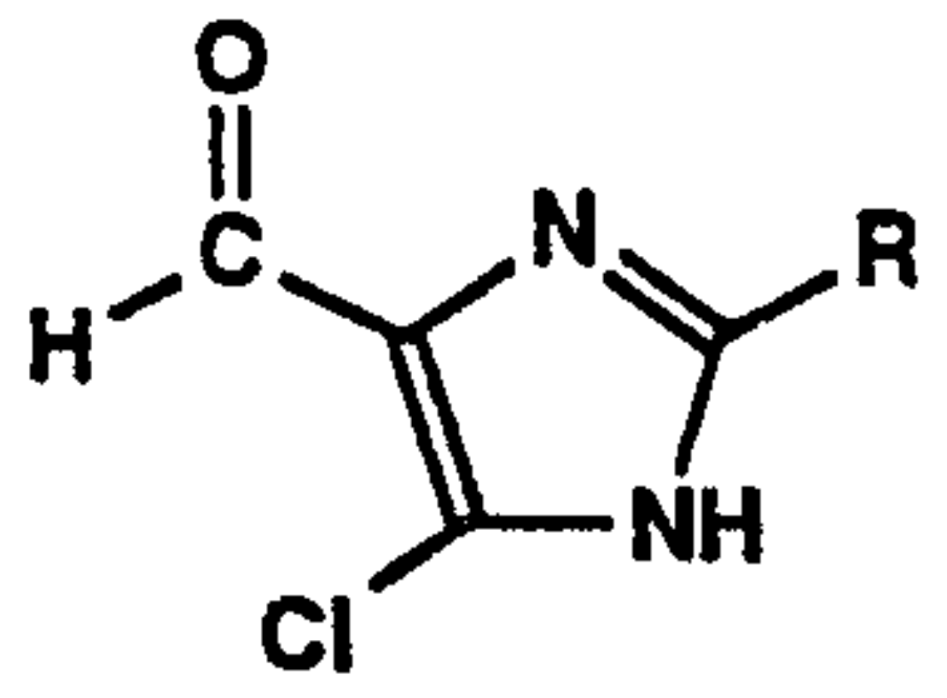
(I)

(57) **Abrégé/Abstract:**

A novel process for the preparation of 2-substituted 5-chloroimidazole-4-carbaldehydes of the general formula: (see formula I) wherein R represents hydrogen or an alkyl, alkenyl, cycloalkyl, arylalkyl or aryl group, is described. In this process a glycine ester hydrohalide is ring-closed with an imidate ester to give a 2-substituted 3,5-dihydroimidazol-4-one, which is converted into an N,N-substituted aminomethyleneimidazolinone using an N,N-substituted formamide acetal and finally chlorinated. The 5-chloroimidazole-4-carbaldehydes (I) are important intermediates in the preparation of hypotensive pharmaceuticals.

ABSTRACT OF THE DISCLOSURE

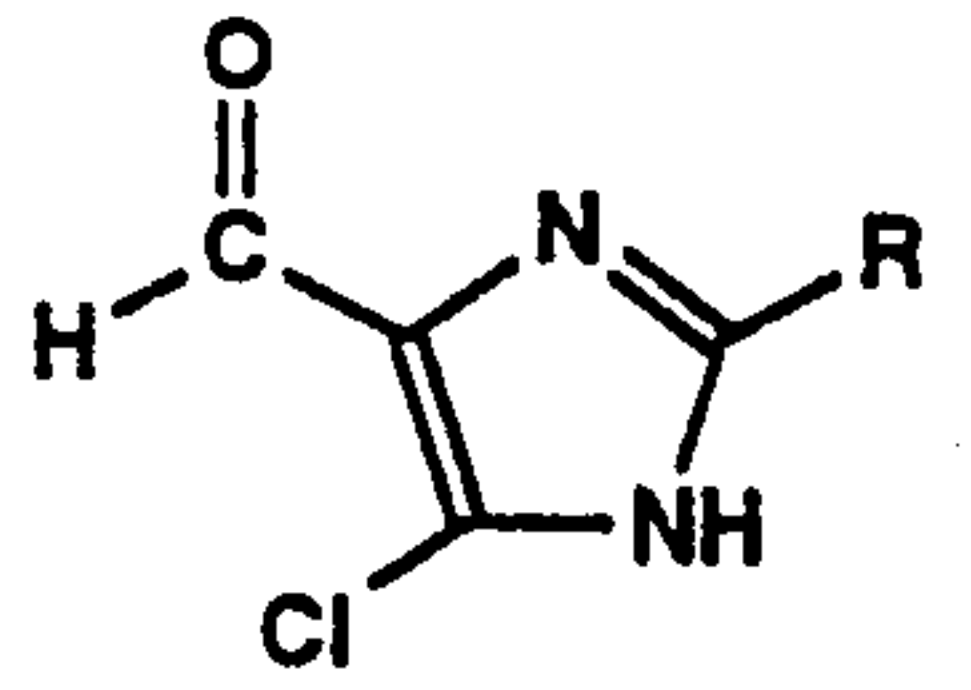
A novel process for the preparation of 2-substituted 5-chloroimidazole-4-carbaldehydes of the general formula:



(I)

wherein R represents hydrogen or an alkyl, alkenyl, cycloalkyl, arylalkyl or aryl group, is described. In this process a glycine ester hydrohalide is ring-closed with an imidate ester to give a 2-substituted 3,5-dihydroimidazol-4-one, which is converted into an N,N-substituted aminomethyleneimidazolinone using an N,N-substituted formamide acetal and finally chlorinated. The 5-chloroimidazole-4-carbaldehydes (I) are important intermediates in the preparation of hypotensive pharmaceuticals.

This invention relates to a novel process for preparing 2-substituted 5-chloroimidazole-4-carbaldehydes of the general formula:


(I)

in which R is hydrogen, an alkyl group, an alkenyl group, a cycloalkyl group, an arylalkyl group or an aryl group.

The 2-substituted 5-chloroimidazole-4-carbaldehydes of general formula I are important starting materials for the preparation of hypotensive pharmaceuticals (US Patent 4,355,040) or of herbicidally active compounds (DE-A 2804435).

Several routes for the preparation of the compounds according to general formula I are known.

Thus, US Patent 4,355,040 describes a process according to which 2-amino-3,3-dichloroacrylonitrile is reacted with an aldehyde to give the corresponding azomethine intermediate and further with a halohydrocarbon and water to give the 2-substituted 5-haloimidazole-4-carbaldehyde. Experimental details are lacking in the patent specification mentioned. A great disadvantage of the synthesis is that the 2-amino-3,3-dichloroacrylonitrile employed first has to be prepared starting from dichloroacetonitrile by reaction thereof with hydrocyanic acid/

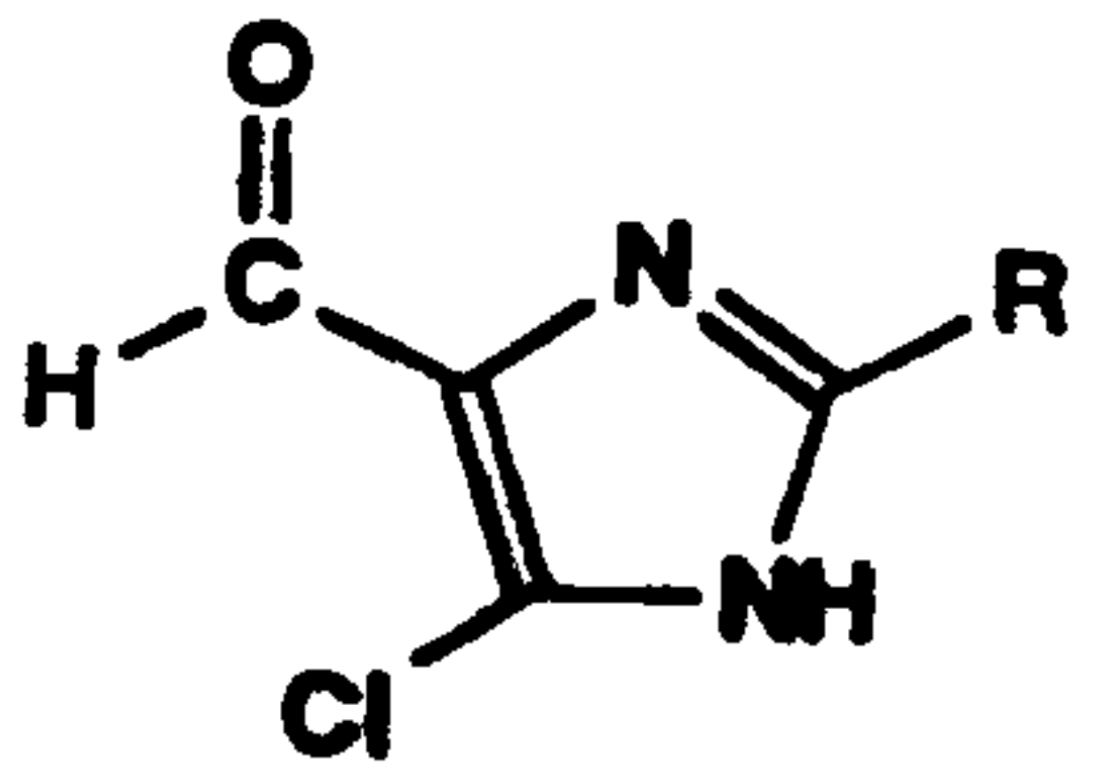
sodium cyanide. The extremely toxic reactants and the safety measures associated therewith, which are necessary even for the preparation of the starting material, make the entire process unsuitable industrially.

US Patent 4,355,040 discloses in a further variant a 3-stage process, in which in a first stage an amidine hydrochloride is ring-closed with dihydroxyacetone at a high NH_3 pressure, and the imidazole alcohol is halogenated and finally oxidized to the aldehyde. It has been shown that pressures of over 20 bar are necessary for the ring-closure reaction. The oxidation of the alcohol additionally works in the presence of chromium oxide.

It is obvious that an oxidation using heavy metal oxides, which as a rule are not recyclable, is no longer practicable, in light of environmental concerns.

It was therefore the object of the invention to develop a process which avoids the disadvantages mentioned.

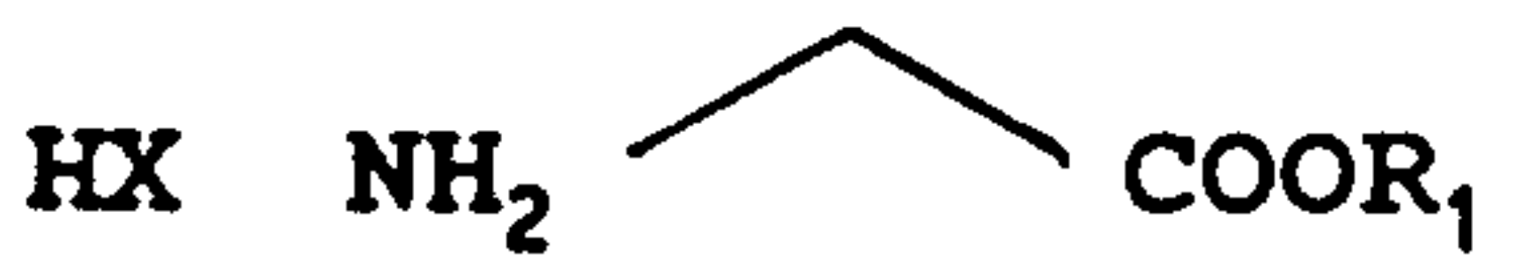
Accordingly, the present invention provides a process for the preparation of 5-chloroimidazole-4-carbaldehydes of the general formula:



(I)

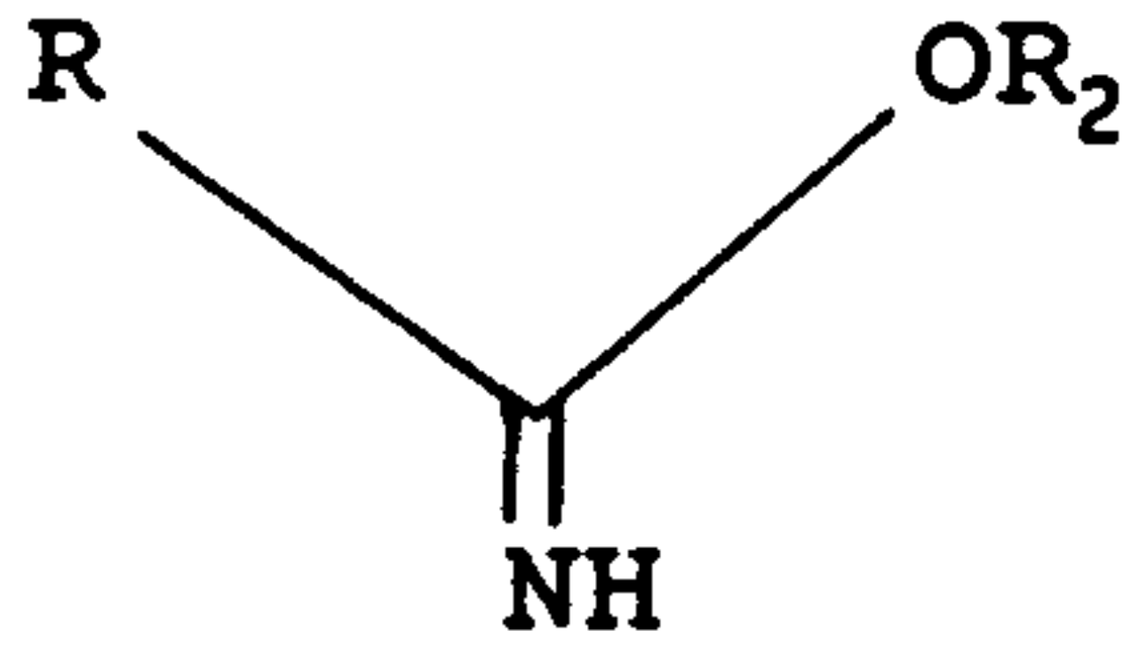
in which R is hydrogen, an alkyl group, an alkenyl group, a cycloalkyl group, an arylalkyl group or an aryl group, which comprises:

in a first stage, reacting a glycine ester hydrohalide of the general formula:



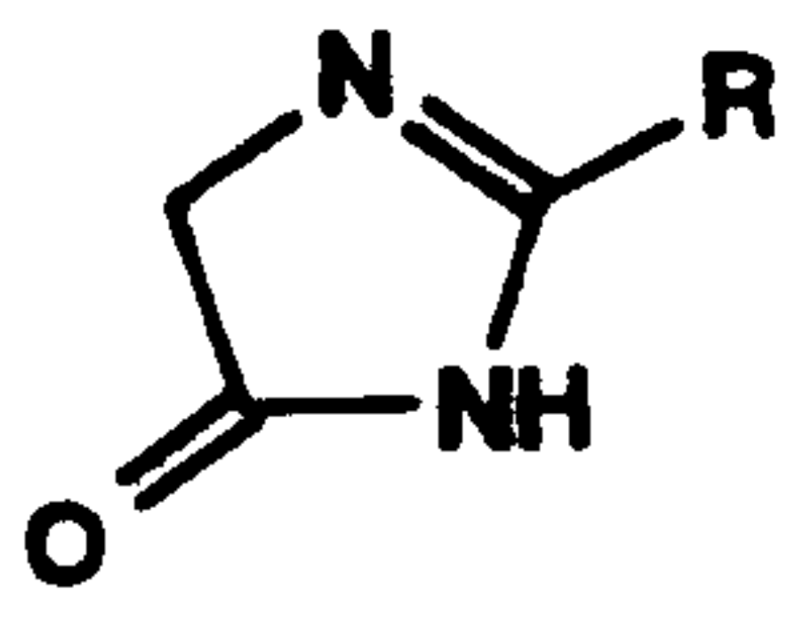
(II)

in which R_1 is an alkyl group and X is a halogen atom, with an imidate ester of the general formula:



(III)

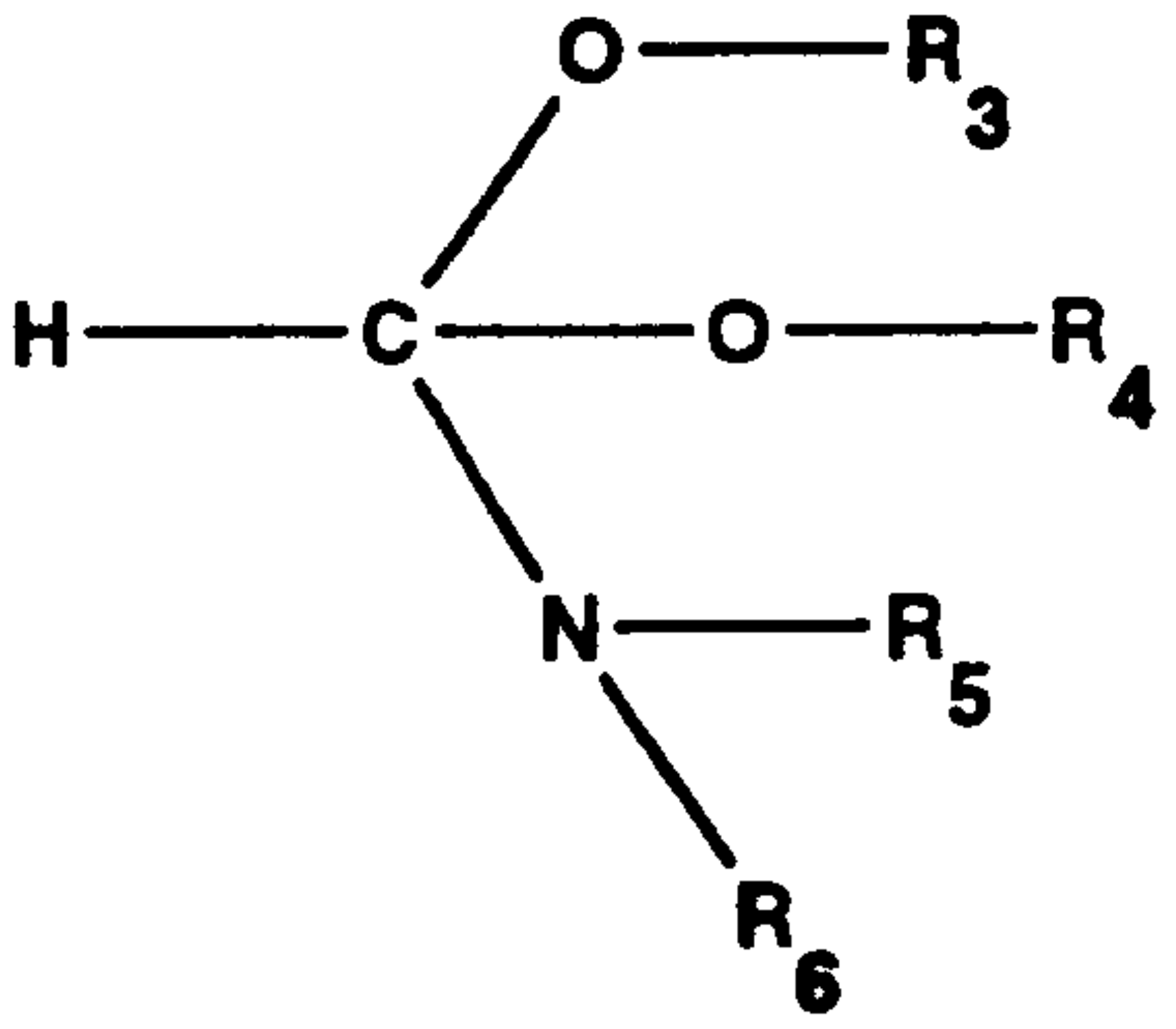
in which R has the meaning mentioned and R_2 is an alkyl group, in the presence of a base to give a 2-substituted 3,5-dihydroimidazol-4-one of the general formula:



(IV)

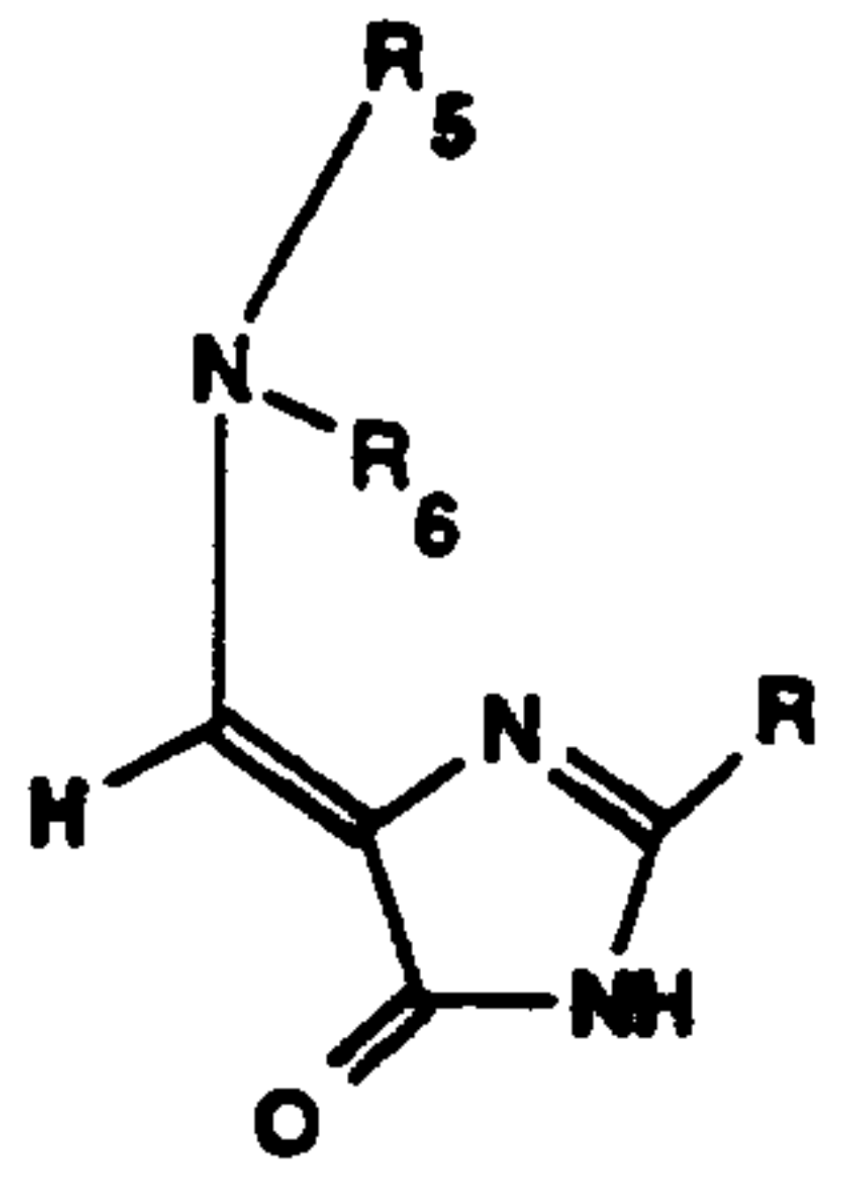
in which R has the meaning mentioned,

converting the compound IV in a second stage with an N,N-substituted formamide acetal of the general formula:



(V)

in which R_3 and R_4 are identical or different and each represents an alkyl group or an arylalkyl group, and R_5 and R_6 are identical or different and each represents an alkyl group or an aryl group, to give an N,N-substituted aminomethyleneimidazolinone of the general formula:



(VI)

in which R, R_5 and R_6 have the meaning mentioned, and

chlorinating the compound VI in a third stage with phosphorus oxychloride or phosgene and hydrolyzing the reaction mixture to give the final product of formula I.

The general names of the groups in substituents R, R_1, R_2, R_3, R_4, R_5 and R_6 in general formulae I to VI have the following meanings.

An alkyl group is understood to mean a straight-chain or branched $(C_1$-$C_6)$-alkyl group, in particular methyl,

ethyl, n-propyl, i-propyl, n-butyl, sec.-butyl, tert.-butyl, pentyl and its isomers or hexyl and its isomers. A preferred alkyl group for R is the n-butyl group. A preferred alkyl group for R_1, R_2, R_3, R_4, R_5 and R_6 is a $(C_1$-$C_4)$-alkyl group.

An alkenyl group is understood to mean a straight-chain or branched $(C_2$-$C_6)$-alkenyl group, such as e.g. 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, pentenyl and its isomers or hexenyl and its isomers. A preferred alkenyl group is the 2- or 3-butenyl group.

Representatives of cycloalkyl groups which may be mentioned are the cyclopropyl group, the cyclobutyl group, the cyclopentyl group or the cyclohexyl group.

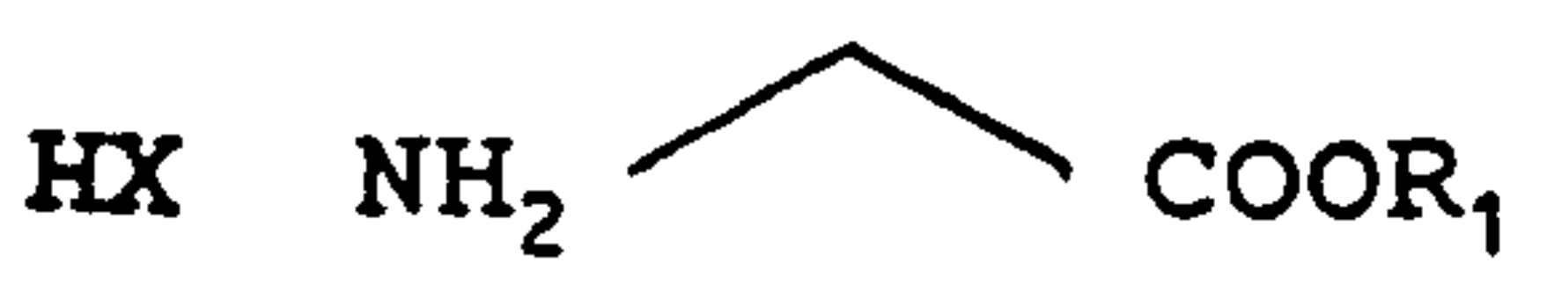
An arylalkyl group can mean a phenyl-$(C_1$-$C_6)$alkyl group, preferably a benzyl group.

Aryl is preferably a phenyl group.

Both the arylalkyl group and the aryl group can have one or more substituents on the aromatic ring, such as e.g. alkyl, halogen, nitro or amino.

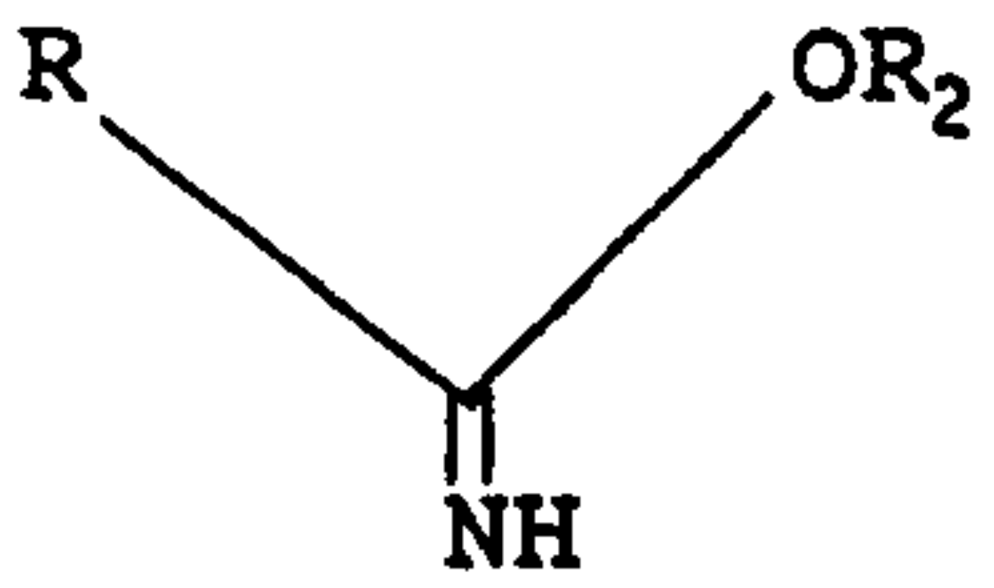
Normally, halogen can be chlorine, bromine or iodine, preferably chlorine.

In the first step of the process according to the invention, a glycine ester hydrohalide of the general formula:



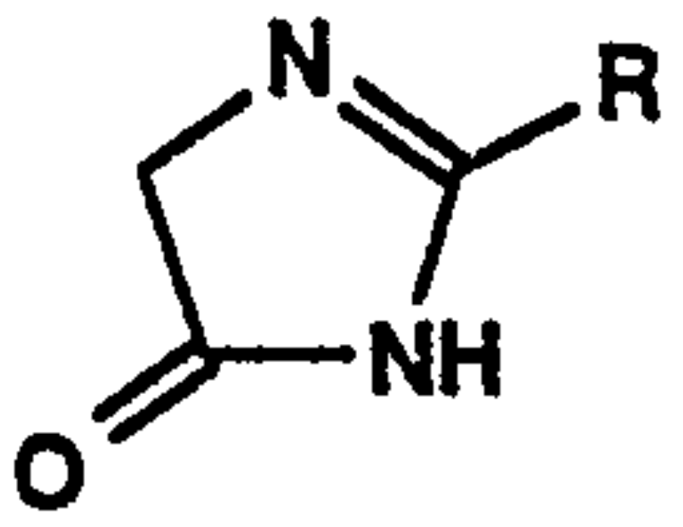
(II)

in which R_1 is an alkyl group and X is a halogen atom, is reacted with an imidate ester of the general formula:



(III)

in which R has the meaning mentioned and R_2 is an alkyl group, in the presence of a base to give a 2-substituted 3,5-dihydroimidazol-4-one of the general formula:



(IV)

in which R has the meaning mentioned.

A procedure can be used in which the glycine ester hydrohalide of general formula II is reacted with the imidate ester of general formula III in the presence of a base. Advantageously, this takes place at a pH of 7 to 12, preferably of 9 to 11.

The glycine ester hydrohalides of general formula II are commercially available stable compounds.

Suitable bases are the alkali metal hydroxides, such as e.g. sodium hydroxide or potassium hydroxide, or alkali metal alkoxides such as e.g. sodium or potassium methoxide, ethoxide or tert.-butoxide.

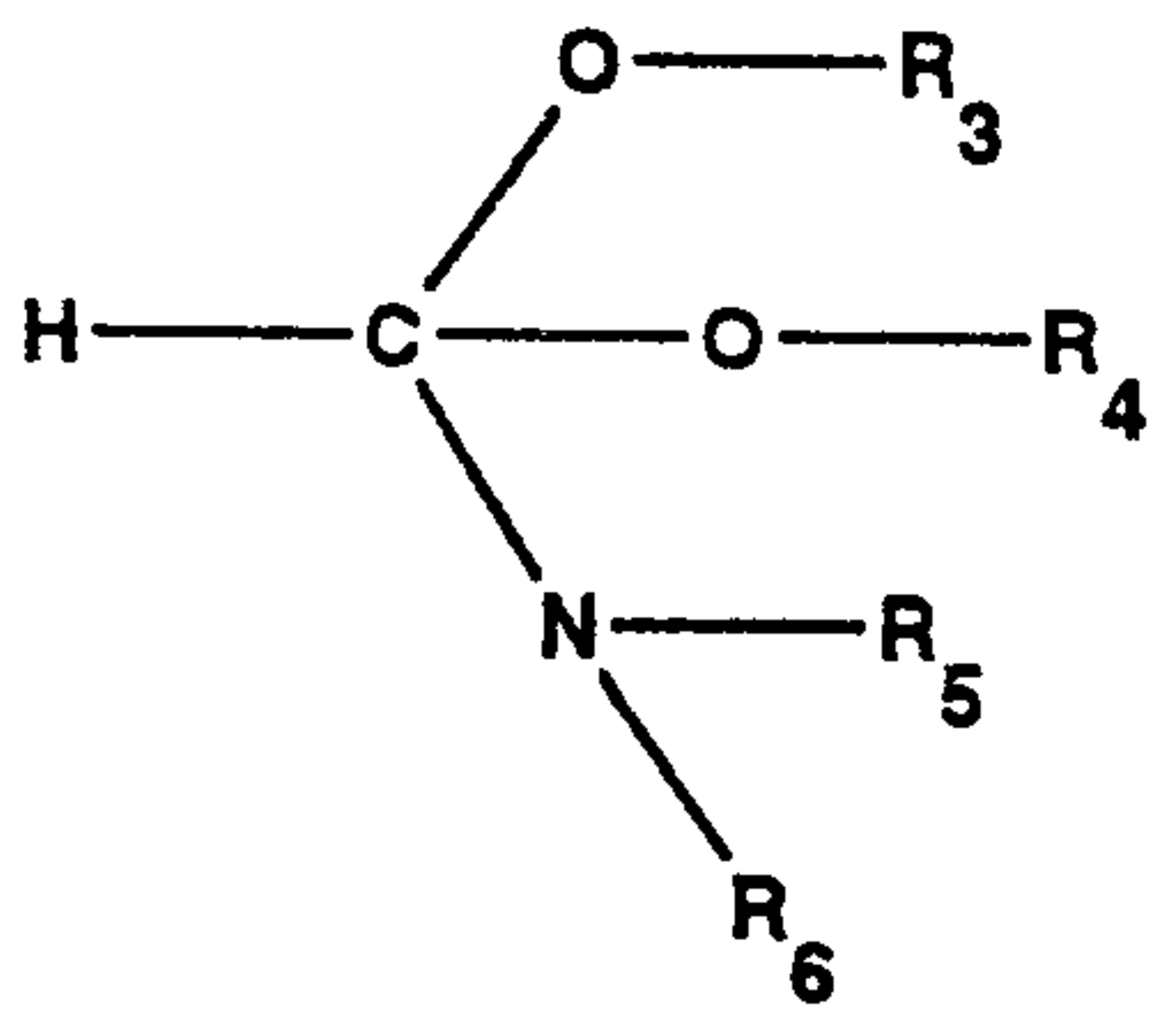
Advantageously, the base is dissolved in a suitable solvent. Particularly suitable solvents are aliphatic alcohols, such as methanol or ethanol. The imidate ester is preferably also added in the form of a solution in an inert solvent. As a rule, aromatic solvents are particularly highly suitable for this purpose, such as e.g. toluene or chlorobenzene or the aliphatic alcohols mentioned.

The reaction of the glycine ester hydrohalide, imidate ester and base advantageously takes place in a stoichiometric ratio of 1:1:1.

The reaction temperature is normally in the range of from -20°C to 50°C, preferably from 0°C to 25°C.

After a reaction time of a few hours, the corresponding 2-substituted 3,5-dihydroimidazol-4-one of the general formula IV can generally be isolated in yields greater than 95% by simple filtration.

Advantageously, however, the imidazolinone of general formula IV is not isolated, but the reactant of the second stage, namely the N,N-substituted formamide acetal of the general formula:



(V)

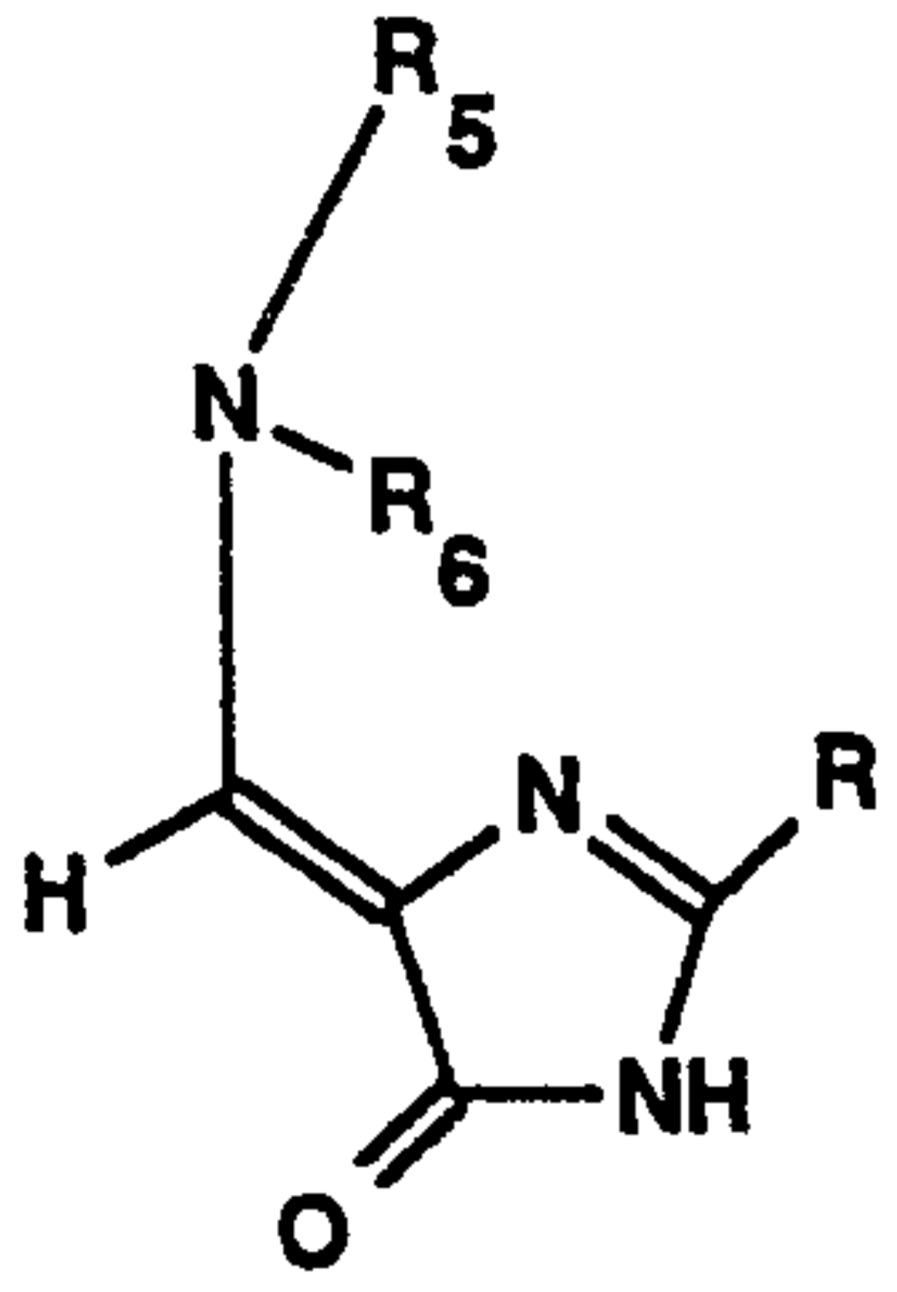
in which R_3 and R_4 are identical or different and each represents an alkyl group or an arylalkyl group, and R_5 and R_6 are identical or different and each represents an alkyl group, an arylalkyl group or an aryl group, is added to the reaction mixture.

Suitable N,N-substituted formamide acetals of general formula V are the N,N-dimethylformamide dialkyl acetals. N,N-Dimethylformamide dimethyl acetal, in which R_3, R_4, R_5 and R_6 are methyl, is particularly preferred.

The reaction in the second stage can be carried out in the presence of an inert solvent such as, for example, an aliphatic alcohol, a halogenated hydrocarbon or an aromatic. It is possible to use methanol, methylene chloride or toluene with good results. However, it is also possible to work without additional solvent, i.e. in the presence of the acetal as a solvent.

The reaction can proceed at a temperature between -50°C and 100°C, but is preferably carried out at room temperature.

The resultant N,N-substituted aminomethylene-imidazolinone of the general formula:



(VI)

in which R, R_5 and R_6 have the meanings mentioned, is not known from the literature and, as an important intermediate in the synthesis according to the invention, is also part of the invention.

The N,N-substituted aminomethyleneimidazolinone mentioned can occur as an E- or Z-isomer.

A particularly preferred imidazolinone of general formula VI is the (Z)-2-butyl derivative, where R = n-butyl and R_5 and R_6 = methyl.

The N,N-substituted aminomethyleneimidazolinone of general formula VI can be isolated from the reaction mixture in a technically customary manner.

However, it is also possible to proceed without isolation of this intermediate to effect the chlorination with phosphorus oxychloride or phosgene in the third and last stage.

The chlorination can be carried out here in the presence of phosphorus oxychloride on its own or in the presence of the so-called Vilsmeier reagent, which consists of phosphorus oxychloride and N,N-dimethylformamide or phosgene and N,N-dimethylformamide, preferably in a molar ratio of 1:1 to 4:1.

The chlorinating agents mentioned are preferably employed in an excess and thus simultaneously serve as a solvent.

However, it is also possible to work in the presence of an additional inert solvent.

The chlorination is preferably carried out at a temperature between 50°C and 150°C.

After a reaction time of about 0.5 to 4 hours, the corresponding 2-substituted 5-chloroimidazole-4-carbaldehyde of general formula I can be obtained in good yield and purity, by treatment of the reaction mixture with water and extraction with a suitable solvent.

The following Examples illustrate the invention.

Example 1

Preparation of (Z)-2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one (VI) from 2-butyl-2-imidazolin-5-one (IV)

N,N-Dimethylformamide dimethyl acetal (2.85 g, content about 92%, 22 mmol) was added to a solution of 2-butyl-2-imidazolin-5-one (2.80 g, 20 mmol) in methanol (20 ml). The temperature rose from 18°C to 26°C. After 45 minutes, the solution was concentrated and dried under high vacuum. 3.88 g of 2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one were obtained with a content of greater than 90% according to ^{1}H-NMR. This corresponds to a yield of about 90% based on the 2-butyl-2-imidazolin-5-one. The product can be recrystallized from ethyl acetate.

M.p.: 114 - 116.5°C

^{1}H-NMR ($CDCl_3$, 400 MHz)	0.95 (3H, t);
	1.42 (2H, m);
	1.68 (2H, m);
	2.53 (2H, t);
	3.17 (3H, br s);
	3.55 (3H, br s);
	7.03 (1H, s);
	10.35 (1H, br s).

Example 2

Preparation of (Z)-2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one (VI) from methyl pentanimidate (III)

Glycine methyl ester hydrochloride (5.00 g, 39.42 mmol) was added in one portion to a solution of sodium hydroxide (1.59 g, 39.42 mmol) in methanol (13 ml) at 0°C, the temperature falling to -10°C. The mixture was stirred for 15 minutes and during this time the temperature rose again to 0°C. Methyl pentanimidate (4.73 g, 39.42 mmol) was added and the mixture was stirred at room temperature for 3 hours. N,N-Dimethylformamide dimethyl acetal (5.62 g, 43.39 mmol) was then added during the course of 5 minutes and the reaction mixture was stirred for a further 3 hours. The solvent was removed on a Rotavapor and the residue was treated with CH_2Cl_2 (40 ml) and water (15 ml). After phase separation, the organic phase was washed with water (10 ml), then the combined H_2O phases were washed twice with 20 ml of CH_2Cl_2 each time. The combined organic phases were dried

($MgSO_4$), filtered, concentrated on the Rotavapor and dried under high vacuum.

6.70 g of 2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one were obtained with a content of about 90% according to ^{1}H-NMR. This corresponds to a yield of about 78% based on the methyl pentanimidate.

Example 3

Preparation of 2-butyl-5-chloroimidazole-4-carbaldehyde (I) from (Z)-2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one (IV)

A mixture of 2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one (1.00 g, 5.12 mmol) and $POCl_3$ (3.20 g, 20.48 mmol) was heated at 100°C for 45 minutes. 1.76 g of $POCl_3$ was distilled off on a Rotavapor and the residue was treated with ethyl acetate (6 ml). The mixture thus obtained was added to water (20 ml) and stirred at room temperature for 5 minutes. The pH was adjusted from 0.34 to 7 using 30% strength sodium hydroxide solution and the mixture was extracted twice using 10 ml of ethyl acetate each time. The combined organic phases were dried ($MgSO_4$), filtered and concentrated and the residue was dried under high vacuum.

0.89 g of 2-butyl-5-chloroimidazole-4-carbaldehyde (purity greater than 95% according to ^{1}H-NMR) was obtained. This corresponds to a yield of 93% based on the 2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one.

Example 4

Preparation of (Z)-2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one (VI) from 2-butyl-2-imidazolin-5-one (IV)

A solution of 2-butyl-2-imidazolin-5-one (5.00 g, 35.67 mmol) and N,N-dimethylformamide diisopropyl acetal (7.02 g, 39.24 mmol) in methylene chloride (25 ml) was stirred at room temperature for 2.5 hours. The solvent was removed on a Rotavapor and the residue was treated with methylene chloride (40 ml). The solution thus obtained was washed twice with 10 ml of water each time, dried ($MgSO_4$) and concentrated on the Rotavapor, and the residue was dried under high vacuum. 5.37 g of 2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one were obtained with a content of greater than 90% according to ^{1}H-NMR. This corresponds to a yield of about 71% based on the 2-butyl-2-imidazolin-5-one.

Example 5

Preparation of (Z)-2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one (VI) from methyl pentanimidate (III)

Glycine methyl ester hydrochloride (5.00 g, 39.42 mmol) was added in one portion to a solution of sodium hydroxide (1.59 g, 39.42 mmol) in methanol (13 ml) at 0°C, the temperature falling to -10°C. The mixture was stirred for 15 minutes and during this time the temperature rose again to 0°C. Methyl pentanimidate (4.73 g, 39.42 mmol) was added and the mixture was stirred at room temperature for 3 hours. N,N-Dimethylformamide dibutyl acetal (9.00 g, 43.36

mmol) was then added during the course of 5 minutes and the reaction mixture was stirred for a further 3 hours. The solvent was removed on a Rotavapor and the residue was treated with CH_2Cl_2 (40 ml) and water (15 ml). After phase separation, the organic phase was washed with water (10 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated on the Rotavapor and the residue was dried under high vacuum. 6.92 g of 2-butyl-4-dimethylaminomethylene-2-imidazolin-5-one were obtained with a content of about 80% according to ^{1}H-NMR. This corresponds to a yield of about 72% based on the methyl pentanimidate.

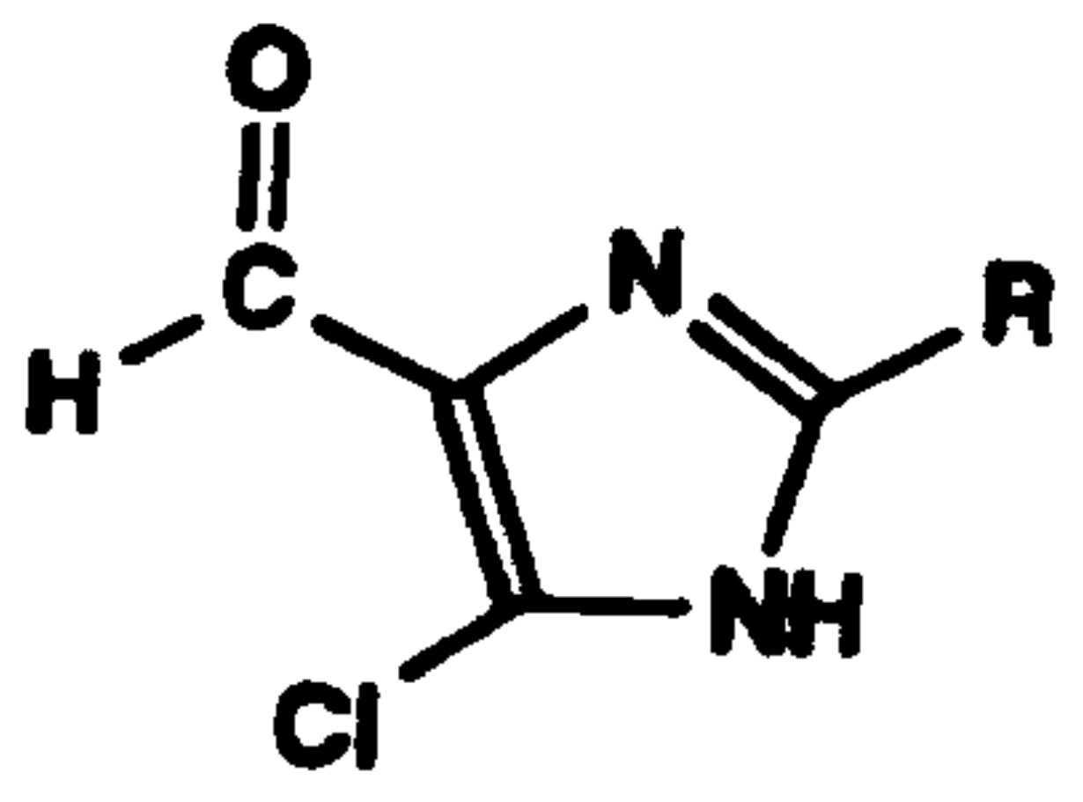
Example 6

Preparation of 2-butyl-5-chloroimidazole-4-carbaldehyde (I) from methyl pentanimidate (III)

Glycine methyl ester hydrochloride (31.72 g, 250 mmol) was added in one portion to a solution of sodium hydroxide (10.13 g, 250 mmol) in methanol (80 ml) at 0°C, the temperature falling to -10°C. The mixture was stirred for 10 minutes and during this time the temperature rose again to 0°C. Methyl pentanimidate (108.25 g of a 26.6% strength solution in toluene, 250 mmol) was added and the mixture was stirred at room temperature for 3 hours. N,N-Dimethylformamide dimethyl acetal (35.64 g, about 92% strength, 275 mmol) was then added during the course of 5 minutes and the reaction mixture was stirred for a further 3 hours. Toluene (200 ml) was added and methanol and water were removed from the mixture by distillation in vacuo. Of the remaining 203.5 g, 91.68 g (corresponding to 112 mmol of methyl pentanimidate) were initially introduced at room temperature and treated with $POCl_3$ (65.09 g, 416 mmol). The mixture was heated at 100°C for 1.5 hours, then 118.5 g of $POCl_3$/toluene were distilled off and the residue was treated with ethyl acetate (121 ml) and water (408 ml). The pH was adjusted to 1 by the addition of 18 ml of 30% strength sodium hydroxide solution and the phases were separated. The aqueous phase was extracted twice with 200 ml of ethyl acetate each time and the combined organic phases were washed with water (200 ml), dried ($MgSO_4$), filtered and concentrated and the residue was dried under high vacuum. 14.07 g of 2-butyl-5-chloroimidazole-4-carbaldehyde (HPLC content 79.9%) were obtained; this corresponds to a yield of 56% based on the methyl pentanimidate.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

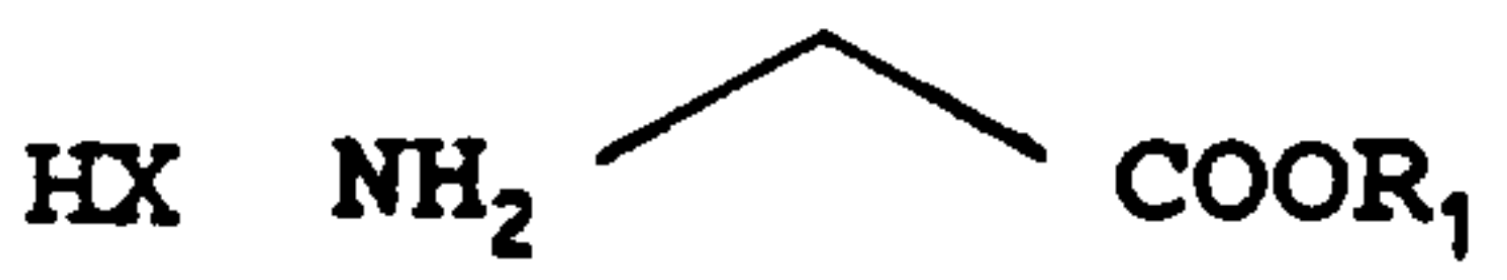
1. A process for the preparation of 5-chloroimidazole-4-carbaldehydes of the general formula:



(I)

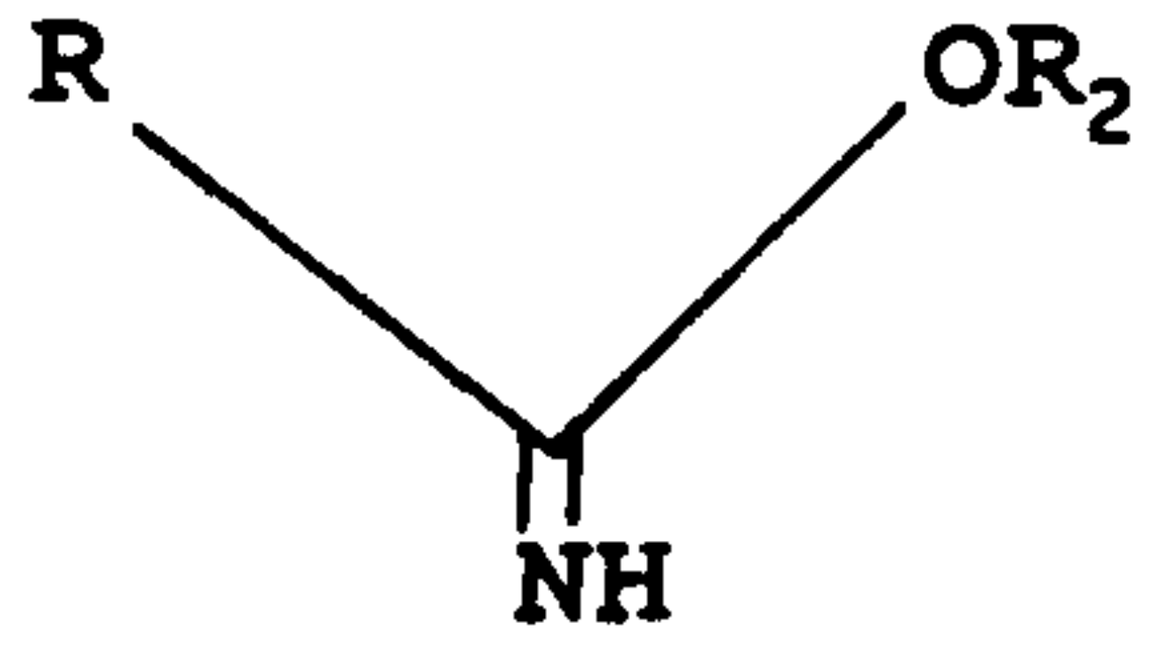
in which R is hydrogen, an alkyl group, an alkenyl group, a cycloalkyl group, an arylalkyl group or an aryl group, which comprises:

in a first step, reacting a glycine ester hydrohalide of the general formula:



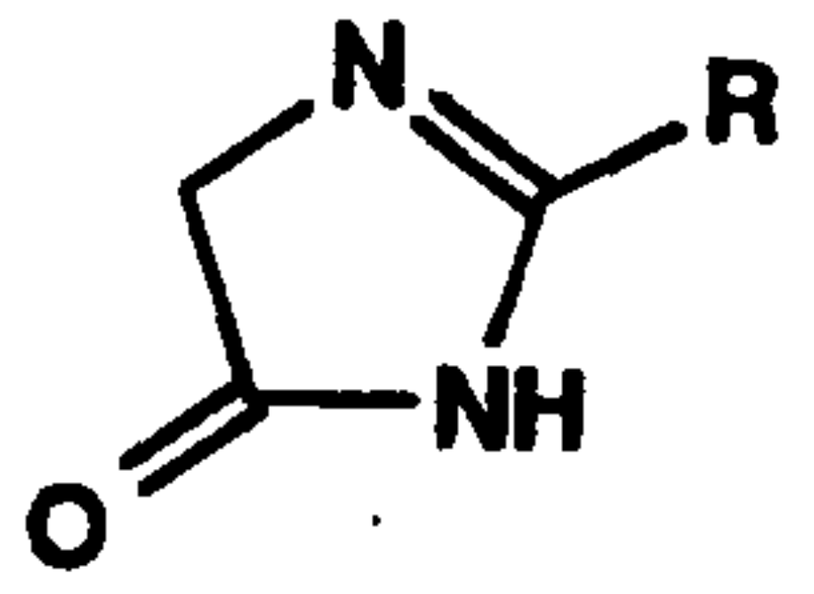
(II)

in which R_1 is an alkyl group and X is a halogen atom, with an imidate ester of the general formula:



(III)

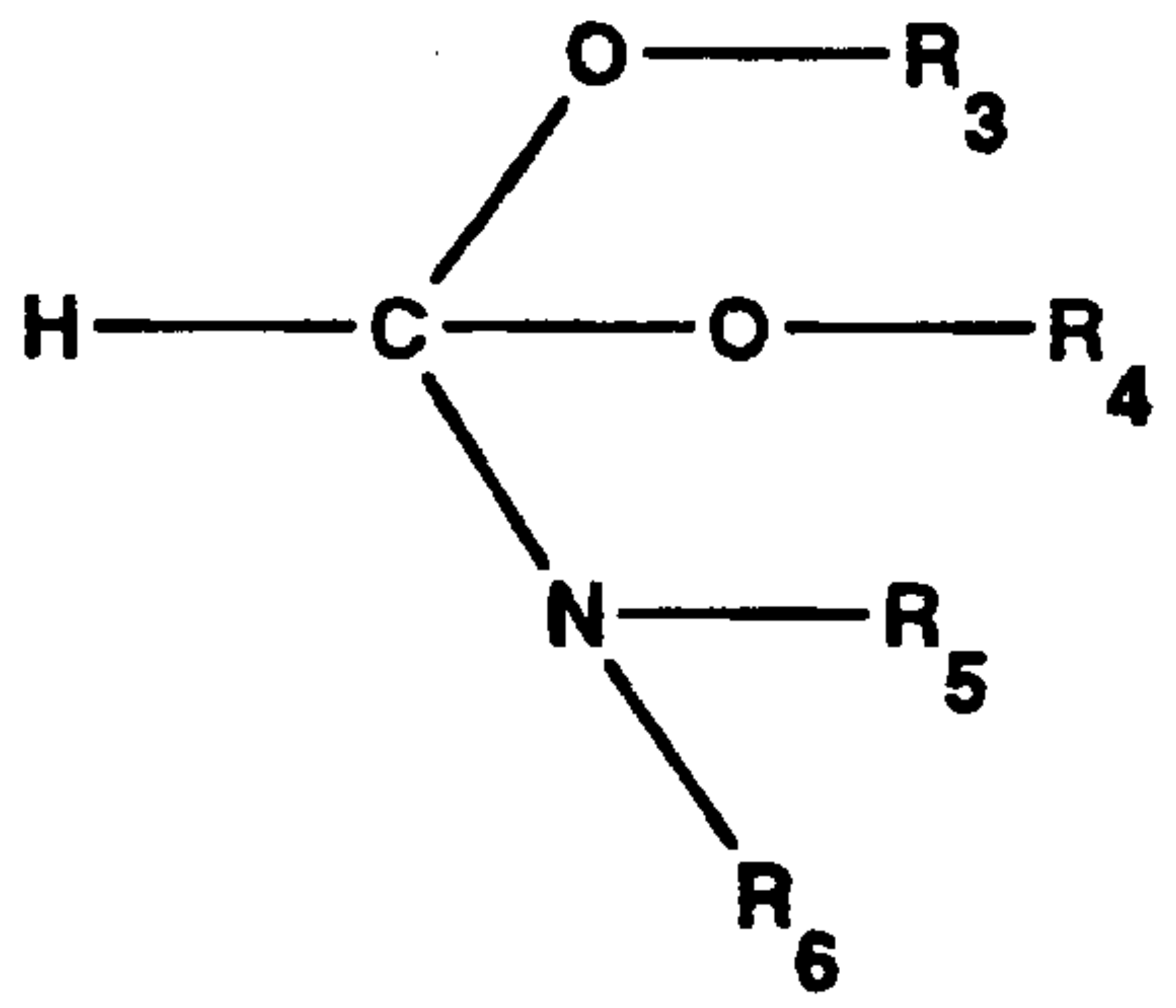
in which R has the above-mentioned meaning and R_2 is an alkyl group, in the presence of a base to give a 2-substituted 3,5-dihydroimidazol-4-one of the general formula:



(IV)

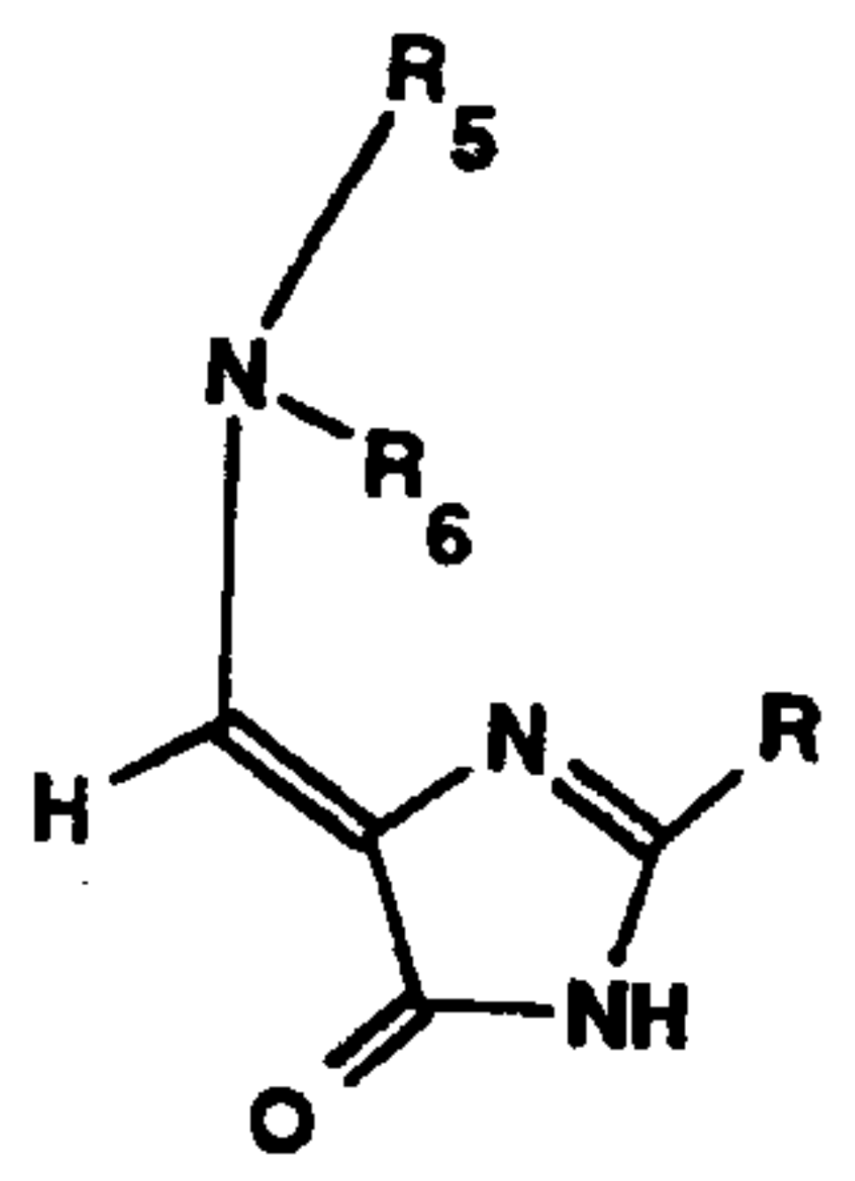
in which R has the above-mentioned meaning,

converting the compound IV in a second step with an N,N-substituted formamide acetal of the general formula:



(V)

in which R_3 and R_4 are identical or different and each represents an alkyl group or an arylalkyl group, and R_5 and R_6 are identical or different and each represents an alkyl group or an aryl group, to give an N,N-substituted aminomethyleneimidazolinone of the general formula:



(VI)

in which R, R_5 and R_6 have the above-mentioned meanings, and chlorinating the compound VI in a third step with phosphorus oxychloride or phosgene and hydrolyzing the reaction mixture to give the final product of formula I.

2. A process according to Claim 1, wherein the intermediates of the general formulae IV and VI are not isolated.

3. A process according to Claim 1, wherein an alkali metal hydroxide or an alkali metal alkoxide is used as a base in the first step.

4. A process according to Claim 1, 2 or 3, wherein the reaction temperature in the first step is between -20° C and 50° C.

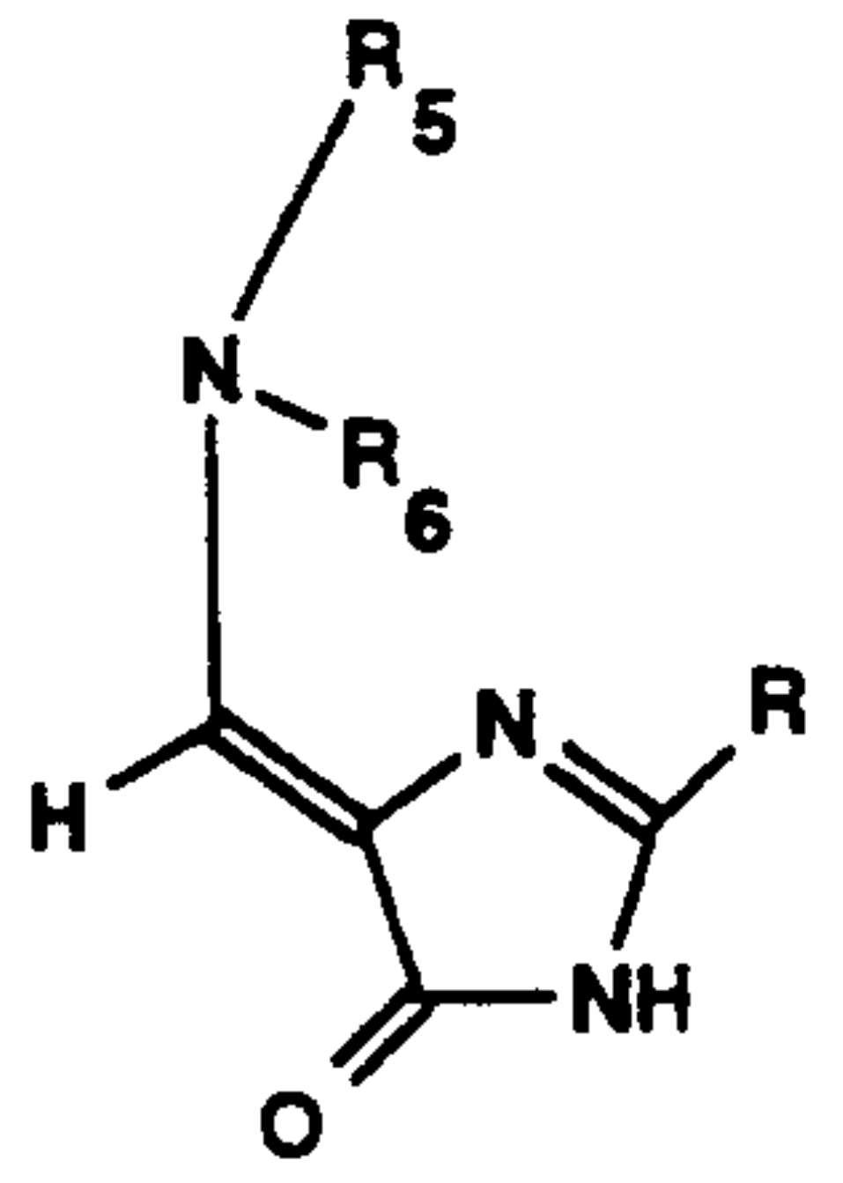
5. A process according to Claim 1, 2 or 3, wherein the reaction in the second step is carried out in the presence of an inert solvent at a temperature between -50° C and 100° C.

6. A process according to Claim 1, 2 or 3, wherein the chlorination with phosphorus oxychloride is carried out at a temperature between 50° C and 150° C.

7. A process according to Claim 1, 2 or 3, wherein the chlorinating step is carried out at a temperature between

50° C and 150° C with phosphorus oxychloride and N,N-dimethylformamide or phosgene and N,N-dimethylformamide.

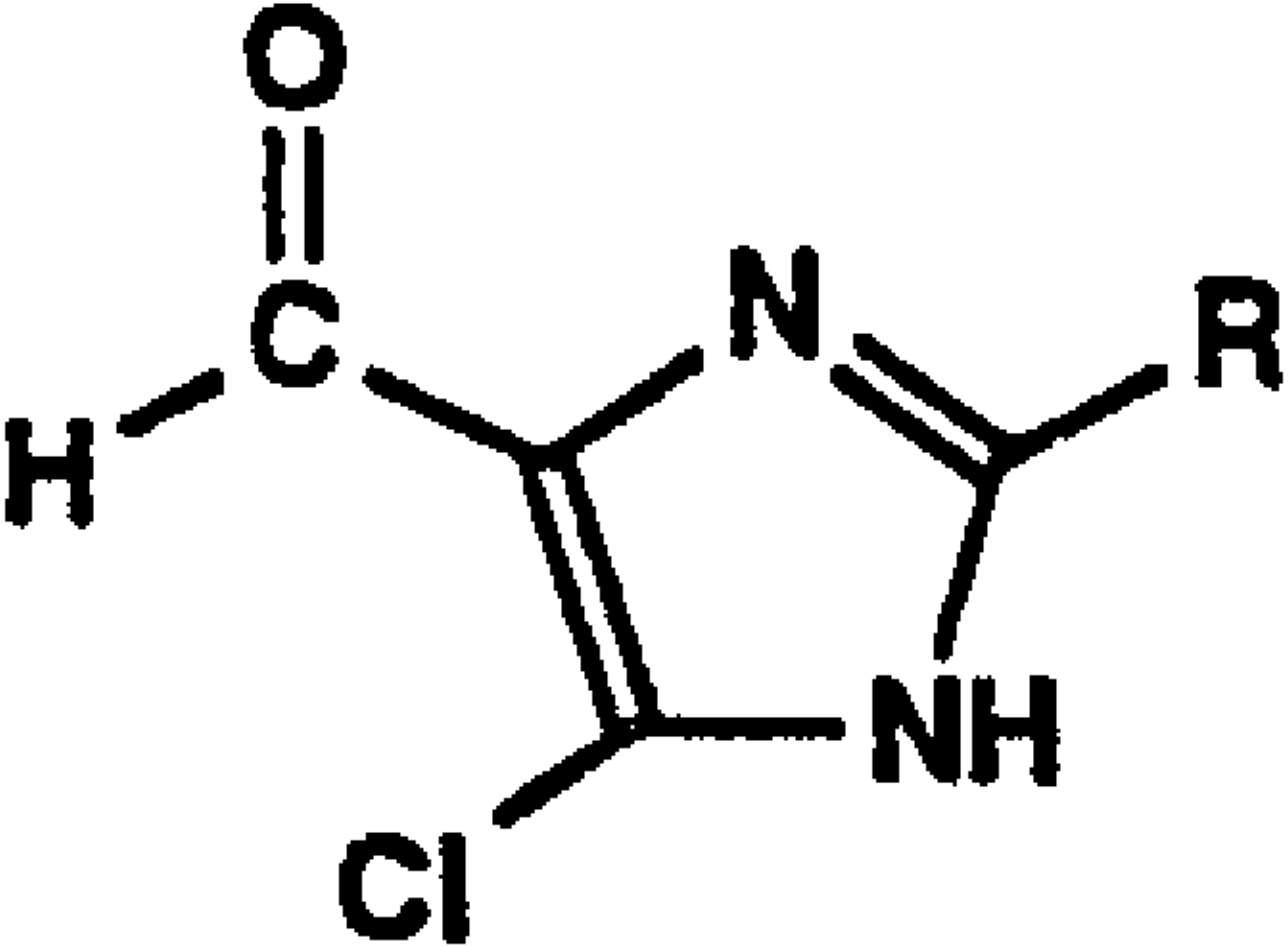
8. An N,N-substituted aminomethyleneimidazolinone of the general formula:



(VI)

in the form of the E- or Z-isomer, wherein R is hydrogen, a (C_1-C_4)-alkyl group, a (C_2-C_6)-alkenyl group, a (C_3-C_6)-cycloalkyl group, an optionally substituted phenyl-(C_1,C_6)-alkyl group or an optionally substituted phenyl group, wherein the substituents of each of the phenyl moieties are selected from the group consisting of (C_1-C_4)-alkyl, halo, nitro and amino, and wherein R_5 and R_6 are identical or different and each is a (C_1-C_4)-alkyl group or an optionally substituted phenyl group, wherein the substituents of the phenol moiety are selected from the group consisting of (C_1-C_4)-alkyl, halo, nitro and amino.

9. The compound according to Claim 8, wherein said compound of the Formula VI is (Z)-2-Butyl-4-dimethylaminomethylene--2-imidazolin--5-one wherein R is n-butyl, R_5 and R_6 are each methyl.



(I)