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Process for the preparation of [(5,6-dicarboxy-3-pyridyl) methyl] ammonium halides

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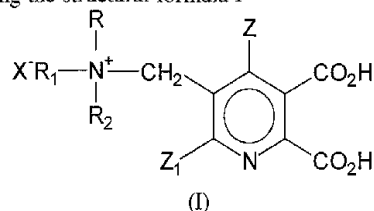
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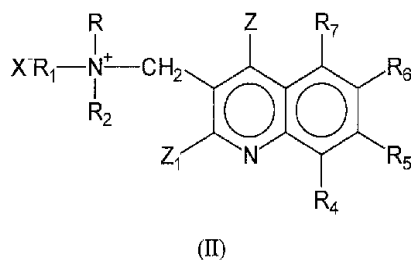
Process for the preparation of [(5,6-dicarboxy-3-pyridyl)methyl] ammonium halides

Abstract

There is provided a process for the preparation of [(5,6-dicarboxy-3-pyridyl)methyl] ammonium halides having the structural formula I



wherein R, R₁ and R₂ are each independently C₁-C₄alkyl, and when taken together, R and R₁ may form a 5- or 6-membered ring optionally interrupted by O, S or NR₃; R₃ is C₁-C₄alkyl; X is Cl, Br or I; Z is hydrogen or halogen; and Z₁ is hydrogen, halogen, cyano or nitro, which process comprises oxidizing a substituted (3-quinolylmethyl)ammonium halide having the structural formula II



wherein R, R₁, R₂, X, Z and Z₁ are as described for formula I above; R₄, R₅, R₆ and R₇ are each independently hydrogen, hydroxy, nitro, OC(O)R₈, halogen, NR₉R₁₀, C₁-C₄alkoxy, SO₃H, SO₂Cl or SH, with the proviso that one of R₄, R₅, R₆ and R₇ is other than hydrogen or halogen; R₈ is C₁-C₄alkyl, C₁-C₄alkoxy, phenyl or NRR; R₉, R₁₀, R₁₁ and R₁₂ are each independently hydrogen, C₁-C₄alkyl or phenyl; the N-oxides thereof; and the acid addition salts thereof, with hydrogen peroxide in the presence of aqueous base.

The [(5,6-dicarboxy-3-pyridyl)methyl]ammonium halides are useful as intermediates in the preparation of herbicidal 5-(alkoxymethyl)-2-(2-imidazolin-2-yl)-nicotinic acids, esters and salts.

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COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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Invention Title: Process for the Preparation of
[(5,6-dicarboxy-3-pyridyl) methyl] ammonium halides

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

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PROCESS FOR THE PREPARATION OF
[(5,6-DICARBOXY-3-PYRIDYL)METHYL]AMMONIUM HALIDES

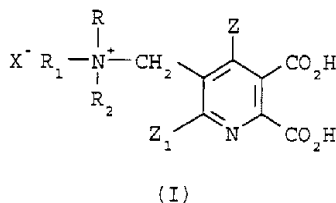
5 BACKGROUND OF THE INVENTION

[(5,6-Dicarboxy-3-pyridyl)methyl]ammonium halides are useful as intermediates in the preparation of herbicidal 5-(alkoxymethyl)-2-(2-imidazolin-2-yl)nicotinic acids, esters and salts. A process for
10 converting 5-methyl-2,3-pyridinedicarboxylic acid derivatives into [(5,6-dicarboxy-3-pyridyl)methyl]-ammonium halides is described in U.S. 5,378,843. Although the process of that patent is useful, there is ongoing research to discover new processes for preparing
15 [(5,6-dicarboxy-3-pyridyl)methyl]ammonium halides.

It is, therefore, an object of the present invention to provide an effective and efficient process for the preparation of [(5,6-dicarboxy-3-pyridyl)methyl]ammonium halides.

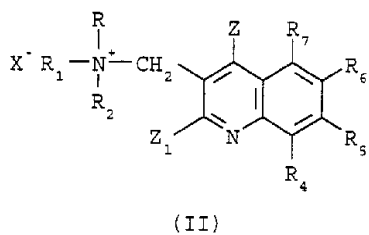
SUMMARY OF THE INVENTION

The present invention provides an effective and efficient process for the preparation of a [(5,6-dicarboxy-3-pyridyl)methyl]ammonium halide having the structural formula I



wherein

- R, R₁ and R₂ are each independently C₁-C₄alkyl, and when taken together, R and R₁ may form a 5- or 6-membered ring optionally interrupted by O, S or NR₃;
 - R₃ is C₁-C₄alkyl;
 - X is Cl, Br or I;
 - Z is hydrogen or halogen; and
 - Z₁ is hydrogen, halogen, cyano or nitro,
- 15 which process comprises oxidizing a substituted (3-quinolylmethyl)ammonium halide having the structural formula II



wherein

- 20 R, R₁, R₂, X, Z and Z₁ are as described for formula I above;

R₄, R₅, R₆ and R₇ are each independently hydrogen, hydroxy, nitro, OC(O)R₈, halogen, NR₉R₁₀, C₁-C₄alkoxy, SO₃H, SO₂Cl or SH, with the proviso that one of R₄, R₅, R₆ and R₇ is other than hydrogen or halogen;

5 R₈ is C₁-C₄alkyl, C₁-C₄alkoxy, phenyl or NR₁₁R₁₂;

R₉, R₁₀, R₁₁ and R₁₂ are each independently hydrogen, C₁-C₄alkyl or phenyl; the N-oxides thereof; and the acid addition salts thereof,

10 with hydrogen peroxide in the presence of aqueous base.

DETAILED DESCRIPTION OF THE INVENTION

In a preferred embodiment of the present invention, a substituted (3-quinolylmethyl)ammonium halide represented by formula II is oxidized with at least about

15 8 molar equivalents of hydrogen peroxide in the presence of at least about 1 molar equivalent, preferably about 4 to 10 molar equivalents, of an aqueous base, preferably in a temperature range of about 50 °C to 100 °C, more preferably about 75 °C to 95 °C.

20 Advantageously, it has been found that [(5,6-dicarboxy-3-pyridyl)methyl]ammonium halides are obtained in high yield and purity by the effective and efficient process of the present invention.

The product [(5,6-dicarboxy-3-pyridyl)methyl]-

25 ammonium halides may be isolated by acidifying the reaction mixture with a mineral acid and collecting the resultant formula I product by standard procedures. Alternatively, the reaction mixture may be integrated into the process used to prepare the final herbicidal

30 agent without isolating the formula I compound.

Exemplary of halogen hereinabove for Z, Z₁, R₄, R₅, R₆ and R₇ are fluorine, chlorine, bromine and iodine with chlorine being preferred.

5 Aqueous bases suitable for use in the process of the present invention include alkali metal hydroxides such as sodium hydroxide and potassium hydroxide, alkaline earth metal hydroxides such as calcium hydroxide, alkali metal carbonates such as sodium carbonate and potassium carbonate, alkaline earth metal carbonates such as
10 calcium carbonate, and mixtures thereof. Preferred aqueous bases include aqueous sodium hydroxide and aqueous potassium hydroxide.

Advantageously, the formula II substituted (3-quinolylmethyl)ammonium halides are highly soluble in the
15 aqueous base. In general, base concentrations from about 35% to 65% on a weight basis are preferred, with base concentrations from about 40% to 60% being more preferred. In the past, certain quinolines have been oxidized with hydrogen peroxide in the presence of
20 aqueous bases having concentrations of up to about 35% on a weight basis (see, e.g., U.S. 4,816,588). However, the use of a more concentrated aqueous base is desirable because it reduces the amount of aqueous waste produced. Another advantage of the process of this invention is
25 that water miscible co-solvents are not required because the substituted (3-quinolylmethyl)ammonium halides are highly soluble in the aqueous base.

A minimum of 8 molar equivalents of hydrogen peroxide is required to completely oxidize a formula II
30 substituted (3-quinolylmethyl)ammonium halide. Preferably, about 8 to 60 molar equivalents of 30% to 50% aqueous hydrogen peroxide, more preferably about 8 to 40 molar equivalents of 30% to 50% aqueous hydrogen peroxide, are used to oxidize the formula II compound.

In a preferred process of the present invention,
R, R₁ and R₂ are each independently C₁-C₄alkyl;

X is Cl or Br;

Z and Z₁ are hydrogen;

5 at least one of R₄, R₅, R₆ and R₇ is hydroxy, nitro or
OC(O)R₈; and

R₈ is C₁-C₄alkyl, C₁-C₄alkoxy or phenyl.

In a more preferred process of the present
invention,

10 R, R₁ and R₂ are methyl;

X is Br;

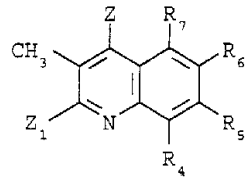
R₅, R₆, R₇, Z and Z₁ are hydrogen;

R₄ is hydroxy, nitro or OC(O)R₈; and

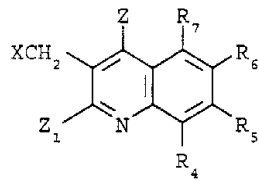
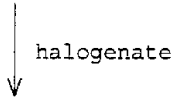
R₈ is C₁-C₄alkyl or C₁-C₄alkoxy.

15 Substituted (3-quinolylmethyl)ammonium halides of
formula II may be prepared by halogenating a substituted
3-methylquinoline of formula III with a halogenating
agent in the presence of a solvent and optionally in the
presence of a catalytic amount of a radical initiator to
20 form a substituted 3-halomethylquinoline of formula IV
and reacting the formula IV compound with at least about
one molar equivalent of an amine of formula V in the
presence of a solvent. The reaction scheme is shown
below in Flow Diagram I.

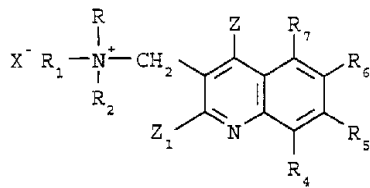
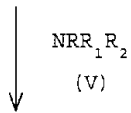
FLOW DIAGRAM I



(III)



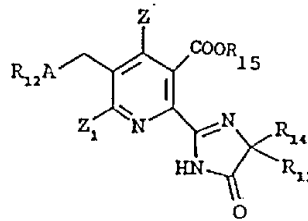
(IV)



(II)

The present invention also provides a process for the preparation of a herbicidal 5-(alkoxymethyl)-2-(2-imidazolin-2-yl)-nicotinic acid, ester and salt compound having the formula

5



(VI)

wherein

10

Z and Z₁ are as defined above;

A is O or S;

R₁₂ is C₁-C₄ alkyl optionally substituted with phenyl optionally substituted with one to three C₁-C₄ alkyl groups or halogen atoms, or

15

phenyl optionally substituted with one to three C₁-C₄ alkyl groups or halogen atoms;

R₁₃ is C₁-C₄ alkyl;

R₁₄ is C₁-C₄ alkyl, C₃-C₆ cycloalkyl or R₁₃ and R₁₄, when taken together with the atom to which they are attached, represent a C₃-C₆ cycloalkyl group optionally substituted with methyl and

20

R₁₅ is hydrogen, diloweralkylimino,

C₁-C₁₂ alkyl optionally substituted with one of the following groups: C₁-C₃ alkoxy, halogen, hydroxy,



C₃-C₆ cycloalkyl, benzyloxy, furyl, phenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, nitrophenyl, carboxyl, loweralkoxycarbonyl, cyano or triloweralkylammonium;

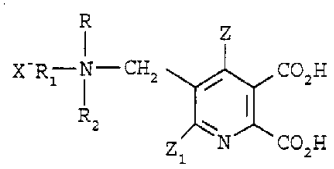
5 C₃-C₁₂ alkenyl optionally substituted with one of the following groups: C₁-C₃ alkoxy, phenyl, halogen or loweralkoxycarbonyl or with two C₁-C₃ alkoxy groups or two halogen groups;

10 C₃-C₆ cycloalkyl optionally substituted with one or two C₁-C₃ alkyl groups; or a cation preferably selected from the group consisting of alkali metals, alkaline earth metals, manganese, copper, iron, zinc, cobalt, lead, silver, nickel, ammonium and organic ammonium; and

15 when R₁₃ and R₁₄ represent different substituents, the optical isomers thereof;

which process comprises:

(a) preparing a compound having the formula I



(I)

wherein Z, Z₁, R, R₁, R₂ and X are as defined above by a process as defined above; and

(b) converting the said compound having formula I into the compound having the formula VI.

The term "lower" as used above in relation to alkyl

and alkoxy groups means that the alkyl or alkoxy group contains 1 to 6, preferably 1 to 4, carbon atoms.

The conversion of the compound having formula I into the compound having formula VI may be carried out in a variety of ways. One may plan routes by combining reactions known for the conversion of one carboxylic acid derivative into another.

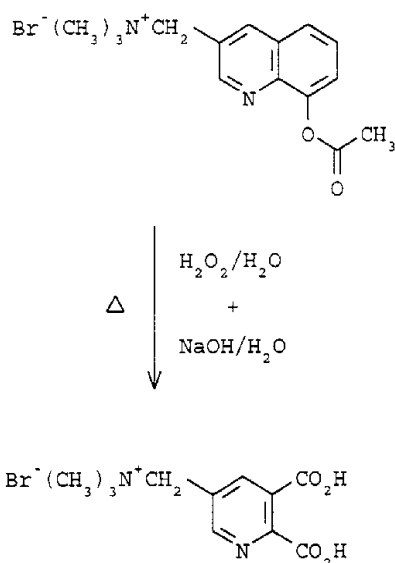
Methods that may be used to create the imidazolinone herbicides are illustrated in the book "The Imidazolinone Herbicides" edited by D.L. Shaner and S.L. O'Connor, published 1991 by CRC Press, Boca Raton, Florida with particular reference to Chapter 2 entitled "Synthesis of the Imidazolinone Herbicides", pages 8-14 and the references cited therein. The following patent literature references also illustrate the methods that may be used to convert the carboxylic acid derivatives into imidazolinone final products:

U.S. Patent Nos. 5,378,843; 5,371,229; 5,520,694;
5,110,930; 5,122,608; 5,206,368; 4,925,944;
4,921,961; 4,959,476; 5,103,009; 4,816,588;
4,757,146; 4,798,619; 4,766,218; 5,001,254;
5,021,078; 4,723,011; 4,709,036; 4,658,030;
4,608,079; 4,719,303; 4,562,257; 4,518,780;
4,4474,962; 4,623,726; 4,750,978; 4,638,068;
4,439,607; 4,459,408; 4,459,409; 4,460,776;
4,125,727 and 4,758,667, and European Patent
Application Nos. EP-A-0-041,623; EP-A-0-331,899 and
EP-A-0-388,619.

In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating more specific details thereof. The invention should not be deemed limited by the examples as the full scope of the invention is defined in the claims.

EXAMPLE 1

Preparation of [(5,6-Dicarboxy-3-pyridyl)methyl]tri-
methylammonium bromide



- 5 Hydrogen peroxide solution (20 g, 30 wt/wt%, 12 equivalents) is added to a stirred solution of [(8-acetoxy-3-quinolyl)methyl]trimethylammonium bromide (5.0 g, 14.7 mmol) and sodium hydroxide solution (9.4 g, 50 wt/wt%, 8 equivalents) at 85 ° to 90 °C over 15 minutes.
- 10 The resultant reaction mixture is stirred at 85 ° to 90 °C for 90 minutes, treated with additional hydrogen peroxide solution (26 g, 30 wt/wt%, 15.6 equivalents) at 85 °C over 30 minutes, and stirred at 85 ° to 90 °C for one hour. LC analysis of the final reaction mixture indicates that the
- 15 title product is produced in 80% yield.

EXAMPLES 2-4

Using essentially the same procedure as described in Example 1, but using various [(8-substituted-3-quinolyl)-methyl]trimethylammonium bromides, [(5,6-dicarboxy-3-
5 pyridyl)methyl]trimethylammonium bromide is produced in the yields shown in Table I.

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6
7
8
9

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TABLE I
Preparation of [(5,6-Dicarboxy-3-pyridyl)methyl]trimethylammonium bromide

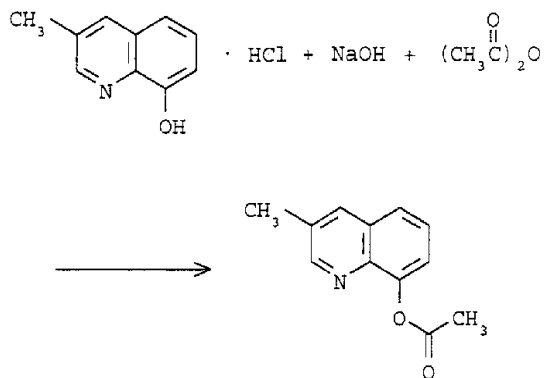


Example	R ₄	Equivalents of 50 wt/wt% NaOH Solution	Equivalents of 30 wt/wt% H ₂ O ₂ Solution	Hours Stirred at 85° to 90°C	% Yield ¹ of I
2	OH	8	38	1.83	86
3	OCO ₂ CH ₃	9.8	58	1.75	83
4	NO ₂	8	32	2.58	45

¹ Determined by LC analysis of reaction mixture

EXAMPLE 5

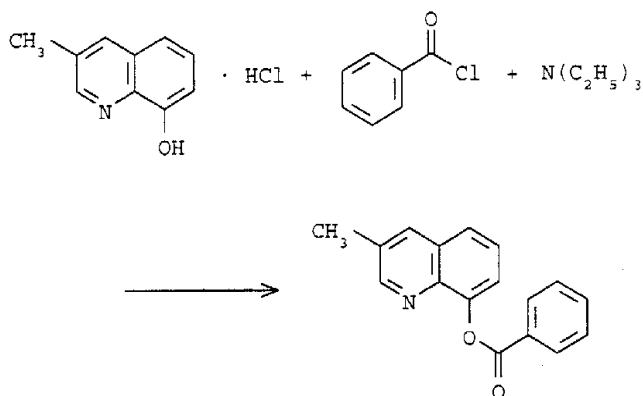
Preparation of 8-Acetoxy-3-methylquinoline



5 A mixture of the hydrochloride salt of 8-hydroxy-3-
methylquinoline (200 g, 1.02 mol) and sodium hydroxide
(102 g, 2.55 mol) in water (1,000 mL) is treated with
acetic anhydride (208 g, 2.04 mol) at 0 ° to 10 °C over 1
hour and stirred at room temperature for 1 hour. An
additional portion of acetic anhydride (50 g, 0.49 mol)
10 is added and the resultant mixture is stirred for one
hour, treated with saturated sodium bicarbonate solution
(100 mL) and filtered to obtain a solid. The solid is
washed with water, dried at 60 °C in a vacuum oven and
recrystallized from an ethyl acetate/heptane solution to
15 give the title product as white needles (168.5 g, 82%
yield).

EXAMPLE 6

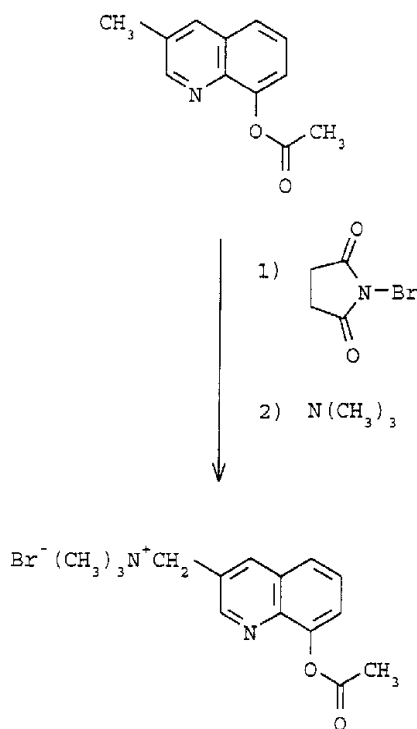
Preparation of 8-Benzoyloxy-3-methylquinoline



A mixture of the hydrochloride salt of 8-hydroxy-3-
5 methylquinoline (10 g, 0.051 mol) and triethylamine
(15.5 g, 0.15 mol) in methylene chloride (100 mL) is
treated with benzoyl chloride (10.8 g, 0.077 mol) at 0 °
to 10 °C over 1 hour, stirred at room temperature for
three hours and diluted with water. The phases are
10 separated, and the organic phase is washed with water,
dried over anhydrous magnesium sulfate and concentrated
in vacuo to obtain solid. The solid is recrystallized
from a heptane/toluene solution to give the title product
as pale yellow crystals (8.8 g, 65% yield).

EXAMPLE 7

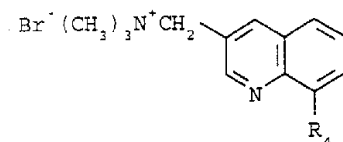
Preparation of [(8-Acetoxy-3-methylquinolyl)methyl]tri-
methylammonium bromide



5 A solution of 8-acetoxy-3-methylquinoline (168.5 g,
0.84 mol), N-bromosuccinimide (177.9 g, 1.00 mol) and
2,2'-azobisisobutyronitrile (6.7 g, 0.04 mol) in
chlorobenzene (1,675 mL) is purged with nitrogen, heated
at 80 ° to 90 °C under nitrogen for 2 hours, cooled to
10 room temperature and filtered. A mixture of the filtrate
in acetone (700 mL) is treated with trimethylamine (75.4

g, 1.28 mol) at 0 ° to 5 °C, stirred at 5 ° to 10 °C for 30 minutes, stirred at room temperature for 1 hour and filtered to obtain a solid. The solid is washed with acetone and dried at 60 °C in a vacuum oven to give the title product as a white solid (180 g, 63% overall yield).

Using essentially the same procedure, but using various 8-substituted-3-methylquinolines, the following compounds are obtained.



R₄

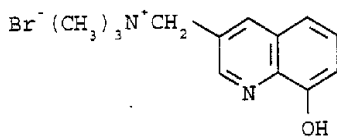
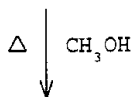
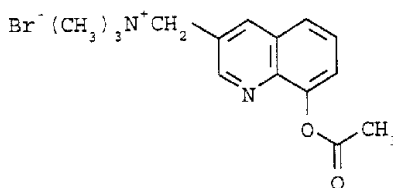
OC(O)C₆H₅

OC(O)OCH₃

NO₂

EXAMPLE 8

Preparation of [(8-Hydroxy-3-quinolyl)methyl]tri-
methylammonium bromide

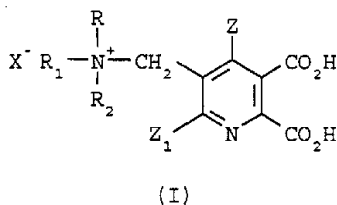


5 A solution of [(8-acetoxy-3-quinolyl)methyl]tri-
methylammonium bromide (5.0 g, 14.7 mmol) in methanol is
refluxed for 13.5 hours and concentrated *in vacuo* to
obtain a residue. The residue is dried in a vacuum oven
at 60 °C to give the title product as an off-white solid
10 (4.4 g, 100% yield).

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~~CLAIM:~~ The claims defining the invention are as follows:

1. A process for the preparation of a [(5,6-dicarboxy-3-pyridyl)methyl]ammonium halide having the structural formula I



wherein

R, R₁ and R₂ are each independently C₁-C₄alkyl, and when taken together, R and R₁ may form a 5- or 6-membered ring optionally interrupted by O, S or NR₃;

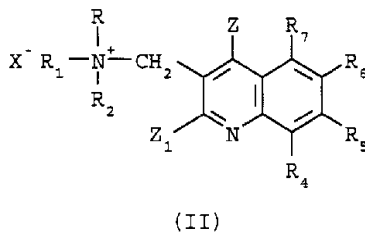
R₃ is C₁-C₄alkyl;

X is Cl, Br or I;

Z is hydrogen or halogen; and

Z₁ is hydrogen, halogen, cyano or nitro,

which process comprises oxidizing a substituted (3-quinolylmethyl)ammonium halide having the structural formula II



wherein

R, R₁, R₂, X, Z and Z₁ are as described for formula I above;

R₄, R₅, R₆ and R₇ are each independently hydrogen, hydroxy, nitro, OC(O)R₈, halogen, NR₉R₁₀, C₁-C₄alkoxy, SO₃H, SO₂Cl or SH, with the proviso that one of R₄, R₅, R₆ and R₇ is other than hydrogen or halogen;

R₈ is C₁-C₄alkyl, C₁-C₄alkoxy, phenyl or NR₁₁R₁₂;

R₉, R₁₀, R₁₁ and R₁₂ are each independently hydrogen, C₁-C₄alkyl or phenyl;

the N-oxides thereof; and

the acid addition salts thereof,

with hydrogen peroxide in the presence of aqueous base.

2. The process according to claim 1 wherein

R, R₁ and R₂ are each independently C₁-C₄alkyl;

X is Cl or Br;

Z and Z₁ are hydrogen;

at least one of R₄, R₅, R₆ and R₇ is hydroxy, nitro or OC(O)R₈; and

R₈ is C₁-C₄alkyl, C₁-C₄alkoxy or phenyl.

3. The process according to claim 2 wherein

R, R₁ and R₂ are methyl;

X is Br;

R₅, R₆, R₇, Z and Z₁ are hydrogen;

R₄ is hydroxy, nitro or OC(O)R₈; and

R₈ is C₁-C₄alkyl or C₁-C₄alkoxy.

4. The process according to claim 1 wherein the hydrogen peroxide is present in an amount from about 8 to 60 molar equivalents relative to the formula II substituted (3-quinolylmethyl)ammonium halide.

5. The process according to claim 1 wherein the aqueous base is present in an amount of at least about one molar equivalent relative to the formula II substituted (3-quinolylmethyl)ammonium halide.

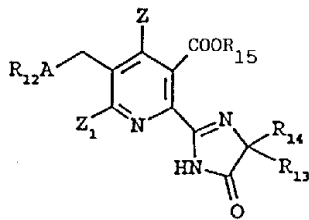
6. The process according to claim 5 wherein the aqueous base is present in an amount from about 4 to 10 molar equivalents.

7. The process according to claim 1 wherein the aqueous base is aqueous sodium hydroxide or aqueous potassium hydroxide.

8. The process according to claim 1 wherein the formula II substituted (3-quinolylmethyl)ammonium halide is oxidized with hydrogen peroxide in the presence of an aqueous base at a temperature range of about 50 °C to 100 °C.

9. The process according to claim 8 wherein the temperature is about 75 °C to 95 °C.

10. A process for the preparation of a herbicidal imidazolinone compound having the formula VI



(VI)

wherein



Z and Z₁ are as defined in claim 1;

A is O or S;

R₁₂ is C₁-C₄ alkyl optionally substituted with phenyl optionally substituted with one to three C₁-C₄ alkyl groups or halogen atoms, or phenyl optionally substituted with one to three C₁-C₄ alkyl groups or halogen atoms;

R₁₃ is C₁-C₄ alkyl;

R₁₄ is C₁-C₄ alkyl, C₃-C₆ cycloalkyl or R₁₃ and R₁₄ when taken together with the atom to which they are attached, represent a C₃-C₆ cycloalkyl group optionally substituted with methyl and

R₁₅ is hydrogen, diloweralkylimino,

C₁-C₁₂ alkyl optionally substituted with one of the following groups: C₁-C₃ alkoxy, halogen, hydroxy, C₃-C₆ cycloalkyl, benzyloxy, furyl, phenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, nitrophenyl, carboxyl, loweralkoxycarbonyl, cyano or triloweralkylammonium;

C₃-C₁₂ alkenyl optionally substituted with one of the following groups: C₁-C₃ alkoxy, phenyl, halogen or loweralkoxycarbonyl or with two C₁-C₃ alkoxy groups or two halogen groups;

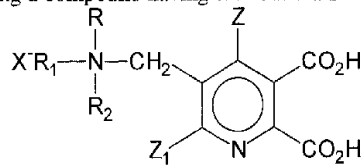
C₃-C₆ cycloalkyl optionally substituted with one or two C₁-C₃ alkyl groups; or

a cation and when

R₁₃ and R₁₄ represent different substituents, the optical isomers thereof;

which process comprises:

(a) preparing a compound having the formula I



wherein Z, Z₁, R, R₁, R₂ and X are defined in claim 1 by a process as claimed in claim
5 1; and

(b) converting the compound having formula I into the compound having the
formula VI.

11. A process for the preparation of a [(5,6-dicarboxy-3-pyridyl)methyl]
ammonium halide, substantially as hereinbefore described with reference to any one of the
10 Examples.

12. A [(5,6-dicarboxy-3-pyridyl)methyl] ammonium halide prepared by the
process of any one of claims 1 to 9 or 11.

13. A process for the preparation of a herbicidal imidazolinone, substantially as
hereinbefore described with reference to any one of the Examples.

15 14. A herbicidal imidazolinone prepared by the process of claim 10 or claim 13.

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