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(54) Titre : PROCEDE POUR LA FABRICATION DE 2-ALKOXYMETHYLACROLEINE
(54) Title: PROCESS FOR THE MANUFACTURE OF 2-ALKOXYMETHYLACROLEIN

(57) Abrégé/Abstract:
There is provided a process for the manufacture of 2-alkoxymethylacrolein compounds via the reaction of an appropriate alcohol and acrolein in the presence of an acid and a trisubstituted amine to form an intermediate and the subsequent reaction of the intermediate with formaldehyde in the presence of an acid and a disubstituted mine. There is also provided a process for the manufacture of 3-alkoxymethyl-quinolines from 2-alkoxymethylacrolein.

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PROCESS FOR THE MANUFACTURE OF 2-ALKOXYMETHYLACROLEIN

ABSTRACT OF THE INVENTION

There is provided a process for the manufacture of 2-alkoxymethylacrolein compounds via the reaction of an appropriate alcohol and acrolein in the presence of an acid and a trisubstituted amine to form an intermediate and the subsequent reaction of the intermediate with formaldehyde in the presence of an acid and a disubstituted amine. There is also provided a process for the manufacture of 3-alkoxymethylquinolines from 2-alkoxymethylacrolein.

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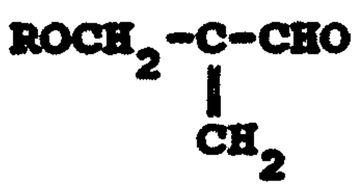
PROCESS FOR THE MANUFACTURE OF 2-ALKOXYMETHYLACROLEIN

This invention provides a convenient and effective method for the manufacture of 2-alkoxymethylacrolein compounds useful in the preparation of pyridine and quinoline herbicide intermediates. There is also provided a process for the manufacture of 3-alkoxymethylquinolines from 2-alkoxymethylacrolein.

The present invention relates to a process for the manufacture of compounds of formula I



(I)

wherein R is C_1 to C_6alkyl.

The formula I alkoxymethylacrolein compound is prepared by reacting an alcohol, ROH wherein R is as described for formula I, with at least one molar equivalent of acrolein in the presence of an acid, a catalytic amount of a trisubstituted amine and a solvent to form an intermediate and reacting said intermediate with at least one molar equivalent of formaldehyde in the presence of an acid, a catalytic amount of disubstituted amine and a solvent to obtain the desired formula I compound.

The invention further relates to a process for the manufacture of 2-alkoxymethylacrolein compounds

of formula I which comprises reacting a suitable compound of formula II

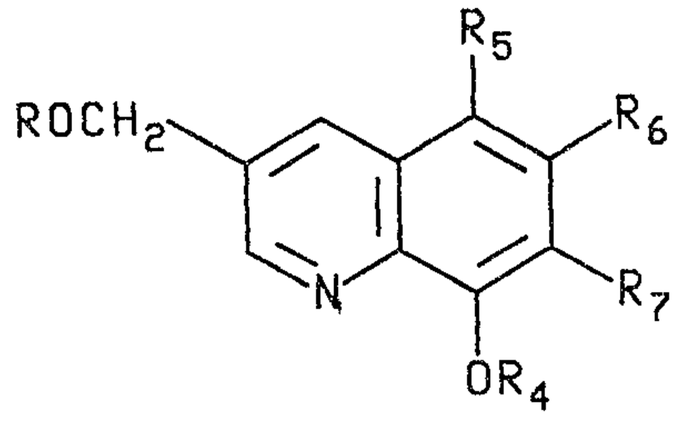
$$ROCH_2CH_2-W$$

(II)

wherein R is as described for formula I and W is CHO or $CH(OR_1)_2$ and R_1 is C_1 to C_4alkyl, with at least one molar equivalent of formaldehyde in the presence of an acid, a catalytic amount of a disubstituted amine and a solvent.

The invention also relates to the use of compounds of formula I in the manufacture of important quinoline and pyridine herbicidal intermediates.

The present invention provides a process for the manufacture of compounds of formula I. The compounds of formula I may be used to prepare 3-alkoxymethylquinolines and 5-alkoxymethylpyridine-2,3-dicarboxylates which are key intermediate compounds in the preparation of 2-(imidazolin-2-yl)nicotinate herbicides. For example, the formula I compounds of the present invention may be used to prepare 3-alkoxymethylquinolines of formula III



(III)

wherein
R is C_1-C_6alkyl;
R_4 is hydrogen or C_1-C_4alkyl; and
R_5, R_6 and R_7 are each independently hydrogen or OR_4.

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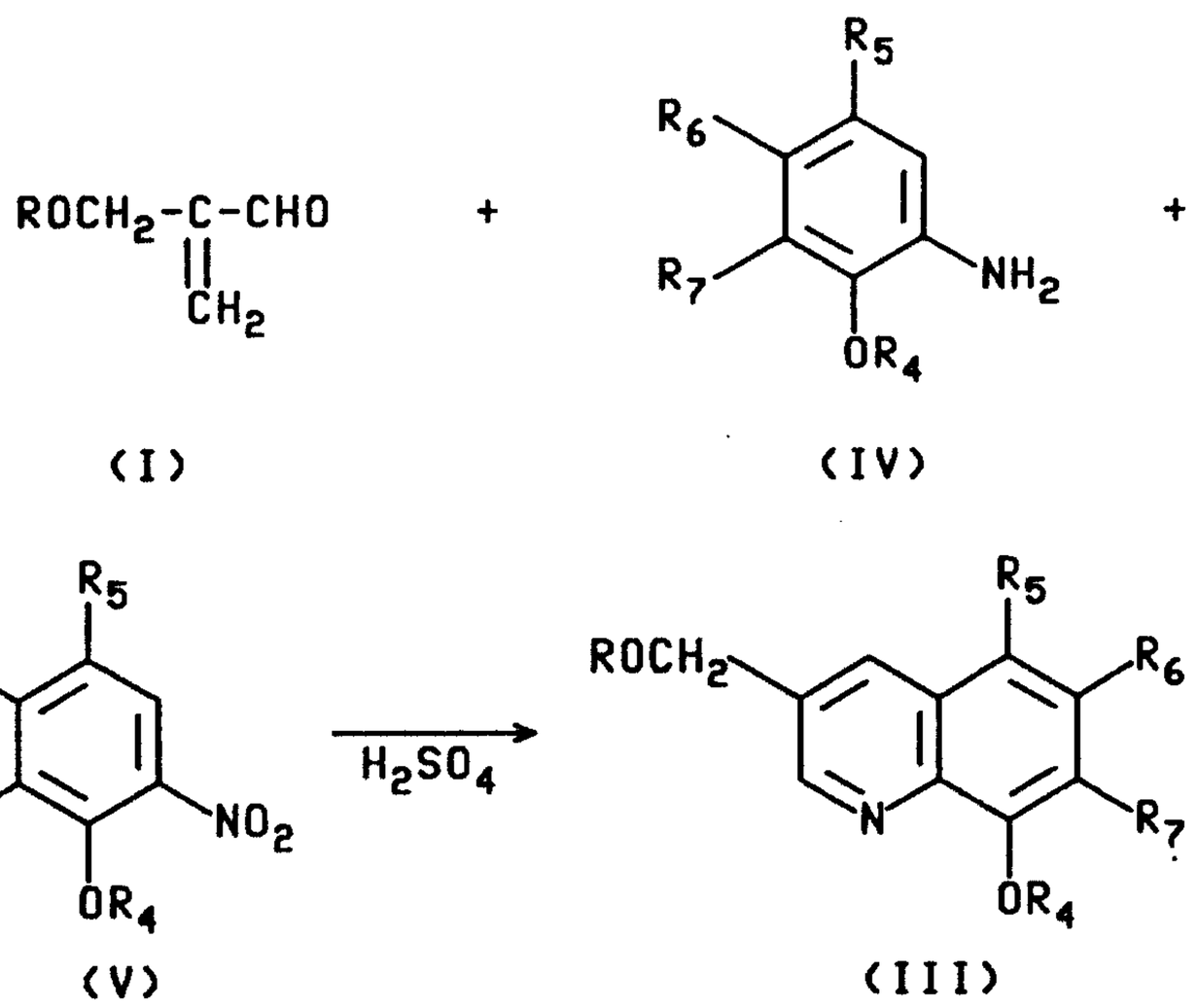
3-Alkoxymethylquinolines may be prepared by reacting a substituted aniline of formula IV with at least one molar equivalent of a 2-alkoxymethylacrolein of formula I in the presence of an acid and a solvent and optionally in the presence of a substituted nitrobenzene of formula V, preferably at an elevated temperature, to form desired formula III compounds. The above reaction scheme is shown in flow diagram I.

FLOW DIAGRAM I

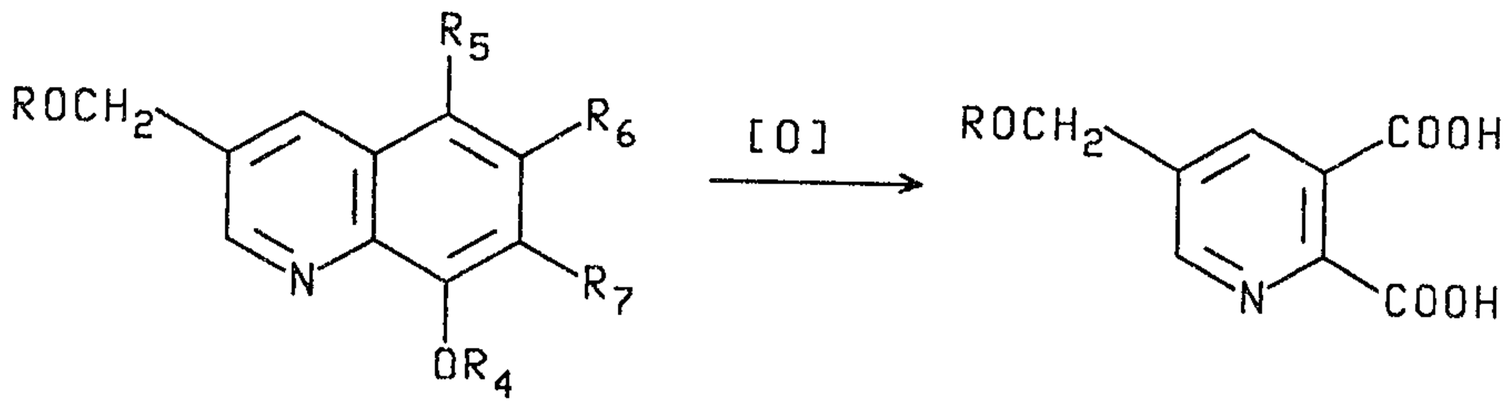


Acids suitable for use in the process used to prepare formula III compounds are strong organic and mineral acids such as sulfuric acid, phosphoric acid, hydrobromic acid and hydrochloric acid. Solvents suitable for use in the process used to prepare formula III compounds are water and ROH alcohols wherein R is C_1-C_6alkyl. **Preferred solvents are ROH alcohols wherein R corresponds to the R of the formula I compound with methanol being a most preferred solvent. Reaction temperatures of from about 30°C to 120°C, preferably about 50°C to**

110°C, are suitable for use in the process used to prepare formula III compounds.

The thus-obtained formula III 3-alkoxymethylquinoline compounds may be oxidized to form 5-alkoxymethylpyridine-2,3-dicarboxylic acids of formula VI. The above reaction scheme is shown in flow diagram II.

FLOW DIAGRAM II

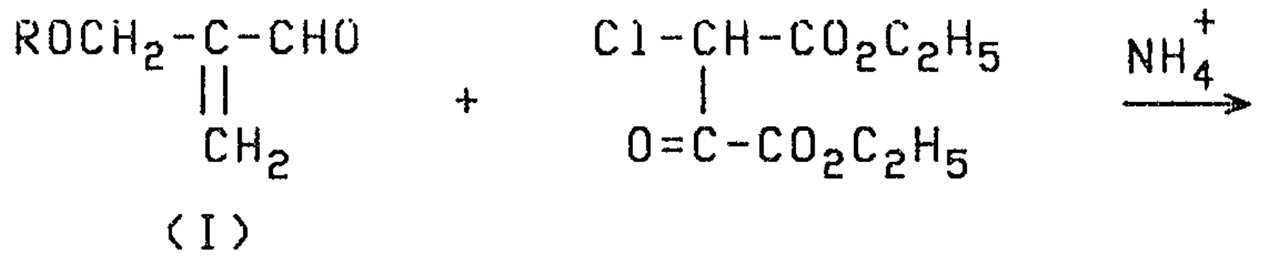


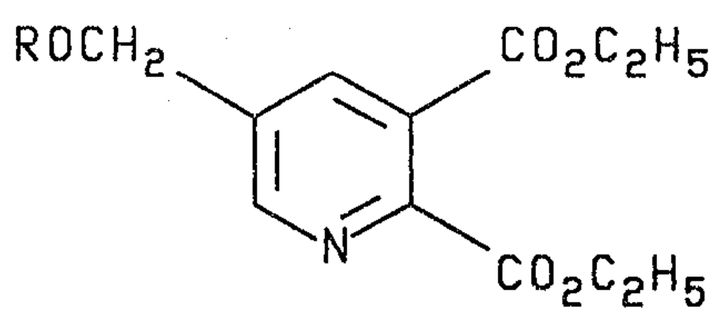
(III) (VI)

Among the methods suitable to oxidize formula III compounds to formula VI compounds are nitric acid oxidation, base peroxide oxidation, base peroxide followed by sodium hypochlorite oxidation, chlorate catalyzed by vanadium oxidation, ozone oxidation and the like.

Advantageously, the formula I compounds of the present invention may also be reacted with an α-halo-β-keto ester in the presence of an ammonium salt to form the corresponding pyridine-2,3-dicarboxylate product as shown in flow diagram III.

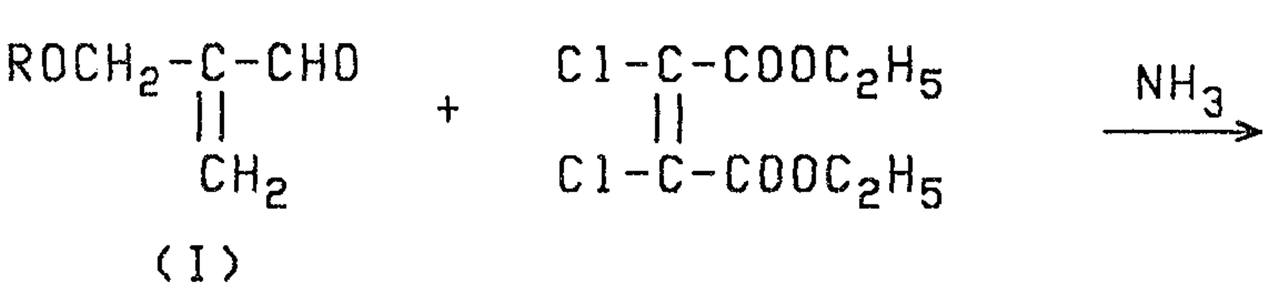
Flow Diagram III

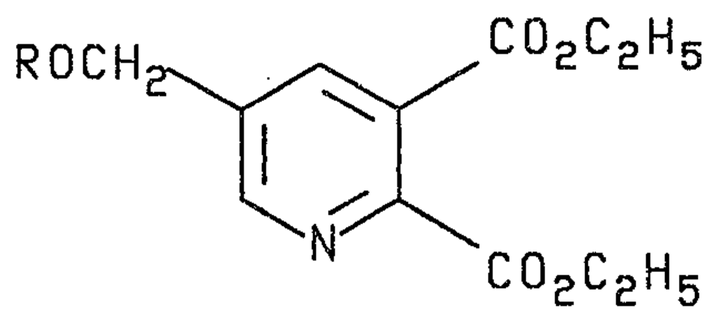




Further, 2-alkoxymethylacrolein compounds of formula I may be reacted with a dialkyl dihalomaleate in the presence of ammonia to form the desired pyridinedicarboxylate product as shown in flow diagram IV.

Flow Diagram IV





It has now been found, that the alkoxymethyl compounds of formula I may be effectively prepared in an efficient process from readily available starting materials. In accordance with the method of invention, an appropriate alcohol having the formula, ROH wherein R is C_1 to C_6 alkyl, may be reacted with at least one molar equivalent of acrolein in the presence of an acid, a catalytic amount of a trisubstituted amine and a solvent to form an intermediate and the intermediate may be reacted with at least one molar equivalent of formaldehyde in the presence of an acid, a disubstituted amine and a solvent to form the desired formula I alkoxymethylacrolein compound. The reaction is shown in flow diagram V.

Flow Diagram V

$$ROH + CH_2{=}CH{-}CHO \xrightarrow[2.\ HCHO]{1.\ H^+,N(R_2)_3} ROCH_2{-}\underset{\underset{CH_2}{\|}}{C}{-}CHO$$

$H^+,NH(R_3)_2$

(I)

In general, the formation of the intermediate and the formula I product are temperature dependent, that is, increased reaction temperature increases the rate of formation. Convenient reaction times may be obtained by increasing the reaction temperature to about 20° to 110°C, preferably about 75° to 100°C. Suitable reaction solvents are water or mixtures of water and a water-miscible organic solvent. Acids suitable for use in the present process are strong

mineral acids, preferably polybasic acids such as sulfuric acid and phosphoric acid. Trisubstituted amines, $N(R_2)_3$, wherein R_2 is C_1-C_4alkyl, C_1-C_4alkanol and the like, preferably triethylamine or triethanolamine, are suitable for use in the present invention. Disubstitued amines, $NH(R_3)_2$, wherein R_3 is C_1-C_6alkyl, preferably dibutylamine, may be used in the inventive process. It is intended formaldehyde be used in any of its readily available forms and preferably as an aqueous solution of about 37% concentration.

Advantageously, compounds of formula I may also be prepared by reacting a compound of formula II

$$ROCH_2CH_2-W$$

(II)

wherein R is C_1-C_6alkyl and W is CHO or $CH(OR_1)_2$ and R_1 is C_1-C_4alkyl, with at least one molar equivalent of formaldehyde in the presence of an acid, a catalytic amount of a disubstituted amine, $NH(R_3)_2$ wherein R_3 is C_1-C_4alkyl, and a solvent. The reaction is shown in flow diagram VI.

Flow Diagram VI

$$ROCH_2CH_2W + HCHO \xrightarrow{1.\ H^+,\ NH(R_3)_2} ROCH_2-\underset{\underset{CH_2}{\|}}{C}-CHO$$

(II) (I)

Compounds of formula II may be prepared according to methods known in the art. The formaldehyde employed in the above process may be in any of its readily available forms and preferably as an

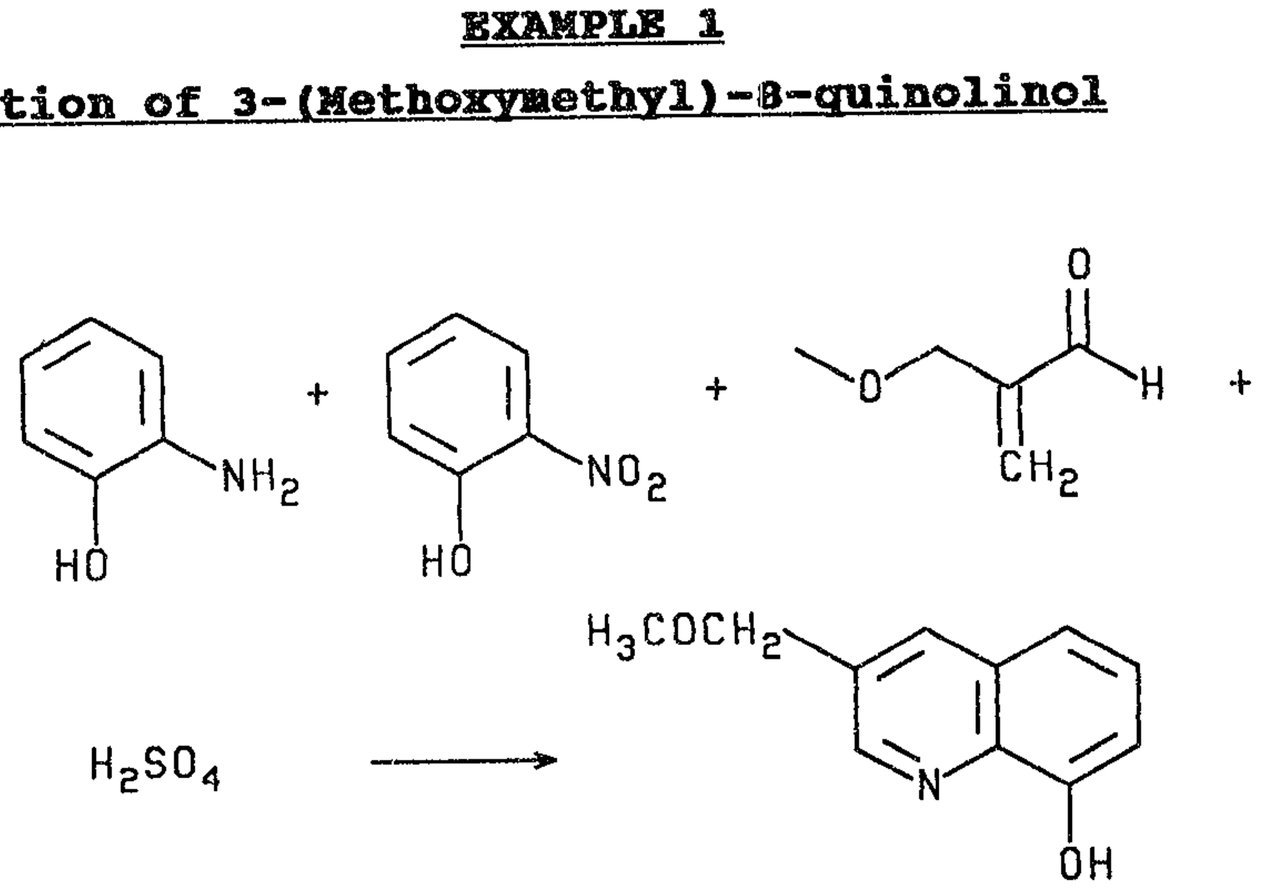
aqueous solution of about 37%. Acids suitable for use are strong mineral acids such as those mentioned hereinabove and preferably sulfuric acid or phosphoric acid. The reaction is temperature dependent, therefore convenient reaction times may be obtained by elevating the reaction temperature to about 20° to 110°C, preferably about 75° to 100°C.

In order to present a more clear understanding of the invention, the following examples are set forth. The examples are primarily for the purpose of demonstrating more specific details thereof and the invention is not to be limited thereby except as defined in the claims.

Unless otherwise noted, all parts are parts by weight. The term NMR designates nuclear magnetic resonance spectroscopy.

EXAMPLE 1

Preparation of 3-(Methoxymethyl)-8-quinolinol



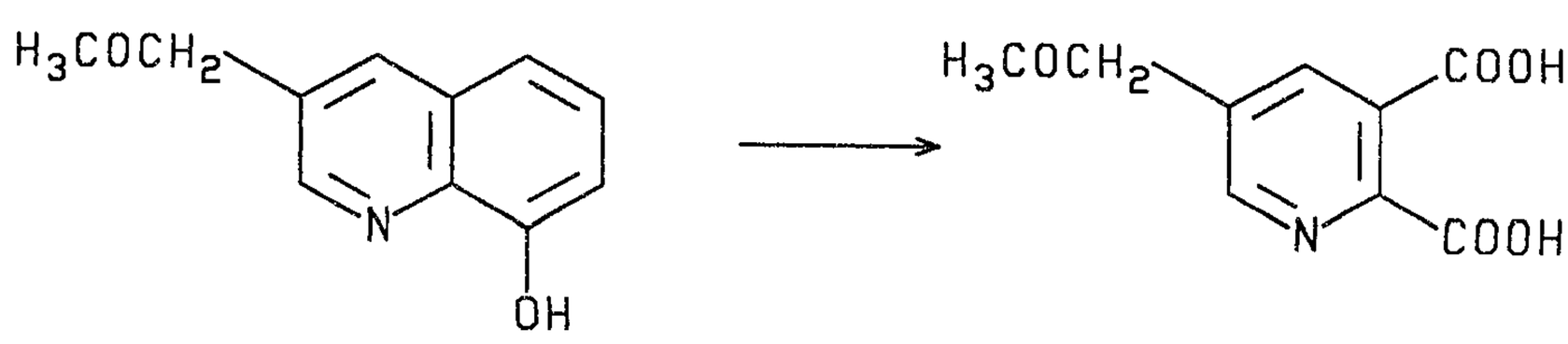
A solution of methanol and sulfuric acid (10.0 g, 0.1 mol) is heated to 65°C, treated with o-aminophenol (4.36 g, 0.04 mol) and o-nitrophenol (2.78 g, 0.02 mol), heated to 70°C, treated with methoxymethacrolein (6.0 g, 0.06 mol) over 40 minutes

at 85° to 90°C and diluted with water. The aqueous mixture is adjusted to about pH 2 with 50% sodium hydroxide solution and filtered. The filtrate is adjusted to about pH 7 with 50% sodium hydroxide solution and extracted with chloroform. The combined organic extracts are concentrated *in vacuo* to give the title product as a solid which is identified by ^{1}H and $^{13}CNMR$ spectral analyses.

Using essentially the same procedure, but substituting *o*-anisidine for *o*-aminophenol, 8-methoxy-3-(methoxymethyl)quinoline is obtained.

EXAMPLE 2

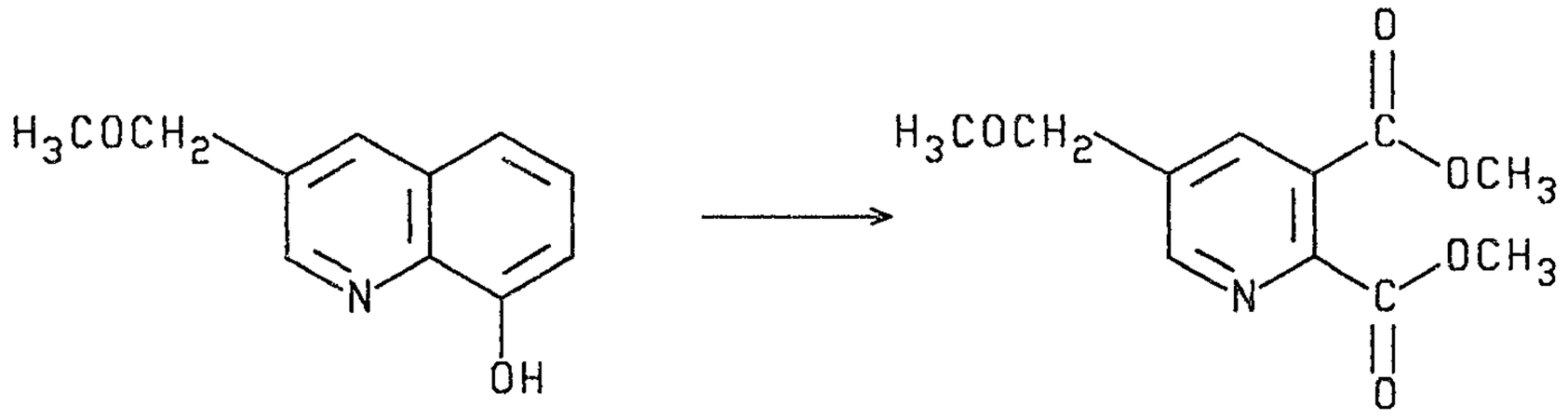
Preparation of 5-(Methoxymethyl)-2,3-pyridinedicarboxylic acid



A mixture of 3-(methoxymethyl)-8-quinolinol (0.92 g, 4.9 mmol) in water is treated with 50% sodium hydroxide solution (1.0 g real, 25.0 mmol), heated to 85°C and treated with 30% hydrogen peroxide solution (3.4 g real, 100.0 mmol) over 2 hours while maintaining the temperature between 65°-90°C. The reaction mixture (26.0 g) is then cooled to room temperature, assayed by HPLC and found to contain 3.15% of the title product (80% yield).

EXAMPLE 3

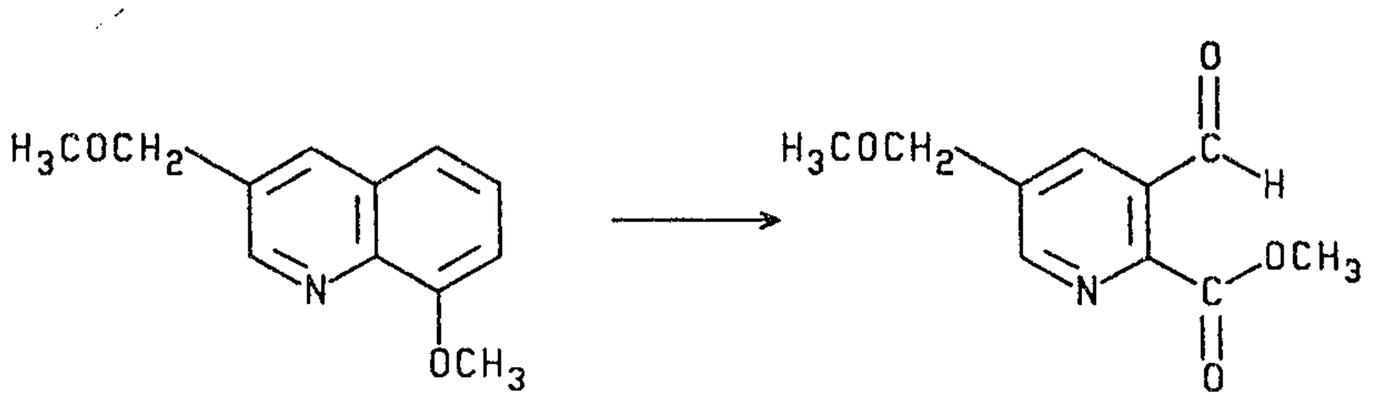
Preparation of Dimethyl 5-(methoxymethyl)-2,3-pyridine-dicarboxylate



Ozone is bubbled through a solution of 3-(methoxymethyl)-8-quinolinol (0.145 g, 0.78 mmol) in 90% acetic acid at room temperature. After 20 minutes, the reaction mixture is concentrated *in vacuo* and the resulting solid is dissolved in 95% ethanol and treated with excess diazomethane. After stirring at room temperature for 14 hours, the reaction mixture is treated with acetic acid and concentrated *in vacuo* to give a yellow oil. Flash chromatography of the oil using silica gel and a 4:1 to 2:1 hexanes/ethyl acetate solution gives the title product as a colorless oil, 0.072 g (41% yield), which is identified by ^{1}H and $^{13}CNMR$ spectral analyses.

EXAMPLE 4

Preparation of Methyl 3-formyl-5-(methoxymethyl)-picolinate



Ozone is bubbled through a solution of 8-methoxy-3-(methoxymethyl)quinoline (0.134 g, 0.66 mmol) in a 9:1 acetonitrile/water mixture at 0°C. After 10 minutes, the reaction mixture is concentrated *in vacuo* and the resulting oil is dissolved in methanol and treated with excess diazomethane. After stirring for 14 hours at room temperature, the reaction mixture is treated with acetic acid and concentrated *in vacuo* to obtain a red oil. Flash chromatography of the oil using silica gel and a 3:1 hexanes/ethyl acetate mixture gives the title product as a colorless oil which is identified by ^{1}HNMR spectral analysis.

Using essentially the same procedure, but substituting 90% acetic acid for the 9:1 acetonitrile/water mixture, the title product is obtained as a colorless oil which is identified by ^{1}HNMR spectral analysis.

EXAMPLE 5

Preparation of 2-methoxymethylacrolein from acrolein

A stirred mixture of acrolein (112g, 2.0 mole), methanol (310g, 9.08 mole), triethanolamine (7.5g, 0.05 mole) and 85% phosphoric acid (5.7g, 0.049 mole) in water is heated at reflux temperature for 9 hours, cooled to room temperature and filtered. The filtrate is diluted with water and treated with a 37% formaldehyde solution (162g, 2.0 mole formaldehyde), concentrated sulfuric acid (11.6g, 0.11 mole), and dibutylamine (27g, 0.21 mole), heated at reflux temperature for 4 hours, cooled to room temperature and extracted with methylene chloride. The extracts are combined and concentrated and the concentrate is vacuum distilled to give the title product, 88g (44% yield) bp 64-66°/70mm Hg, identified by NMR analysis.

EXAMPLE 6

Preparation of 2-ethoxymethylacrolein from acrolein

A stirred mixture of anhydrous ethanol (235.5g, 5.12 mole) and acrolein (77.3g, 1.38 mole) is treated with 0.7 ml concentrated HCl and NH_4Cl (6.0g, 0.11 mole) and heated to reflux temperature over a 3 hour period. The reaction mixture is heated at reflux temperatures for 18 hours in a flask fitted with a 1 Dean Stark trap. The trap is removed and the reaction mixture is vacuum distilled. The distillate is redistilled, and 42g is added to a stirred mixture of water, 0.8g of concentrated H_2SO_4, hydroquinone (0.05g, 0.45 mmole) and dibutylamine (1.78g, 0.014 mole). A 37% formaldehyde solution (19.5g, 0.24 mole) is added to the reaction mixture simultaneously at 80°-85°C. The reaction mixture is stirred for 6 hours at 80°-85°C, cooled to room temperature and extracted with hexanes. The extracts are combined and fractionally distilled to yield the title product, identified by NMR analysis.

EXAMPLE 7

Preparation of 2-methoxymethylacrolein from 1,1,3-trimethoxypropane

To a mixture of 96% sulfuric acid (3.0g, 0.024 mole), dibutylamine (6.7g, 0.052 mole) and hydroquinone (1.6g, 0.013 mole) in water at 85°C, is added a mixture of 1,1,3-trimethoxypropane (120.6g, 0.90 mole) and 37% formaldehyde solution (84g, 1.1 mole formaldehyde) over a 1.25 hour period. The reaction mixture is heated at reflux temperature for 5 hours, cooled to room temperature and extracted with methylene chloride. The extracts are combined and fractionally distilled to give the title product, identified by NMR analysis.

EXAMPLE 8

Preparation of 2-methoxymethylacrolein from β-methoxymethylpropionaldehyde

A mixture of β-methoxymethylpropionaldehyde (44g, 0.43 mole), 37% formaldehyde (40.5g, 0.52 mole), dibutylamine (6.8g, 0.053 mole), 96% sulfuric acid (3.0g, 0.029 mole) and hydroquinone (0.6g, 0.055 mole) in water is heated at reflux temperature for 2 hours, cooled to room temperature and extracted with methylene chloride. The extracts are combined and fractionally distilled to give the title product, 20.5g (48% yield), identified by NMR analysis.

EXAMPLE 9

Preparation of 2-alkoxymethylacrolein from β-alkoxymethylpropionaldehyde

Using essentially the same procedure described in Example 4 and substituting the appropriate β-alkoxymethylpropionaldehyde, the following compounds are obtained: 2-butoxymethylacrolein, 1.4g (28% yield), identified by NMR analysis and 2-isopropoxymethylacrolein, 1.4g (22% yield), identified by NMR analysis.

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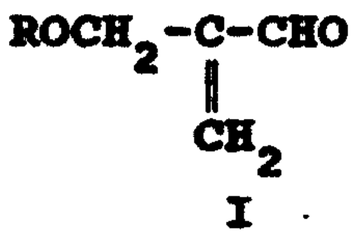
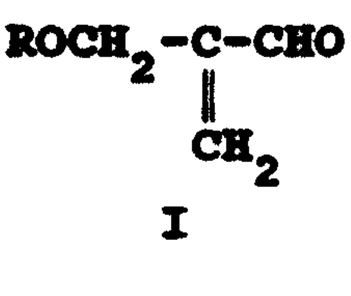
CLAIMS:

1. A process for the manufacture of a compound of formula I



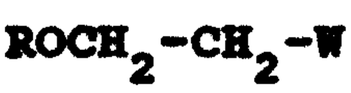
wherein R is C_1 to C_6 alkyl, comprising
reacting ROH wherein R is C_1 to C_6 alkyl with at least one molar equivalent of acrolein in the presence of a mineral acid, a catalytic amount of a trisubstituted amine and a solvent, wherein the solvent is water or a mixture of water and a water-miscible organic solvent, to form an intermediate and reacting said intermediate with at least one molar equivalent of formaldehyde in the presence of a mineral acid, a catalytic amount of a disubstituted amine and a solvent, wherein the solvent is water or a mixture of water and a water-miscible organic solvent, to form the formula I compound.

2. A process for the manufacture of a compound of formula I



I

wherein R is C_1 to C_6alkyl, comprising
reacting a compound of formula II



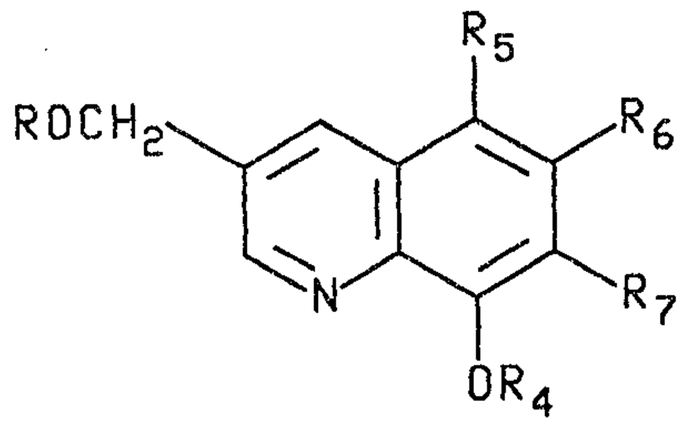
II

wherein R is C_1 to C_6 alkyl and W is CHO or $CH(OR_1)_2$ and R_1 is C_1-C_4 alkyl, with at least one molar equivalent of formaldehyde in the presence of a mineral acid, a catalytic amount of a disubstituted amine and a solvent, wherein the solvent is water or a mixture of water and a water-miscible organic solvent.

3. The process according to claim 1 or 2, wherein the reaction temperature is about 20°C to 110°C; the acid is selected from the group consisting of sulfuric acid, phosphoric acid, hydrochloric acid and hydrobromic acid; the trisubstituted amine is selected from the group consisting of tri(C_1-C_4-alkyl)amine and tri(C_1-C_4alkanol)amine and wherein the disubstituted amine is di(C_1-C_4alkyl)amine.

4. The process according to claim 1 or 2 wherein the trisubstituted amine is triethylamine or triethanolamine and wherein the disubstituted amine is dibutylamine.

5. A compound having the structural formula



wherein

R is C_1-C_6alkyl;

R_4 is hydrogen or C_1-C_4alkyl; and

R_5, R_6 and R_7 are each independently hydrogen or OR_4.

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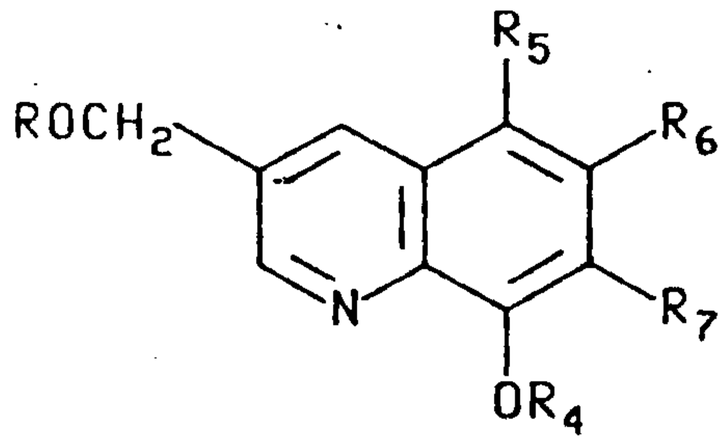
6. The compound according to claim 5 selected from the group consisting of 3-(methoxymethyl)-8-quinolinol and 8-methoxy-3-(methoxymethyl)quinoline.

7. A process for the preparation of a compound of formula III



(III)

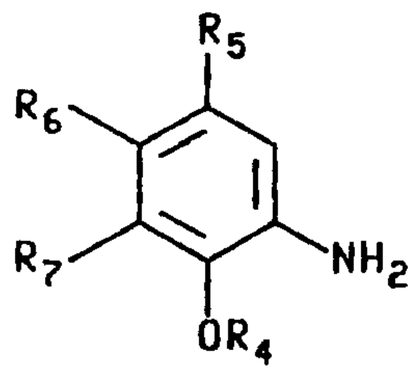
wherein

R is C_1-C_6alkyl;

R_4 is hydrogen or C_1-C_4alkyl; and

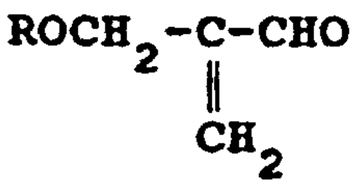
R_5, R_6 and R_7 are each independently hydrogen or OR_4,

comprising reacting a compound of formula IV



(IV)

wherein R_4, R_5, R_6 and R_7 are as defined above with at least one molar equivalent of a compound of formula I



(I)

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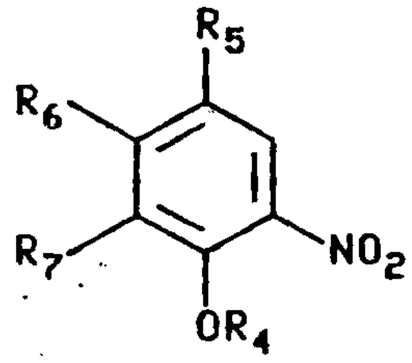
wherein R is as defined above in the presence of an **acid and a solvent and optionally in the presence of a compound of formula V**

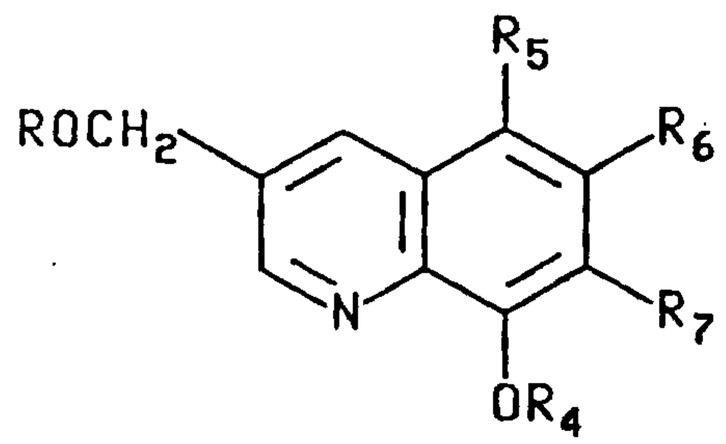


(V)

wherein R_4, R_5, R_6 and R_7 are as defined above to **form the formula III compound.**

8. The process according to claim 7 wherein the formula V compound is present; the reaction temperature is about 30°C to 120°C and the acid is selected from the group consisting of sulfuric acid, phosphoric acid and hydrochloric acid.

9. A process for the preparation of a compound of formula III



(III)

wherein

R is C_1-C_6 alkyl;

R_4 is hydrogen or C_1-C_4 alkyl; and

R_5, R_6 and R_7 are each independently hydrogen or OR_4,

comprising reacting ROH wherein R is C_1

to C_6 alkyl with at least one molar equivalent of

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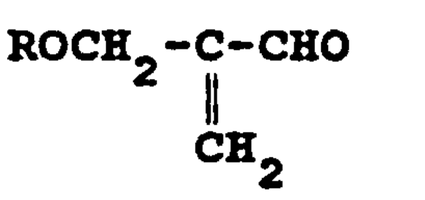
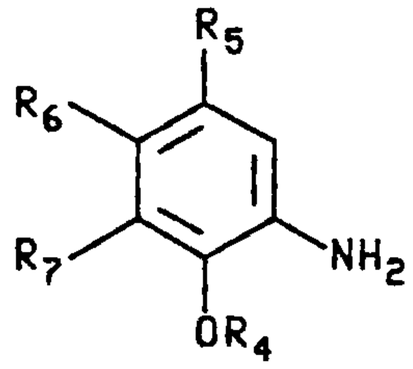
acrolein in the presence of a mineral acid, a catalytic amount of a trisubstituted amine of the formula $N(R_2)_3$, wherein R_2 is C_1-C_4 alkyl or C_1-C_4 alkanol, and a first solvent wherein the first solvent is water or a mixture of water and a water-miscible organic solvent, to form an intermediate and reacting said intermediate with at least one molar equivalent of formaldehyde in the presence of a mineral acid, a catalytic amount of a disubstituted amine of the formula $NH(R_3)_2$, wherein R_3 is C_1-C_6 alkyl, and a second solvent wherein the second solvent is water or a mixture of water and a water-miscible organic solvent to form a compound of formula I



(I)

wherein R is as defined above, reacting at least one molar equivalent of the compound of formula I with a compound of formula IV



(IV)

wherein R_4, R_5, R_6, and R_7 are as defined above, in the presence of an acid and a third solvent and optionally in the presence of a compound of formula V

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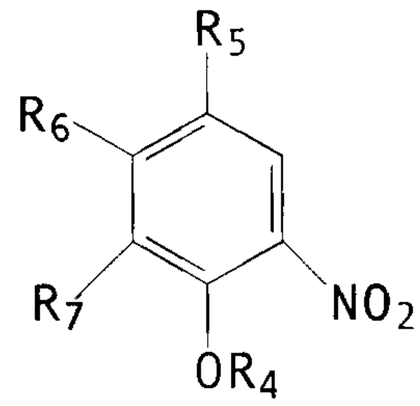

(V)

wherein R_4, R_5, R_6 and R_7 are as defined above to form the formula III compound.

10. The process according to claim 9 wherein the formula V compound is present; the reaction temperature is about 30°C to 120°C in the reaction of the compound of formula I with the compound of formula IV and the compound of formula V; the acid is selected from the group consisting of sulfuric acid, phosphoric acid and hydrochloric acid; and wherein the third solvent is selected from the group consisting of water and a C_1-C_6alcohol.

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