IDOS



33257-00

# PROCESS FOR THE PREPARATION OF 5-(ALKOXYMETHYL)-2,3-PYRIDINEDICARBOXIMIDE COMPOUNDS

## BACKGROUND OF THE INVENTION

5-(Alkoxymethyl)-2,3-pyridinedicarboximide compounds are useful as intermediates in the preparation of herbicidal 5-(alkoxymethyl)-2-(2-imidazolin-2-yl)nicotinic acid, ester and salt compounds. Methods for the preparation of 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are rather limited, and those methods that are available may require extensive purification methods to provide high purity 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds.

European patent application number 308,084-A1 generically discloses that a 5-(alkoxymethyl)-2,3-pyridinedicarboximide compound may be prepared by reacting a substituted oxime compound with a halomaleimide compound optionally in the presence of an inorganic base. However, that method is not satisfactory because it produces a mixture that contains the desired 5-(alkoxymethyl)-2,3-pyridinedicarboximide compound and a relatively high percentage of an undesirable 5-methyl-2,3-pyridinedicarboximide compound. Arduous or time consuming purification methods are then required to obtain high purity 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds. If the mixture is not highly purified, the 5-(alkoxymethyl)-2-(2-imidazolin-2-yl)nicotinic acid, ester or salt compound prepared from the mixture will be

This Sheet Has Been Replaced

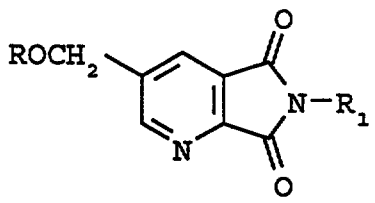
THIS SHEET HAS BEEN REPLACED

contaminated with a 5-methyl-2-(2-imidazolin-2-yl)nicotinic acid, ester or salt compound which has different herbicidal properties than the desired compound.

It is, therefore, an object of the present invention to provide a process for the preparation of high purity 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds.

## SUMMARY OF THE INVENTION

The present invention provides an effective and efficient process for the preparation of a 5-(alkoxymethyl)-2,3-pyridinedicarboximide compound having the structural formula I



(I)

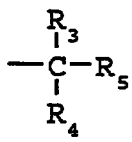
wherein

R is $C_1$-$C_6$alkyl;

$R_1$ is hydrogen, $C_1$-$C_6$alkyl, $C(O)R_2$,

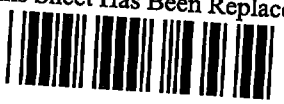
phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups,

benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or



;

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

$R_2$ is $C_1$-$C_6$alkyl,

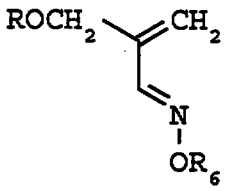
phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or

benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups;

$R_3$ and $R_4$ are each independently $C_1$-$C_4$alkyl; and

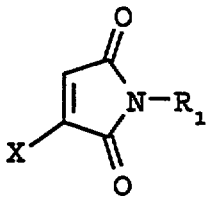
$R_5$ is cyano or $CONH_2$,

which process comprises reacting an oxime of a 2-(alkoxymethyl)-2-propen-1-one compound having the structural formula II



(II)

wherein R is as described above and $R_6$ is hydrogen or $C_1$-$C_6$alkyl with a substituted maleimide compound having the structural formula III



(III)

wherein $R_1$ is as described above and X is halogen, phenylsulfinyl or 1-imidazolyl and a base selected from

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

the group consisting of a tri($C_2$-$C_4$alkyl)amine, an alkali metal acetate and mixtures thereof in the presence of a solvent at an elevated temperature.

Surprisingly, it has been found that 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are obtained in high purity when prepared by the effective and efficient process of the present invention.

In one preferred embodiment of the present invention, an oxime of a 2-(alkoxymethyl)-2-propen-1-one compound represented by formula II is reacted with at least about one molar equivalent of a substituted maleimide compound represented by formula III, and at least about one molar equivalent of a tri($C_2$-$C_4$alkyl)amine or an alkali metal acetate or a mixture thereof, suitably at a temperature of at least 75 °C, e.g. a temperature of at least 90 °C, preferably in a temperature range of about 75 °C to 150 °C, more preferably about 90 °C to 135 °C, in the presence of a solvent having a boiling point of at least about 75 °C.

Advantageously, it has now been found that 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are obtained in high purity by the effective and efficient process of the present invention. In contrast, 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are contaminated with significant amounts of 5-methyl-2,3-pyridinedicarboximide compounds when prepared according to the procedure described in EP 308,084-A1.

The 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds may be isolated by diluting the reaction mixture with water and filtering the formula I product from the aqueous mixture. The product formula I compounds may also be isolated by concentrating the reaction mixture *in vacuo* and filtering the formula I product from the concentrated

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

mixture. Alternatively, the reaction mixture may be integrated into the process used to prepare the final herbicidal agent without isolating the formula I compound.

Exemplary of halogen hereinabove are fluorine, chlorine, bromine and iodine.

The base is an especially important element of the present invention because it significantly reduces the production of 5-methyl-2,3-pyridinedicarboximide compounds. Tri($C_2$-$C_4$alkyl)amines suitable for use in the process of the present invention include triethylamine, N,N-diethylisopropylamine, N,N-diisopropylethylamine and the like with triethylamine being preferred. Alkali metal acetates suitable for use in the process of this invention include sodium acetate, potassium acetate and the like with sodium acetate and potassium acetate being preferred. The base may suitably be used in an amount of at least one molar equivalent relative to the Formula I compound.

In another preferred embodiment of the present invention, a phase transfer catalyst is present. Preferably, the phase transfer catalyst is present when the alkali metal acetate is present. Phase transfer catalysts suitable for use in the present invention include any conventional phase transfer catalysts. Preferred phase transfer catalysts include crown ethers such as 18-crown-6 and 15-crown-5.

Solvents suitable for use in the process of the present invention preferably have a boiling point of at least about 75 °C and include aromatic hydrocarbons such as toluene, xylenes, mesitylene and mixtures thereof; halogenated aromatic hydrocarbons such as mono- and dihalobenzenes and mixtures thereof; polynuclear aromatic hydrocarbons such as naphthalene, alkylnaphthalenes and mixtures thereof; glycols such as 1,2-diethoxyethane and mixtures thereof; and mixtures thereof. Preferred solvents

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

include toluene, xylenes, mesitylene, 1,2-diethoxyethane and mixtures thereof with toluene being more preferred.

In another embodiment of the present invention, an alkali metal carbonate such as sodium carbonate, potassium carbonate and the like is present. Preferably, the alkali metal carbonate is present when the tri($C_2$-$C_4$alkyl)amine is present.

The process of the present invention is especially useful for the preparation of 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds wherein

R is methyl; and/or

$R_1$ is methyl, phenyl or $-\overset{\overset{CH_3}{|}}{\underset{\underset{CH(CH_3)_2}{|}}{C}}-R_5$; and/or

$R_5$ is cyano or $CONH_2$.

Oximes of 2-(alkoxymethyl)-2-propen-1-one compounds and substituted maleimide compounds which are particularly useful in the process of this invention are those wherein R and $R_6$ are methyl; and/or

$R_1$ is methyl, phenyl or $-\overset{\overset{CH_3}{|}}{\underset{\underset{CH(CH_3)_2}{|}}{C}}-R_5$; and/or

$R_5$ is cyano or $CONH_2$; and/or

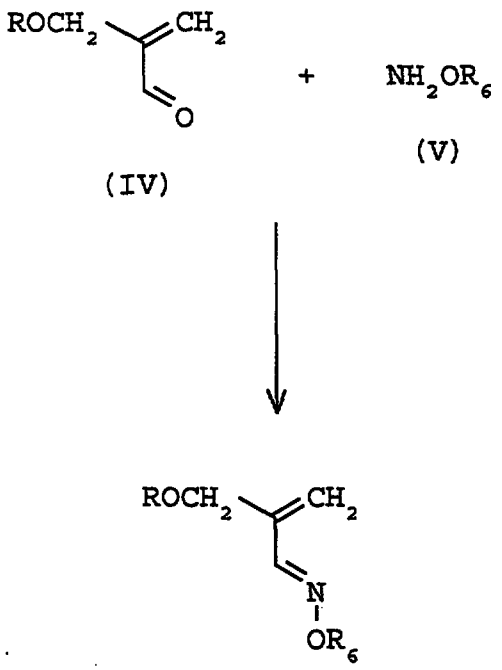
X is Cl or Br.

The formula II oxime compounds of the present invention may be prepared by reacting a 2-alkoxymethyl-acrolein of formula IV with a substituted hydroxylamine of formula V optionally in the presence of a base. The reaction is shown below in Flow Diagram I.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

**FLOW DIAGRAM I**

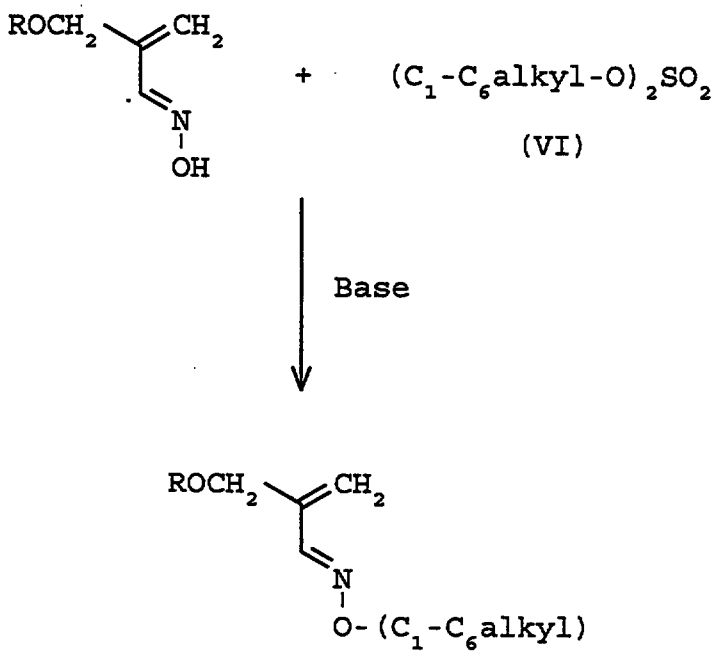



Alternatively, oxime compounds of formula II wherein $R_6$ is $C_1$-$C_6$alkyl may be prepared by reacting a formula II compound wherein $R_6$ is hydrogen with a dialkyl sulfate of formula VI and a base such as sodium hydroxide or an alkali metal alkoxide optionally in the presence of a phase transfer catalyst. The reaction scheme is shown in Flow Diagram II.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

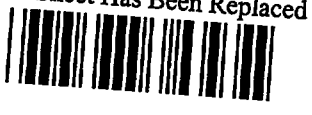
**FLOW DIAGRAM II**




A method for the preparation of formula IV 2-alkoxymethylacroleins is described in U.S. 5,177,266. Formula III substituted maleimide compounds wherein X is halogen and $R_1$ is hydrogen, $C_1$-$C_6$alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl or $-CR_3R_4R_5$ are known in the art and may be prepared according to the procedures described in EP 308,084-A1.

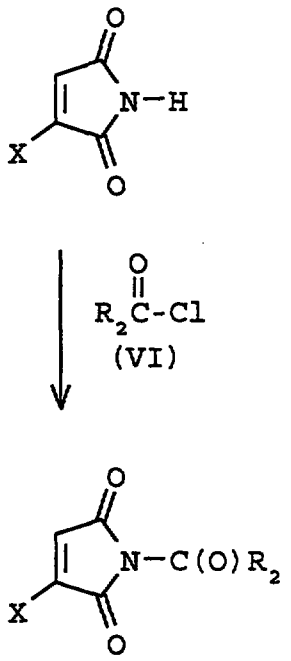
Substituted maleimide compounds wherein $R_1$ is $C(O)R_2$ may be prepared by reacting a formula III compound wherein $R_1$ is hydrogen with an acid chloride of formula VI in the presence of a solvent as shown in Flow Diagram III.

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

**FLOW DIAGRAM III**

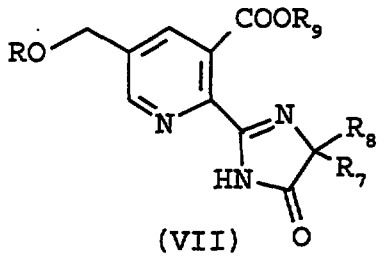



Formula III compounds wherein X is 1-imidazolyl may be prepared by reacting a formula III compound wherein X is Cl or Br with imidazole and a base such as a tri($C_1$-$C_4$alkyl)amine in the presence of a solvent. And formula III compounds wherein X is phenylsulfinyl may be prepared by reacting a formula III compound wherein X is Cl or Br with thiophenol and a base such as an alkali metal acetate in the presence of a solvent to form an intermediate compound and oxidizing the intermediate compound with a conventional oxidizing agent in the presence of a solvent to form the desired formula III compound wherein X is phenylsulfinyl.

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

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED



(VII)

wherein

R is as defined above;

$R_7$ is $C_1$-$C_4$ alkyl;

$R_8$ is $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl or $R_7$ and $R_8$ when taken together with the atom to which they are attached, represent a $C_3$-$C_6$ cycloalkyl group optionally substituted with methyl and

$R_9$ is hydrogen, diloweralkylimino,

$C_1$-$C_{12}$ alkyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, halogen, hydroxy, $C_3$-$C_6$ cycloalkyl, benzyloxy, furyl, phenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, nitrophenyl, carboxyl, loweralkoxycarbonyl, cyano or triloweralkylammonium;

$C_3$-$C_{12}$ alkenyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, phenyl, halogen or loweralkoxycarbonyl or with two $C_1$-$C_3$ alkoxy groups or two halogen groups;

$C_3$-$C_6$ cycloalkyl optionally substituted with one or two $C_1$-$C_3$ 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,

This Sheet Has Been Replaced

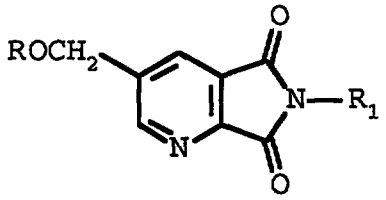


THIS SHEET HAS BEEN PLACED

ammonium and organic ammonium;

which process comprises:

(a) preparing a compound having the formula I



(I)

wherein R and $R_1$ 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 VII.

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. When used herein as a group or part of a group the term alkyl includes straight or branched chain alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl and t-butyl.

The conversion of the compound having formula I into the compound having formula VII 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

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

literature references also illustrate the methods that may be used to convert the carboxylic acid derivatives into imidazolinone final products:

U.S. Patent Nos. 5,371,229; 5,334,576; 5,250,694; 5,276,157; 5,110,930; 5,122,608; 5,206,368; 4,925,944; 4,921,961; 4,959,476; 5,103,009; 4,816,588; 4,748,244; 4,754,033; 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; 4,459,408; 4,459,409; 4,460,776; 4,125,727 and 4,758,667, and European Patent Application Nos. EP-A-0-041,623 and EP-A-0-308,084.

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.

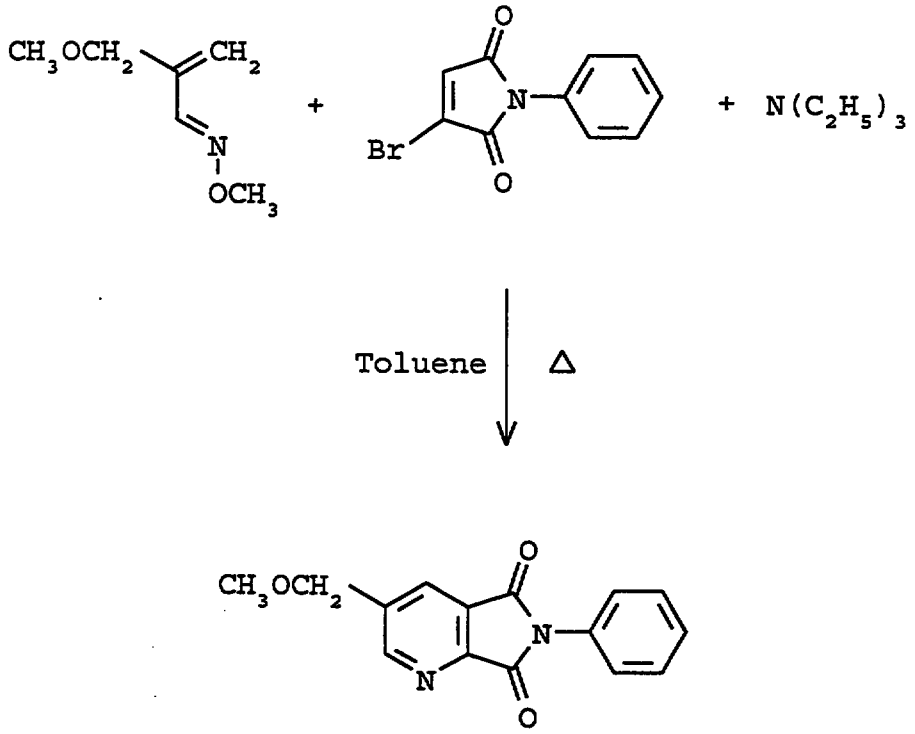
This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

**EXAMPLE 1**

**Preparation of 5-(Methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide**




A solution of the O-methyloxime of 2-(methoxymethyl)-2-propen-1-one (9.0 g, 96% pure, 67 mmol) in toluene (112 g) is heated at 97 °C for 27 hours. During the heating period, 2-bromo-N-phenylmaleimide (27.75 g, 110 mmol) and triethylamine (17.9 g, 177 mmol) are added portionwise to the reaction mixture. The final reaction mixture is filtered to remove solids, washed with water and concentrated *in vacuo* to give the title product as an orange solid (10.9 g, 61% yield) having a 5-(methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide to 5-methyl-N-phenyl-2,3-pyridinedicarboximide ratio of 233:1.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

**EXAMPLES 2-9**

The procedure of Example 1 is repeated using a variety of conditions and the results are summarized in Table I.

As can be seen from the data in Examples 1-9, the process of the present invention (Examples 1-7) produces 5-(methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide which is contaminated with a significantly smaller amount of 5-methyl-N-phenyl-2,3-pyridinedicarboximide than the process described in EP 308,084-A1 (Examples 8 and 9).

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

This Sheet Has Been Replaced



## TABLE I

Preparation of 5-(Methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide

| Example | Eq. of 2-bromo-N-phenylmaleimide | Base/Eq. | Eq. of 18-Crown-6 | Solvent | Temp. (°C) | Time (hrs) | %Yield[1] | Ratio[2] |
|---|---|---|---|---|---|---|---|---|
| 2 | 1.3 | $N(C_2H_5)_3$/3 | - | toluene | reflux | 23 | 51 | 180:1 |
| 3 | 1.2 | NaOAc/7 | - | 1,2-diethoxyethane | 100 | 35 | 44 | 30:1 |
| 4 | 2.0 | $Na_2CO_3$/3.1 $N(C_2H_5)_3$/1 | - | toluene | reflux | 34 | 62 | 179:1 |
| 5 | 2.7 | KOAc/4.2 | 0.01 | toluene | reflux | 37 | 52 | 54:1 |
| 6 | 2.2 | $(CH_3)_2CHNC_2H_5$/3.1 | - | toluene | 100 | 33 | 31 | 28:1 |
| 7 | 1.0 | NaOAc/5 | - | toluene | 95 | 28 | 47 | 28:1 |
| 8 | 1.0 | $K_2CO_3$/7.3 | - | toluene | reflux | 22 | 31 | 1:1 |
| 9 | 1.0 | $K_2CO_3$/1.8 | - | toluene | 98 | 19 | 44 | 4:1 |

[1] Determined by GC analysis of reaction mixture.

[2] Ratio of 5-(methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide to 5-methyl-N-phenyl-2,3-pyridinedicarboximide.

THIS SHEET HAS BEEN REPLACED

**EXAMPLES 10-12**

Using essentially the same procedure as described in Example 1, but substituting 2-chloro-N-phenylmaleimide for 2-bromo-N-phenylmaleimide, 5-methoxymethyl-N-phenyl-2,3-pyridinedicarboximide is produced in the yields shown in Table II.

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

This Sheet Has Been Replaced

## TABLE II

Preparation of 5-(Methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide

| Example | Eq. of 2-chloro-N-phenylmaleimide | Base/Eq. | Eq. of 18-Crown-6 | Solvent | Temp. (°C) | Time (hrs) | %Yield[1] | Ratio[2] |
|---|---|---|---|---|---|---|---|---|
| 10 | 1.7 | $N(C_2H_5)_3$/2.7 | - | toluene | 95 | 43 | 59 | 224:1 |
| 11 | 3.0 | KOAc/4.1 | 0.05 | toluene | reflux | 37 | 70 | 45:1 |
| 12 | 1.1 | NaOAc/4.5 | - | toluene | 90 | 55 | 59 | 68:1 |

[1] Determined by GC analysis of reaction mixture.

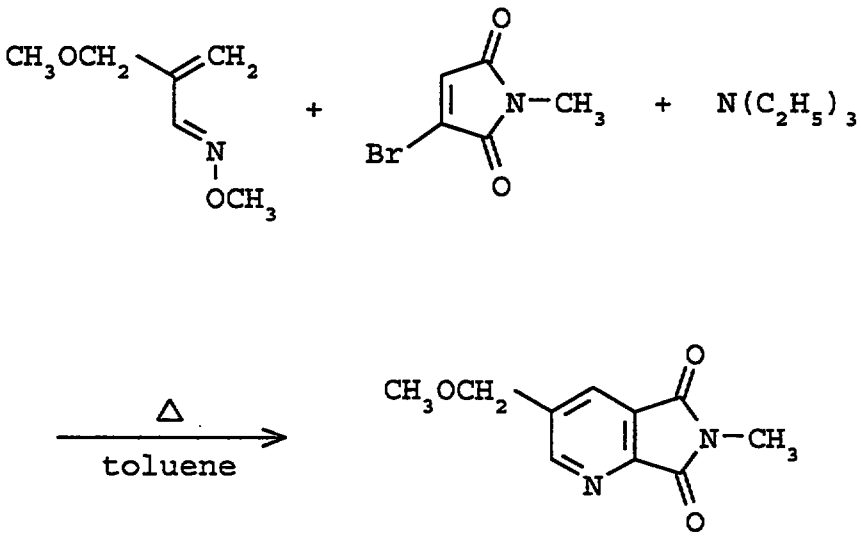
[2] Ratio of 5-(methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide to 5-methyl-N-phenyl-2,3-pyridinedicarboximide.



THIS SHEET HAS BEEN REPLACED

**EXAMPLE 13**

**Preparation of 5-(Methoxymethyl)-N-methyl-2,3-pyridinedicarboximide**




A solution of O-methyloxime of 2-(methoxymethyl)-2-propen-1-one (9.9 g, 84% pure, 64 mmol) in toluene (112 g) is heated at 100 °C for 44 hours. During the heating period, 2-bromo-N-methylmaleimide (20.35 g, 107 mmol) and triethylamine (16.9 g, 167 mmol) are added portionwise to the reaction mixture. The final reaction mixture is filtered to remove solids, washed with water and concentrated *in vacuo* to give the title product as an orange solid (8.1 g, 61% yield) having a 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide to 5-methyl-N-methyl-2,3-pyridinedicarboximide ratio of 316:1.

**EXAMPLES 14 and 15**

Using essentially the same procedure as described in Example 13, 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide is produced in the yields shown in Table III.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

This Sheet Has Been Replaced

**TABLE III**

**Preparation of 5-(Methoxymethyl)-N-methyl-2,3-pyridinedicarboximide**

| Example | Eq. of 2-bromo-N-methylmaleimide | Base/Eq. | Eq. of 18-Crown-6 | Solvent | Temp. (°C) | Time (hrs) | %Yield[1] | Ratio[2] |
|---|---|---|---|---|---|---|---|---|
| 14 | 1.0 | NaOAc/6.5 | - | toluene | 100 | 44 | 60 | 70:1 |
| 15 | 2.4 | KOAc/4.1 | 0.01 | toluene | reflux | 30 | 52 | 175:1 |



[1] Determined by GC analysis of reaction mixture.

[2] Ratio of 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide to 5-methyl-N-methyl-2,3-pyridinedicarboximide.

THIS SHEET HAS BEEN REPLACED

**EXAMPLES 16-18**

Using essentially the same procedure as described in Example 13, but substituting 2-chloro-N-methylmaleimide for 2-bromo-N-methylmaleimide, 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide is produced in the yields shown in Table IV.

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

This Sheet Has Been Replaced

## TABLE IV

**Preparation of 5-(Methoxymethyl)-N-methyl-2,3-pyridinedicarboximide**

| Example | Eq. of 2-chloro-N-methylmaleimide | Base/Eq. | Eq. of 18-Crown-6 | Solvent | Temp. (°C) | Time (hrs) | %Yield[1] | Ratio[2] |
|---|---|---|---|---|---|---|---|---|
| 16 | 1.3 | $Na_2CO_3$/3.1<br>$N(C_2H_5)_3$/1 | - | toluene | reflux | 29 | 51 | 166:1 |
| 17 | 1.6 | KOAc/4.2 | 0.01 | toluene | reflux | 33 | 50 | 110:1 |
| 18 | 1.5 | $N(C_2H_5)_3$/2.7 | - | toluene | 100 | 40 | 65 | 177:1 |



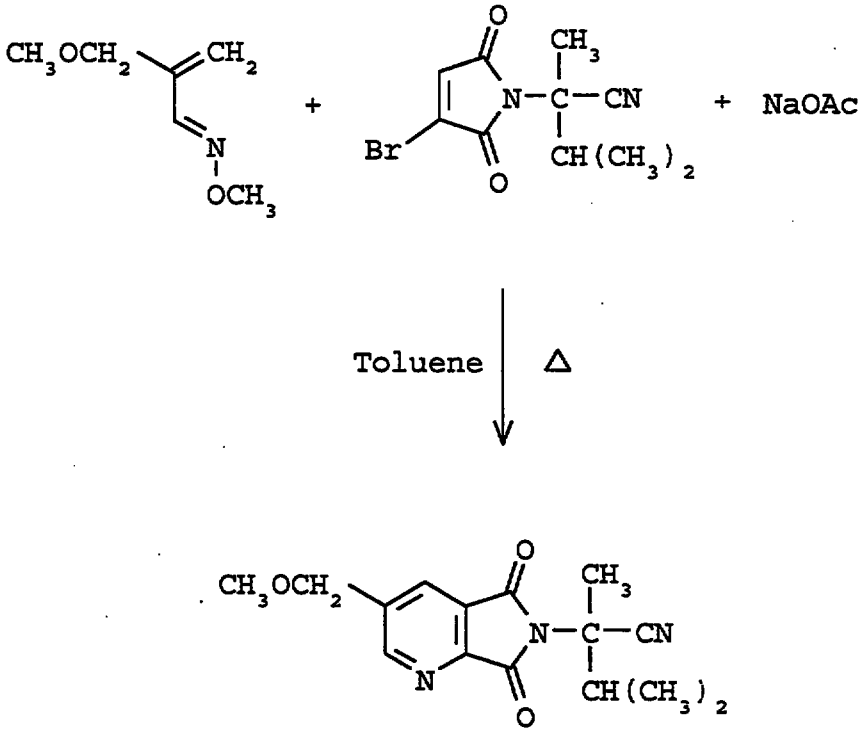
[1] Determined by GC analysis of reaction mixture.

[2] Ratio of 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide to 5-methyl-N-methyl-2,3-pyridinedicarboximide.

THIS SHEET HAS BEEN REPLACED

**EXAMPLE 19**

**Preparation of 5,7-Dihydro-α-isopropyl-3-(methoxymethyl)-α-methyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile**




A mixture of 3-bromo-2,5-dihydro-α-isopropyl-α-methyl-2,5-dioxopyrrole-1-acetonitrile (0.6 g, 90% pure, 1.99 mmol) in toluene (12 g) is heated at 95 °C for 41 hours. During the heating period, the O-methyloxime of 2-(methoxymethyl)-2-propen-1-one (0.27 g, 2.0 mmol) and sodium acetate (0.76 g, 9.2 mmol) are added portionwise to the reaction mixture. The final reaction mixture is filtered to remove solids, washed with water and concentrated in vacuo to give the title product as a red oil (0.40 g, 70% yield) having a 5,7-dihydro-α-isopropyl-3-(methoxymethyl)-α-methyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile to 5,7-dihydro-α-isopropyl-3,α-

This Sheet Has Been Replaced



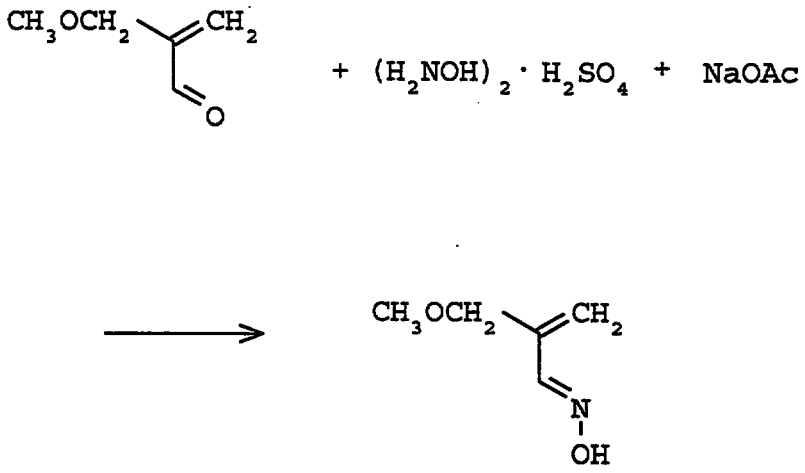
THIS SHEET HAS BEEN REPLACED

dimethyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile ratio of 61:1.

Using essentially the same procedure, but in the absence of a base, 5,7-dihydro-α-isopropyl-3-(methoxymethyl)-α-methyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile is obtained in 32% yield with a 5,7-dihydro-α-isopropyl-3-(methoxymethyl)-α-methyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile to 5,7-dihydro-α-isopropyl-3,α-dimethyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile ratio of 2:1.

**EXAMPLE 20**

**Preparation of the Oxime of 2-(methoxymethyl)-2-propen-1-one**



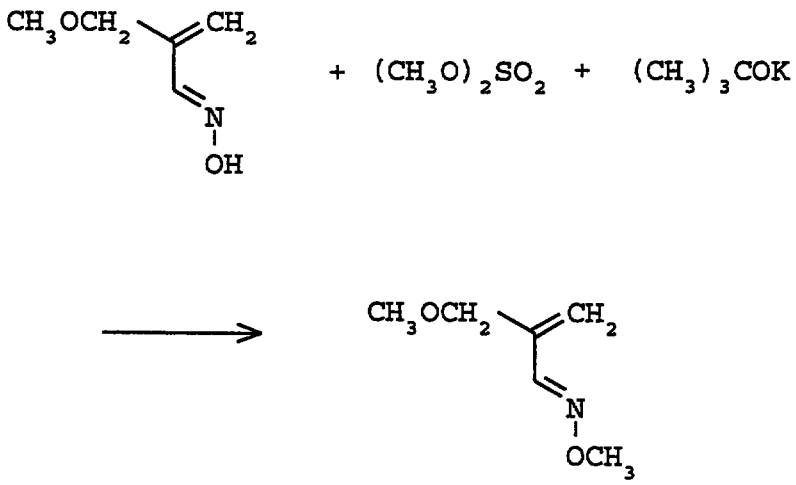
A mixture of hydroxylamine sulfate (3.81 g, 23.2 mmol) and sodium acetate (3.52 g, 4.29 mmol) in water (30 g) is treated dropwise with 2-methoxymethylacrolein (5.1 g, 70% pure) over 15 minutes, stirred at room temperature for 5 hours and extracted with methylene chloride. The organic extract is dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title product as a yellow oil (3.3 g, 80% yield).

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

**EXAMPLE 21**

**Preparation of the O-methyloxime of 2-(methoxymethyl)-2-propen-1-one**



A mixture of the oxime of 2-(methoxymethyl)-2-propen-1-one (1.8 g, 10.4 mmol, 67% pure) and potassium *tert*-butoxide (1.93 g, 17.2 mmol) in tetrahydrofuran (40 g) is stirred at 5 ° to 10 °C for 10 minutes, treated dropwise with dimethyl sulfate (2.37 g, 18.8 mmol), stirred for 1.2 hours, filtered to remove solids and concentrate *in vacuo* to obtain a residue. The residue is dissolved in methylene chloride and the resultant solution is washed sequentially with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title product as a yellow oil (1.4 g, 74% yield).

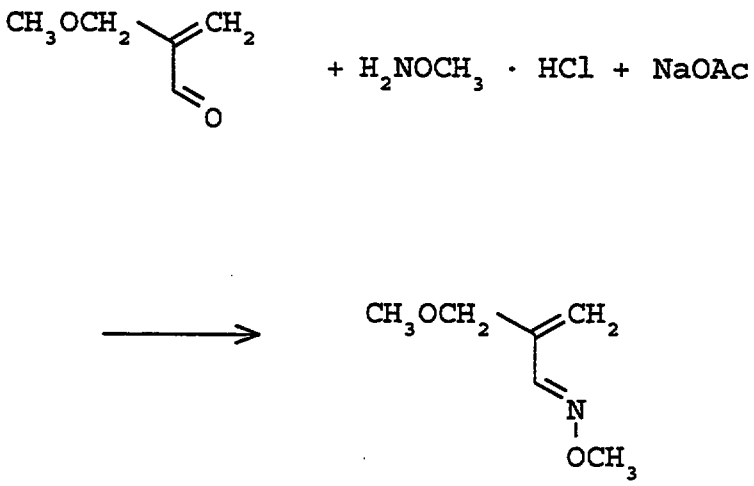
This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

**EXAMPLE 22**

**Preparation of the O-methyloxime of 2-(methoxymethyl)-2-propen-1-one**



A mixture of methoxylamine hydrochloride (21.0 g, 0.25 mol) and sodium acetate (22.4 g, 0.27 mol) in water (159 g) is treated dropwise with 2-methoxymethylacrolein (21.0 g, 90% pure, 0.19 mol) over ten minutes at 21° to 29°C, stirred overnight at room temperature and extracted with methylene chloride. The organic extract is washed sequentially with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title product as a yellow oil (26.1 g). A portion of the yellow oil is distilled under reduced pressure (50° to 70°C, 16 mm Hg) to give the title product as a clear, colorless oil.

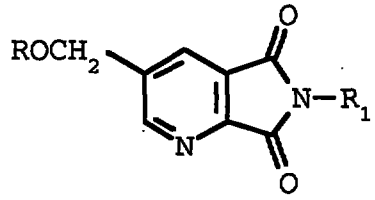
This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

CLAIMS

1. A process for the preparation of a 5-(alkoxymethyl)-2,3-pyridinedicarboximide compound having the structural formula I



(I)

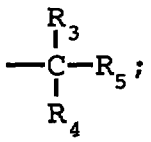
wherein

R is $C_1$-$C_6$alkyl;

$R_1$ is hydrogen, $C_1$-$C_6$alkyl, C(O)$R_2$,

phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups,

benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or



;

$R_2$ is $C_1$-$C_6$alkyl,

phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or

benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups;

$R_3$ and $R_4$ are each independently $C_1$-$C_4$alkyl; and

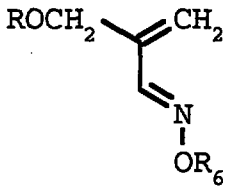
This Sheet Has Been Replaced





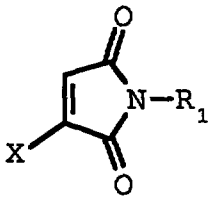

THIS SHEET HAS BEEN REPLACED

$R_5$ is cyano or $CONH_2$,
which process comprises reacting an oxime of a 2-(alkoxymethyl)-2-propen-1-one compound having the structural formula II



(II)

wherein R is as described above and $R_6$is hydrogen or $C_1$-$C_4$alkyl with a substituted maleimide compound having the structural formula III



(III)

wherein $R_1$ is as described above and X is halogen, phenylsulfinyl or 1-imidazolyl and a base selected from the group consisting of a tri($C_2$-$C_4$alkyl)amine, an alkali metal acetate and mixtures thereof in the presence of a solvent at an elevated temperature.

2. The process according to claim 1 wherein the base is selected from the group consisting of triethylamine, sodium acetate and potassium acetate and is present in an amount of at least about one molar equivalent relative to the formula I compound.

This Sheet Has Been Replaced





THIS SHEET HAS BEEN REPLACED

3. The process according to claim 1 or claim 2 further comprising a phase transfer catalyst selected from 18-crown-6 or 15-crown-5.

4. The process according to any one of claims 1 to 3 further comprising an alkali metal carbonate selected from sodium carbonate and potassium carbonate.

5. The process according to any one of claims 1 to 4 wherein R and $R_6$ are methyl and/or

$R_1$ is methyl, phenyl or $-\overset{\overset{CH_3}{|}}{\underset{\underset{CH(CH_3)_2}{|}}{C}}-R_5$;

and/or

X is Cl or Br.

6. The process according to any one of claims 1 to 5 wherein the solvent is selected from the group consisting of an aromatic hydrocarbon, a halogenated aromatic hydrocarbon, a polynuclear aromatic hydrocarbon, a glycol and mixtures thereof, and the boiling point of the solvent is at least about 75 °C.

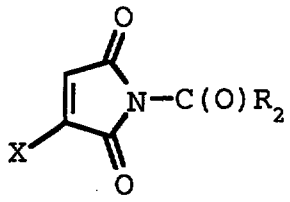
7. The process according to any one of claims 1 to 6 wherein the formula II compound is reacted with the formula III compound and the base at a temperature of above about 75 °C.

8. A compound having the structural formula

This Sheet Has Been Replaced

* C L M S *

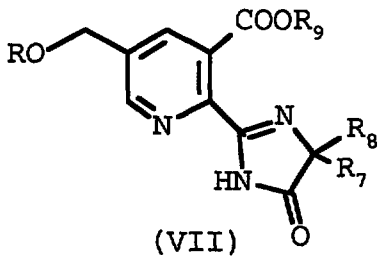
THIS SHEET HAS BEEN REPLACED



wherein
X is halogen; and
$R_2$ is $C_1$-$C_6$alkyl,
phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or
benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups.

9. The compound according to claim 8 wherein X is Cl or Br and $R_2$ is $C_1$-$C_4$alkyl, phenyl or benzyl.

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



(VII)

wherein
R is as defined in Claim 1;
$R_7$ is $C_1$-$C_4$ alkyl;
$R_8$ is $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl or $R_7$ and $R_8$ when taken together with the atom to which they are attached, represent a $C_3$-$C_6$ cycloalkyl group optionally

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

substituted with methyl and

$R_9$ is hydrogen, diloweralkylimino,

$C_1$-$C_{12}$ alkyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, halogen, hydroxy, $C_3$-$C_6$ cycloalkyl, benzyloxy, furyl, phenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, nitrophenyl, carboxyl, loweralkoxy-carbonyl, cyano or triloweralkylammonium;

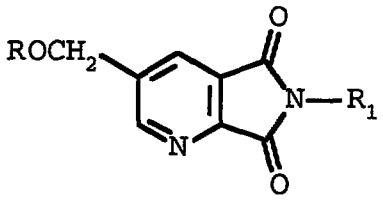
$C_3$-$C_{12}$ alkenyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, phenyl, halogen or loweralkoxycarbonyl or with two $C_1$-$C_3$ alkoxy groups or two halogen groups;

$C_3$-$C_6$ cycloalkyl optionally substituted with one or two $C_1$-$C_3$ alkyl groups;

or a cation;

which process comprises:

(a) preparing a compound having the formula I



(I)

wherein R and $R_1$ are as defined in Claim 1 by a process as claimed in Claim 1; and

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

This Sheet Has Been Replaced

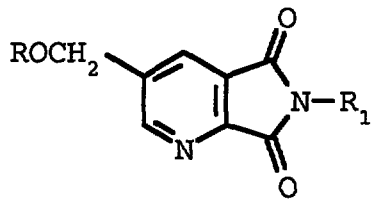
* C L M S *

THIS SHEET HAS BEEN REPLACED

## ABSTRACT

## PROCESS FOR THE PREPARATION OF 5-(ALKOXYMETHYL)-2,3-PYRIDINEDICARBOXIMIDE COMPOUNDS

There is provided a process for the preparation of 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds having the structural formula I



(I).

The 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are useful as intermediates in the preparation of herbicidal 5-(alkoxymethyl)-2-(2-imidazolin-2-yl)nicotinic acid, ester and salt compounds.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

REPLACEMENT SHEET
29 AUG 1997



# PROCESS FOR THE PREPARATION OF 5-(ALKOXYMETHYL)-2,3-PYRIDINEDICARBOXIMIDE COMPOUNDS

## BACKGROUND OF THE INVENTION

5-(Alkoxymethyl)-2,3-pyridinedicarboximide compounds are useful as intermediates in the preparation of herbicidal 5-(alkoxymethyl)-2-(2-imidazolin-2-yl)nicotinic acid, ester and salt compounds. Methods for the preparation of 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are rather limited, and those methods that are available may require extensive purification methods to provide high purity 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds.

European patent application number 308,084-A1 generically discloses that a 5-(alkoxymethyl)-2,3-pyridinedicarboximide compound may be prepared by reacting a substituted oxime compound with a halomaleimide compound optionally in the presence of an inorganic base. However, that method is not satisfactory because it produces a mixture that contains the desired 5-(alkoxymethyl)-2,3-pyridinedicarboximide compound and a relatively high percentage of an undesirable 5-methyl-2,3-pyridinedicarboximide compound. Arduous or time consuming purification methods are then required to obtain high purity 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds. If the mixture is not highly purified, the 5-(alkoxymethyl)-2-(2-imidazolin-2-yl)nicotinic acid, ester or salt compound prepared from the mixture will be

REPLACEMENT SHEET
29 AUG 1997

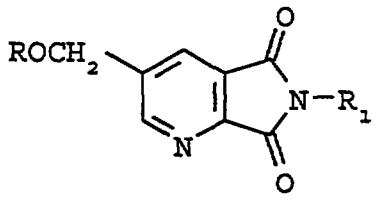


contaminated with a 5-methyl-2-(2-imidazolin-2-yl)nicotinic acid, ester or salt compound which has different herbicidal properties than the desired compound.

It is, therefore, an object of the present invention to provide a process for the preparation of high purity 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds.

## SUMMARY OF THE INVENTION

The present invention provides an effective and efficient process for the preparation of a 5-(alkoxymethyl)-2,3-pyridinedicarboximide compound having the structural formula I



(I)

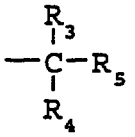
wherein

R is $C_1$-$C_6$alkyl;

$R_1$ is hydrogen, $C_1$-$C_6$alkyl, $C(O)R_2$,

phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups,

benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or



;

REPLACEMENT SHEET
29 AUG 1997



$R_2$ is $C_1$-$C_6$alkyl,

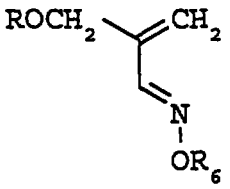
phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or

benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups;

$R_3$ and $R_4$ are each independently $C_1$-$C_4$alkyl; and

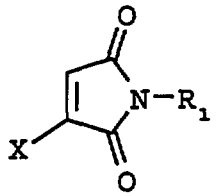
$R_5$ is cyano or $CONH_2$,

which process comprises reacting an oxime of a 2-(alkoxymethyl)-2-propen-1-one compound having the structural formula II



(II)

wherein R is as described above and $R_6$ is hydrogen or $C_1$-$C_6$alkyl with a substituted maleimide compound having the structural formula III



(III)

wherein $R_1$ is as described above and X is halogen, phenylsulfinyl or 1-imidazolyl and a base selected from

REPLACEMENT SHEET
29 AUG 1997



the group consisting of a tri($C_2$-$C_4$alkyl)amine, an alkali metal acetate and mixtures thereof in the presence of a solvent at an elevated temperature.

Surprisingly, it has been found that 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are obtained in high purity when prepared by the effective and efficient process of the present invention.

In one preferred embodiment of the present invention, an oxime of a 2-(alkoxymethyl)-2-propen-1-one compound represented by formula II is reacted with at least about one molar equivalent of a substituted maleimide compound represented by formula III, and at least about one molar equivalent of a tri($C_2$-$C_4$alkyl)amine or an alkali metal acetate or a mixture thereof, suitably at a temperature of at least 75 °C, e.g. a temperature of at least 90 °C, preferably in a temperature range of about 75 °C to 150 °C, more preferably about 90 °C to 135 °C, in the presence of a solvent having a boiling point of at least about 75 °C.

Advantageously, it has now been found that 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are obtained in high purity by the effective and efficient process of the present invention. In contrast, 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are contaminated with significant amounts of 5-methyl-2,3-pyridinedicarboximide compounds when prepared according to the procedure described in EP 308,084-A1.

The 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds may be isolated by diluting the reaction mixture with water and filtering the formula I product from the aqueous mixture. The product formula I compounds may also be isolated by concentrating the reaction mixture *in vacuo* and filtering the formula I product from the concentrated

REPLACEMENT SHEET
29 AUG 1997



mixture. Alternatively, the reaction mixture may be integrated into the process used to prepare the final herbicidal agent without isolating the formula I compound.

Exemplary of halogen hereinabove are fluorine, chlorine, bromine and iodine.

The base is an especially important element of the present invention because it significantly reduces the production of 5-methyl-2,3-pyridinedicarboximide compounds. Tri($C_2$-$C_4$alkyl)amines suitable for use in the process of the present invention include triethylamine, N,N-diethylisopropylamine, N,N-diisopropylethylamine and the like with triethylamine being preferred. Alkali metal acetates suitable for use in the process of this invention include sodium acetate, potassium acetate and the like with sodium acetate and potassium acetate being preferred. The base may suitably be used in an amount of at least one molar equivalent relative to the Formula I compound.

In another preferred embodiment of the present invention, a phase transfer catalyst is present. Preferably, the phase transfer catalyst is present when the alkali metal acetate is present. Phase transfer catalysts suitable for use in the present invention include any conventional phase transfer catalysts. Preferred phase transfer catalysts include crown ethers such as 18-crown-6 and 15-crown-5.

Solvents suitable for use in the process of the present invention preferably have a boiling point of at least about 75 °C and include aromatic hydrocarbons such as toluene, xylenes, mesitylene and mixtures thereof; halogenated aromatic hydrocarbons such as mono- and dihalobenzenes and mixtures thereof; polynuclear aromatic hydrocarbons such as naphthalene, alkylnaphthalenes and mixtures thereof; glycols such as 1,2-diethoxyethane and mixtures thereof; and mixtures thereof. Preferred solvents

REPLACEMENT SHEET
29 AUG 1997



include toluene, xylenes, mesitylene, 1,2-diethoxyethane and mixtures thereof with toluene being more preferred.

In another embodiment of the present invention, an alkali metal carbonate such as sodium carbonate, potassium carbonate and the like is present. Preferably, the alkali metal carbonate is present when the tri($C_2$-$C_4$alkyl)amine is present.

The process of the present invention is especially useful for the preparation of 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds wherein

R is methyl; and/or

$R_1$ is methyl, phenyl or $-\overset{CH_3}{\underset{CH(CH_3)_2}{C}}-R_5$; and/or

$R_5$ is cyano or $CONH_2$.

Oximes of 2-(alkoxymethyl)-2-propen-1-one compounds and substituted maleimide compounds which are particularly useful in the process of this invention are those wherein R and $R_6$ are methyl; and/or

$R_1$ is methyl, phenyl or $-\overset{CH_3}{\underset{CH(CH_3)_2}{C}}-R_5$; and/or

$R_5$ is cyano or $CONH_2$; and/or

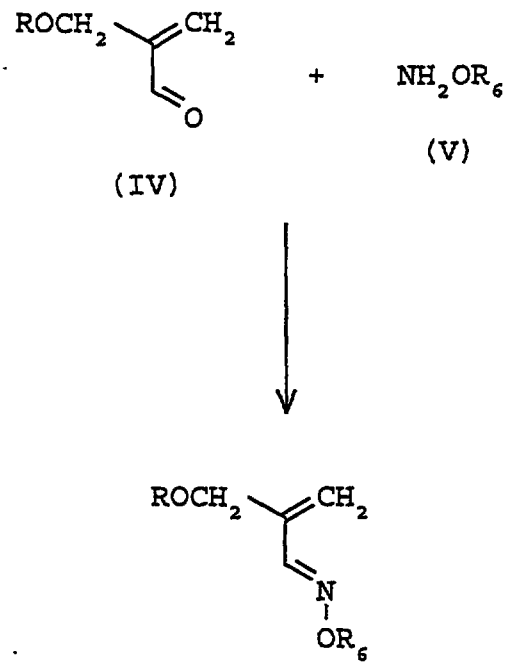
X is Cl or Br.

The formula II oxime compounds of the present invention may be prepared by reacting a 2-alkoxymethyl-acrolein of formula IV with a substituted hydroxylamine of formula V optionally in the presence of a base. The reaction is shown below in Flow Diagram I.

REPLACEMENT SHEET
29 AUG 1997



**FLOW DIAGRAM I**

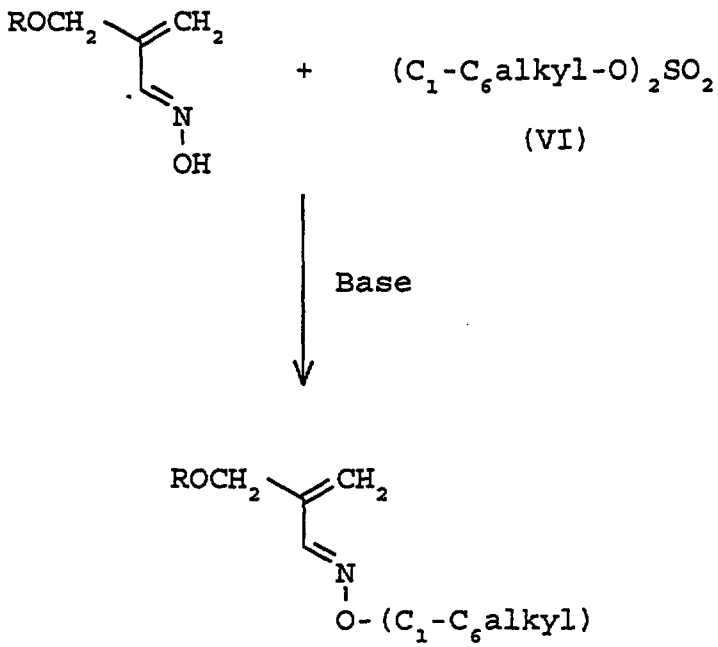



Alternatively, oxime compounds of formula II wherein $R_6$ is $C_1$-$C_6$alkyl may be prepared by reacting a formula II compound wherein $R_6$ is hydrogen with a dialkyl sulfate of formula VI and a base such as sodium hydroxide or an alkali metal alkoxide optionally in the presence of a phase transfer catalyst. The reaction scheme is shown in Flow Diagram II.

REPLACEMENT SHEET
29 AUG 1997



**FLOW DIAGRAM II**



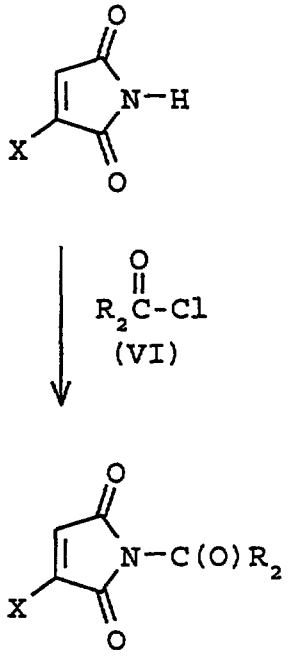

A method for the preparation of formula IV 2-alkoxymethylacroleins is described in U.S. 5,177,266. Formula III substituted maleimide compounds wherein X is halogen and $R_1$ is hydrogen, $C_1$-$C_6$alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl or $-CR_3R_4R_5$ are known in the art and may be prepared according to the procedures described in EP 308,084-A1.

Substituted maleimide compounds wherein $R_1$ is $C(O)R_2$ may be prepared by reacting a formula III compound wherein $R_1$ is hydrogen with an acid chloride of formula VI in the presence of a solvent as shown in Flow Diagram III.

REPLACEMENT SHEET
29 AUG 1997



FLOW DIAGRAM III

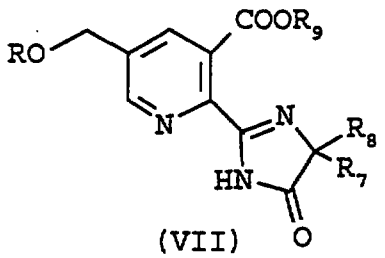



Formula III compounds wherein X is 1-imidazolyl may be prepared by reacting a formula III compound wherein X is Cl or Br with imidazole and a base such as a tri($C_1$-$C_4$alkyl)amine in the presence of a solvent. And formula III compounds wherein X is phenylsulfinyl may be prepared by reacting a formula III compound wherein X is Cl or Br with thiophenol and a base such as an alkali metal acetate in the presence of a solvent to form an intermediate compound and oxidizing the intermediate compound with a conventional oxidizing agent in the presence of a solvent to form the desired formula III compound wherein X is phenylsulfinyl.

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

REPLACEMENT SHEET
29 AUG 1997





(VII)

wherein

R is as defined above;

$R_7$ is $C_1$-$C_4$ alkyl;

$R_8$ is $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl or $R_7$ and $R_8$ when taken together with the atom to which they are attached, represent a $C_3$-$C_6$ cycloalkyl group optionally substituted with methyl and

$R_9$ is hydrogen, diloweralkylimino,

$C_1$-$C_{12}$ alkyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, halogen, hydroxy, $C_3$-$C_6$ cycloalkyl, benzyloxy, furyl, phenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, nitrophenyl, carboxyl, loweralkoxycarbonyl, cyano or triloweralkylammonium;

$C_3$-$C_{12}$ alkenyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, phenyl, halogen or loweralkoxycarbonyl or with two $C_1$-$C_3$ alkoxy groups or two halogen groups;

$C_3$-$C_6$ cycloalkyl optionally substituted with one or two $C_1$-$C_3$ 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,

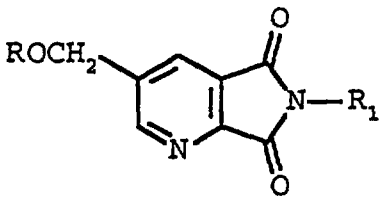
REPLACEMENT SHEET
29 AUG 1997



ammonium and organic ammonium;

which process comprises:

(a) preparing a compound having the formula I



(I)

wherein R and $R_1$ 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 VII.

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. When used herein as a group or part of a group the term alkyl includes straight or branched chain alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl and t-butyl.

The conversion of the compound having formula I into the compound having formula VII 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

REPLACEMENT SHEET
29 AUG 1997



literature references also illustrate the methods that may be used to convert the carboxylic acid derivatives into imidazolinone final products:

U.S. Patent Nos. 5,371,229; 5,334,576; 5,250,694; 5,276,157; 5,110,930; 5,122,608; 5,206,368; 4,925,944; 4,921,961; 4,959,476; 5,103,009; 4,816,588; 4,748,244; 4,754,033; 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; 4,459,408; 4,459,409; 4,460,776; 4,125,727 and 4,758,667, and European Patent Application Nos. EP-A-0-041,623 and EP-A-0-308,084.

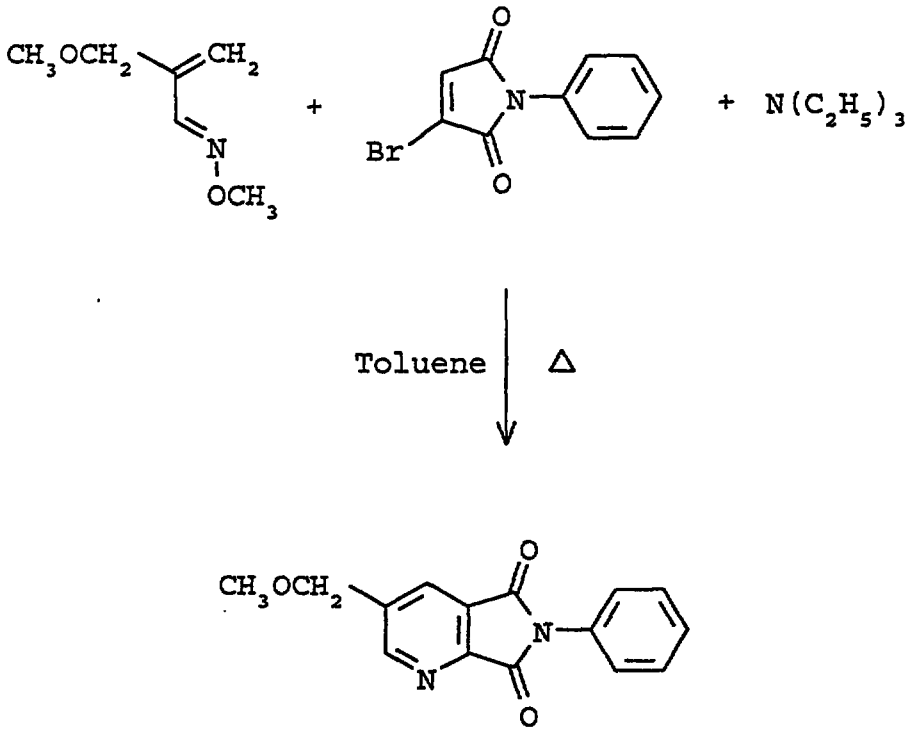
In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating more specific details thereof. The invention should not be deemed limited by the examples as the full scope of the invention is defined in the claims.

REPLACEMENT SHEET
29 AUG 1997



**EXAMPLE 1**

**Preparation of 5-(Methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide**




A solution of the O-methyloxime of 2-(methoxymethyl)-2-propen-1-one (9.0 g, 96% pure, 67 mmol) in toluene (112 g) is heated at 97 °C for 27 hours. During the heating period, 2-bromo-N-phenylmaleimide (27.75 g, 110 mmol) and triethylamine (17.9 g, 177 mmol) are added portionwise to the reaction mixture. The final reaction mixture is filtered to remove solids, washed with water and concentrated *in vacuo* to give the title product as an orange solid (10.9 g, 61% yield) having a 5-(methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide to 5-methyl-N-phenyl-2,3-pyridinedicarboximide ratio of 233:1.

REPLACEMENT SHEET
29 AUG 1997



**EXAMPLES 2-9**

The procedure of Example 1 is repeated using a variety of conditions and the results are summarized in Table I.

As can be seen from the data in Examples 1-9, the process of the present invention (Examples 1-7) produces 5-(methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide which is contaminated with a significantly smaller amount of 5-methyl-N-phenyl-2,3-pyridinedicarboximide than the process described in EP 308,084-A1 (Examples 8 and 9).

## TABLE I

Preparation of 5-(Methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide

| Example | Eq. of 2-bromo-N-phenylmaleimide | Base/Eq. | Eq. of 18-Crown-6 | Solvent | Temp. (°C) | Time (hrs) | %Yield[1] | Ratio[2] |
|---|---|---|---|---|---|---|---|---|
| 2 | 1.3 | $N(C_2H_5)_3$/3 | - | toluene | reflux | 23 | 51 | 180:1 |
| 3 | 1.2 | NaOAc/7 | - | 1,2-diethoxyethane | 100 | 35 | 44 | 30:1 |
| 4 | 2.0 | $Na_2CO_3$/3.1 $N(C_2H_5)_3$/1 | - | toluene | reflux | 34 | 62 | 179:1 |
| 5 | 2.7 | KOAc/4.2 | 0.01 | toluene | reflux | 37 | 52 | 54:1 |
| 6 | 2.2 | $(CH_3)_2CHNC_2H_5$/3.1 | - | toluene | 100 | 33 | 31 | 28:1 |
| 7 | 1.0 | NaOAc/5 | - | toluene | 95 | 28 | 47 | 28:1 |
| 8 | 1.0 | $K_2CO_3$/7.3 | - | toluene | reflux | 22 | 31 | 1:1 |
| 9 | 1.0 | $K_2CO_3$/1.8 | - | toluene | 98 | 19 | 44 | 4:1 |

[1] Determined by GC analysis of reaction mixture.

[2] Ratio of 5-(methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide to 5-methyl-N-phenyl-2,3-pyridinedicarboximide.



REPLACEMENT SHEET
29 AUG 1997

REPLACEMENT SHEET
29 AUG 1997



**EXAMPLES 10-12**

Using essentially the same procedure as described in Example 1, but substituting 2-chloro-N-phenylmaleimide for 2-bromo-N-phenylmaleimide, 5-methoxymethyl-N-phenyl-2,3-pyridinedicarboximide is produced in the yields shown in Table II.

## TABLE II

Preparation of 5-(Methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide

| Example | Eq. of 2-chloro-N-phenylmaleimide | Base/Eq. | Eq. of 18-Crown-6 | Solvent | Temp. (°C) | Time (hrs) | %Yield[1] | Ratio[2] |
|---|---|---|---|---|---|---|---|---|
| 10 | 1.7 | $N(C_2H_5)_3$/2.7 | - | toluene | 95 | 43 | 59 | 224:1 |
| 11 | 3.0 | KOAc/4.1 | 0.05 | toluene | reflux | 37 | 70 | 45:1 |
| 12 | 1.1 | NaOAc/4.5 | - | toluene | 90 | 55 | 59 | 68:1 |

[1] Determined by GC analysis of reaction mixture.

[2] Ratio of 5-(methoxymethyl)-N-phenyl-2,3-pyridinedicarboximide to 5-methyl-N-phenyl-2,3-pyridinedicarboximide.



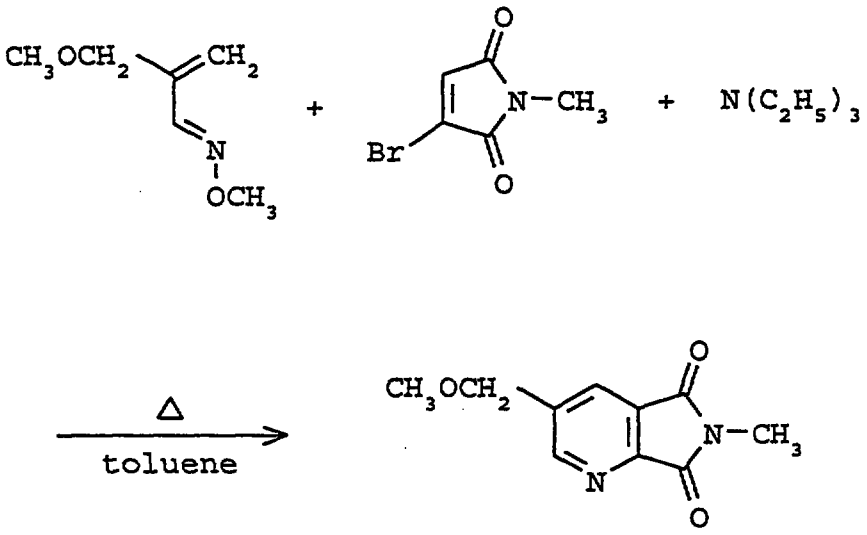
REPLACEMENT SHEET
29 AUG 1997

REPLACEMENT SHEET
29 AUG 1997



## EXAMPLE 13

**Preparation of 5-(Methoxymethyl)-N-methyl-2,3-pyridinedicarboximide**




A solution of O-methyloxime of 2-(methoxymethyl)-2-propen-1-one (9.9 g, 84% pure, 64 mmol) in toluene (112 g) is heated at 100 °C for 44 hours. During the heating period, 2-bromo-N-methylmaleimide (20.35 g, 107 mmol) and triethylamine (16.9 g, 167 mmol) are added portionwise to the reaction mixture. The final reaction mixture is filtered to remove solids, washed with water and concentrated *in vacuo* to give the title product as an orange solid (8.1 g, 61% yield) having a 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide to 5-methyl-N-methyl-2,3-pyridinedicarboximide ratio of 316:1.

## EXAMPLES 14 and 15

Using essentially the same procedure as described in Example 13, 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide is produced in the yields shown in Table III.

## TABLE III

Preparation of 5-(Methoxymethyl)-N-methyl-2,3-pyridinedicarboximide

| Example | Eq. of 2-bromo-N-methylmaleimide | Base/Eq. | Eq. of 18-Crown-6 | Solvent | Temp. (°C) | Time (hrs) | %Yield[1] | Ratio[2] |
|---|---|---|---|---|---|---|---|---|
| 14 | 1.0 | NaOAc/6.5 | - | toluene | 100 | 44 | 60 | 70:1 |
| 15 | 2.4 | KOAc/4.1 | 0.01 | toluene | reflux | 30 | 52 | 175:1 |



[1] Determined by GC analysis of reaction mixture.

[2] Ratio of 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide to 5-methyl-N-methyl-2,3-pyridinedicarboximide.

REPLACEMENT SHEET
29 AUG 1997

REPLACEMENT SHEET
29 AUG 1997



**EXAMPLES 16-18**

Using essentially the same procedure as described in Example 13, but substituting 2-chloro-N-methylmaleimide for 2-bromo-N-methylmaleimide, 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide is produced in the yields shown in Table IV.

TABLE IV

Preparation of 5-(Methoxymethyl)-N-methyl-2,3-pyridinedicarboximide

| Example | Eq. of 2-chloro-N-methylmaleimide | Base/Eq. | Eq. of 18-Crown-6 | Solvent | Temp. (°C) | Time (hrs) | %Yield[1] | Ratio[2] |
|---|---|---|---|---|---|---|---|---|
| 16 | 1.3 | $Na_2CO_3$/3.1 $N(C_2H_5)_3$/1 | - | toluene | reflux | 29 | 51 | 166:1 |
| 17 | 1.6 | KOAc/4.2 | 0.01 | toluene | reflux | 33 | 50 | 110:1 |
| 18 | 1.5 | $N(C_2H_5)_3$/2.7 | - | toluene | 100 | 40 | 65 | 177:1 |



[1] Determined by GC analysis of reaction mixture.

[2] Ratio of 5-(methoxymethyl)-N-methyl-2,3-pyridinedicarboximide to 5-methyl-N-methyl-2,3-pyridinedicarboximide.

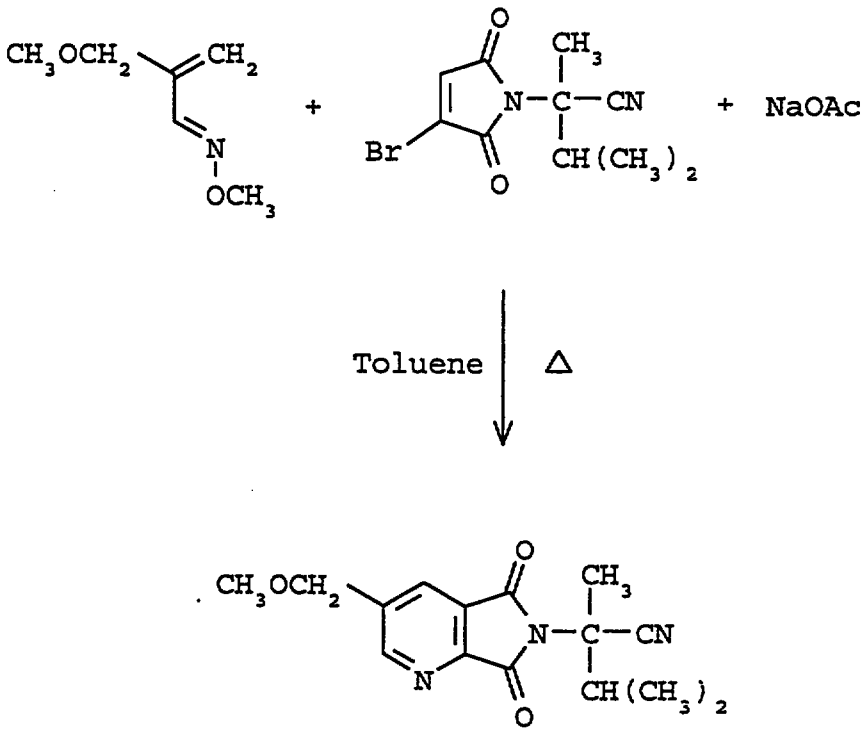
REPLACEMENT SHEET
29 AUG 1997

REPLACEMENT SHEET
29 AUG 1997



**EXAMPLE 19**

**Preparation of 5,7-Dihydro-α-isopropyl-3-(methoxymethyl)-α-methyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile**




A mixture of 3-bromo-2,5-dihydro-α-isopropyl-α-methyl-2,5-dioxopyrrole-1-acetonitrile (0.6 g, 90% pure, 1.99 mmol) in toluene (12 g) is heated at 95 °C for 41 hours. During the heating period, the O-methyloxime of 2-(methoxymethyl)-2-propen-1-one (0.27 g, 2.0 mmol) and sodium acetate (0.76 g, 9.2 mmol) are added portionwise to the reaction mixture. The final reaction mixture is filtered to remove solids, washed with water and concentrated in vacuo to give the title product as a red oil (0.40 g, 70% yield) having a 5,7-dihydro-α-isopropyl-3-(methoxymethyl)-α-methyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile to 5,7-dihydro-α-isopropyl-3,α-

REPLACEMENT SHEET
29 AUG 1997

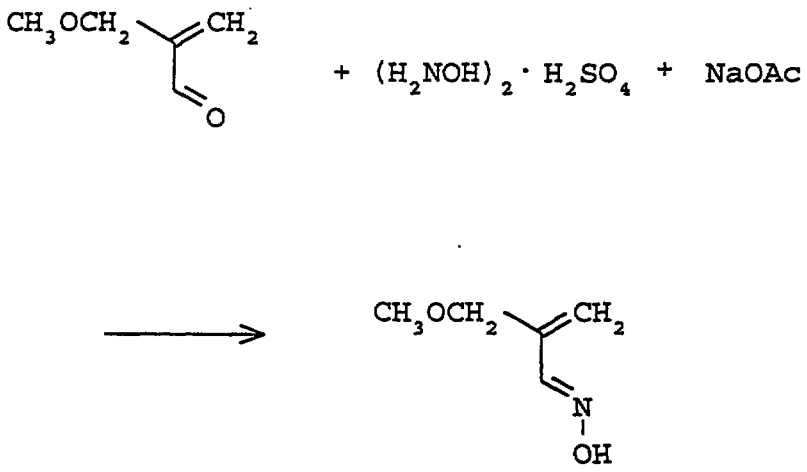


dimethyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile ratio of 61:1.

Using essentially the same procedure, but in the absence of a base, 5,7-dihydro-α-isopropyl-3-(methoxymethyl)-α-methyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile is obtained in 32% yield with a 5,7-dihydro-α-isopropyl-3-(methoxymethyl)-α-methyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile to 5,7-dihydro-α-isopropyl-3,α-dimethyl-5,7-dioxo-6H-pyrrolo[3,4-b]pyridine-6-acetonitrile ratio of 2:1.

## EXAMPLE 20

**Preparation of the Oxime of 2-(methoxymethyl)-2-propen-1-one**



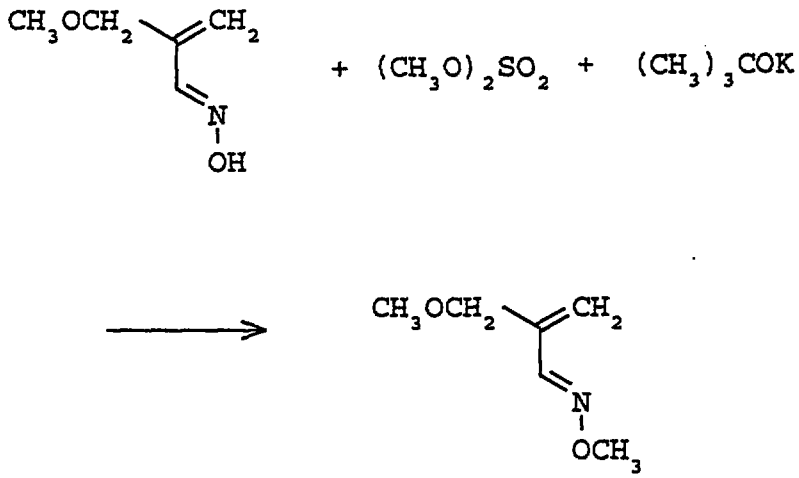
A mixture of hydroxylamine sulfate (3.81 g, 23.2 mmol) and sodium acetate (3.52 g, 4.29 mmol) in water (30 g) is treated dropwise with 2-methoxymethylacrolein (5.1 g, 70% pure) over 15 minutes, stirred at room temperature for 5 hours and extracted with methylene chloride. The organic extract is dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title product as a yellow oil (3.3 g, 80% yield).

REPLACEMENT SHEET
29 AUG 1997



**EXAMPLE 21**

**Preparation of the O-methyloxime of 2-(methoxymethyl)-2-propen-1-one**



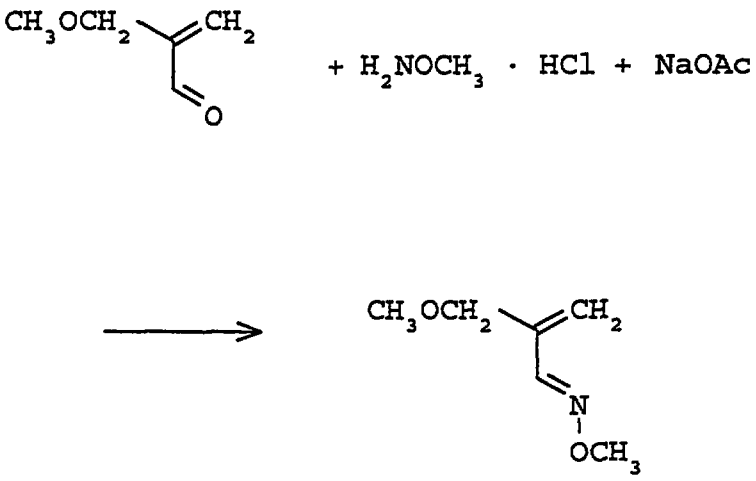
A mixture of the oxime of 2-(methoxymethyl)-2-propen-1-one (1.8 g, 10.4 mmol, 67% pure) and potassium tert-butoxide (1.93 g, 17.2 mmol) in tetrahydrofuran (40 g) is stirred at 5 ° to 10 °C for 10 minutes, treated dropwise with dimethyl sulfate (2.37 g, 18.8 mmol), stirred for 1.2 hours, filtered to remove solids and concentrate *in vacuo* to obtain a residue. The residue is dissolved in methylene chloride and the resultant solution is washed sequentially with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title product as a yellow oil (1.4 g, 74% yield).

REPLACEMENT SHEET
29 AUG 1997



**EXAMPLE 22**

**Preparation of the O-methyloxime of 2-(methoxymethyl)-2-propen-1-one**



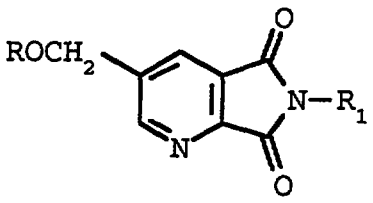
A mixture of methoxylamine hydrochloride (21.0 g, 0.25 mol) and sodium acetate (22.4 g, 0.27 mol) in water (159 g) is treated dropwise with 2-methoxymethylacrolein (21.0 g, 90% pure, 0.19 mol) over ten minutes at 21° to 29°C, stirred overnight at room temperature and extracted with methylene chloride. The organic extract is washed sequentially with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title product as a yellow oil (26.1 g). A portion of the yellow oil is distilled under reduced pressure (50° to 70°C, 16 mm Hg) to give the title product as a clear, colorless oil.

REPLACEMENT SHEET
29 AUG 1997



CLAIMS

1. A process for the preparation of a 5-(alkoxymethyl)-2,3-pyridinedicarboximide compound having the structural formula I



(I)

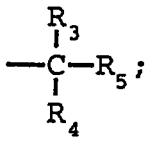
wherein

R is $C_1$-$C_6$alkyl;

$R_1$ is hydrogen, $C_1$-$C_6$alkyl, C(O)$R_2$,

phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups,

benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or



$R_2$ is $C_1$-$C_6$alkyl,

phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or

benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups;

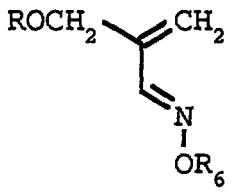
$R_3$ and $R_4$ are each independently $C_1$-$C_4$alkyl; and

*CLMS*

REPLACEMENT SHEET
29 AUG 1997

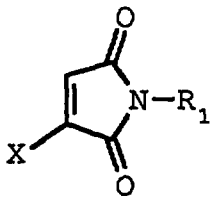


$R_5$ is cyano or $CONH_2$,
which process comprises reacting an oxime of a 2-(alkoxymethyl)-2-propen-1-one compound having the structural formula II



(II)

wherein R is as described above and $R_6$is hydrogen or $C_1$-$C_4$alkyl with a substituted maleimide compound having the structural formula III



(III)

wherein $R_1$ is as described above and X is halogen, phenylsulfinyl or 1-imidazolyl and a base selected from the group consisting of a tri($C_2$-$C_4$alkyl)amine, an alkali metal acetate and mixtures thereof in the presence of a solvent at an elevated temperature.

2. The process according to claim 1 wherein the base is selected from the group consisting of triethylamine, sodium acetate and potassium acetate and is present in an amount of at least about one molar equivalent relative to the formula I compound.

* C L M S *

REPLACEMENT SHEET
29 AUG 1997



3. The process according to claim 1 or claim 2 further comprising a phase transfer catalyst selected from 18-crown-6 or 15-crown-5.

4. The process according to any one of claims 1 to 3 further comprising an alkali metal carbonate selected from sodium carbonate and potassium carbonate.

5. The process according to any one of claims 1 to 4 wherein R and $R_6$ are methyl and/or

$R_1$ is methyl, phenyl or $-\overset{\overset{CH_3}{|}}{\underset{\underset{CH(CH_3)_2}{|}}{C}}-R_5$;

and/or

X is Cl or Br.

6. The process according to any one of claims 1 to 5 wherein the solvent is selected from the group consisting of an aromatic hydrocarbon, a halogenated aromatic hydrocarbon, a polynuclear aromatic hydrocarbon, a glycol and mixtures thereof, and the boiling point of the solvent is at least about 75 °C.

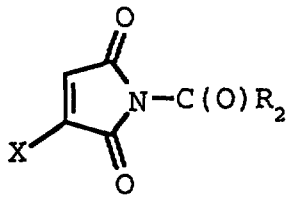
7. The process according to any one of claims 1 to 6 wherein the formula II compound is reacted with the formula III compound and the base at a temperature of above about 75 °C.

8. A compound having the structural formula

* C L M S *
This Sheet Has Been Replaced

REPLACEMENT SHEET
29 AUG 1997

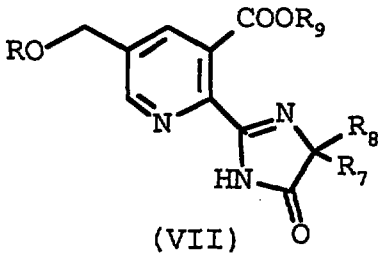




wherein
X is halogen; and
$R_2$ is $C_1$-$C_6$alkyl,
phenyl optionally substituted with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups, or
benzyl optionally substituted on the phenyl ring with any combination of from one to four halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, nitro or cyano groups.

9. The compound according to claim 8 wherein X is Cl or Br and $R_2$ is $C_1$-$C_4$alkyl, phenyl or benzyl.

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



(VII)

wherein
R is as defined in Claim 1;
$R_7$ is $C_1$-$C_4$ alkyl;
$R_8$ is $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl or $R_7$ and $R_8$ when taken together with the atom to which they are attached, represent a $C_3$-$C_6$ cycloalkyl group optionally

*CLMS*
This Sheet Has Been Replaced

REPLACEMENT SHEET
29 AUG 1997



substituted with methyl and

$R_9$ is hydrogen, diloweralkylimino,

$C_1$-$C_{12}$ alkyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, halogen, hydroxy, $C_3$-$C_6$ cycloalkyl, benzyloxy, furyl, phenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, nitrophenyl, carboxyl, loweralkoxy-carbonyl, cyano or triloweralkylammonium;

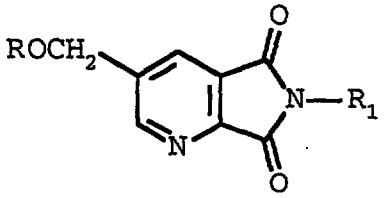
$C_3$-$C_{12}$ alkenyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, phenyl, halogen or loweralkoxycarbonyl or with two $C_1$-$C_3$ alkoxy groups or two halogen groups;

$C_3$-$C_6$ cycloalkyl optionally substituted with one or two $C_1$-$C_3$ alkyl groups;

or a cation;

which process comprises:

(a) preparing a compound having the formula I



(I)

wherein R and $R_1$ are as defined in Claim 1 by a process as claimed in Claim 1; and

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

This Sheet Has Been Replaced



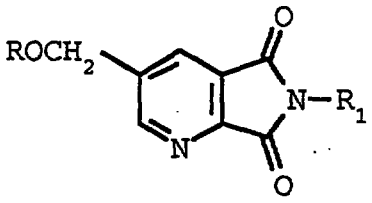
REPLACEMENT SHEET
29 AUG 1997



## ABSTRACT


### PROCESS FOR THE PREPARATION OF 5-(ALKOXYMETHYL)-2,3-PYRIDINEDICARBOXIMIDE COMPOUNDS

There is provided a process for the preparation of 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds having the structural formula I




(I).

The 5-(alkoxymethyl)-2,3-pyridinedicarboximide compounds are useful as intermediates in the preparation of herbicidal 5-(alkoxymethyl)-2-(2-imidazolin-2-yl)nicotinic acid, ester and salt compounds.

REPLACEMENT SHEET
24 APR 2000



3. The process according to claim 1 or claim 2 further comprising a phase transfer catalyst selected from 18-crown-6 or 15-crown-5.

4. The process according to any one of claims 1 to 3 further comprising an alkali metal carbonate selected from sodium carbonate and potassium carbonate.

5. The process according to any one of claims 1 to 4 wherein R and $R_6$ are methyl and/or

$R_1$ is methyl, phenyl or $-\!-\!\overset{\overset{CH_3}{|}}{\underset{\underset{CH(CH_3)_2}{|}}{C}}\!-\!R_5$;

and/or

X is Cl or Br.

6. The process according to any one of claims 1 to 5 wherein the solvent is selected from the group consisting of an aromatic hydrocarbon, a halogenated aromatic hydrocarbon, a polynuclear aromatic hydrocarbon, a glycol and mixtures thereof, and the boiling point of the solvent is at least about 75 °C.

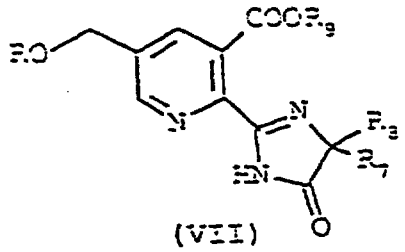
7. The process according to any one of claims 1 to 6 wherein the formula II compound is reacted with the formula III compound and the base at a temperature of above about 75 °C.

* C L M S *

REPLACEMENT SHEET
24 APR 2000



8. A process for the preparation of a herbicidal imidazolinone compound having the formula VII



(VII)

wherein

R is as defined in Claim 1;

$R_7$ is $C_1$-$C_4$ alkyl;

$R_8$ is $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl or $R_7$ and $R_8$ when taken together with the atom to which they are attached, represent a $C_3$-$C_6$ cycloalkyl group optionally substituted with methyl and

$R_9$ is hydrogen, diloweralkylimino, $C_1$-$C_{12}$ alkyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, halogen, hydroxy, $C_3$-$C_6$ cycloalkyl, benzyloxy, furyl, phenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, nitrophenyl, carboxyl, loweralkoxy-carbonyl, cyano or triloweralkylammonium;

$C_3$-$C_{12}$ alkenyl optionally substituted with one of the following groups: $C_1$-$C_3$ alkoxy, phenyl, halogen or loweralkoxycarbonyl or with two $C_1$-$C_3$ alkoxy groups or two halogen groups;

$C_3$-$C_6$ cycloalkyl optionally substituted with one or two $C_1$-$C_3$ alkyl groups;

or a cation;

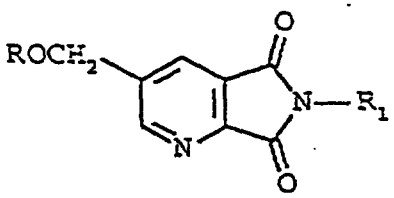
which process comprises:

* C L M S *

REPLACEMENT SHEET
24 APR 2000



(a) preparing a compound having the formula I



(I)

wherein R and $R_1$ are as defined in Claim 1 by a process as claimed in Claim 1; and

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

* C L M S *