METHOD FOR THE PREPARATION OF SUBSTITUTED AND UNSUBSTITUTED 2,3-PYRIDINE AND QUINOLINEDICARBOXYLIC ACIDS

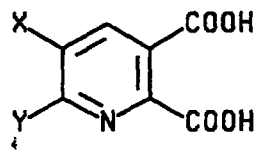
The discovery, development and commercialization of the 2-(2-imidazolin-2-yl) pyridines and quinolines as herbicidal agents has given new meaning to the term "weed control"; for within this series of compounds it has been found that some are broad-spectrum or total vegetation herbicides with activity in both herbaceous and woody plants. Others are highly selective weed control agents useful as weed control agents in the presence of crops. The broad-spectrum compounds have been widely accepted for use in cleaning industrial sites and rights-of-way for railroads and power lines while the selective herbicides are used extensively as weed control agents in the presence of soybeans, snapbeans, peas and alfalfa. Such acceptance has stirred the interest of many researchers in the field of agricultural chemistry and has led to development of a variety of synthetic routes to the preparation of the herbicidally active 2-(2-imidazolin-2-yl)-pyridines and quinolines.

Several of these processes involve the preparation of 2,3-pyridinedicarboxylic acid anhydrides from 2,3-pyridinedicarboxylic acids, but methods for the preparation of the 2,3-pyridinedicarboxylic acids are rather limited and those processes that are

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available may be arduous, time-consuming or multi-step processes that are not entirely satisfactory.

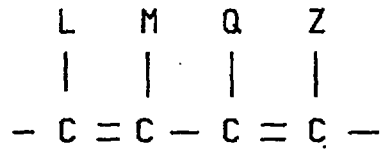
The present invention is directed to a method for the preparation of substituted and unsubstituted 2,3-pyridine and quinolinedicarboxylic acids of formula I



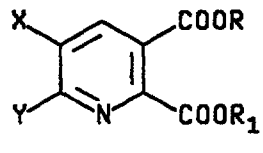
(I)

wherein

X and Y are each independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxyalkyl, C_1-C_6 alkoxy, C_1-C_4 alkylthio, phenoxy, C_1-C_4 haloalkyl, nitro, cyano, C_1-C_4 alkylamino, diloweralkylamino, C_1-C_4 alkylsulfonyl or phenyl optionally substituted with a C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen group; and, when taken together, X and Y may form a ring in which XY is represented by the structure



wherein L, M, Q and Z are each hydrogen, halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; by hydrolyzing a 2,3-pyridine or quinolinedicarboxylic acid diester of formula II



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wherein R and R_1 each represent a C_1-C_6 alkyl group and X and Y are as described above for formula I; by heating the dicarboxylic acid diester in the presence of water and an acid having an ionization constant pK_a of less than 3.0 at a temperature between about 50°C and 110°C, separating water and alcohol from the reaction mixture, cooling the remaining reaction mixture to a temperature between about 20°C and 35°C, treating the remaining reaction mixture with base, if the reaction mixture has a pH value less than pH 1.3, to adjust the pH of said mixture to a value between 1.3 and 2.0 and separating the formula I 2,3-pyridine or quinolinedicarboxylic acid from the pH adjusted mixture.

One of the embodiments of the present invention relates to a method for the preparation of acid salts of formula I substituted and unsubstituted 2,3-pyridine and quinolinedicarboxylic acids by hydrolyzing a formula II 2,3-pyridine or quinolinedicarboxylic acid diester in the presence of water and an acid having a pK_a of less than 3.0 at a temperature between about 50°C and 110°C, cooling the heated mixture to a temperature between about 20°C and 40°C, washing the cooled mixture with a volatile chlorinated hydrocarbon, an ether or a water-immiscible alcohol, adding to the washed mixture 1,1'-oxybis[2-methoxyethane]; 2,5,8,11-tetraoxadodecane or 2,5,8,11,14-pentaoxapentadecane and separating water to obtain the formula I 2,3-pyridine or quinolinedicarboxylic acid as the acid salt and optionally dispersing said acid salt in water or aqueous base to obtain the formula I 2,3-pyridine or quinolinedicarboxylic acid.

The method of the present invention is especially efficacious for the preparation of 5-ethyl-2,3-pyridinedicarboxylic acid, 2,3-pyridinedicarboxylic

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acid, 5-methoxymethyl-2,3-pyridinedicarboxylic acid, 5-methyl-2,3-pyridinedicarboxylic acid and 2,3-quinolinedicarboxylic acid.

The product formula I 2,3-pyridine and quinolinedicarboxylic acids may be isolated by filtration of the formula I product or by extraction of the reaction mixture with a suitable solvent. In the isolation procedure suitable extraction solvents include tetrahydrofuran and water-immiscible alcohols.

Acids having an ionization constant pK_a of greater than 3.0 are unable to fully protonate the pyridine or quinoline ring of a formula I 2,3-pyridine or quinolinedicarboxylic acid. This lack of protonation leads to decomposition of the desired formula I dicarboxylic acid through decarboxylation. Therefore, it is desirable to employ acids having an ionization constant pK_a of less than 3.0 to avoid this unwanted decarboxylation while effectively hydrolyzing formula II dicarboxylic diesters to the desired formula I dicarboxylic acids of the present invention.

Representative acids for use in the present invention include both mineral acids and organic acids having an ionization constant pK_a of less than 3.0, as shown below, with sulfuric acid, hydrobromic acid and hydrochloric acid being preferred. At least 1.1 molar equivalents of the acid is required to hydrolyze a formula II dicarboxylic acid diester. Typically about 1.5 to 5 molar equivalents and preferably 3 to 5 molar equivalents of acid is employed to hydrolyze a formula II diester.

Acid	pK_a
Sulfuric	-3.0
Sulfurous	1.9
Hydrochloric	-6.1
Hydrobromic	-9.0
Trifluoroacetic	0.5
Trichloroacetic	0.5
β-Naphthalene sulfonic	0.6
Benzene sulfonic	2.6
p-Toluene sulfonic	0.9
p-Ethylbenzene sulfonic	0.9
Dichloroacetic	1.3
Phosphoric	2.5

Bases suitable for use in the present invention include aqueous bases such as alkali metal and alkaline earth metal hydroxides and carbonates with aqueous sodium hydroxide and potassium hydroxide being preferred.

Volatile chlorinated hydrocarbons suitable for use in the present invention include dichloromethane, carbon tetrachloride, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane and the like with dichloromethane being preferred. Ethers suitable for use in the present invention include diethyl ether, tetrahydrofuran and the like with tetrahydrofuran being preferred. Water-immiscible alcohols which may be employed in the method of the present invention include n-butanol, n-hexanol, n-pentanol and the like.

Water and alcohol form an azeotrope at elevated temperatures and this azeotrope is separated from the reaction mixture of the present invention by continuous distillation. Since the by-product alcohol is continuously separated from the reaction mixture, the reaction mixture is unable to establish an

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equilibrium and proceeds until all of the formula II dicarboxylic acid diester is hydrolyzed to the desired formula I 2,3-pyridine or quinolinedicarboxylic acid.

Acid salts of formula I 2,3-pyridine and quinolinedicarboxylic acids generally cannot be isolated from aqueous solutions. Therefore, when a high boiling solvent such as 1,1'-oxybis[2-methoxyethane], 2,5,8,11-tetraoxadodecane, 2,5,8,11,14-pentaoxapentadecane and the like is added to the washed reaction mixture of the present invention to allow for the separation of water via distillation at an elevated temperature and/or at reduced pressure. Since the water is now removed, the above acid salt may be isolated in high yield.

In order to facilitate a further understanding of the invention, the following examples are presented to illustrate more specific details thereof. The invention is not to be limited thereby except as defined in the claims.

EXAMPLE 1

Preparation of 5-Methoxymethyl-2,3-pyridinedicarboxylic acid using sulfuric acid

A mixture of 5-methoxymethyl-2,3-pyridinedicarboxylic acid dimethyl ester (12.0 g, 0.05 mol), sulfuric acid (14.7 g, 0.15 mol) and water (40 g, 2.2 mol) is heated at 70° to 110°C. A mixture of methanol and water is continuously distilled from the reaction mixture and heating is continued until the reaction is complete by chromatographic analysis. The reaction mixture is cooled to room temperature and the pH is adjusted to 1.3 to 2.0 with 50% sodium hydroxide. The title product is isolated by filtration, washed with water (20 mL) and dried *in vacuo*. The title product is identified by ^{1}HNMR and mass spectroscopy and analyzed by high pressure liquid chromatography to be >96% pure.

EXAMPLE 2

Preparation of 5-Methoxymethyl-2,3-pyridinedicarboxylic acid using hydrochloric acid

A mixture of 5-methoxymethyl-2,3-pyridinedicarboxylic acid dimethyl ester (12.0 g, 0.05 mol), hydrochloric acid (9.1 g, 0.25 mol) and water (36 g) is heated at 70° to 110°C. A mixture of methanol, water and hydrochloric acid is continuously distilled from the reaction mixture, and heating is continued until the reaction is complete by chromatographic analysis. The reaction mixture is cooled to room temperature and the pH is adjusted to 1.3 to 2.0 with 50% sodium hydroxide. The title product is isolated by filtration, washed with water (20 mL) and dried *in vacuo*. The title product is identified by ^{1}HNMR and mass spectroscopy and analyzed by high pressure liquid chromatography to be >92% pure.

EXAMPLE 3

Preparation of 5-Methyl-2,3-pyridinedicarboxylic acid using phosphoric acid

A stirred mixture of 5-methyl-2,3-pyridinedicarboxylic acid dimethyl ester (20.9 g, 0.1 mol), phosphoric acid (29.4g, 0.3 mol) and water (60 g, 3.3 mol) is heated at 70° to 110°C. A mixture of methanol and water is continuously distilled from the reaction mixture and heating is continued until the reaction is complete by chromatographic analysis. The mixture is cooled to room temperature and the title product is allowed to precipitate. The title product is isolated by filtration, washed with water (30 mL) and dried *in vacuo*. The title product is identified by ^{1}HNMR and mass spectroscopy and analyzed by high pressure liquid chromatography to be >97% pure.

EXAMPLE 4

Preparation of 5-Methyl-2,3-pyridinedicarboxylic acid using hydrochloric acid

A stirred mixture of 5-methyl-2,3-pyridinedicarboxylic acid dimethyl ester (20.9 g, 0.1 mol), hydrochloric acid (18.2g, 0.5 mol) and water (72g) is heated at 70° to 110°C. A mixture of methanol and water and hydrochloric acid is continuously distilled from the reaction mixture and heating is continued until the reaction is complete by chromatographic analysis. The reaction mixture is concentrated *in vacuo* and diluted with water. The title product is isolated by filtration, washed with water (30 mL) and dried *in vacuo*. The title product is identified by ^{1}HNMR and mass spectroscopy and analyzed by high pressure liquid chromatography to be >96% pure.

EXAMPLE 5

Preparation of 5-Methyl-2,3-pyridinedicarboxylic acid using hydrobromic acid

A stirred mixture of 5-methyl-2,3-pyridinedicarboxylic acid dimethyl ester (20.9 g, 0.1 mol), hydrobromic acid (40.5g, 0.5 mol) and water (50g) is heated at 70° to 110°C. A mixture of methanol, water and hydrobromic acid is continuously distilled from the reaction mixture and heating is continued until the reaction is completed by chromatographic analysis. The mixture is concentrated *in vacuo* and diluted with water. The title product is isolated by filtration, washed with water (30 mL) and dried *in vacuo*. The title product is identified by ^{1}HNMR and mass spectroscopy and analyzed by high pressure liquid chromatography to be >96% pure.

EXAMPLE 6

Preparation of 5-Ethyl-2,3-pyridinedicarboxylic acid using sulfuric acid

A mixture of 5-ethyl-2,3-pyridinedicarboxylic acid diethyl ester (25 g, 0.1 mol), sulfuric acid (30g, 0.3 mol) and water (60 g, 3.3 mol) is heated at 70° to 110°C. A mixture of ethanol, water and hydrochloric acid is continuously distilled from the reaction mixture, and heating is continued until the reaction is complete by chromatographic analysis. The mixture is cooled to room temperature and the pH is adjusted to pH 1.3 to pH 2.0 with 50% sodium hydroxide. The title product is isolated by filtration, washed with water (20 mL) and dried in vacuo. The title product is identified by ^{1}HNMR and mass spectroscopy and analyzed by high pressure liquid chromatography to be >98% pure.

EXAMPLE 7

Preparation of 5-Ethyl-2,3-pyridinedicarboxylic acid using hydrochloric acid

A mixture of 5-ethyl-2,3-pyridinedicarboxylic acid diethyl ester (182 g, 0.73 mol), hydrochloric acid (93g, 2.5 mol) and water (60 g, 3.3 mol) is heated at 70° to 110°C. A mixture of ethanol, water and hydrochloric acid is continuously distilled from the reaction mixture and replaced with 18% aqueous hydrochloric acid. The reaction mixture is held at this temperature until the reaction is complete by chromatographic analysis. The reaction mixture is cooled to room temperature and the pH is adjusted to pH 1.3 to pH 2.0 with 50% sodium hydroxide. The title product is isolated by filtration, washed with water (20 mL) and dried in vacuo. The title product is identified by ^{1}HNMR and mass spectroscopy and analyzed by high pressure liquid chromatography to be >96% pure.

EXAMPLE 8

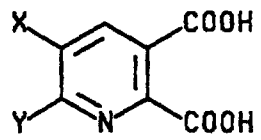
Preparation of 5-Ethyl-2,3-pyridinedicarboxylic acid using hydrochloric acid and diglyme

A mixture of 5-ethyl-2,3-pyridinedicarboxylic acid diethyl ester (44.2 g, 0.18 mol), hydrochloric acid (23.3 g, 0.64 mol) and water (103 g, 5.7 mol) is heated at 80°C for 18 hours. The reaction mixture is cooled to 30°C and washed with methylene chloride. Diglyme is added to the mixture and the mixture is concentrated in vacuo, diluted with methylene chloride and filtered. The filter cake is washed with diglyme and methylene chloride to give the hydrochloride salt of the title compound. The filter cake is then slurried with water, filtered and dried to give the title compound. The title product is identified by ^{1}HNMR and mass spectroscopy and analyzed by high pressure liquid chromatography to be >99% pure.

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I CLAIM:

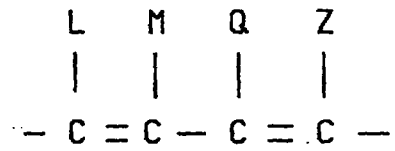
1. A method for the preparation of a formula I 2,3-pyridine or quinolinedicarboxylic acid having the structure



(I)

wherein

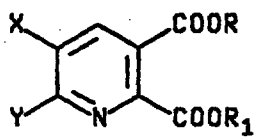
X and Y are each independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxyalkyl, C_1-C_6 alkoxy, C_1-C_4 alkylthio, phenoxy, C_1-C_4 haloalkyl, nitro, cyano, C_1-C_4 alkylamino, diloweralkylamino, C_1-C_4 alkylsulfonyl or phenyl optionally substituted with a C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen group; and, when taken together, X and Y may form a ring in which XY is represented by the structure



wherein L, M, Q and Z are each hydrogen, halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; characterized by hydrolyzing a formula II 2,3-pyridine or quinolinedicarboxylic acid diester having the structure

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(II)

wherein R and R_1 each represent a C_1-C_6 alkyl group and X and Y are as described above for formula I; by heating said dicarboxylic acid diester in the presence of water and an acid having an ionization constant pK_a of less than 3.0 at a temperature between about 50°C and 110°C, separating water and alcohol from said reaction mixture, cooling the remaining reaction mixture to a temperature between about 20°C and 35°C, treating the remaining reaction mixture with base, if the reaction mixture has a pH value less than pH 1.3, to adjust the pH of said mixture to a value between 1.3 and 2.0 and separating the formula I 2,3-pyridine or quinolinedicarboxylic acid from the pH adjusted mixture.

2. The method according to claim 1 wherein the acid employed in the hydrolysis is sulfuric, sulfurous, hydrochloric, hydrobromic, trifluoroacetic, trichloroacetic, β-naphthalene sulfonic, benzene sulfonic, p-toluene sulfonic, p-ethylbenzene sulfonic, dichloracetic or phosphoric acid and is used at about 3 to 5 molar equivalent per mole of diester treated.

3. The method according to claim 1 wherein the base is an aqueous solution of an alkali metal hydroxide.

4. The method according to claim 1 wherein the reaction mixture which has been adjusted to a pH value

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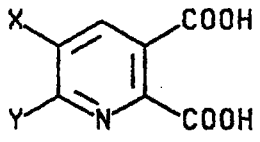
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between pH 1.3 and pH 2.0 is filtered to obtain the formula I 2,3-pyridinedicarboxylic acid.

5. The method according to claim 1 wherein the acid is sulfuric, hydrochloric or hydrobromic acid and the base is sodium hydroxide.

6. The method according to claim 1 wherein the 2,3-pyridine or quinolinedicarboxylic acid is 5-ethyl-2,3-pyridinedicarboxylic acid, 5-methoxymethyl-2,3-pyridinedicarboxylic acid, 2,3-pyridinedicarboxylic acid, 5-methyl-2,3-pyridinedicarboxylic acid or 2,3-quinolinedicarboxylic acid; the acid is sulfuric, hydrochloric or hydrobromic acid and the base is sodium hydroxide.

7. A method for the preparation of an acid salt of a formula I 2,3-pyridine or quinolinedicarboxylic acid having the structure

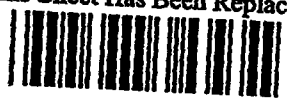


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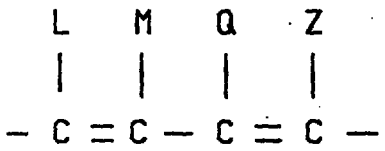
wherein

X and Y are each independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxyalkyl, C_1-C_6 alkoxy, C_1-C_4 alkylthio, phenoxy, C_1-C_4 haloalkyl, nitro, cyano, C_1-C_4 alkylamino, diloweralkylamino, C_1-C_4 alkylsulfonyl or phenyl optionally substituted with a C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen group; and, when taken together, X and Y may form a ring in which XY is represented by the structure

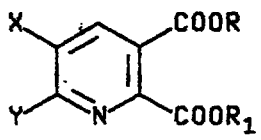
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wherein L, M, Q, and Z are each hydrogen, halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; characterized by hydrolyzing a formula II 2,3-pyridine or quinolinedicarboxylic acid diester having the structure



(II)

wherein R and R_1 each represent a C_1-C_6 alkyl group and X and Y are as described above for formula I, in the presence of water and an acid having a pK_a of less than 3.0 at a temperature between about 50°C and 110°C, cooling said heated mixture to a temperature between about 20°C and 40°C, washing said cooled mixture with a volatile chlorinated hydrocarbon, an ether or a water-immiscible alcohol, adding to the washed mixture 1,1'-oxybis[2-methoxyethane]; 2,5,8,11-tetraoxadodecane or 2,5,8,11,14-pentaoxapentadecane and separating water to obtain the formula I 2,3-pyridine or quinolinedicarboxylic acid as the acid salt and optionally dispersing said acid salt in water or aqueous base to obtain the formula I 2,3-pyridine or quinolinedicarboxylic acid.

8. The method according to claim 7 wherein the 2,3-pyridine or quinolinedicarboxylic acid is 5-ethyl-2,3-pyridinedicarboxylic acid, 5-methoxymethyl-2,3-pyridinedicarboxylic acid, 2,3-pyridinedicarboxylic acid, 5-methyl-2,3-pyridinedicarboxylic acid or 2,3-quinolinedicarboxylic acid.

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9. The method according to claim 7 wherein the acid used is hydrochloric acid and is used at about 1.5 to 5 molar equivalents of acid per mole of diester.

10. The method according the claim 7 wherein the volatile chlorinated hydrocarbon is dichloromethane, chloroform or carbon tetrachloride; the ether is diethyl ether or tetrahydrofuran; and the water-immiscible alcohol is n-butanol, n-hexanol or n-pentanol.