Description

The present invention relates to novel methods for preparing quinoline-2,3-dicarboxylic acids. These acids are useful intermediates in the preparation of herbicidal pyridine and quinoline imidazolinone herbicidal compounds.

The herbicidal pyridine and quinoline imidazolinone compounds prepared from the present compounds include 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)quinoline-3-carboxylic acid, esters and salts thereof and are disclosed in European Patent Application 0 041 623, incorporated herein by reference. These herbicidal imidazolinyl quinolinecarboxylic acids may be prepared by the procedure described in United States Patent 4,518,780 (incorporated herein by reference) by cyclization, under basic conditions, with an appropriately substituted 2-carbamoyl quinoline-3-carboxylic acid, that, in turn, is prepared by the reaction of a substituted quinoline-2,3-dicarboxylic acid anhydride and appropriately substituted aminocarboxamide or aminothiocarboxamide. Quinoline-2,3-dicarboxylic acid anhydrides are readily prepared from the diacids by procedures well known in the art. However,the diacids themselves are not readily available.

Existing procedures for preparing esters of quinoline-2,3-dicarboxylic acid include the Friedlander reaction of 2-aminobenzaldehyde with diethyloxalacetate, as described by L. Hozer and S. von Niementowski, J. Prakt. Chem., 116(2):43 (1927) and P. Caluwe, Tetranedron, 36:2359 (1984), and the ozonolysis of acridine as described by A. Godard, G. Zueguiner, P. Pastour in Bull. Soc. Chim. France, 906 (1971). These methods are not suitable for the manufacture of large quantities of materials because of difficulty in preparing and storing 2-aminobenzaldehyde. 2-aminobenzaldehyde is not only unstable, but there are limited supplies of acridine in order to prepare said 2-aminobenzaldehyde. Therefore, other routes have been preferred.

On such other synthesis is disclosed in pending application for United States Letters Patent of Robert Doehner, Serial Number 698,192 filed February 4, 1985 (incorporated herein by reference) which describes a method for the preparation of quinoline-2,3-dicarboxylic acid and esters thereof by reacting a beta-anilino-alpha,beta-unsaturated ester with an immonium salt (commonly called a Vilsmeir reagent). The beta-anilino-alpha,beta-unsaturated esters are obtained by the reaction of appropriately substituted anilines with ketoesters or dialkyl acetylene dicarboxylates.

Unfortunately, the availability of ketoesters and dialkyl acetylene dicarboxylates, such as diethyloxalacetate and diethyl acetylenedicarboxylate is limited, thereby restricting the quantities of anilinofumarate, a precursor to quinoline-2,3-dicarboxylic acid.

Co-pending applications for United States Letters Patent of D. Maulding filed concurrently herewith provide effective methods for the preparation of anilinofumarate by reacting dichlorosuccinates with specified amines.

SUMMARY OF THE INVENTION

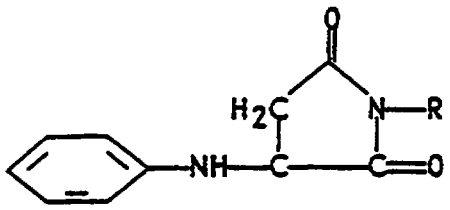
Although other routes exist for the preparation of anilinofumarates in order to prepare quinoline-2,3-dicarboxylic acids for producing the herbicidal agents 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-quinoline-3-carboxylic acids, esters and salts thereof, the present invention relates to a process for the preparation of quinoline-2,3-dicarboxylic acid with the use of aniline and maleic anhydride to obtain a ready source of acridine.

It is an object of the present invention, therefore, to provide a ready source of starting materials to form quinoline-2,3-dicarboxylic acid. This objective is fulfilled by reacting an oxidized anilinosuccimide with dimethylformamide dimethylacetal or dimethyl formamide and phosphorous oxychlorid, cyclizing the resulting reactant to result in an acridinimide and hydrolyzing the acridinimide to obtain the quinoline-2,3-dicarboxylic acids.

These and other objects of the invention will become more apparent by the detailed description of the invention provided hereinbelow.

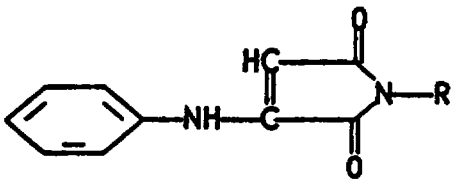
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel method for the preparation of quinoline-2,3-dicarboxylic acid, said method comprising oxidizing an N-substituted-3-anilinosuccinimide of formula I



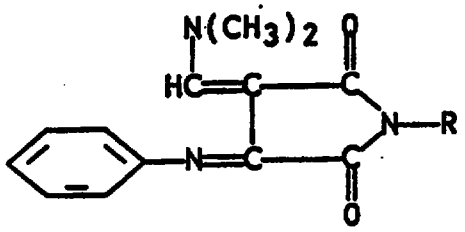
I

wherein R is phenyl or C_1-C_6 alkyl in an inert solvent; reacting the thus-formed formula II 3-anilino-N-substituted-maleimide



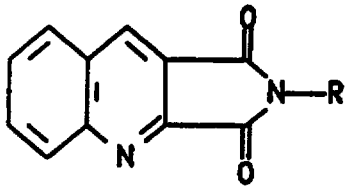
II

wherein R is as defined hereinabove with a minimum of 2 molar equivalents (2 molar equivalents or greater) of dimethylformamide dimethyl acetal in an inert hydrocarbon aromatic hydrocarbon, chlorinated hydrocarbon or chlorinated aromatic hydrocarbon solvent, or with one molar equivalent of a Vilsmeier reagent prepared from dimethylformamide and two molar equivalents of $POCl_3$ in dichloromethane at reflux; isolating the resulting formula III 3-phenylimino-4-dimethylaminomethylene-N-substituted-succinimide



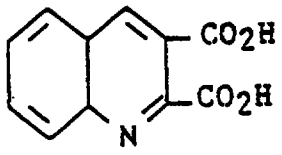
III

wherein R is as defined hereinabove; cyclizing the formula III compound by treatment with polyphosphoric acid at 130°C to 145°C to yield formula IV substitutedacridinimide



IV

wherein R is as defined hereinabove; hydrolyzing the formula IV acridinimide with a minimum one (1) molar equivalent base (one molar equivalent or greater) in a solvent of water or an aqueous alcohol; cooling the reaction mixture; isolating the thus formed quinoline-2,3-dicarboxylic, formula V



V

acid by acidification of said cooled reaction mixture; and collecting the precipitated product.

It has been found that the reaction of formula II 3-anilino-N-substituted-maleimides compounds readily prepared by oxidation of formula I N-substituted-3-anilinosuccinimide with oxidising agents such as MnO_2 or chloranil, in an inert solvent at a temperature of about 25°C to 150°C, preferably at reflux with one molar equivalent of a Vilsmeir reagent prepared from dimethyl formamide and $POCl_3$ in refluxing methylene chloride, or preferably with a minimum of two molar equivalents of dimethylformamide dimethyl acetal in solvents such as toluene, xylene, benzene, methylene chloride, ethylene chloride, chloro-benzene at a temperature of about 25°C to 140°C yields formula IV compounds. These formula IV compounds are easily cyclized to formula IV acridinimides when treated with polyphosphoric acid at a temperature of about 130°C to 145°C.

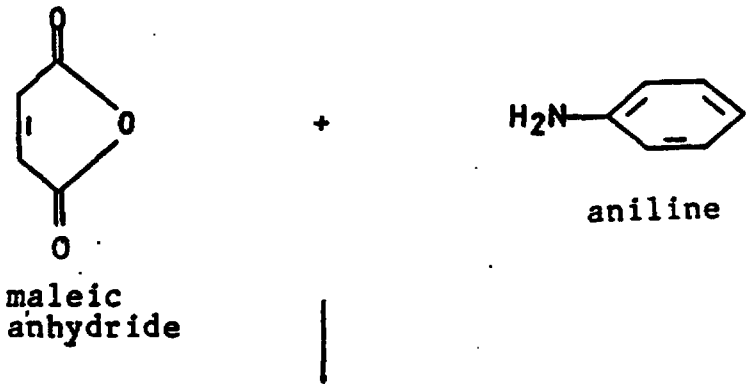
Additionallly, it has been found that the formula IV acridinimides are readily hydrolysed in water or aqueous-alcoholic solvent systems with a minimum of two molar equivalents of base (2 molar equivalents or greater). Preferable bases are sodium hydroxide, potassium hydroxide, or mixtures thereof at concentrations of 5% to 50%, on a weight basis, giving quinoline-2,3-dicarboxylic acid as its salt. This is then isolated as the free acid by acidification of the cooled reaction mixture and collection of the precipitated product.

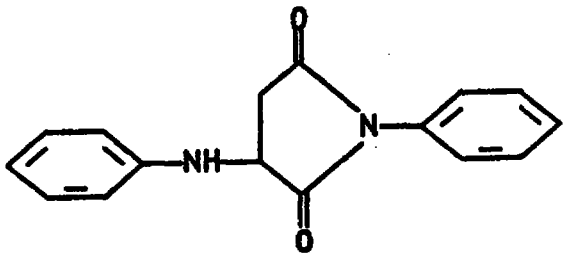
Advantageously, the above method provides a novel route to quinoline-2,3-dicarboxylic acid utilizing formula I 3-anilinosuccinimides which may be prepared in high yields from maleic anhydride, a ready source of starting material available in large quantities, by known procedures, such as those described by S. I. Burmistrov. et al., J. Org. Chem. U.S.S.R., 8:1102 (1972), and L. E. Coleman, Jr. et al., J. Org. Chem., 24:135 (1959) (incorporated herein by reference).

The present invention is further illustrated by the following which are provided as illustrations of the invention.

EXAMPLE 1

Preparation of 3-anilino-N-phenylsuccinimide

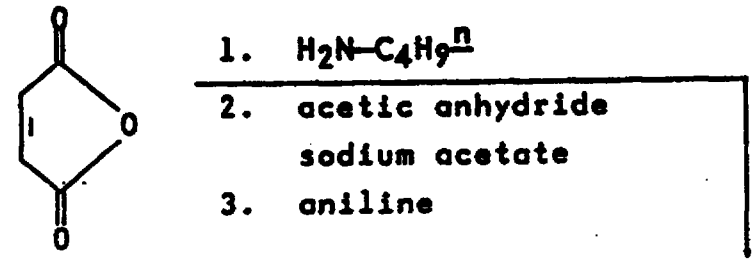


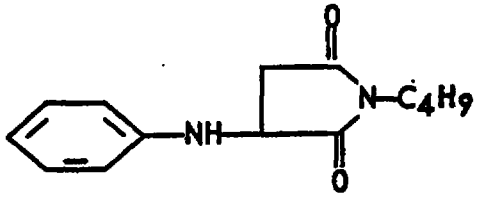


A mixture of 9.8 g (0.1 mol) of maleic anhydride, 18.6 g (0.20 mol) of aniline and 75 mL of o-dichlorobenzene is heated while stirring at 175-180°C for one hour. At 175°C all of the solid goes into solution. A Dean Stark trap is used to collect the condensate during the reaction. Cooling gives a thick precipitate, which is stirred in 50 mL of ethanol, cooled in ice and collected by filtration to give 16.6 g of the product having m.p. 211-214.5°C. Concentration of the filtrate and slurrying in 50 mL of ethanol gives another 3.0 g of product, giving a total yield of 74%.

EXAMPLE 2

Preparation of 3-anilino-N-butylsuccinimide

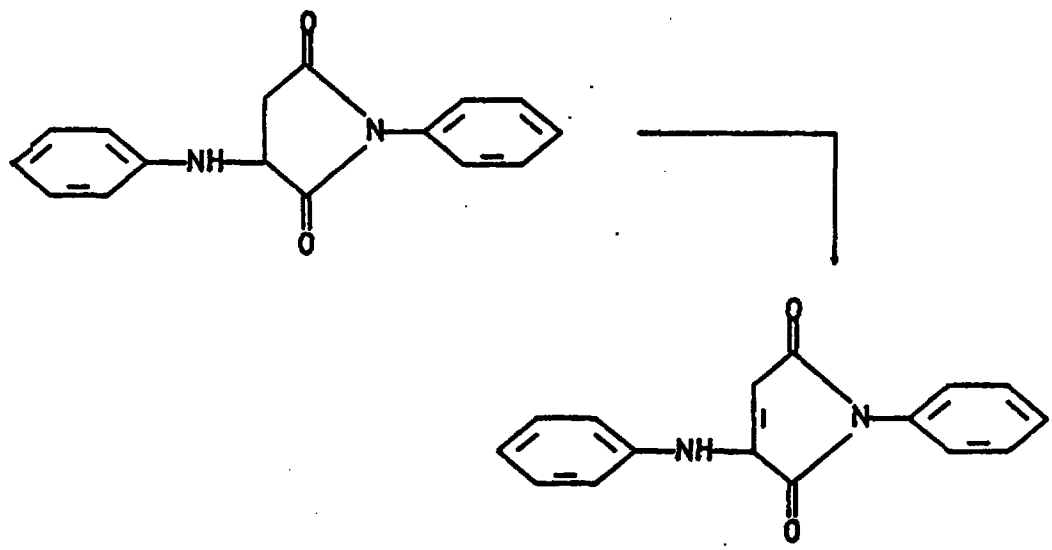




Maleic anhydride is reacted with n-butylamine under the conditions reported by L. E. Coleman et al., in J. Org. Chem., 24:135, (1959). A mixture containing the thus-formed n-butylmaleamic acid (12.0 g, 0.07 mol), anhydrous sodium acetate (2.7 g) and acetic anhydride (29 mL) is heated at 85°C to 90°C for 30 minutes. The solution is cooled to 40°C and poured into 55 mL of water. The layers are stirred at room temperature for 15 minutes, then diluted to 275 mL. A dark oil precipitates. Extraction with 100 mL of CH_2Cl_2, then another 25 mL of CH_2Cl_2, and evaporation of solvent gives 9.9 g of n-butylmaleimide as an oil, ir, 1735 (sh) and 1700 cm-1. A solution of 9.9 g (0.065 mol) of the n-butylmaleimide and 35 mL of acetic acid is treated with 6.51 g (0.07 mol) of aniline , with the resulting solution heated at 120°C for 30 minutes. The solution is cooled and poured into 280 mL of water. The amorphous material is collected and recrystallized from isopropyl alcohol to give 9.3 g of n-butyl anilinosuccinimide as off-white crystals, m.p. 97-100°C, ir, 3350, 1720 (sh), 1680, 1600 cm-1; mass spec, (ci) m/e 247. Anal. Calcd. for C14H18N202: C, 68.29; H, 7.32; N, 11.38. Found: C, 68.46; H, 7.28; N, 11.25.

EXAMPLE 3

Preparation of 3-anilino-N-phenylmaleimide



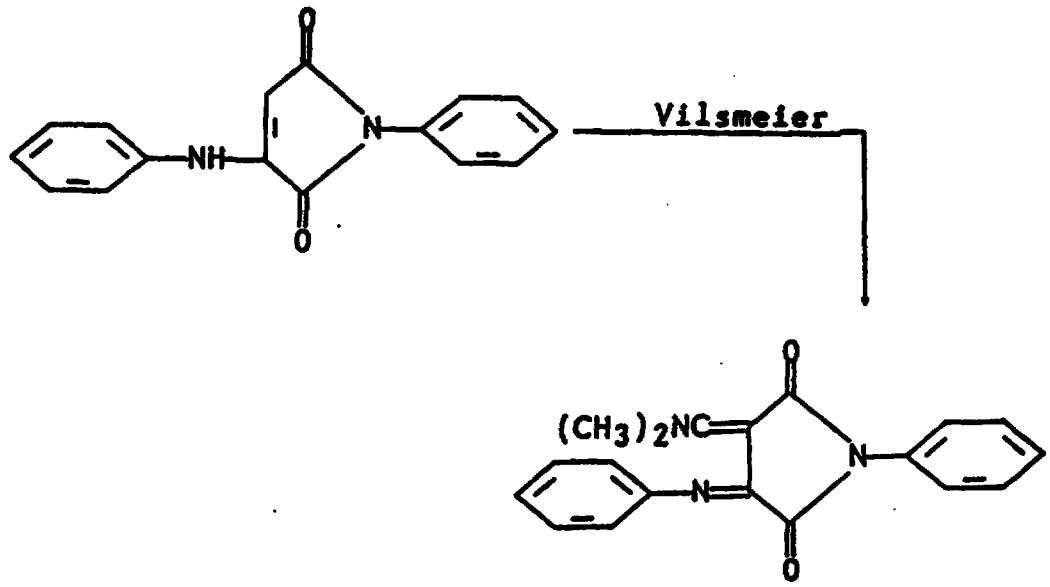
A. A mixture of 1.98 g (7.5 mmol) of the anilinosuccinimide prepared in Example 1 above and 1.96 g (22.5 mmol) of MnO_2 in 45 mL of toluene is refluxed for six hours. The mixture is filtered, while hot, and the resulting solid is heated in another 50 mL of boiling toluene and filtered again while hot. Cooling the combined toluene filtrates gives 450 mg of the title product as yellow-orange needles. Concentration of the toluene solution gives another 360 mg; m.p. 228-233 °C (lit (7) m.p. 230-230.5 °C).

B. A mixture of 1.32 g (5.0 mmol) of the anilinosuccinimide 1.22 g (5.0 mmol) of chloranil and 30 mL of xylene are refluxed for four hours. The mixture is cooled to room temperature and the precipitate collected and recrystallized from acetonitrile to give 0.86 g (65%); m.p. 233-235 °C.

Utilizing the procedure above and substituting N-butylanilinosuccinimide for the 3-amino-N-phenylsuccinimide yields 93% of N-butylanilinomaleimide which upon crystallization from isopropyl alcohol has a m.p. of 128-130 °C. Anal. Calcd. for $C_{14}H_{16}N_2O_2$: 68.85; H, 6.56; N, 11.48. Found: C, 68.58; H, 6.45; N, 11.38.

EXAMPLE 4

Preparation of 3-phenylimino-4-dimethylaminomethylene-N-phenylsuccinimide



A. A solution of 13.2 g (0.05 mol) of the anilinomaleimide prepared in Example 3, 11.9 g (0.10 mol) of dimethylformamide dimethyl acetal and 250 mL of toluene is refluxed for three hours. Cooling the solution gives a dark maroon solid which is stirred in 200 mL of hot ethanol and collected to give the title product 12.3 g (77%) having m.p. 196-200.5 °C. Recrystallization from acetonitrile gives brown-gold crystals, mp 199.5-201.5 °C (dec).

Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.47; H, 5.33; N, 13.17. Found: C, 71.42; H, 5.56; N, 12.98.

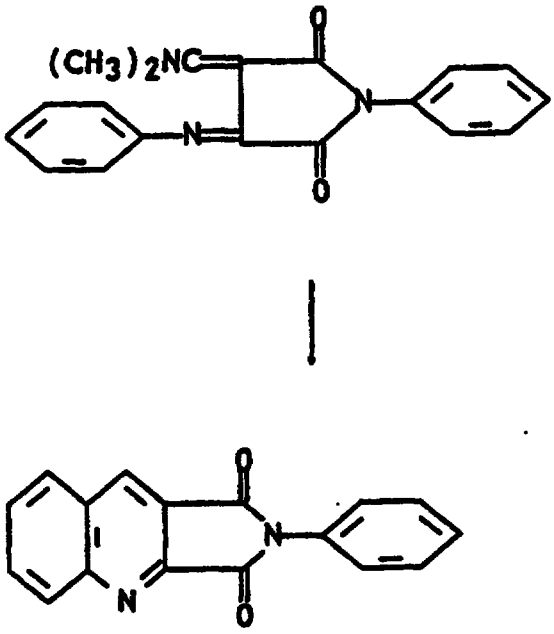
B. To a solution of 0.37 g (5. mmol) of DMF and 15 mL of methylene chloride is added dropwise, with cooling (15 °C-20 °C), 1.68 g (11 mmol) of $POCl_3$. The slurry is stirred at room temperature for 30 minutes, and the anilinomaleimide is added as a solid. The mixture is refluxed for three hours, and a dark maroon solution forms. The solution is cooled in ice, and 20 mL of methylene chloride and 10 mL of water are added. Aqueous Na_2CO_3 is added until the aqueous phase is alkaline, and the two layers are stirred for 15 minutes and filtered. The organic phase is separated and evaporated to give a viscous oil, which is dissolved in 40 mL of ethanol. Cooling gives 200 mg of the title product as an orange solid, m.p. 189-195 °C. Evaporation of solvent and recrystallization from ethyl acetate gives another 200 mg.

When the Vilsmeier reaction using DMF is attempted in refluxing monochlorobenzene, toluene or ethylene chloride, only polymeric material is obtained.

Utilizing procedure A above and substituting the N-butylanilinomaleide for 3-anilino-N-phenylmaleimide yields the corresponding 3-phenylimino-4-dimethylaminomethylene-N-butylsuccinimide.

EXAMPLE 5

Preparation of N-phenylacridinimide

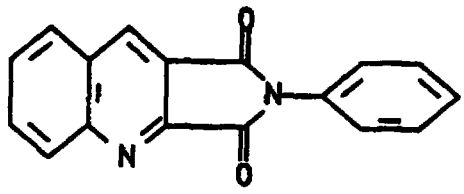


A solution of 2.0 g of the N-phenylsuccinimide, prepared as in Example 4, in 60 g of polyphosphoric acid, is heated at 140°C-145°C, with occasional stirring, for 20 minutes. The red maroon solution is cooled and poured into 400 g of ice and water. The crude product is collected, stirred in 100 mL of hot ethanol and isolated as an off-white solid, weighing 1.54 g (90%) having a m.p. 315-321°C.

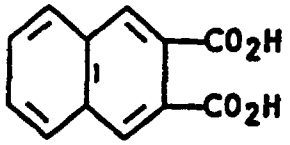
Utilizing the above procedure substituting the N-butylsuccinimide prepared in Example 4 for the N-phenylsuccinimide yields N-butylacridinimide in 47% yield, which upon crystallization has m.p. 165-167°C. Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found C, 70.78; N, 5.41; N, 10.96.

EXAMPLE 6

Preparation of Quinoline-2,3-dicarboxylic acid



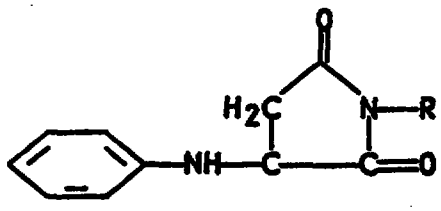
base



A mixture of 274 mg (1.0 mmol) of N-phenylacridinimide, 160 mg (4.0 mmol) of NaOH in 1.5 mL of water and 10 mL of ethanol is heated at reflux for three hours. Water (10 mL) is added, while the ethanol is removed by distillation, and the resulting solution is then heated at reflux for two hours. The solution is cooled in an ice bath and conc HCl is added, dropwise, until the mixture is acidic. The thick mixture is filtered, washed with water and dried in a vacuum oven at 60 °C to give 179 mg of the product with m.p. 279 °C-281 °C (dec with loss of CO_2 at 105 °C-120 °C).

Claims

1. A method for the preparation of quinoline-2,3-dicarboxylic acid, said method comprising: oxidizing an N-substituted-3-anilinosuccinimide of formula I

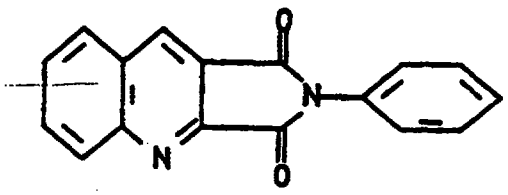


I

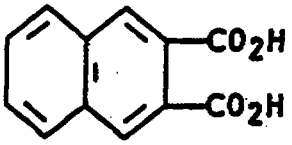
wherein R is phenyl or C_1-C_6 alkyl in an inert solvent; reacting the thus formed formula II 3-anilino-N-substituted-maleimide

EXAMPLE 6

Preparation of Quinoline-2,3-dicarboxylic acid



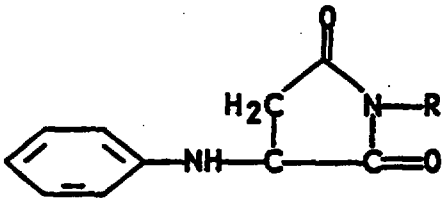
base



A mixture of 274 mg (1.0 mmol) of N-phenylacridinimide, 160 mg (4.0 mmol) of NaOH in 1.5 mL of water and 10 mL of ethanol is heated at reflux for three hours. Water (10 mL) is added, while the ethanol is removed by distillation, and the resulting solution is then heated at reflux for two hours. The solution is cooled in an ice bath and conc HCl is added, dropwise, until the mixture is acidic. The thick mixture is filtered, washed with water and dried in a vacuum oven at 60 °C to give 179 mg of the product with m.p. 279 °C-281 °C (dec with loss of CO_2 at 105 °C-120 °C).

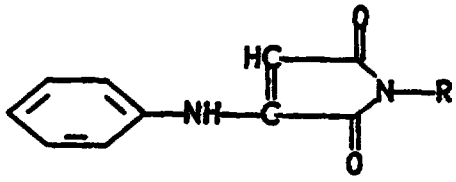
Claims

1. A method for the preparation of quinoline-2,3-dicarboxylic acid, said method comprising: oxidizing an N-substituted-3-anilinosuccinimide of formula I



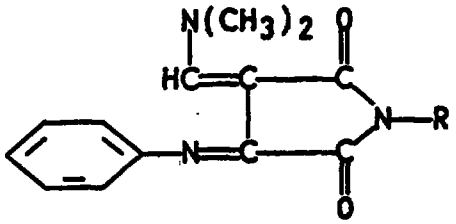
I

wherein R is phenyl or C_1-C_6 alkyl in an inert solvent; reacting the thus formed formula II 3-anilino-N-substituted-maleimide



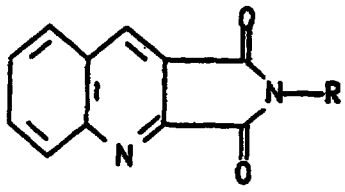
II

wherein R is as defined hereinabove with a minimum of 2 molar equivalents of dimethylformamide dimethylacetal in an inert hydrocarbon aromatic hydrocarbon, chlorinated hydrocarbon or chlorinated aromatic hydrocarbon solvent, or one molar equivalent of a Vilsmeier reagent prepared from dimethylformamide and two molar equivalents of $POCl_3$ in dichloromethane at reflux; isolating the resulting formula III 3-phenylimino-4-dimethylaminomethylene-N-substituted-succinimide



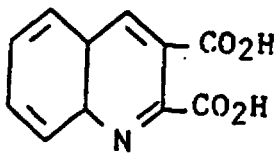
III

wherein R is as defined hereinabove: cyclizing the formula III compound by treatment with polyphosphoric acid at 130 °C to 145 °C to yield a formula IV substituted-acridinimide



IV

wherein R is as defined hereinabove; hydrolyzing the formula IV acridinimide with a minimum one molar equivalent base in a solvent of water or an aqueous alcohol; cooling the reaction mixture; isolating the thus formed quinoline-2,3-dicarboxylic acid (formula V) by acidification of the cooled reaction mixture;



V

and collecting the precipitated product.

2. A method according to Claim 1, wherein said formula II 3-anilino-N-substituted maleimide is reacted with a minimum of two molar equivalents of dimethylformamide dimethyl acetal, in an inert solvent, at a temperature of about 25 °C to 140 °C.

3. A method according to Claim 2, wherein said solvent is toluene, benzene, xylene, methylene chloride, ethylene chloride, chlorobenzene, or mixtures thereof.

4. A method according to Claim 3, wherein said formula I N-substituted 3-anilinosuccinimide is oxidized with MnO_2 or chloranil in toluene or xylene at reflux.

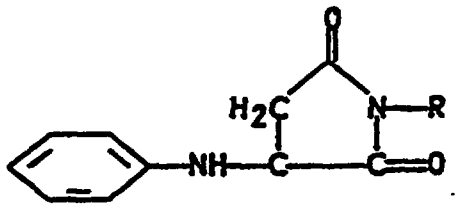
5. A method according to Claim 4, wherein said base to hydrolyze said formula IV N-substituted-acridinimide is aqueous or aqueous alcoholic sodium hydroxide, potassium hydroxide, or mixtures thereof, at a concentration of about 5% to 50%, on a weight basis.

6. A method according to Claim 5, wherein said base used is two or more molar equivalents.

7. A method according to Claim 6, wherein said formula IV N-substituted-acridinimide is hydrolyzed at reflux for about two to six hours.

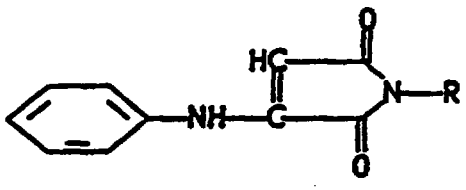
Patentansprüche

1. Verfahren zur Herstellung von Chinolin-2,3-dicarbonsäure, umfassend:
das Oxidieren eines N-substituierten 3-Anilinosuccinimids der Formel I,



I

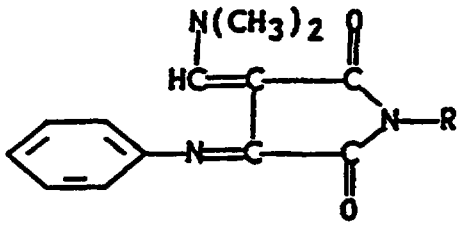
in der R Phenyl oder C_1-C_6-Alkyl ist, in einem inerten Lösungsmittel;
das Umsetzen des so gebildeten 3-Anilino-N-substituiertenmaleimids der Formel II,



II

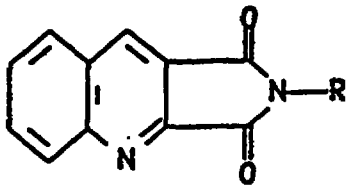
in der R wie oben definiert ist, mit einem Minimum von 2 Moläquivalenten Dimethylformamiddimethylacetal in einem inerten Kohlenwasserstoff-, aromatischen Kohlenwasserstoff-, chlorierten Kohlenwasserstoff- oder chlorierten aromatischen Kohlenwasserstoff-Lösungsmittel oder 1 Moläquivalent eines Vilsmeier-Reagenz, hergestellt aus Dimethylformamid und 2 Moläquivalenten $POCl_3$, in Dichlormethan unter Rückfluß; das Isolieren des resultierenden 3-Phenylimino-4-dimethylaminomethylen-N-substituierten-succinimids der Formel III,

* C L M S *



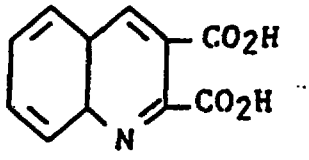
III

in der R wie oben definiert ist; das Cyclisieren der Verbindung der Formel III durch Behandlung mit Polyphosphorsäure bei 130 °C bis 145 °C, um ein substituiertes Acridinimid der Formel IV zu liefern,



IV

in der R wie oben definiert ist; das Hydrolysieren des Acridinimids der Formel IV mit einem Minimum von 1 Moläquivalent Base in einem Lösungsmittel aus Wasser oder einem wäßrigen Alkohol; das Abkühlen der Reaktionsmischung; das Isolieren der so gebildeten Chinolin-2,3-dicarbonsäure (Formel V) durch Ansäuern der abgekühlten Reaktionsmischung;



V

und das Sammeln des ausgefallenen Produkts.

2. Verfahren nach Aspruch 1, in dem das 3-Anilino-N-substituierte-maleimid der Formel II mit einem Minimum von zwei Moläquivalenten Dimethylformamiddimethylacetal in einem inerten Lösungsmittel bei einer Temperatur von ungefähr 25 °C bis 140 °C umgesetzt wird.

3. Verfahren nach Anspruch 2, in dem das Lösungsmittel Toluol, Benzol, Xylol, Methylenchlorid, Ethylenchlorid, Chlorbenzol oder Mischungen derselben ist.

4. Verfahren nach Anspruch 3, in dem das N-substituierte 3-Anilinosuccinimid der Formel I mit MnO_2 oder Chloranil in Toluol oder Xylol unter Rückfluß oxidiert wird.

5. Verfahren nach Anspruch 4, in dem die Base zum Hydrolysieren des N-substituierten Acridinimids der Formel IV wäßriges oder wäßrig-alkoholisches Natriumhydroxid, Kaliumhydroxid oder deren Mischungen bei einer Konzentration von ungefähr 5% bis 50% auf Gewichtsbasis ist.

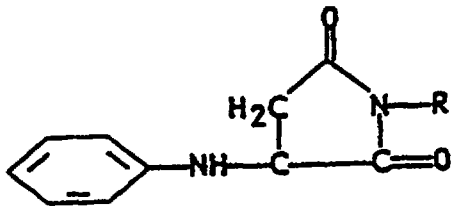
6. Verfahren nach Anspruch 5, in dem die verwendete Base zwei oder mehr Moläquivalente ausmacht.

* C L M S *

7. Verfahren nach Anspruch 6, in dem das N-substituierte Acridinimid ungefähr zwei bis sechs Stunden unter Rückfluß hydrolysiert wird.

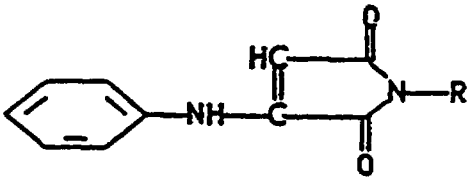
Revendications

1. Procédé pour la préparation d'acide quinoléine-2,3-dicarboxylique, ledit procédé comprenant : l'oxydation d'un 3-anilinosuccinimide N-substitué de formule I



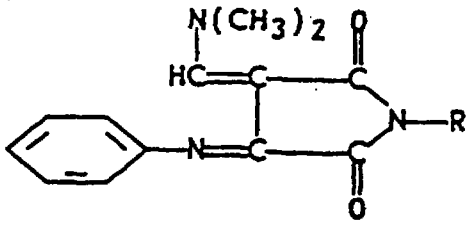
I

où R est un groupe phényle ou alkyle en C_1-C_6, dans un solvant inerte ; la réaction du 3-anilinomaléimide N-substitué ainsi formé de formule II



II

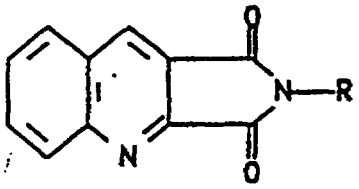
où R est tel que défini ci-dessus, avec au moins 2 équivalents molaires d'acétal diméthylique de diméthylformamide dans un solvant inerte du type hydrocarbure, hydrocarbure aromatique, hydrocarbure chloré ou hydrocarbure aromatique chloré, ou avec 1 équivalent molaire d'un réactif de Vilsmeier préparé à partir de diméthylformamide et de 2 équivalents molaires de $POCl_3$ dans le dichlorométhane au reflux ; l'isolement du 3-phénylimino-4-diméthylaminométhylène-succinimide N-substitué résultant de formule III



III

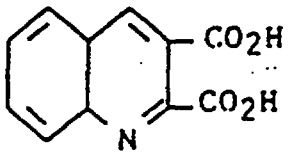
où R est tel que défini ci-dessus ; la cyclisation du composé de formule III par traitement avec l'acide polyphosphorique entre 130 °C et 145 °C pour former l'acridinimide substitué de formule IV

* C L M S *



IV

où R est tel que défini ci-dessus ; l'hydrolyse de l'acridinimide de formule IV avec au moins 1 équivalent molaire d'une base dans un solvant constitué d'eau ou d'un alcool aqueux ; refroidir le mélange réactionnel ; l'isolement de l'acide quinoléine-2,3-dicarboxylique ainsi formé (formule V) par acidification du mélange réactionnel refroidi ;



V

et la collecte du produit précipité.

2. Procédé selon la revendication 1, dans lequel ledit 3-anilinomaléimide N-substitué de formule II est amené à réagir avec au moins 2 équivalents molaires d'acétal diméthylique de diméthylformamide, dans un solvant inerte, à une température d'environ 25 °C à 140 °C.

3. Procédé selon la revendication 2, dans lequel ledit solvant est le toluène, le benzène, le xylène, le chlorure de méthylène, le chlorure d'éthylène, le chlorobenzène ou leurs mélanges.

4. Procédé selon la revendication 3, dans lequel ledit 3-anilinosuccinimide N-substitué de formule I est oxydé avec MnO_2 ou le chloranile dans le toluène ou le xylène au reflux.

5. Procédé selon la revendication 4, dans lequel ladite base utilisée pour hydrolyser ledit acridinimide N-substitué de formule IV est une solution aqueuse ou aqueuse-alcoolique d'hydroxyde de sodium, d'hydroxyde de potassium ou de mélanges d'entre eux, à une concentration d'environ 5 % à 50 % en poids.

6. Procédé selon la revendication 5, dans lequel ladite base est utilisée en une quantité de 2 équivalents molaires ou plus.

7. Procédé selon la revendication 6, dans lequel ledit acridinimide N-substitué de formule IV est hydrolysé au reflux pendant environ deux à six heures.

* C L M S *