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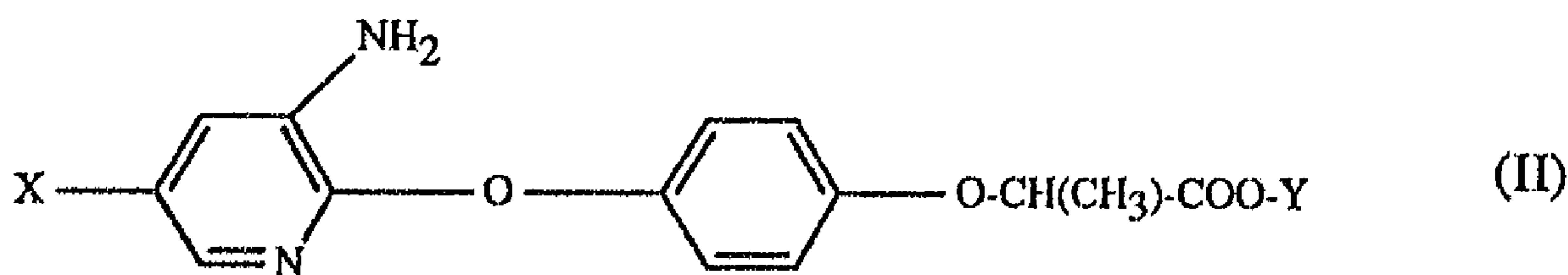
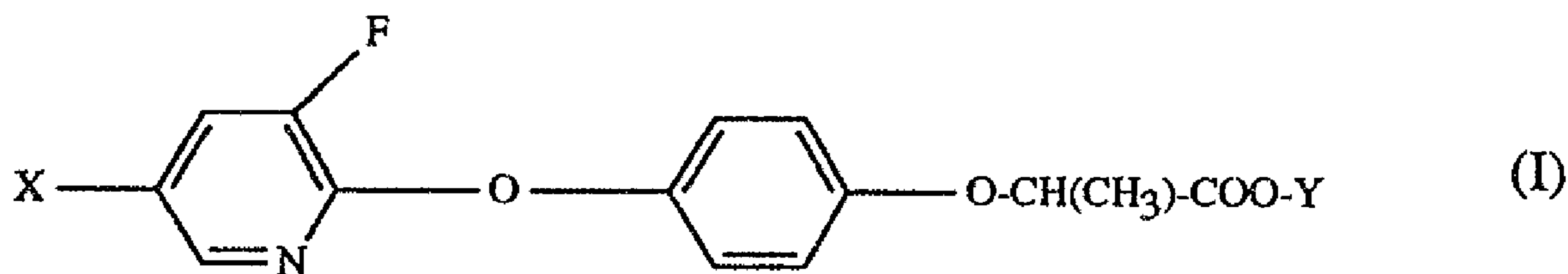
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(54) Titre : METHODE DE PREPARATION D'ACIDES (3-FLUOROPYRIDIN-2-YLOXY)PHENOXYPROPIONIQUES

(54) Title: PROCESS FOR THE PREPARATION OF (3-FLUOROPYRIDIN-2-YLOXY)PHENOXYPROPIONIC ACIDS



(57) Abrégé/Abstract:

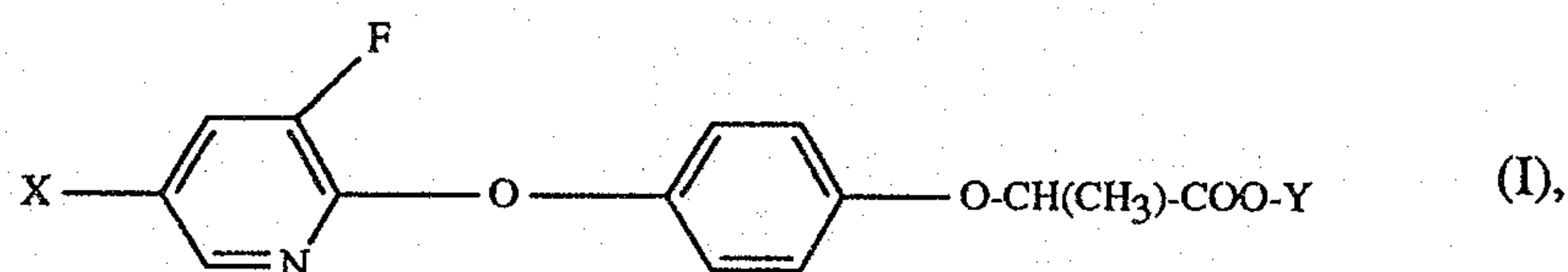
(3-Fluoropyridin-2-yloxy)phenoxypropionic acids of formula I (see formula I) wherein X is hydrogen, fluoro, chloro, bromo or trifluoromethyl and Y is hydrogen, sodium or potassium, are prepared by reacting a compound of formula II (see formula II) wherein X and Y are as defined for formula I, in an anhydrous medium, with hydrogen fluoride and a diazotising agent, and converting the diazonium fluoride so produced by thermal decomposition into the (3-fluoropyridin-2-yloxy)phenoxypropionic acid of formula I.



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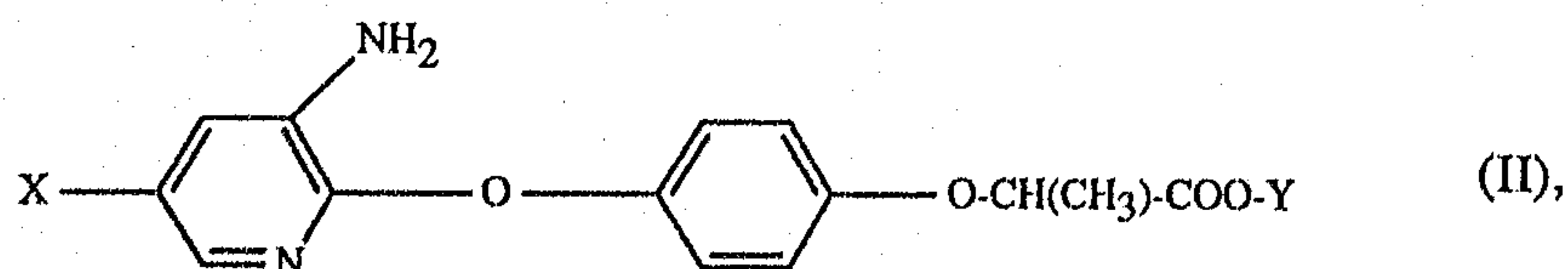
Process for the preparation of (3-fluoropyridin-2-yloxy)phenoxypropionic acidsAbstract of the Disclosure

(3-Fluoropyridin-2-yloxy)phenoxypropionic acids of formula I



wherein X is hydrogen, fluoro, chloro, bromo or trifluoromethyl and Y is hydrogen, sodium or potassium,

are prepared by reacting a compound of formula II

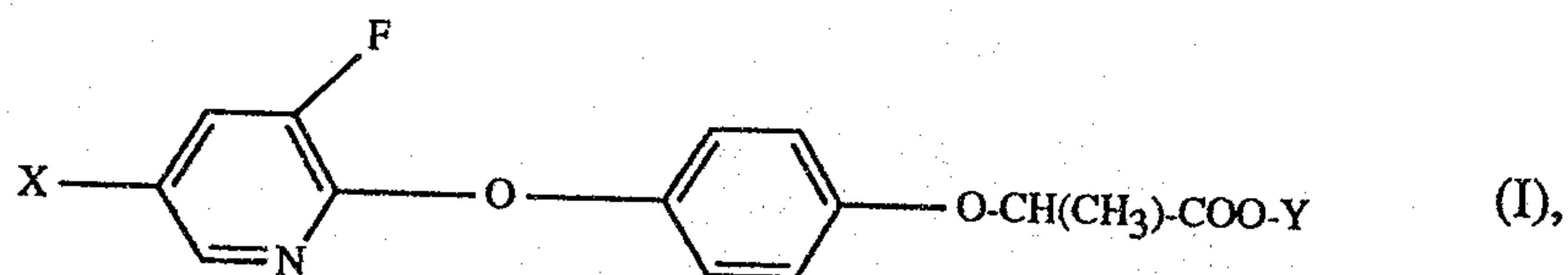


wherein X and Y are as defined for formula I, in an anhydrous medium, with hydrogen fluoride and a diazotising agent, and converting the diazonium fluoride so produced by thermal decomposition into the (3-fluoropyridin-2-yloxy)phenoxypropionic acid of formula I.

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Process for the preparation of (3-fluoropyridin-2-yloxy)phenoxypropionic acids

The present invention relates to a process for the preparation of (3-fluoropyridin-2-yloxy)-phenoxypropionic acids of formula I

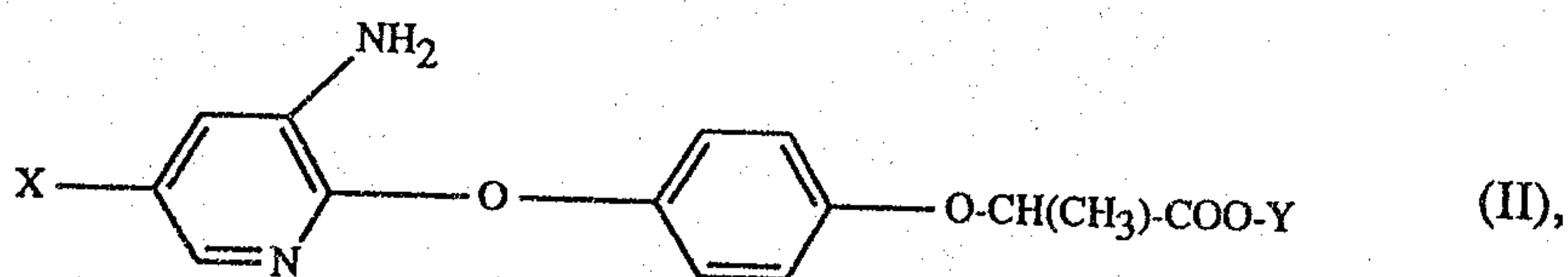


wherein X is hydrogen, fluoro, chloro, bromo or trifluoromethyl and Y is hydrogen, sodium or potassium.

The (3-fluoropyridin-2-yloxy)phenoxypropionic acids and salts of formula I have herbicidal properties. Furthermore, they are useful intermediates for the synthesis of the herbicidally active (3-fluoropyridin-2-yloxy)phenoxypropionates disclosed, inter alia, in published European patent applications EP-A-0 083 556 and EP-A-0 248 968.

It is the object of this invention to provide a process which allows (3-fluoropyridin-2-yloxy)phenoxypropionic acids to be prepared in simple manner and in good yield, starting from readily accessible starting materials, and which is particularly suitable as an industrial production process.

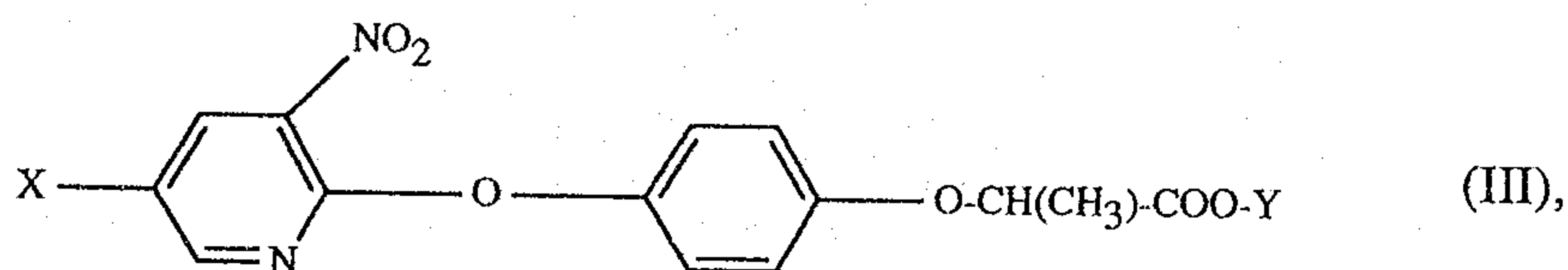
It has now been found that (3-fluoropyridin-2-yloxy)phenoxypropionic acids of formula I can be prepared in advantageous manner by reacting a compound of formula II



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wherein X and Y are as defined for formula I, in an anhydrous medium, with hydrogen fluoride and a diazotising agent, and converting the diazonium fluoride so produced by thermal decomposition into the (3-fluoropyridin-2-yloxy)phenoxypropionic acid of formula I.

The final products of the process of this invention are known. The starting materials of formula II are novel and also constitute an object of this invention. They can be obtained by reduction methods from the corresponding nitro compounds of formula III



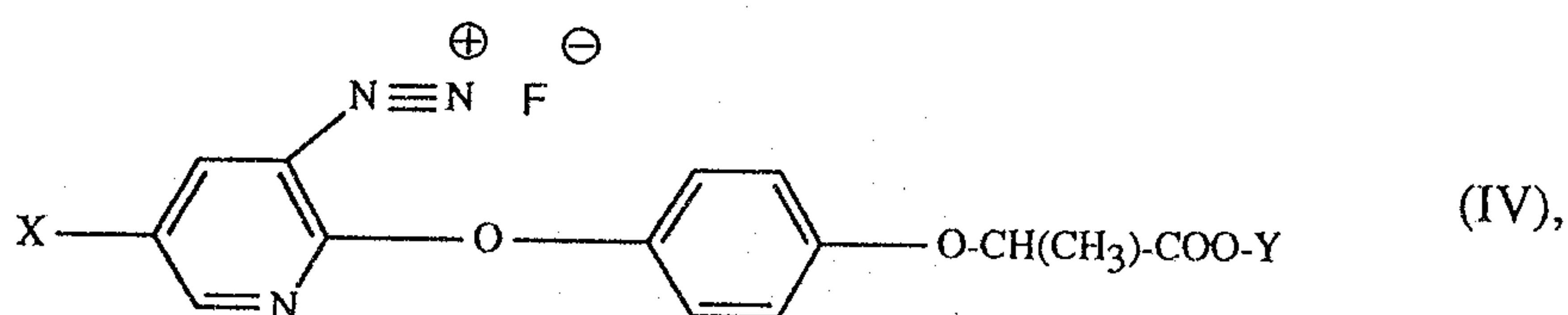
wherein X and Y are as defined for formula I. All standard methods described in the literature can be used for reducing the nitro compounds of formula III to the amino compounds of formula II. The reduction can typically be carried out with advantage in aqueous medium in the presence of iron, tin or zinc and hydrochloric acid. Other suitable methods are reduction processes using complex hydrides such as lithium aluminium hydride, or catalytic reduction with hydrogen using platinum, palladium or nickel catalysts.

The compounds of formula III, which are used as starting materials for the preparation of the compounds of formula II, are likewise novel and constitute yet a further object of the invention. The compounds of formula III can be prepared by methods which are known per se, typically by reacting the corresponding 2-chloro-3-nitropyridines with 2-(4-hydroxy)phenoxypropionic acid in the presence of a base. Such processes are described, for example, in EP-A-0 248 968. The 2-chloro-3-nitropyridines required for the preparation of the compounds of formula III, as well as the 2-(4-hydroxy)phenoxypropionic acid, are known or can be obtained by methods which are known to the skilled person.

The diazotisation can be carried out in the temperature range from -20 to +25°C, preferably from -10 to +10°C.

Preferred diazotising agents are sodium nitrite, potassium nitrite, N_2O_3 , NOF , $NOCl$, iso-amyl nitrite or tert-butyl nitrite. A particularly preferred diazotising agent is sodium nitrite.

The thermal decomposition of the diazonium fluoride of formula IV



wherein X and Y are as defined for formula I, is normally carried out in the temperature range from 15 to 100°C, preferably from 30 to 60°C. A particularly preferred temperature range is from 45 to 60°C.

A suitable anhydrous medium is hydrogen fluoride or a mixture of hydrogen fluoride and an inert polar aprotic solvent. Preferred solvents are dimethyl sulfoxide, sulfolane (tetrahydrothiophene-1,1-dioxide), N,N-dimethylformamide, N-methyl-2-pyrrolidinone, dimethyl aniline, as well as cyclic and open-chain ethers such as diisopropyl ether, tetrahydrofuran or 1,4-dioxane. A particularly preferred reaction medium is a mixture of hydrogen fluoride and dimethyl sulfoxide. In the solvent-free variant of the process of the invention, the reaction is conveniently carried out under pressure. A preferred pressure range is from 1 to 5 MPa (megapascal), most preferably 2 to 4 MPa.

A preferred embodiment of the invention comprises adding the diazotising agent to hydrogen fluoride and the compound of formula II in the anhydrous medium.

A particularly preferred embodiment of the invention comprises charging a mixture of hydrogen fluoride and the compound of formula II to the reactor under a pressure of 1 to 5 MPa, preferably 2 to 4 MPa, and then adding a mixture of the diazotising agent and hydrogen fluoride.

The process of this invention can be carried out in two steps as well as in one step. In the

two-step variant of the process, the diazonium fluoride is prepared in the first step and thermally decomposed in the second step. In the particularly preferred single step variant of the process, the diazotisation is carried out at the decomposition temperature of the diazonium fluoride which forms *in situ* and is converted direct into the compound of formula I.

A particularly preferred variant of the process of the invention comprises reacting a mixture of hydrogen fluoride and 4-(5-chloro-3-aminopyridin-2-yloxy)phenoxypropionic acid in the presence of dimethyl sulfoxide at a temperature in the range from 45 to 60°C with sodium nitrite.

A further preferred variant of the process of the invention comprises reacting a mixture of 4-(5-chloro-3-aminopyridin-2-yloxy)phenoxypropionic acid and hydrogen fluoride under a pressure of 2 to 4 MPa and in the temperature range from 45 to 60°C with a mixture of sodium nitrite and hydrogen fluoride.

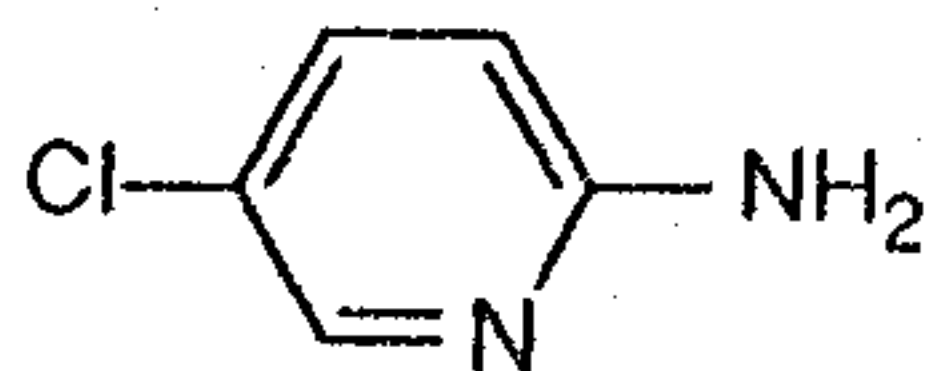
By means of the process of this invention it is possible to prepare the 4-(5-chloro-3-aminopyridin-2-yloxy)phenoxypropionic acids of formula I from readily accessible starting materials in simple manner and in good yield and in high selectivity and purity. A particular advantage of the process of this invention is that the unstable and explosive diazonium salt intermediates do not have to be isolated from the reaction medium. In addition, no environmentally undesirable fluoride or boron trifluoride wastes form, as the excess hydrogen fluoride can be recycled in simple manner.

The following Examples illustrate the process of the invention in more detail.

Working Examples:

A) Preparation of the starting materials

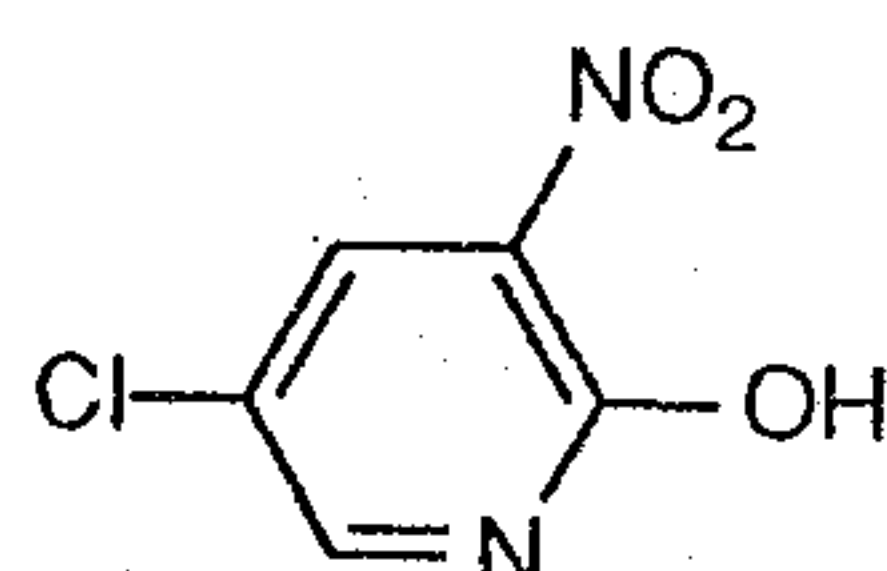
Example A1: Preparation of 5-chloro-2-aminopyridine



941 g of 2-aminopyridine are added at a temperature of 10°C over 30 minutes to 4 l of

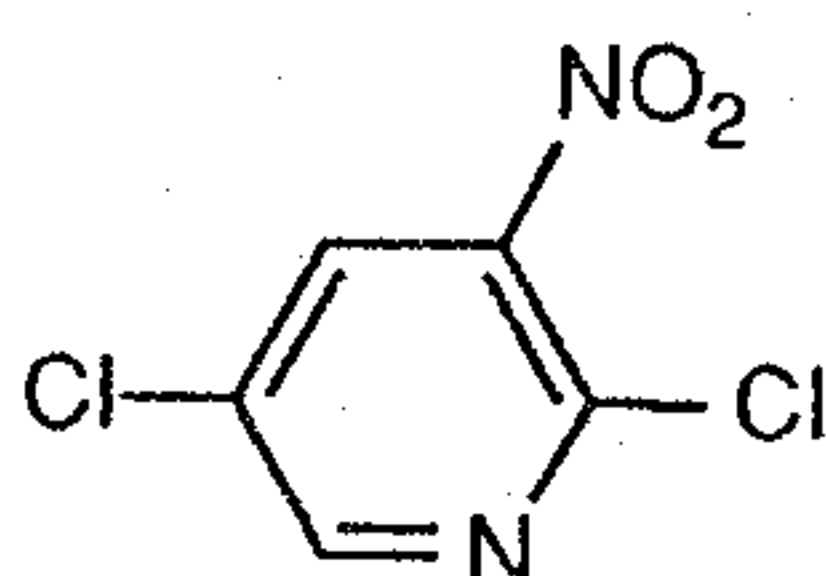
concentrated hydrochloric acid. Then 745 g of chlorine gas is introduced over 8 1/2 hours at a temperature of 10°C. The reaction mixture is stirred for 18 hours and then neutralised at a temperature of 10-20°C with 5.9 l of concentrated sodium hydroxide solution to a pH of 7-8. The precipitated crude product is isolated by filtration, washed with ice-water and subsequently dried at 40°C. For purification, the crude product is suspended in water and then collected by filtration. The product is suspended in petroleum ether, isolated by filtration and dried, giving 991 g (77.1 % of theory) of 5-chloro-2-aminopyridine with a melting point of 128-130°C in 95% purity.

Example A2: Preparation of 5-chloro-2-hydroxy-3-nitropyridine



321 g of 5-chloro-2-aminopyridine are added dropwise to 1.25 l of concentrated sulfuric acid. The reaction mixture is then stirred until the educt has completely dissolved. Then 172.5 g of sodium nitrite, dissolved in 240 ml of water, are added at a temperature of 40-45°C and the reaction mixture is stirred for 15 minutes. Subsequently 125 ml of 100 % nitric acid are added dropwise at 50°C over 40 minutes. The reaction mixture is kept for 1 hour at 55°C and then poured onto 5 kg of ice-water. The product in the form of a yellow precipitate is isolated by filtration, washed copiously with water and subsequently dried at 60°C, giving 351 g of 5-chloro-2-hydroxy-3-nitropyridine (80.5 % of theory) with a melting point of 229-231°C.

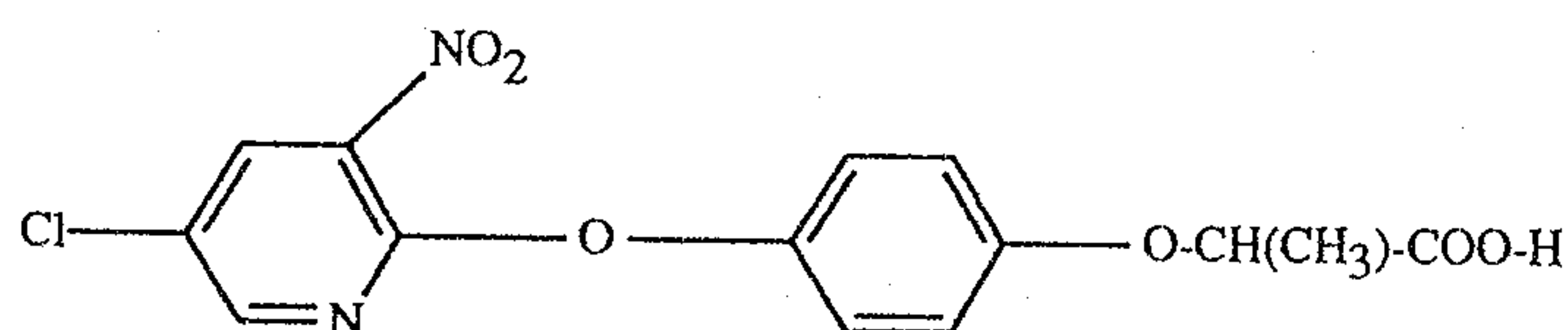
Example A3: Preparation of 2,5-dichloro-3-nitropyridine



75 g of phosgene are introduced at a temperature of 85-95°C over 1 hour into a mixture of 87.5 g of 5-chloro-2-hydroxy-3-nitropyridine in 500 ml of toluene and 3 ml of N,N-dimethylformamide. The reaction mixture is kept for 2 hours under reflux at 85-95°C

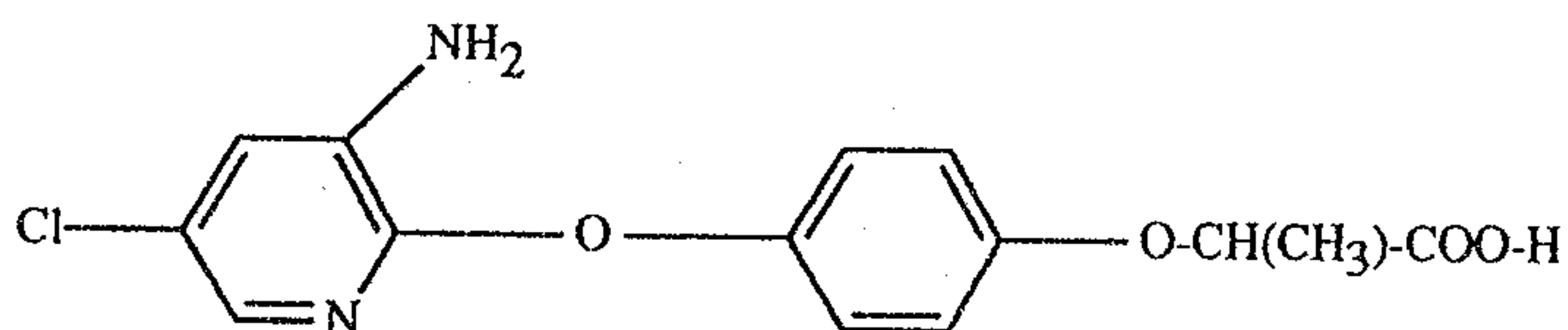
and then allowed to cool to room temperature over a period of 18 hours. The reaction mixture is washed 3 times with water and the organic phase is dried over sodium sulfate and thereafter concentrated by evaporation. The crude product, obtained in the form of a brown oil, is crystallised from 200 ml of n-hexane, giving 67.5 g of 2,5-dichloro-3-nitropyridine (70 % of theory) with a melting point of 38-39°C.

Example A4: Preparation of 2-(4-(5-chloro-3-nitropyridin-2-yloxy)phenoxy)propionic acid:



56.1 g of a 50 % aqueous solution of potassium hydroxide are added dropwise at room temperature to a suspension of 91 g of water and 92.3 g of 2-(4-hydroxy)phenoxypropionic acid. After the removal of water by distillation, the potassium salt so obtained is dissolved in 390 g of N,N-dimethylformamide, and then 108.1 g of 2,5-dichloro-3-nitropyridine in 95 g of N,N-dimethylformamide are added dropwise at 85°C. The reaction mixture is stirred for 90 minutes at 85°C, then poured into water and 100 ml of concentrated hydrochloric acid are added dropwise. The oily crude product is extracted with toluene. The organic phase is concentrated by evaporation, giving 188 g (92 % of theory) of 2-(4-(5-chloro-3-nitropyridin-2-yloxy)phenoxy)propionic acid.

Example A5: Preparation of 2-(4-(5-chloro-3-aminopyridin-2-yloxy)phenoxy)propionic acid

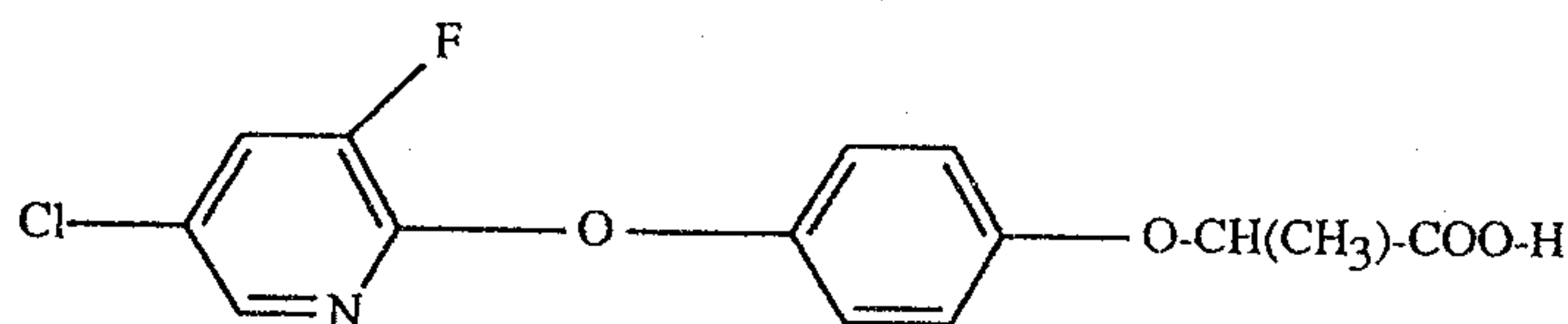


20 g of Raney nickel catalyst are added to a solution of 196 g of 2-(4-(5-chloro-3-nitropyridin-2-yloxy)phenoxy)propionic acid in 615 g of dioxane, and hydrogenation is

subsequently carried out at 20-22°C under normal pressure. After separating the catalyst the solvent is removed, giving 98 g of 2-(4-(5-chloro-3-aminopyridin-2-yloxy)phenoxy)propionic acid as crude product (55 % of theory) which has a melting point of 152-154°C and can be recrystallised from toluene.

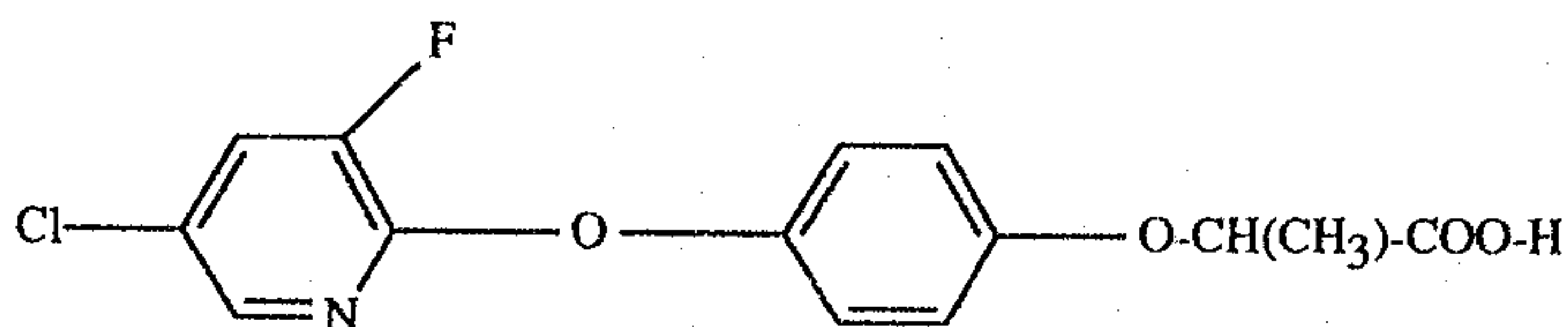
B) Preparation of the final products

Example B1: Preparation of 2-(4-(5-chloro-3-fluoropyridin-2-yloxy)phenoxy)propionic acid:



A polyethylene reactor is charged with 150 g of hydrogen fluoride and cooled to -78°C. Then a solution of 31.2 g of 2-(4-(5-chloro-3-aminopyridin-2-yloxy)phenoxy)propionic acid in 82.5 g of dimethyl sulfoxide is added dropwise over 1 hour at a temperature of -20 to +10°C. The reaction mixture is slowly heated to 50°C and 7.4 g of sodium nitrite are then added in portions at a maximum temperature of 60°C over a period of 90 minutes. The reaction mixture is thereafter cooled to room temperature and, after addition of ethyl acetate, is stirred into ice and then neutralised with concentrated ammonia to pH 3-4. After repeated extraction with ethyl acetate, the organic phases are extracted with water until the pH is 8. The pH of the aqueous phase is then adjusted with concentrated hydrochloric acid to below 2. The solvent is removed, giving 30 g of 2-(4-(5-chloro-3-fluoropyridin-2-yloxy)phenoxy)propionic acid (88% of theory) in 90 to 95 % purity and with a melting point of 90-92°C. The product can be recrystallised from methanol/water or toluene.

Example B2: Preparation of 2-(4-(5-chloro-3-fluoropyridin-2-yloxy)phenoxy)propionic acid:



A polyethylene reactor is charged with 75 g of hydrogen fluoride and cooled to -78°C . Then 7.4 g of sodium nitrite are added in portions at a temperature of -10 to 0°C . The solution is run into an evacuated, pressure-resistant autoclave. The pressure is then increased to 3 MPa by introducing nitrogen and the temperature is kept at 0°C .

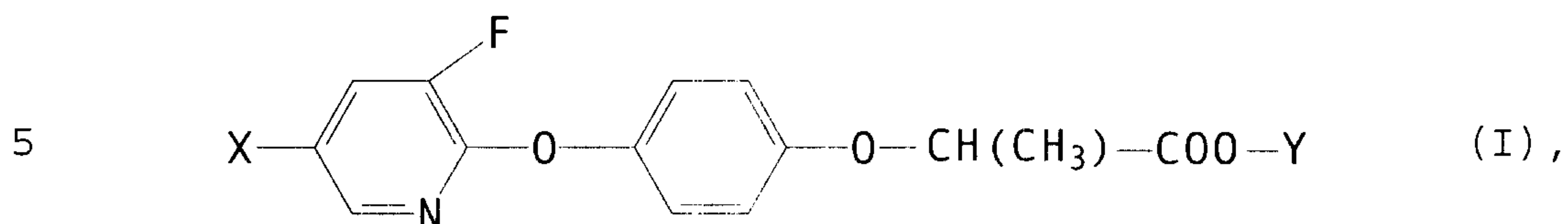
A pressure-resistant autoclave is charged with 31.2 g of 2-(4-(5-chloro-3-aminopyridin-2-yloxy)phenoxy)propionic acid, evacuated and cooled to -78°C . Then 50 g of hydrogen fluoride are added and the reaction mixture is heated to 50°C . At this temperature a solution of sodium nitrite and hydrogen fluoride in liquid form, which is under a pressure of 3 MPa, is run in over 1 hour. The reaction mixture is stirred for 1 hour at 50°C and under a pressure of 2.4 MPa, then cooled to room temperature. The pressure in the autoclave is reduced to normal pressure, excess hydrogen fluoride is removed with suction and the oily residue is washed with cold water and neutralised with concentrated ammonia to pH 3. The organic phase is separated and the aqueous phase is extracted 3 times with ethyl acetate. The combined organic phases are extracted with water until the pH is 8, and the pH of the aqueous phase is adjusted with concentrated hydrochloric acid to below 2. After extraction with toluene and removal of the solvent, 26.5 g of 2-(4-(5-chloro-3-fluoropyridin-2-yloxy)phenoxy)propionic acid (77% of theory) are obtained in 90 to 95% purity and with a melting point of $90-92^{\circ}\text{C}$. The product can be recrystallised from methanol/water or toluene.

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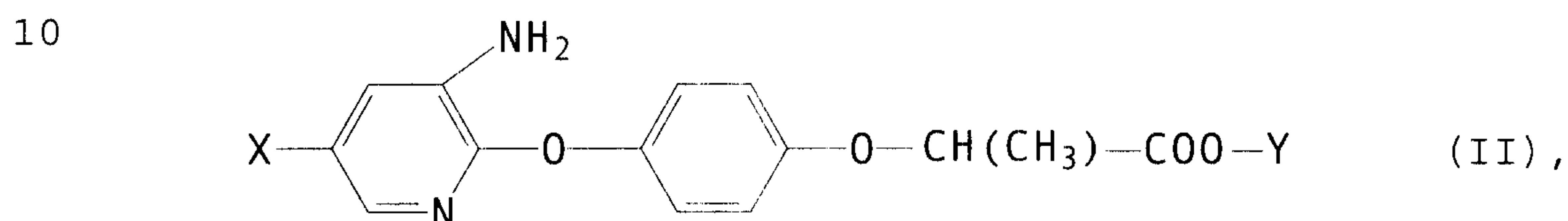
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CLAIMS:

1. A process for the preparation of a (3-fluoropyridin-2-yloxy)phenoxypropionic acid of formula I



wherein X is hydrogen, fluoro, chloro, bromo or trifluoromethyl and Y is hydrogen, sodium or potassium, which process comprises reacting a compound of formula II



wherein X and Y are as defined for formula I with a diazotising agent, and converting the resulting diazonium fluoride by thermal decomposition into the (3-fluoropyridin-2-yloxy)phenoxypropionic acid of formula I or the sodium or potassium salt thereof, wherein the reaction takes place in an anhydrous medium of hydrogen fluoride and dimethylsulfoxide under normal pressure.

20 2. A process according to claim 1, wherein the thermal decomposition is carried out in the temperature range from 30 to 60°C.

3. A process according to claim 1, wherein the thermal decomposition is carried out in the temperature range from 45 to 60°C.

4. A process according to claim 1, 2 or 3, wherein sodium nitrite, potassium nitrite, N₂O₃, NOF, NOCl, isoamyl

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nitrite or tert-butyl nitrite is used as the diazotising agent.

5. A process according to claim 4, wherein sodium nitrite is used as the diazotising agent.

5 6. A process according to any one of claims 1 to 5, which comprises adding the diazotising agent to hydrogen fluoride, dimethylsulfoxide and the compound of formula II in the anhydrous medium.

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PATENT AGENTS

