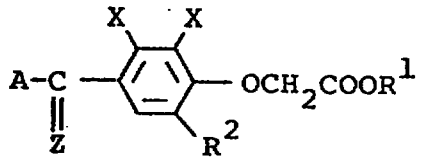
Description

This invention relates to a phenoxyacetic acid derivative and processes for preparing the same. More particularly, it relates to a phenoxyacetic acid derivative of the formula:



(I)

wherein A is a 5-pyrazolyl group having one substituent selected from an alkyl (C_{1-10}) group and an alkoxy (C_{1-6})-alkyl (C_{1-6}) group, R^1 is a hydrogen atom, R^2 is a hydrogen atom, X is a halogen atom and Z is an oxygen atom or a methylene group, or a salt thereof.

Known diuretic agents include thiazide diuretics such as chlorothiazide or hydrochlorothiazide and loop diuretics such as furosemide or ethacrynic acid. These agents are useful to increase urine volume and electrolyte excretion by inhibiting reabsorption of water and electrolytes from renal tubules. However, these known diuretics are not satisfactory in that they are liable to cause hyperuricemia which often results in interstitial nephritis or gout due to deposition of uric acid in tissue of living body. Therefore, it has been wanted to develop diuretics which can promote excretion of not only water and electrolytes but also uric acid.

BURGER - Medicinal Chemistry 1980, pages 207, 208 and following discloses a variety of diuretics including 2,3 dichlorophenoxyacetic acid derivatives.

We have now found that the phenoxyacetic acid derivative (I) and its salts have potent diuretic, saluretic and uricosuric activities. For example, when the effect of a test compound on urine volume was examined by administering a carboxymethylcellulose solution thereof (dose : 100 mg/kg) orally to saline-loaded rats, each one of [2,3-dichloro-4-(1-ethoxymethyl-5-pyrazolylcarbonyl)phenoxy]acetic acid, [2,3-dichloro-4-(1-methoxymethyl-5-pyrazolylcarbonyl)phenoxy]acetic acid, [2,3-dichloro-4-(1-ethyl-5-pyrazolylcarbonyl) phenoxy]acetic acid and [2,3-dichloro-4-(1-isopropyl-5-pyrazolylcarbonyl)phenoxy]acetic acid showed more than 100 % increase in the urine volume as compared with a control group of rats. Moreover, the oral administration of {2,3-dichloro-4-[1-(1-methyl-5-pyrazolyl)vinyl]phenoxy}acetic acid to said saline-loaded rats produced more than 100 % increase in the uric acid excretion as compared with a control group of rats.

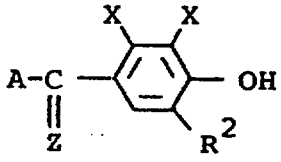
Examples of the compound of the present invention include those of the formula (I) in which A is a 5-pyrazolyl group having one substituent selected from an alkyl (C_{1-10})group and an alkoxy (C_{1-6})-alkyl (C_{1-6}) group; R^1 is hydrogen atom; R^2 is hydrogen atom; X is a halogen atom such as chlorine, bromine or iodine; and Z is an oxygen atom or a methylene group.

A is a substituted 5-pyrazolyl group, having one substituent selected from an alkyl (C_{1-10}) group such as methyl, ethyl, propyl, isopropyl, butyl or pentyl; an alkoxy (C_{1-6})alkyl (C_{1-6}) group such as methoxymethyl or ethoxymethyl.

According to the present invention, the phenoxyacetic acid derivative (I) or a salt thereof can be prepared by the step or steps of:

(A)

-i) reacting a phenol compound of the formula:



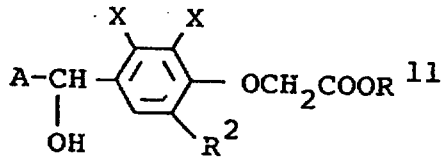
(II)

wherein A, R^2, X and Z are the same as defined above, with an acetic acid compound of the formula:

$Y\text{-}CH_2COOR^{11}$ (III)

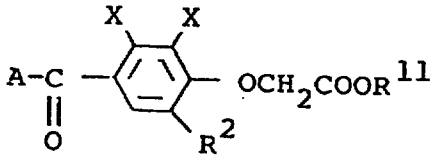
wherein Y is a reactive residue and R^{11} is a hydrogen atom or an alkyl (C_{1-6}) group or

-ii) oxidizing a compound of the formula:



(IV)

wherein A, R^{11},R^2 and X are the same as defined above, to give a compound of the formula:



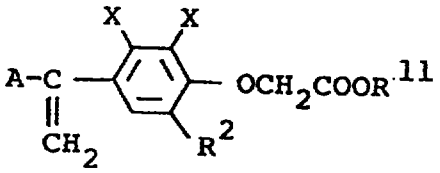
(I-A)

wherein A, R^{11},R^2 and X are the same as defined above; or

-iii) reacting the compound (I-A) with an ylide compound of the formula:

$(C_6H_5)_3P=CH_2$ (V)

to give a compound of the formula:



(I-B)

wherein A, R^{11}, R^2 and X are the same as defined above and

(B) when R^{11} of the compound obtained in the step (A)-i), -ii) or -iii) is an alkyl (C_{1-6}) group, hydrolyzing said compound to give a compound (I); and

(C) if required, further converting the product into a salt thereof.

Examples of the reactive residue Y in the starting compound (III) include a halogen atom such as chlorine, bromine or iodine, tosyloxy and methanesulfonyloxy.

The reaction of the phenol compound (II) with the acetic acid compound (III) can be carried out in a solvent in the presence of an acid acceptor. The acid acceptor includes, for example, alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides such as calcium hydroxide or barium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkali metal bicarbonates such as sodium bicarbonate or potassium bicarbonate, alkali metal hydrides such as sodium hydride or potassium hydride, alkali metal lower alkoxides such as sodium ethoxide or potassium t-butoxide, lithium diisopropylamide, sodium aide, lithium amide, alkali metal fluorides such as potassium fluoride or cesium fluoride, or an organic bases such as triethylamine or tributylamine. Lower alkanones such as acetone or methylethylketone, lower alkanols such as methanol or ethanol, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulfoxide or a mixture of water and the aforementioned organic solvent is preferably used as the solvent. It is preferred to carry out the reaction at a temperature of 0 to 100 °C, especially 20 to 80 °C.

The oxidation of the compound (IV) can be carried out by treatment with an oxidizing agent in a solvent. Methylene chloride, chloroform, lower alkanones such as acetone or methylethylketone, benzene, toluene,

hexane, petroleum ether, acetonitrile, dimethylformamide, dimethylsulfoxide, acetic acid, tetrahydrofuran, dioxane or a mixture of water and the afore-mentioned organic solvent is preferably used as the solvent. Suitable examples of the oxidizing agent include manganese dioxide, chromic acid anhydride, potassium permanganate, acetic anhydride-dimethylsulfoxide, chloranil, 2,3-dichloro-5,6-dicyanobenzoquinone,dinitrogen tetraoxide. It is preferred to carry out the reaction at a temperature of -78 to 100 °C, especially 0 to 50 °C.

The reaction of the ketone compound (I-A) with the ylide compound (V) can be carried out in a solvent. Tetrahydrofuran, dimethylsulfoxide, dioxane, ether, sulfolane or a mixture thereof is preferably used as the solvent. It is preferred to carry out the reaction at a temperature of 0 to 60 °C, especially 20 to 40 °C.

The hydrolysis of the phenoxyacetate compound can be carried out by treating said compound with an acid or a base in a solvent. Examples of the acid include mineral acids such as hydrochloric acid, hydrobromic acid or sulfuric acid, and examples of the base include alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides such as barium hydroxide. Lower alkanols such as methanol or ethanol, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulfoxide or a mixture thereof is preferably used as the solvent. It is preferred to carry out the reaction at a temperature of 0 to 80 °C, especially at 0 to 50 °C in case the acid is used, or at 20 to 60 °C in case the base is used.

When A is the 5-pyrazolyl group having an alkoxy (C_{1-6}) alkyl (C_{1-6}) group, optional removal of said substituent can be carried out in a conventional manner such as, for example, acid treatment, base treatment, hydrolysis or reduction.

The thus-obtained compound (I) of the present invention can be converted into a salt thereof in a traditional manner, for example, by reacting said compound with a substantially equimolar amount of an acid or a base in a solvent.

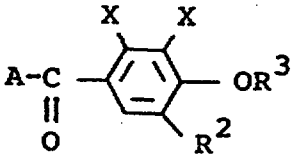
As mentioned hereinbefore, the phenoxyacetic acid derivative (I) of the present invention and a salt thereof show potent diuretic, saluretic and uricosuric activities, and are useful for treatment and /or prophylaxis of congestive heart failure, a wide variety of edema (e.g., hepatic edema, renal edema, cardiac edema, hydrops gravidarum (= edema of pregnancy), lymphatic edema, drug-induced edema, pulmonary edema), hydrops abdominis, exudative pleurisy, interstitial nephritis, gout or hyperuremia.

The compound (I) of the present invention can be used for pharmaceutical use either in the free form or in the form of a salt thereof. Examples of the salt of the compound (I) include alkali metal salts such as sodium salt or potassium salt, alkaline earth metal salts such as calcium salt, inorganic acid addition salts such as hydrochloride or hydrobromide, oragnic acid addition salts such as methanesulfonate or oxalate, and the like.

The compound (I) or a salt thereof can be administered either orally or parenterally. For oral administration, the compound (I) and a salt thereof may be used in the solid form such as tablets, powders, capsules or granules, which may contain conventional carriers, binders, diluents, disintegrators, wetting agents and the like. They may also be used in liquid form such as aqueous or oily suspensions, solutions, syrups or elixiles. On the other hand, for parenteral administration, the compound (I) and a salt thereof may be used, for example, in the form of injections or suppositories.

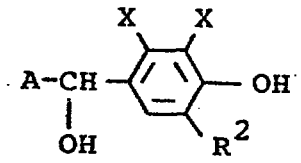
The dose of the compound (I) or a salt thereof may vary over a wide range depending on the administration route, the age, body weight or conditions of patients and the kind and severity of diseases to be treated. In general, however, preferred daily dose of the compound (I) or a salt thereof is in the range of 0.3 to 200 mg/kg/day, especially 1 to 100 mg/kg/day.

Concomitantly, the starting compound (II) in which Z is oxygen atom (said compound is hereinafter referred as the compound (II-A)) may be prepared by treating a compound of the formula:



(VI)

wherein R^3 is a lower alkyl group, and A, R^2 and X are the same as defined above, with hydrobromic acid, an alkali metal cyanide, an alkali metal thioacetate, boron tribromide and the like, or by oxidizing a compound of the formula:



(VII)

wherein A, R^2 and X are the same as defined above.

The starting compound (II) in which Z is methylene group may be prepared by reacting the thus-obtained compound (II-A) with the ylide compound (V).

On the other hand, the starting compound (IV) of the present invention may be prepared by reacting the compound (VII) with the acetic acid compound (III).

Example 1

0.63 g of 2,3-dichloro-4-(1-ethoxymethyl-5-pyrazolylcarbonyl)phenol, 0.58 g of bromoacetic acid and 1.11 g of potassium carbonate are added to 40 ml of acetone, and the mixture is refluxed for 48 hours. The reaction mixture is concentrated to remove solvent, and water is added to the residue. The aqueous mixture is washed with ethyl acetate, acidified with 10 % hydrochloric acid and then extracted with ethyl acetate. The extract is washed with a saturated sodium chloride solution, dried and evaporated to remove solvent. The residue is crystallized with water, and the crystals are separated by filtration, washed successively with water and isopropyl ether, and dried to give 0.42 g of [2,3-dichloro-4-(1-ethoxymethyl-5-pyrazolylcarbonyl)-phenoxy]acetic acid.

M.p. 148 - 149 °C

Mass(m/e): 372 (M^+)

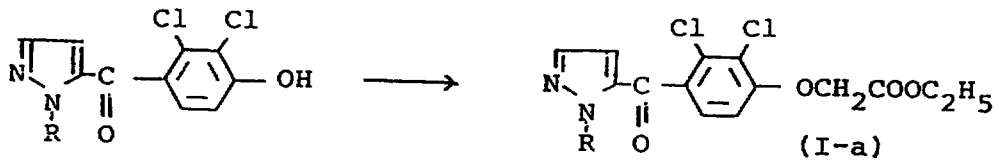
NMR($CDCl_3$ + DMSO-d_6)δ: 1.17(t, 3H, J=7Hz), 3.61(q, 2H, J=7Hz), 4.76(s, 2H), 5.90(s,2H), 6.47(d, 1H, J=2Hz), 6.84(d, 1H, J=9Hz), 7.32(d, 1H, J=9Hz), 7.53(d, 1H, J=2Hz)

sodium salt monohydrate: M.p. 194 - 196.5 °C

Example 2 to 6

1.67g of the corresponding phenol derivatives and 1.15g ethyl bromoacetate and 1.68 g of potassium carbonate are added to 60 ml of acetone, and the mixture is refluxed for 1 hour. The reaction mixture is filtered and the filtrate is evaporated to remove solvent. The residue is dissolved in benzene, and the solution is treated with activated charcoal and evaporated to give an oil, which is then crystallized from isopropyl ether to give the compounds as shown in Table 1.

Table 1



Ex. Nos.	Compound(I-a) R	Properties
2	CH_2OCH_3	M.p. 78 -79 °C Mass(m/e): 386(M^+)
3	$CH(CH_3)_2$	M.p. 79 - 80 °C Mass(m/e): 384(M^+)
4	$(CH_2)_5CH_3$	oil IRν_{max}^{liquid} (cm^{-1}): 1755, 1660, 1580, 1550, 1500 Mass(m/e): 426(M^+)

In Example 5 ethanol is used as the crystallization solvent instead of isopropyl ether.

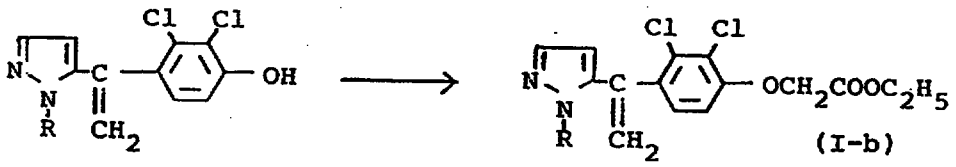
5	CH_3	M.p. 79 - 80 °C Mass(m/e): 356(M^+)
6	C_2H_5	M.p. 79 - 81 °C Mass(m/e): 370(M^+)

Example 7 to 9

The corresponding phenol derivative and ethyl bromoacetate are treated in the same manner as described in Example 2 to 6 to give the compounds as shown in Table 2.

In Example 7 , a mixture of isopropyl ether and hexane is used as the crystallization solvent instead of isopropyl ether in Example 2 to 6.

Table 2



Ex. Nos.	Compound (I-b) R	Properties
7	CH_3	M.p. 88 - 89 °C Mass(m/e): 354(M^+)
8	C_2H_5	oil IRν_{max}^{liquid} (cm^{-1}): 1750 Mass(m/e): 368(M^+)
9	$CH_2OC_2H_5$	oil IRν_{max}^{liquid} (cm^{-1}): 1750, 1620, 1590, 1560, 1515 Mass(m/e): 398(M^+)

Example 10

0.9 g of ethyl [2,3-dichloro-4-(1-ethoxymethyl-5-pyrazolylcarbonyl)phenoxy]acetate is suspended in 20 ml of ethanol, and 10 ml of an aqueous 10% sodium hydroxide solution are added thereto. The mixture is stirred at room temperature for 1 hour. The reaction mixture is concentrated to remove ethanol and adjusted to pH 1 - 2 with 10% hydrochloric acid. The resulting crystals are collected by filtration, washed successively with water and isopropyl ether, and dried to give 0.82 g of [2,3-dichloro-4-(1-ethoxymethyl-5-pyrazolylcarbonyl)phenoxy]acetic acid.

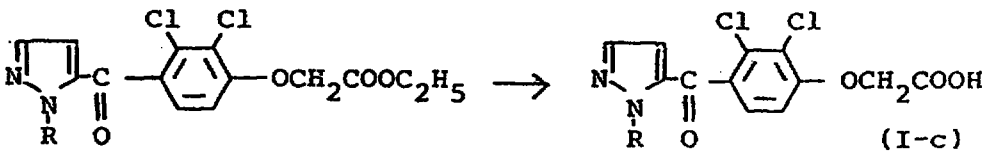
The physico-chemical properties of the thus-obtained product are identical with those of the compound obtained in Example 1.

Example 11 to 15

The corresponding phenoxyacetate derivatives are treated in the sane manner as described in Example 10 to give the compounds as shown in Table 3.

Isopropyl ether - hexane (Example 13 or ethyl acetate (Example 14) is used as the crystallization solvent.

Table 3



(I-c)

Ex. Nos.	Compound (I-c) R	Properties
11	CH_2OCH_3	M.p. 179 - 180.5 °C Mass(m/e): 358(M^+) NMR($CDCl_3$+DMSO-d_6)δ:3.37(s, 3H), 4.81(s, 2H), 5.84(s, 2H), 6.54 (d, 1H, J=2Hz), 6.97(d, 1H, J=8.6 Hz), 7.39(d, 1H, J=8.6Hz), 7.57(d, 1H, J=2Hz)

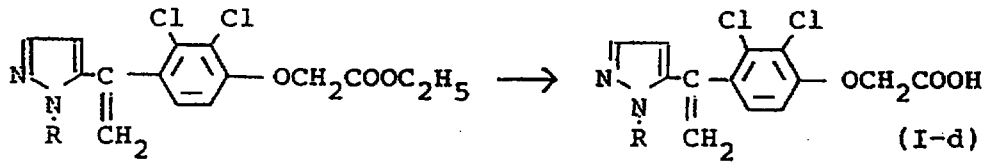
12	$CH(CH_3)_2$	M.p. 223 - 225 °C Mass(m/e): 356(M^+) NMR($CDCl_3$+DMSO-d_6)δ: 1.55(d, 6H, J=6.6Hz), 4.77(s, 2H), 5.52(sept., 1H, J=6.6Hz), 6.39(d, 1H, J=2Hz), 6.89(d, 1H, J=8.7Hz), 7.34(d, 1H, J=8.7Hz), 7.48(d, 1H, J=2Hz), 8.45(br s, 1H)
13	$(CH_2)_5CH_3$	M.p. 114 - 115 °C Mass(m/e): 398(M^+)
14	CH_3	M.p. 230 - 231 °C Mass(m/e): 328(M^+)
15	C_2H_5	M.p. 203 - 204 °C Mass(m/e): 342(M^+) NMR($CDCl_3$+DMSO-d_6)δ:1.47(t, 3H, J=7Hz), 4.63(q, 2H, J=7Hz), 4.81(s, 2H), 6.43(d, 1H, J=2Hz), 6.97(d, 1H, J=8.5Hz), 7.38(d, 1H,J=8.5Hz) 7.45(d, 1H, J=2Hz)

Example 16 to 18

The corresponding phenoxyacetate derivatives are treated in the same manner as described in Example 10 to give the compounds as shown in Table 4.

In Example 18, ethanol-isopropyl ether is used as the crystallization solvent.

Table 4



Ex. Nos.	Compound (I-d) R	Properties
16	CH_3	M.p. 186.5 - 187.5 °C Mass(m/e): 326(M^+) NMR($CDCl_3$+DMSO-d_6)δ:3.75(s, 3H), 4.71(s, 2H), 5.53(s-like, 1H), 5.61(s-like, 1H), 6.03(d, 1H, J=2 Hz), 6.79(d, 1H, J=8.5Hz), 7.16(d, 1H, J=8.5Hz), 7,38(d, 1H, J=2Hz)
17	$CH_2OC_2H_5$	M.p. 151.5 - 153.5 °C Mass(m/e): 370(M^+) NMR($CDCl_3$+DMSO-d_6)δ:1.16(t, 3H, J=7Hz), 3.63(q, 2H, J=7Hz), 4.72(s, 2H), 5.43(s, 2H), 5.53(s-like, 1H), 5.97(s-like, 1H), 6.83(d, 1H, J=8.5Hz), 7.25(d, 1H, J=8.5Hz), 7.42(d-like, 2H)
18	C_2H_5	M.p. 163.5 - 153.5 °C Mass(m/e): 340(M^+)

[Preparation of Starting Compounds]

Preparation 1

(1) 4.13 ml of 1.6 M n-butyl lithium in hexane are added dropwise to a tetrahydrfuran solution of 0.76 g of 1-ethoxymethylpyrazole at - 60 °C under argon gas atmosphere. mixture is stirred at - 63 to - 50 °C for 1 hour. A solution of 1.23 g of 2,3-dichloro-4-methoxybenzaldehyde in tetrahydrofuran is added to the mixture, and the mixture is stirred at - 50 °C to room temperature for 1 hour. An aqueous saturated ammonium chloride solution and water are added to the mixture under ice-cooling and the mixture is concentrated to remove tetrahydrofuran. The residual aqueous layer is extracted with ethyl acetate and the extract is washed with water, dried and evaporated to give colorless crystals, which are then washed with isopropyl ether and dried to give 1.62 g of α-(1-ethoxymethyl-5-pyrazolyl)-2,3-dichloro-4-methoxybenzylalcohol.
M.p. 155 - 157 °C

(2) 2.72 g of manganese dioxide are added to a solution of 1.04 g of α-(1-ethoxymethyl-5-pyrazolyl)-2,3-dichloro-4-methoxybenzylalcohol in methylene chloride and the mixture is stirred at room temperature for 27 hours. The reaction mixture is filtered and the filtrate is condensed to an oily residue, which is then crystallized from isopropyl ether to give 0.93 g of (2,3-dichloro-4-methoxyphenyl)(1-ethoxymethyl-5-pyrazolyl)methanone.
M.p. 74 - 76 °C
(3) 9.45 g of potassium thiolacetate are added to a solution of 5.45 g of (2,3-dichloro-4-methoxyphenyl)-(1-ethoxymethyl-5-pyrazolyl)methanone in dimethylsulfoxide and the mixture is stirred at 90 - 100 °C under argon gas atmosphere for 4 hours. After cooling the solution, cold water is added thereto, and the mixture is adjusted to pH 5 - 6 with acetic acid and then extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove solvent. The residue is purified by silica gel column chromatography to give 3.72 g of 2,3-dichloro-4-(1-ethoxymethyl-5-pyrazolylcarbonyl)phenol.
M.p. 115 - 117 °C

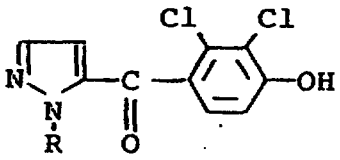
Preparation 2

(1) 6.0 g of 1-methylpyrazole are treated in the same manner as described in Preparation 1-(1). 18.0 g of α-(1-methyl-5-pyrazolyl)2,3-dichloro-4-methxybenzylalcohol are obtained.
M.p. 169 - 171 °C
(2) 2.23 g of α-(1-methyl-5-pyrazolyl)-2,3-dichloro-4-methxybenzylalcohol are dissolved in a mixture of acetic acid, acetone and water, and 0.90 g of chromic acid anhydride is added to the solution. The mixture is stirred at room temperature for 2.5 hours and isopropanol is added thereto to ecompose excess oxidizing agent. The mixture is filtered and the filtrate is evaporated. Water is added to the residue and the mixture is extracted with chloroform. The extract is washed, dried and evaporated to remove solvent. The residue is crystallized with methanol to give 2.07 g of (2,3-dichloro-4-methoxyphenyl) (1-methyl-5-pyrazolyl)methanone.
M.p. 150 - 152 °C
(3) 20 ml of 47% hydrobromic acid are added to 1.0 g of (2,3-dichloro-4-methoxyphenyl) (1-methyl-5-pyrazolyl)methanone, and the mixture is refluxed for 4 hours. The reaction mixture is evaporated to remove solvent and the residue is dissolved in an aqueous 10% sodium hydroxide solution. The solution is filtered, and the filtrate is adjusted to pH 4 - 5 with acetic acid. The resultant crystals are collected, washed with water and dried to give 0.88 g of 2,3-dichloro-4-(1-methylpyrazolylcarbonyl)phenol.
M.p. 220 - 222 °C

Prepararion 3 - 6

The corresponding starting compounds are treated in the same manner as described in Preparation 1 or 2 to give the compounds as shown in Table 5

Table 5



(II-a)

Pr. Nos.	Compound (II-a) R	Melting points (°C)
3	CH_2OCH_3	134 - 135
4	$CH(CH_3)_2$	191 - 192
5	$(CH_2)_5CH_3$	110 - 111.5
6	C_2H_5	180 - 181

Preparation 7

(1) A suspension of 8.35 g of 2,3-dichloro-4-(1-methyl-5-pyrazolylcarbonyl)phenol, 5.59 g of allyl bromide and 10.64 g of potassium carbonate in acetone is refluxed for 3 hours.
The reaction mixture is filtered and the filtrate is evaporated to remove solvent. The residue is dissolved in toluene, and the solution is treated with activated charcoal and then evaporated to give 8.36 g of (2,3-dichloro-4-allyloxyphenyl)(1-methyl-5-pyrazolyl)methanone.
M.p. 118 - 119 °C
(2) A suspension of 8.20 g of (2,3-dichloro-4-allyloxyphenyl)(1-methyl-5-pyrazolyl)methanone in N,N-dimethylaniline is stirred at 200 °C under argon gas atmosphere for 25 hours and cooled. The reaction mixture is diluted with ether and extracted with an aqueous 5% sodium hydroxide solution. The aqueous extract is washed with ether, adjusted to pH 5 - 6 with acetic acid and then extracted with chloroform. The organic layer is washed with water, dried and evaporated to give a solid, which is then purified by silica gel column chromatography to give 5.16 g of 6-allyl-2,3-dichloro-4-(1-methyl-5-pyrazolylcarbonyl)-phenol.
M.p. 141 - 143 °C

Preparation 8

A solution of 2.71 g of 2,3-dichloro-4-(1-methyl-5-pyrazolylcarbonyl)phenol in tetrahydrofuran-dimethylsulfoxide is added dropwise to an ylide solution prepared from a solution of 8.57 g of methyltriphenylphophonium bromide in tetrahydrofurandimethylsulfoxide and 13.8 ml of 1.6 M n-butyl lithium in hexane. The mixture is stirred at room temperature for 18 hours, and further stirred at 65 °C for 2 hours. The reaction mixture is poured into an aqueous saturated ammonium chloride solution and then extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove solvent. The residue is purified by silica gel column chromatography to give 2.41 g of 2,3-dichloro-4-[1-(1-methyl-5-pyrazolyl)vinyl]-phenol.
M.p. 185 - 186.5 °C

Preparation 9 and 10

The corresponding ketone compounds are treated in the same manner as described in Preparation 8 to give the following compounds.

(9) 2,3-dichloro-4-[1-(1-ethyl-5-pyrazolyl)vinyl]phenol
M.p. 180 - 182.5 °C

(10) 2,3-dichloro-4-[1-(1-ethoxymethyl-5-pyrazolyl)vinyl]phenol
M.p. 162 - 164 °C

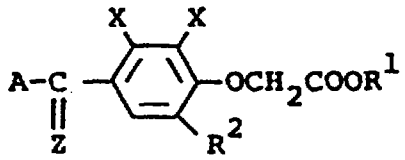
Preparation 11

(1) A solution of 5.51 g of boron tribromide in methylene chloride is added dropwise to a solution of 2.05 g of 2,3-dichloro-4-methoxybenzaldehyde in methylene chloride.
The mixture is stirred at room temperature for 4 hours, poured into ice-water and then extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove solvent. 10 % hydrochloric acid and methanol are added to the residue and the mixture is stirred for 3 hours under ice-cooling and extracted with ethyl acetate again. The extract is washed with water, dried and evaporated to remove solvent. The residue is crystallized with isopropyl ether to give 1.82 g of 4-hydroxy-2,3-dichlorobenzaldehyde.
(2) 18.1 ml of 1.6 M n-butyl lithium in hexane are added to a tetrahydrofuran solution of 3.56 g of 1-ethoxymethylpyrazole at -55 to -53 °C under argon gas atmosphere and the mixture is stirred at the same temperature for 1 hour. A solution of 2.45 g of 2,3-dichloro-4-hydroxybenzaldehyde in tetrahydrofuran is added to the above mixture, and the reaction mixture is stirred at -55 to -60 °C for 3 hours. 4.9 ml of hexamethylphosphoric triamide are then added and the whole mixture is stirred at room temperature for 16 hours. An aqueous saturated ammonium chloride solution is added and the mixture is extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove solvent. The residue is purified by silica gel column chromatography and crystallized with a mixture of ethyl acetate and isopropyl ether to give 2.69 g of α-(1-ethoxymethyl-5-pyrazolyl)-2,3-dichloro-4-hydroxybenzylalcohol.
M.p. 149.5 - 150 °C

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A phenoxyacetic acid derivative of the formula:



(I)

wherein A is a 5-pyrazolyl group having one substituent selected from an alkyl (C_{1-10}) group and an alkoxy (C_{1-6})-alkyl (C_{1-6}) group, R^1 is a hydrogen atom, R^2 is a hydrogen atom, X is a halogen atom and Z is an oxygen atom or a methylene group, or a salt thereof.

2. The compound according to Claim 1, in which X is a chlorine atom.

3. The compound according to Claim 2, in which A is a 1-(C_{1-6})alkyl-5-pyrazolyl group or a 1-alkoxy-(C_{1-6})-alkyl-(C_{1-6})-5-pyrazolyl group.

4. The compound according to Claim 3, which is [2,3-dichloro-4-(1-ethyl-5-pyrazolylcarbonyl)phenoxy]-acetic acid or a salt thereof.

5. The compound according to Claim 3, which is {2,3-dichloro-4-[1-(1-methyl-5-pyrazolyl)vinyl]-phenoxy}acetic acid or a salt thereof.

6. A pharmaceutical composition which comprises a therapeutically effective amount of the compound

The corresponding ketone compounds are treated in the same manner as described in Preparation 8 to give the following compounds.

(9) 2,3-dichloro-4-[1-(1-ethyl-5-pyrazolyl)vinyl]phenol
M.p. 180 - 182.5 °C

(10) 2,3-dichloro-4-[1-(1-ethoxymethyl-5-pyrazolyl)vinyl]phenol
M.p. 162 - 164 °C

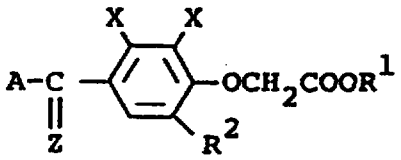
Preparation 11

(1) A solution of 5.51 g of boron tribromide in methylene chloride is added dropwise to a solution of 2.05 g of 2,3-dichloro-4-methoxybenzaldehyde in methylene chloride.
The mixture is stirred at room temperature for 4 hours, poured into ice-water and then extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove solvent. 10 % hydrochloric acid and methanol are added to the residue and the mixture is stirred for 3 hours under ice-cooling and extracted with ethyl acetate again. The extract is washed with water, dried and evaporated to remove solvent. The residue is crystallized with isopropyl ether to give 1.82 g of 4-hydroxy-2,3-dichlorobenzaldehyde.
(2) 18.1 ml of 1.6 M n-butyl lithium in hexane are added to a tetrahydrofuran solution of 3.56 g of 1-ethoxymethylpyrazole at -55 to -53 °C under argon gas atmosphere and the mixture is stirred at the same temperature for 1 hour. A solution of 2.45 g of 2,3-dichloro-4-hydroxybenzaldehyde in tetrahydrofuran is added to the above mixture, and the reaction mixture is stirred at -55 to -60 °C for 3 hours. 4.9 ml of hexamethylphosphoric triamide are then added and the whole mixture is stirred at room temperature for 16 hours. An aqueous saturated ammonium chloride solution is added and the mixture is extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove solvent. The residue is purified by silica gel column chromatography and crystallized with a mixture of ethyl acetate and isopropyl ether to give 2.69 g of α-(1-ethoxymethyl-5-pyrazolyl)-2,3-dichloro-4-hydroxybenzylalcohol.
M.p. 149.5 - 150 °C

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A phenoxyacetic acid derivative of the formula:



(I)

wherein A is a 5-pyrazolyl group having one substituent selected from an alkyl (C_{1-10}) group and an alkoxy (C_{1-6})-alkyl (C_{1-6}) group, R^1 is a hydrogen atom, R^2 is a hydrogen atom, X is a halogen atom and Z is an oxygen atom or a methylene group, or a salt thereof.

2. The compound according to Claim 1, in which X is a chlorine atom.

3. The compound according to Claim 2, in which A is a 1-(C_{1-6})alkyl-5-pyrazolyl group or a 1-alkoxy-(C_{1-6})-alkyl-(C_{1-6})-5-pyrazolyl group.

4. The compound according to Claim 3, which is [2,3-dichloro-4-(1-ethyl-5-pyrazolylcarbonyl)phenoxy]-acetic acid or a salt thereof.

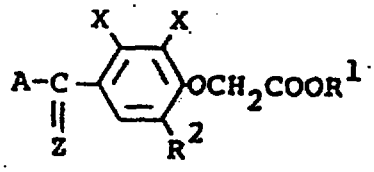
5. The compound according to Claim 3, which is {2,3-dichloro-4-[1-(1-methyl-5-pyrazolyl)vinyl]-phenoxy}acetic acid or a salt thereof.

6. A pharmaceutical composition which comprises a therapeutically effective amount of the compound

* C L M S *

claimed in Claim 1 and a pharmaceutically acceptable carrier therefor.

7. A process for preparing a phenoxyacetic acid derivative of the formula:

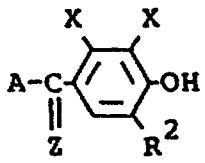


(I)

wherein A is a 5-pyrazolyl group having one substituent selected from an alkyl (C_{1-10}) group and an alkoxy (C_{1-6})-alkyl (C_{1-6}) group, R^1 is a hydrogen atom, R^2 is a hydrogen atom, X is a halogen atom and Z is an oxygen atom or a methylene group, or a salt thereof, which comprises the step or steps of:

(A)

-i) reacting a phenol compound of the formula:



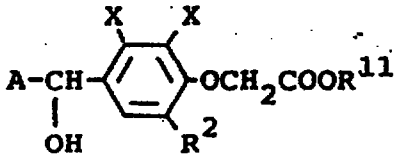
(II)

wherein A, R^2, X and Z are the same as defined above, with an acetic acid compound of the formula:

$Y\text{-}CH_2COOR^{11}$ (III)

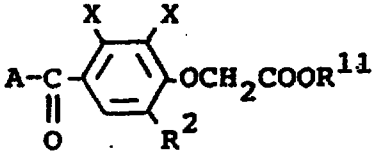
wherein Y is a reactive residue and R^{11} is a hydrogen atom or an alkyl (C_{1-6}) group; or

-ii) oxidizing a compound of the formula:



(IV)

wherein A, R^{11}, R^2 and X are the same as defined above, to give a compound of the formula:



(I-A)

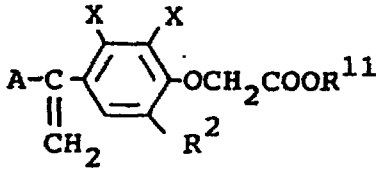
wherein A, R^{11}, R^2 and x are the same as defined above; or

-iii) reacting the compound (I-A) with an ylide compound of the formula:

$(C_6H_5)_3P=CH_2$ (V)

to give a compound of the formula:

* C L M S *



(I-B)

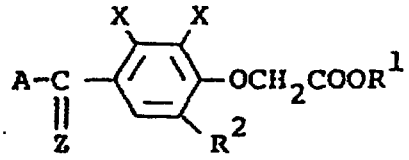
wherein A, R^{11}, R^2 and X are the same as defined above; and

(B) when R^{11} of the compound obtained in the step (A)-i), -ii) or -iii) is an alkyl (C_{1-6}) group, hydrolyzing said compound to give a compound (I); and

(C) if required, further converting the product into a salt thereof.

Claims for the following Contracting State : GR

1. A phenoxyacetic acid derivative of the formula:



(I)

wherein A is a 5-pyrazolyl group having one substituent selected from an alkyl (C_{1-10}) group and an alkoxy (C_{1-6})-alkyl (C_{1-6}) group, R^1 is a hydrogen atom, R^2 is a hydrogen atom, X is a halogen atom and Z is an oxygen atom or a methylene group, or a salt thereof.

2. The compound according to Claim 1, in which X is a chlorine atom.

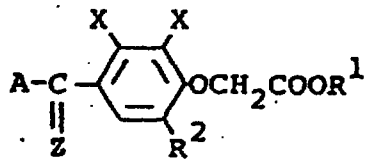
3. The compound according to Claim 2, in which A is a 1-(C_{1-6})alkyl-5-pyrazolyl group or a 1-alkoxy-(C_{1-6})-alkyl-(C_{1-6})-5-pyrazolyl group.

4. The compound according to Claim 3, which is [2,3-dichloro-4-(1-ethyl-5-pyrazolylcarbonyl)phenoxy]-acetic acid or a salt thereof.

5. The compound according to Claim 3, which is {2,3-dichloro-4-[1-(1-methyl-5-pyrazolyl)vinyl]-phenoxy}acetic acid or a salt thereof.

6. A composition which comprises a therapeutically effective amount of the compound claimed in Claim 1 and a carrier therefor.

7. A process for preparing a phenoxyacetic acid derivative of the formula:



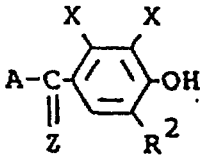
(I)

wherein A is a 5-pyrazolyl group having one substituent selected from an alkyl (C_{1-10}) group and an alkoxy (C_{1-6})-alkyl (C_{1-6}) group, R^1 is a hydrogen atom, R^2 is a hydrogen atom, X is a halogen atom and Z is an oxygen atom or a methylene group, or a salt thereof, which comprises the step or steps of:

(A)

-i) reacting a phenol compound of the formula:

* C L M S *

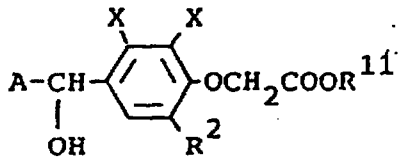


(II)

wherein A, R^2, X and Z are the same as defined above, with an acetic acid compound of the formula:

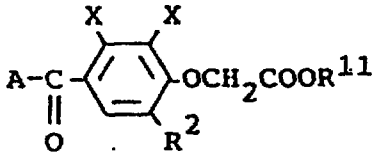
$Y\text{-}CH_2COOR^{11}$ (III)

wherein Y is a reactive residue and R^{11} is a hydrogen atom or an alkyl (C_{1-6}) group; or
-ii) oxidizing a compound of the formula:



(IV)

wherein A, R^{11}, R^2 and X are the same as defined above, to give a compound of the formula:

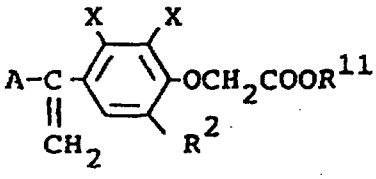


(I-A)

wherein A, R^{11}, R^2 and X are the same as defined above; or
-iii) reacting the compound (I-A) with an ylide compound of the formula:

$(C_6H_5)_3P=CH_2$ (V)

to give a compound of the formula:



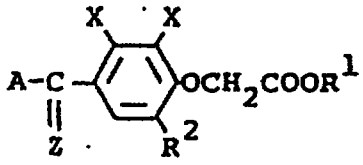
(I-B)

wherein A, R^{11}, R^2 and X are the same as defined above; and
(B) when R^{11} of the compound obtained in the step (A)-i), -ii) or -iii) is an alkyl (C_{1-6}) group, hydrolyzing said compound to give a compound (I); and
(C) if required, further converting the product into a salt thereof.

Claims for the following Contracting State : ES

1. A process for preparing a phenoxyacetic acid derivative of the formula:

* C L M S *

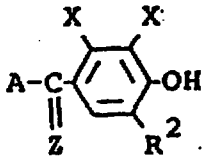


(I)

wherein A, is a 5-pyrazolyl group having one substituent selected from an alkyl (C_{1-10}) group and an alkoxy (C_{1-6})-alkyl (C_{1-6}) group, R^1 is a hydrogen atom, R^2 is a hydrogen atom, X is a halogen atom and Z is an oxygen atom or a methylene group, or a salt thereof, which comprises the step or steps of:

(A)

-i) reacting a phenol compound of the formula:



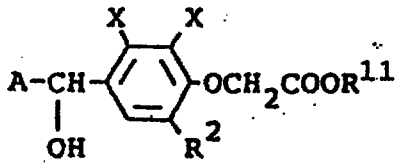
(II)

wherein A, R^2, x and Z are the same as defined above, with an acetic acid compound of the formula:

$Y\text{-}CH_2COOR^{11}$ (III)

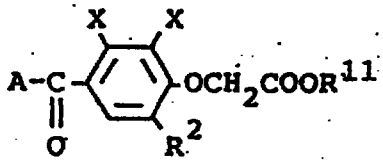
wherein Y is a reactive residue and R^{11} is a hydrogen atom or an alkyl (C_{1-6}) group; or

-ii) oxidizing a compound of the formula:



(IV)

wherein A, R^{11}, R^2 and X are the same as defined above, to give a compound of the formula:



(I-A)

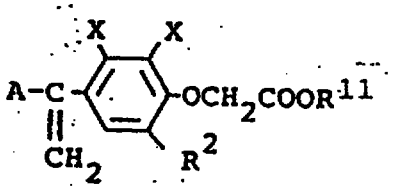
wherein A, R^{11}, R^2 and X are the same as defined above; or

-iii) reacting the compound (I-A) with an ylide compound of the formula:

$(C_6H_5)_3P=CH_2$ (V)

to give a compound of the formula:

* C L M S *



(I-B)

wherein A, R^{11}, R^2 and X are the same as defined above; and

(B) when R^{11} of the compound obtained in the step (A)-i), -ii) or -iii) is an alkyl (C_{1-6}) group, hydrolyzing said compound to give a compound (I); and

(C) if required, further converting the product into a salt thereof.

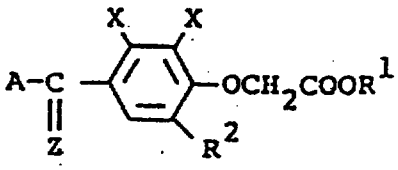
2. The process according to Claim 1 for the production of the compound [2,3-dichloro-4-(1-ethyl-5-pyrazolylcarbonyl)phenoxy]acetic acid or a salt thereof.

3. The process according to Claim 1 for the production of the compound {2,3-dichloro-4-[1-(1-methyl-5-pyrazolyl)vinyl]phenoxy}acetic acid or a salt thereof.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Dérivé d'acide phénoxyacétique de formule :



(I)

dans laquelle A est un groupe 5-pyrazolyle portant un substituant choisi entre un groupe alkyle en C_1 à C_{10} et un groupe (alkoxy en C_1 à C_6)-(alkyle en C_1 à C_6), R^1 est un atome d'hydrogène, R^2 est un atome d'hydrogène, X est un atome d'halogène et Z est un atome d'oxygène ou un groupe méthylène, ou un sel de ce dérivé.

2. Composé suivant la revendication 1, dans Lequel X est un atome de chlore.

3. Composé suivant la revendication 2, dans lequel A est un groupe 1-(alkyle en C_1 à C_6)-5-pyrazolyle ou un groupe 1-(alkoxy en C_1 à C_6)-(alkyle en C_1 à C_6)-5-pyrazolyle.

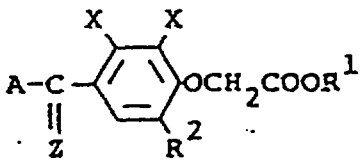
4. Composé suivant la revendication 3, qui est l'acide [2,3-dichloro-4-(1-éthyl-5-pyrazolylcarbonyl)-phénoxy]acétique ou un sel de cet acide.

5. Composé suivant la revendication 3, qui est l'acide {2,3-dichloro-4-[1-(1-méthyl-5-pyrazolyl)vinyl]-phénoxy}acétique ou un sel de cet acide.

6. Composition pharmaceutique, qui comprend une quantité à effet thérapeutique du composé suivant la revendication 1 et un support pharmaceutiquement acceptable pour ce composé.

7. Procédé de préparation d'un dérivé d'acide phénoxyacétique de formule :

* C L M S *

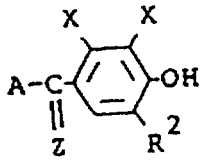


(I)

dans laquelle A est un groupe 5-pyrazolyle portant un substituant choisi entre un groupe alkyle en C_1 à C_6 et un groupe (alkoxy en C_1 à C_6)-(alkyle en C_1 à C_6), R^1 est un atome d'hydrogène, R^2 est un atome d'hydrogène, X est un atome d'halogène et Z est un atome d'oxygène ou un groupe méthylène, ou d'un sel de ce dérivé, qui comprend une ou plusieurs étapes consistant :

(A)

-i) à faire réagir un composé phénolique de formule :



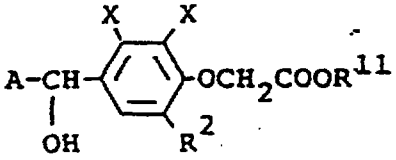
(II)

dans laquelle A, R^2, X et Z ont les définitions données ci-dessus, avec un composé d'acide acétique de formule :

$Y\text{-}CH_2COOR^{11}$ (III)

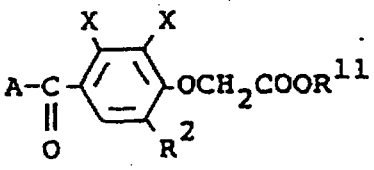
dans laquelle Y est un résidu réactif et R^{11} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 ; ou

-ii) à oxyder un composé de formule :



(IV)

dans laquelle A, R^1, R^2 et X ont les définitions données ci-dessus, pour obtenir un composé de formule :



(I-A)

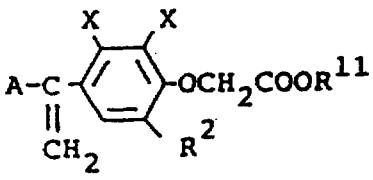
dans laquelle A, R^{11}, R^2 et X ont les définitions données ci-dessus ; ou bien

-iii) à faire réagir le composé (I-A) avec un ylide de formule :

$(C_6H_5)_3P=CH_2$ (V)

pour obtenir un composé de formule :

* C L M S *



(I-B)

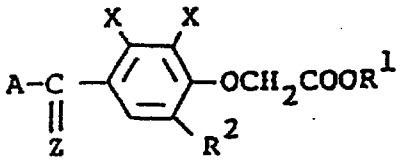
dans laquelle A, R^{11}, R^2 et X ont les définitions données ci-dessus ; et

(B) lorsque R^{11} du composé obtenu dans l'étape (A)-i), -ii) ou -iii) est un groupe alkyle en C_1 à C_6, à hydrolyser ledit composé pour obtenir un composé (I) ; et

(C) le cas échéant, à transformer encore le produit en un sel.

Revendications pour l'Etat contractant suivant : GR

1. Dérivé d'acide phénoxyacétique de formule :



(I)

dans laquelle A est un groupe 5-pyrazolyle portant un substituant choisi entre un groupe alkyle en C_1 à C_{10} et un groupe (alkoxy en C_1 à C_6)-(alkyle en C_1 à C_6), R^1 est un atome d'hydrogène, R^2 est un atome d'hydrogène, X est un atome d'halogène et Z est un atome d'oxygène ou un groupe méthylène, ou un sel de ce dérivé.

2. Composé suivant la revendication 1, dans lequel X est un atome de chlore.

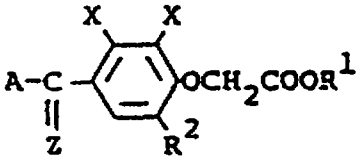
3. Composé suivant la revendication 2, dans lequel A est un groupe 1-(alkyle en C_1 à C_6)-5-pyrazolyle ou un groupe 1-(alkoxy en C_1 à C_6)-(alkyle en C_1 à C_6)-5-pyrazolyle.

4. Composé suivant la revendication 3, qui est l'acide [2,3-dichloro-4-(1-éthyl-5-pyrazolylcarbonyl)-phénoxy]acétique ou un sel de cet acide.

5. Composé suivant la revendication 3, qui est l'acide {2,3-dichloro-4-[1-(1-méthyl-5-pyrazolyl)vinyl]-phénoxy}acétique ou un sel de cet acide.

6. Composition qui comprend une quantité à effet thérapeutique du composé suivant la revendication 1 et un support approprié.

7. Procédé de préparation d'un dérivé d'acide phénoxyacétique de formule :



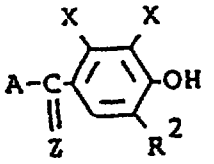
(I)

dans laquelle A est un groupe 5-pyrazolyle portant un substituant choisi entre un groupe alkyle en C_1 à C_{10} et un groupe (alkoxy en C_1 à C_6)-(alkyle en C_1 à C_6), R^1 est un atome d'hydrogène, R^2 est un atome d'hydrogène, X est un atome d'halogène et Z est un atome d'oxygène ou un groupe méthylène, ou d'un sel de ce dérivé, qui comprend l'étape ou les étapes consistant :

(A)

* C L M S *

-i) à faire réagir un composé phénolique de formule :

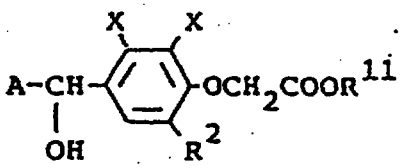


(II)

dans laquelle A, R^2, X et Z ont les définitions données ci-dessus, avec un composé d'acide acétique de formule :

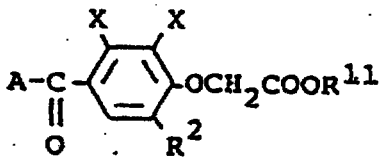
$Y\text{-}CH_2COOR^{11}$ (III)

dans laquelle Y est un résidu réactif et R^{11} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 ; ou
-ii) à oxyder un composé de formule :



(IV)

dans laquelle A, R^{11}, R^2 et X sont tels que définis ci-dessus, pour obtenir un composé de formule :

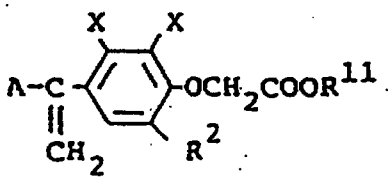


(I-A)

dans laquelle A, R^{11}, R^2 et X ont les définitions données ci-dessus ; ou bien
-iii) à faire réagir le composé (I-A) avec un ylide de formule :

$(C_6H_5)_3P=CH_2$ (V)

pour former un composé de formule :



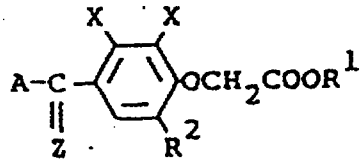
(I-B)

dans laquelle A, R^{11}, R^2 et X ont les définitions données ci-dessus ; et
(B) lorsque R^{11} du composé obtenu dans l'étape (A)-i), -ii) ou -iii) est un groupe alkyle en C_1 à C_6, à hydrolyser ledit composé pour former un composé (I) ; et
(C) le cas échéant, à convertir ensuite le produit en un sel.

* C L M S *

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'un dérivé d'acide phénoxyacétique de formule :

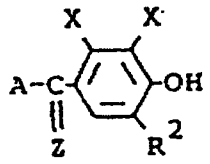


(I)

dans laquelle A est un groupe 5-pyrazolyle portant un substituant choisi entre un groupe alkyle en C_1 à C_{10} et un groupe (alkoxy en C_1 à C_6)-(alkyle en C_1 à C_6), R^1 est un atome d'hydrogène, R^2 est un atome d'hydrogène, X est un atome d'halogène et Z est un atome d'oxygène ou un groupe méthylène, ou d'un sel de ce dérivé, qui comprend une ou plusieurs des étapes consistant :

(A)

-i) à faire réagir un composé phénolique de formule :



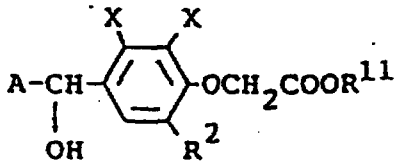
(II)

dans laquelle A, R^2, X et Z ont les définitions données ci-dessus, avec un composé d'acide acétique de formule :

$Y\text{-}CH_2COOR^{11}$ (III)

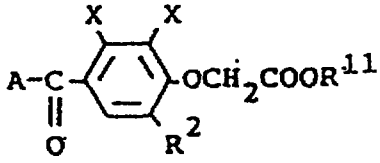
dans laquelle Y est un résidu réactif et R^{11} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 ; ou bien

-ii) à oxyder un composé de formule :



(IV)

dans laquelle A, R^{11}, R^2 et X sont tels que définis ci-dessus, pour former un composé de formule :



(I-A)

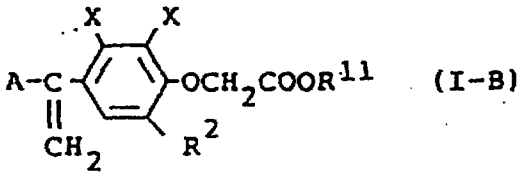
dans laquelle A, R^{11}, R^2 et X sont tels que définis ci-dessus ; ou bien

-iii) à faire réagir le composé (I-A) avec un ylide de formule :

$(C_6H_5)_3P=CH_2$ (V)

* C L M S *

pour former un composé de formule :



(I-B)

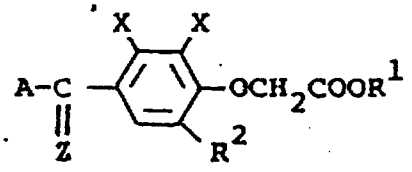
dans laquelle A, R^{11}, R^2 et X sont tels que définis ci-dessus ; et
(B) lorsque R^{11} du composé obtenu dans l'étape (A)-i), -ii) ou -iii) est un groupe alkyle en C_1 à C_6, à hydrolyser ledit composé pour former un composé (I) ; et
(C) le cas échéant, à convertir ensuite le produit en un sel.

2. Procédé suivant la revendication 1, pour la production de l'acide [2,3-dichloro-4-(1-éthyl-5-pyrazolylcarbonyl)phénoxy]acétique ou d'un sel de cet acide.

3. Procédé suivant la revendication 1, pour la production de l'acide (2,3-dichloro-4-[1-(1-méthyl-5-pyrazolyl)vinyl]phénoxy)acétique ou d'un sel de cet acide.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Phenoxyessigsäurederivat der Formel:



(I)

worin A eine 5-Pyrazolylgruppe mit einem Substituenten, ausgewählt unter einer Alkyl-(C_{1-10})-gruppe und einer Alkoxy-(C_{1-6})-alkyl-(C_{1-6})-gruppe, bedeutet, R^1 ein Wasserstoffatom bedeutet, R^2 ein Wasserstoffatom bedeutet, X ein Halogenatom bedeutet und Z ein Sauerstoffatom oder eine Methylengruppe bedeutet, oder ein Salz davon.

2. Verbindung nach Anspruch 1, worin X ein Chloratom bedeutet.

3. Verbindung nach Anspruch 2, worin A eine 1-(C_{1-6})-Alkyl-5-pyrazolylgruppe oder eine 1-Alkoxy-(C_{1-6})-alkyl-(C_{1-6})-5-Pyrazolylgruppe bedeutet.

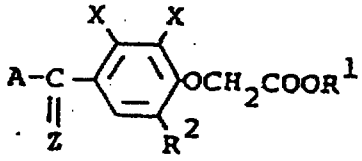
4. Verbindung nach Anspruch 3, nämlich [2,3-Dichlor-4-(1-ethyl-5-pyrazolylcarbonyl)-phenoxy]-essigsäure oder ein Salz davon.

5. Verbindung nach Anspruch 3, nämlich {2,3-Dichlor-4-[1-(1-methyl-5-pyrazolyl)-vinyl]-phenoxy}-essigsäure oder ein Salz davon.

6. Pharmazeutisches Präparat, dadurch **gekennzeichnet,** daß es eine therapeutisch wirksame Menge der Verbindung nach Anspruch 1 und einen pharmazeutisch annehmbaren Träger dafür enthält.

7. Verfahren zur Herstellung eines Phenoxyessigsäurederivats der Formel:

* C L M S *

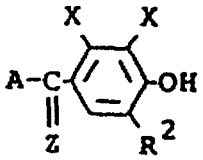


(I)

worin A eine 5-Pyrazolylgruppe mit einem Substituenten ausgewählt unter einer Alkyl-(C_{1-10})-gruppe und einer Alkoxy-(C_{1-6})-alkyl-(C_{1-6})-gruppe, bedeutet, R^1 ein Wasserstoffatom bedeutet, R^2 ein Wasserstoffatom bedeutet, X ein Halogenatom bedeutet und Z ein Sauerstoffatom oder eine Methylengruppe bedeutet, oder eines Salzes davon, **gekennzeichnet** durch die Stufe(n):

(A)

-i) Umsetzung einer Phenolverbindung der Formel:



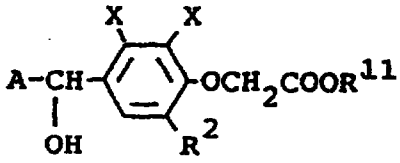
(II)

worin A, R^2, X und Z die oben gegebenen Definitionen besitzen, mit einer Essigsäureverbindung der Formel:

$Y\text{-}CH_2COOR^{11}$ (III)

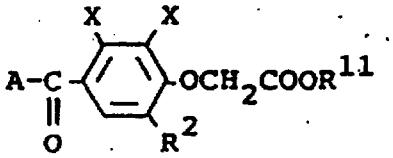
worin Y einen reaktiven Rest bedeutet und R^{11} ein Wasserstoffatom oder eine Alkyl-(C_{1-6})-gruppe bedeutet; oder

-ii) Oxidation einer Verbindung der Formel:



(IV)

worin A, R^{11}, R^2 und X die oben gegebenen Definitionen besitzen, wobei eine Verbindung der Formel:



(I-A)

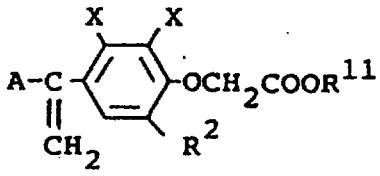
erhalten wird, worin A, R^{11}, R^2 und X die oben gegebenen Definitionen besitzen; oder

-iii) Umsetzung der Verbindung (I-A) mit einer Ylidverbindung der Formel:

$(C_6H_5)_3P=CH_2$ (V)

wobei eine Verbindung der Formel:

* C L M S *

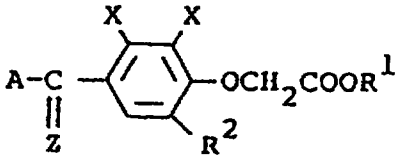


(I-B)

erhalten wird, worin A, R^{11}, R^2 und X die oben gegebenen Definitionen besitzen; und
(B) wenn R^{11} der Verbindung, die bei der Stufe (A)-i), -ii) oder -iii) erhalten wird, eine Alkyl-(C_{1-6})-gruppe bedeutet, Hydrolyse der Verbindung unter Bildung einer Verbindung der Formel (I); und
(C) gegebenenfalls weitere Umwandlung des Produktes in ein Salz davon.

Patentansprüche für folgenden Vertragsstaat : GR

1. Phenoxyessigsäurederivat der Formel:



(I)

worin A eine 5-Pyrazolylgruppe mit einem Substituenten, ausgewählt unter einer Alkyl-(C_{1-10})-gruppe und einer Alkoxy-(C_{1-6})-alkyl-(C_{1-6})-gruppe, bedeutet, R^1 ein Wasserstoffatom bedeutet, R^2 ein Wasserstoffatom bedeutet, X ein Halogenatom bedeutet und Z ein Sauerstoffatom oder eine Methylengruppe bedeutet, oder ein Salz davon.

2. Verbindung nach Anspruch 1, worin X ein Chloratom bedeutet.

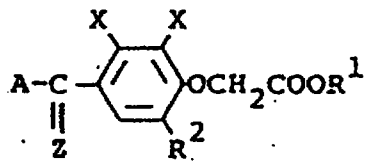
3. Verbindung nach Anspruch 2, worin A eine 1-(C_{1-6})-Alkyl-5-pyrazolylgruppe oder eine 1-Alkoxy-(C_{1-6})-alkyl-(C_{1-6})-5-pyrazolylgruppe bedeutet.

4. Verbindung noch Anspruch 3, nämlich [2,3-Dichlor-4-(1-ethyl-5-pyrazolylcarbonyl)-phenoxy]-essigsäure oder ein Salz davon.

5. Verbindung nach Anspruch 3, nämlich {2,3-Dichlor-4-[1-(1-methyl-5-pyrazolyl)-vinyl]-phenoxy}-essigsäure oder ein Salz davon.

6. Präparat, dadurch **gekennzeichnet,** daß es eine therapeutisch wirksame Menge der Verbindung nach Anspruch 1 und einen Träger dafür enthält.

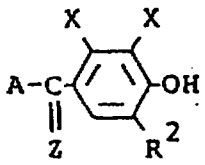
7. Verfahren zur Herstellung eines Phenoxyessigsäurederivats der Formel:



(I)

worin A eine 5-Pyrazolylgruppe mit einem Substituenten, ausgewählt unter einer Alkyl-(C_{1-10})-Gruppe und einer Alkoxy-(C_{1-6})-alkyl-(C_{1-6})-gruppe, bedeutet, R^1 ein Wasserstoffatom bedeutet, R^2 ein Wasserstoffatom bedeutet, X ein Halogenatom bedeutet und Z ein Sauerstoffatom oder eine Methylengruppe bedeutet, oder eines Salzes davon, **gekennzeichnet** durch die Stufe(n):
(A)
-i) Umsetzung einer Phenolverbindung der Formel:

* C L M S *



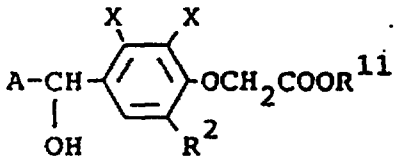
(II)

worin A, R^2, X und Z die oben gegebenen Definitionen besitzen, mit einer Essigsäureverbindung der Formel:

$Y\text{-}CH_2COOR^{11}$ (III)

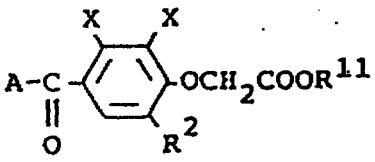
worin Y einen reaktiven Rest bedeutet und R^{11} ein Wasserstoffatom oder eine Alkyl-(C_{1-6})-gruppe bedeutet; oder

-ii) Oxidation einer Verbindung der Formel:



(IV)

worin A, R^{11}, R^2 und X die oben gegebenen Definitionen besitzen, wobei eine Verbindung der Formel:



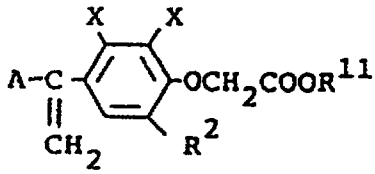
(I-A)

erhalten wird, worin A, R^{11}, R^2 und X die oben gegebenen Definitionen besitzen; oder

-iii) Umsetzung der Verbindung (I-A) mit einer Ylidverbindung der Formel:

$(C_6H_5)_3P=CH_2$ (V)

wobei eine Verbindung der Formel:



(I-B)

erhalten wird, worin A, R^{11}, R^2und X die oben gegebenen Definitionen besitzen; und

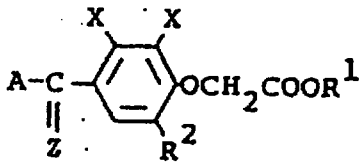
(B) wenn R^{11} der Verbindung, die bei der Stufe (A)-i), -ii) oder -iii) erhalten wird, eine Alkyl-(C_{1-6})-gruppe bedeutet, Hydrolyse der Verbindung unter Bildung einer Verbindung der Formel (I); und

(C) gegebenenfalls weitere Umwandlung des Produktes in ein Salz davon.

Patentansprüche für folgenden Vertragsstaat : ES

* C L M S *

1. Verfahren zur Herstellung eines Phenoxyessigsäurederivats der Formel:

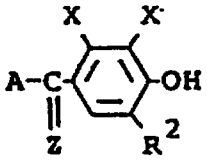


(I)

worin A eine 5-Pyrazolylgruppe mit einem Substituenten, ausgewählt unter einer Alkyl-(C_{1-10})-gruppe und einer Alkoxy-(C_{1-6})-alkyl-(C_{1-6})-gruppe, bedeutet, R^1 ein Wasserstoffatom bedeutet, R^2 ein Wasserstoffatom bedeutet, X ein Halogenatom bedeutet und Z ein Sauerstoffatom oder eine Methylengruppe bedeutet, oder eines Salzes davon, **gekennzeichnet** durch die Stufe(n):

(A)

-i) Umsetzung einer Phenolverbindung der Formel:



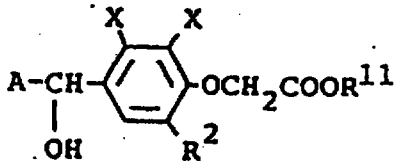
(II)

worin A, R^2, X und Z die oben gegebenen Definitionen besitzen, mit einer Essigsäureverbindung der Formel:

$Y\text{-}CH_2COOR^{11}$ (III)

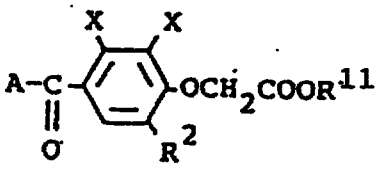
worin Y einen reaktiven Rest bedeutet und R^{11} ein Wasserstoffatom oder eine Alkyl-(C_{1-6})-gruppe bedeutet; oder

-ii) Oxidation einer Verbindung der Formel:



(IV)

worin A, R^{11}, R^2 und X die oben gegebenen Definitionen besitzen, wobei eine Verbindung der Formel:



(I-A)

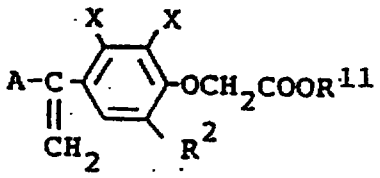
erhalten wird, worin A, R^{11}, R^2 und X die oben gegebenen Definitionen besitzen; oder

-iii) Umsetzung der Verbindung (I-A) mit einer Ylidverbindung der Formel:

$(C_6H_5)_3P=CH_2$ (V)

* C L M S *

wobei eine Verbindung der Formel:



(I-B)

erhalten wird, worin A, R^{11}, R^2 und X die oben gegebenen Definitionen besitzen; und
(B) wenn R^{11} der Verbindung, die bei der Stufe (A)-i), -ii) oder -iii) erhalten wird, eine Alkyl-(C_{1-6})-gruppe bedeutet, Hydrolyse der Verbindung unter Bildung einer Verbindung der Formel (I); und
(C) gegebenenfalls weitere Umwandlung des Produktes in ein Salz davon.

2. Verfahren nach Anspruch 1, dadurch **gekennzeichnet,** daß die Verbindung [2,3-Dichlor-4-(-1-ethyl-5-pyrazolylcarbonyl)-phenoxy]-essigsäure oder ein Salz davon hergestellt wird.

3. Verfahren nach Anspruch 1, dadurch **gekennzeichnet,** daß die Verbindung {2,3-Dichlor-4-[1-(1-methyl-5-pyrazolyl)-vinyl]-phenoxy}-essigsäure oder ein Salz davon hergestellt wird.

* C L M S *