PATENT SPECIFICATION (11) 1 572 309

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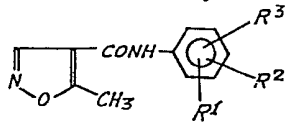
(19)

(54) PROCESS FOR THE MANUFACTURE OF 5-METHYL ISOXAZOLE-4-CARBOXYLIC ACID ANILIDE DERIVATIVES

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt/Main 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

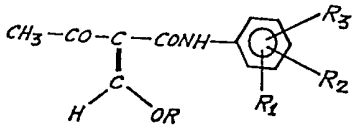
This invention relates to a process for the manufacture of isoxazole derivatives and is an improvement in or modification of the invention forming the subject of specification No. 1547452, which provides a 5-methyl-isoxazole-4-carboxylic acid anilide of the general formula I



(I)

in which R^1, R^2 and R^3, which may be identical or different, each represents an alkyl group having 1, 2 or 3 carbon atoms, an alkoxy group having 1, 2 or 3 carbon atoms, an alkylthio group having 1, 2 or 3 carbon atoms, the alkyl group of which may be completely or partially substituted by identical or different halogen atoms, for example, fluorine, chlorine, bromine and iodine atoms; or represents a halogen atom, for example, a fluorine, chlorine, bromine or iodine atom, or represents a nitro or cyano group, or an alkoxycarbonyl group having 1, 2 or 3 carbon atoms in the alkyl moiety, and in which R^1 and R^2 may each further represent a hydrogen atom, provided that when both represent hydrogen atoms R^3 cannot represent a methyl group, and when one or both of R^1 or R^2 represents hydrogen, R^3 may additionally represent a phenyl or phenoxy group which may carry one or two substituents selected from fluorine, chlorine, bromine and iodine atoms, alkyl groups having 1, 2 or 3 carbon atoms and alkoxy groups having 1, 2 or 3 carbon atoms, or

in which R^1 denotes a hydrogen atom and R^2 and R^3 together represent a methylenedioxy group or, together with the phenyl ring to which they are linked, represent a naphthalene ring, and which furthermore, provides a process for the manufacture of the compound of the formula I, which comprises treating a 2-alkoxymethyleneacetoacetic acid anilide of the formula IV

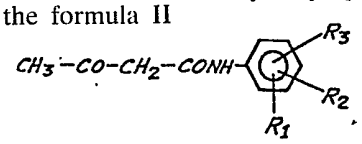


(IV)

in which R_1, R_2 and R_3 are as defined above and R represents an alkyl group having 1 to 4 carbon atoms with hydroxylamine in an organic solvent, an aqueous/organic solvent, or a

mixture of two or more organic solvents.

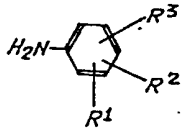
The acetoacetic acid anilides of formula IV may be prepared by a process wherein an acetoacetic acid anilide of the formula II



(II)

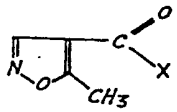
in which R_1, R_2 and R_3 are as defined above, is heated with an orthoformic acid ester of the formula III $HC(OR)_3$ (III) wherein R represents an alkyl group having 1 to 4 carbon atoms and preferably with an acid anhydride.

The present invention provides a process for the manufacture of a 5-methyl-isoxazole-4-carboxylic acid anilide of the general formula I, wherein an aniline of the general formula V



(V)

in which R^1, R^2 and R^3 have the abovementioned meanings, is reacted with a compound of the formula VI



(VI)

in which X denotes a halogen atom, preferably a chlorine or bromine atom, a carbodiimide group, or a YO-group or a ZO-CO-O- group, Y representing a phenyl group which may be monosubstituted, disubstituted or trisubstituted by the same or different substituents, as appropriate, selected from fluorine, chlorine, bromine, and iodine atoms, methyl, ethyl, methoxy, ethoxy, nitro and cyano groups, or denotes the acyl radical corresponding to the formula VI and Z representing an alkyl group having from 1 to 4 carbon atoms or a benzyl or phenyl group.

When a phenyl or phenoxy group R^3 carries two substituents, these are preferably the same, and when Y represents a phenyl group carrying two or three substituents, these are preferably the same.

Advantageously, the reaction is carried out in a partitioning agent or solvent which has an inert behaviour towards the reactants, for example, a nitrile, for example, acetonitrile; an ether, for example, diethyl ether, tetrahydrofuran or dioxane; or an alcohol, for example, methanol, ethanol, propanol or isopropanol.

A preferred process for the preparation of the compound of the formula I is the reaction of the carboxylic acid chloride of the formula VI with an aniline of the formula V. It is advantageous in this case to carry out the reaction in the presence of an acid-binding agent, for example, potassium carbonate or sodium carbonate, an alkali metal or alkaline earth metal hydroxide or alcoholate, an organic base, for example triethylamine, pyridine, picoline or quinoline or an excess of the particular aniline employed, at a temperature of from 0 to 160°C, preferably from 20 to 80°C. The reaction times generally range from a few minutes to two hours.

The reactive derivatives of the 5-methylisoxazole-4-carboxylic acid of the formula VI required as starting materials from the process according to the invention, may be obtained in a manner which is in itself known (compare German Patent Specification No. 634 286) by the reaction of an ethoxymethylideneacetoacetic acid ester with hydroxylamine to give a 5-methyl-isoxazole-4-carboxylic acid ester, by acid saponification of the ester thus obtained, preferably using a mixture of glacial acetic acid and concentrated hydrochloric acid in a ratio of 1:1, to give 5-methyl-isoxazole-4-carboxylic acid, and by activation of this carboxylic acid group, for example, by formation of the carboxylic acid halides, ester or anhydrides. The 5-methylisoxazole-4-carboxylic acids can also be activated by reaction with a carbodiimide, for example dicyclohexylcarbodiimide.

Examples of the carboxylic acid derivatives of formula VIa are 5-methylisoxazole-4-carboxylic acid phenyl esters, in particular the 2,4-dichloro-phenyl ester and the 2,4,6-trichlorophenyl ester, and furthermore 5-methylisoxazole-4-carboxylic acid anhydrides, in particular those in which X denotes a methoxycarbonyloxy radical, an ethoxycarbonyloxy radical or a benzyloxycarbonyloxy radical.

The compounds of the formula I are pharmacologically active, having a strong antiphlogistic and analgesic action.

The invention also provides a pharmaceutical preparation which comprises a compound of the general formula I which itself forms part of this invention in admixture or conjunction with a pharmaceutically suitable carrier.

The following Examples illustrate the invention.

Example

5-methylisoxazole-4-carboxylic acid 4-fluoro-anilide

a_1) A solution of 7.3 g (0.05 mole) of 5-methylisoxazole-4-carboxylic acid chloride of the formula VI in 20 ml of acetonitrile is added dropwise, whilst stirring, at room temperature to 0.1 mole of 4-fluoroaniline of the formula V (11.1 g), dissolved in 200 ml of acetonitrile. After stirring for a further 15 minutes, the crystals which have precipitated are filtered off and rinsed with twice 20 ml of acetonitrile and the combined filtrates are brought to dryness under reduced pressure. This gives 10.8 g (98% of theory) of an oily residue which crystallizes after trituration.

Melting point after recrystallisation from water: 117 to 118°C.

a_2) When 0.05 mole of triethylamine (10.1 g) is used as the acid-binding agent instead of the 4-fluoroaniline of the formula V, the oily residue is digested with water. The crystals thus obtained are filtered off and washed with water. After drying in air, this gives 10.6 g (96% of theory) of colorless crystals which, after recrystallization from water, melt at 117 to 118°C.

b) 0.1 mole of 4-fluoroaniline of the formula V (11.1 g) and 0.1 mole of 4-bromophenyl 5-methylisoxazole-4-carboxylate of the formula VI (28.2 g) dissolved in 50 ml of acetonitrile are heated under reflux for 90 minutes. Subsequently the solution is evaporated under reduced pressure and the residue is digested with petroleum ether. This gives 15.6 g (71% of theory) of an oily residue which crystallizes after spreading out. Melting point after recrystallization from water: 117 to 118°C.

c) 0.1 mole of 4-fluoroaniline of the formula V (11.1 g) and 0.1 mole of ethoxycarbonyl 5-methylisoxazole-4-carboxylate of the formula VI (19.9 g), dissolved in 60 ml of tetrahydrofurane, are heated under reflux for 60 minutes. The reaction mixture is then brought to dryness and this gives 17.1 g (78% of theory) of a crystalline residue which, after recrystallization from water, melts at 117 to 118°C.

The compounds listed in Table 1 were prepared by the process indicated above.

TABLE 1:

5-methylisoxazole-4-carboxylic acid anilides of the formula I

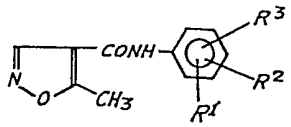
No	R^1	R^2	R^3	Melting point °C
1	H	H	4–F	117 – 118
2	H	H	4–Cl	151
3	H	H	4–Br	162 – 163
4	H	H	4–I	173 – 173.5
5	H	3 Cl	4–Cl	146
6	H	3 Cl	4–F	123 – 124
7	H	3,4	–O CH_2 –O	125 – 126
8	H	3 F	4–F	107 – 109
9	H	3 F	4–Cl	105 – 107
10	H	2–F	4–F	123
11	H	2–F	5–CF_3	107 – 108

The numbers in Table 1 denote:

1. 5-Methylisoxazole-4-carboxylic acid 4-fluoro-anilide
2. 5-Methylisoxazole-4-carboxylic acid 4-chloro-anilide
3. 5-Methylisoxazole-4-carboxylic acid 4-bromo-anilide
4. 5-Methylisoxazole-4-carboxylic acid 4-iodo-anilide
5. 5-Methylisoxazole-4-carboxylic acid 3,4-dichloro-anilide
6. 5-Methylisoxazole-4-carboxylic acid 3-chloro-4-fluoro-anilide
7. 5-Methylisoxazole-4-carboxylic acid 3,4-methylenedioxy-anilide
8. 5-Methylisoxazole-4-carboxylic acid 3,4-difluoro-anilide
9. 5-Methylisoxazole-4-carboxylic acid 4-chloro-3-fluoro-anilide
10. 5-Methylisoxazole-4-carboxylic acid 2,4-difluoro-anilide
11. 5-Methylisoxazole-4-carboxylic acid 2-fluoro-5-trifluoromethyl anilide

WHAT WE CLAIM IS:

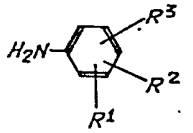
1. A process for the manufacture of a 5-methyl-isoxazole-4-carboxylic acid anilide of the general formula I



(I)

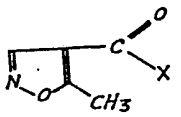
in which R^1, R^2 and R^3, which may be identical or different, each represents an alkyl group having 1, 2 or 3 carbon atoms, an alkoxy group having 1, 2 or 3 carbon atoms, an alkylthio group having 1, 2 or 3 carbon atoms, the alkyl group of which may be completely or partially substituted by identical or different halogen atoms; or represents a halogen atom, or represents a nitro or cyano group, or an alkoxycarbonyl group having 1, 2 or 3 carbon atoms in the alkyl moiety, and in which R^1 and R^2 may each further represent a hydrogen atom, provided that when both represent hydrogen atoms R^3 cannot represent a methyl group, and when one or both of R^1 and R^2 represents hydrogen, R^3 may additionally represent a phenyl or phenoxy group which may carry one or two substituents selected from fluorine, chlorine, bromine and iodine atoms, alkyl groups having 1, 2 or 3 carbon atoms and alkoxy groups having 1, 2 or 3 carbon atoms, or

in which R^1 denotes a hydrogen atom and R^2 and R^3 together represent a methylenedioxy group or, together with the phenyl ring to which they are linked, represent a naphthalene ring, wherein an aniline of the formula V



(V)

in which R^1, R^2 and R^3 have the above meanings, is reacted with a compound of the formula VI



(VI)

in which X denotes a halogen atom, a carbodiimide group, or a YO- group or ZO-CO-O- group, Y representing a phenyl group which may be monosubstituted, disubstituted or trisubstituted by the same or different substituents, as appropriate, selected from fluorine, chlorine, bromine, and iodine atoms, and methyl, ethyl, methoxy, ethoxy, nitro and cyano groups, or represents the acyl radical corresponding to the formua VI, and Z represents an alkyl group having from 1 to 4 carbon atoms, or a benzyl or phenyl group.

2. A process as claimed in claim 1, wherein X represents a chlorine atom and the reaction is carried out at a temperature of from 0 to 160°C in the presence of an acid binding agent.

3. A process as claimed in claim 1, wherein X represents a phenoxy, 2,4-dichlorophenoxy, 2,4,6-trichlorophenoxy, methoxycarbonyloxy, ethoxycarbonyloxy or benzyloxycarbonyloxy group.

4. A process as claimed in claim 1, carried out substantially as described in Example a_1, a_2, b or c herein.

5. A compound of the general formula I as defined in claim 1, whenever produced by a process as claimed in any one of claims 1 to 4.

6. A compound as described in Table 1, whenever produced by a process as claimed in claim 1.

7. A pharmaceutical preparation which comprises a compound as claimed in claim 5 or claim 6 in admixture or conjunction with a pharmaceutically suitable carrier.

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