1 542 315

PATENT SPECIFICATION

(11) 1 542 315

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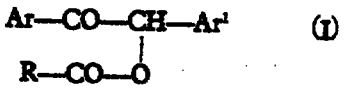
(19)

(54) PROCESS FOR PREPARING OXAZOLES

(71) We, JOHN WYETH & BROTHER LIMITED, a British Company of Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 OPH, 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:—

The invention relates to a method of preparation of 4,5 - diaryloxazol - 2 - ylalkanoic acids and their salts.

(4,5 - Diaryloxazol - 2 - yl) propionic and butyric acids and their salts are known from British Patent Specification No. 1,206,403. They exhibit pharmacological activity, particularly anti - inflammatory activity. The acids are prepared by cyclising keto esters of the general formula



(I)

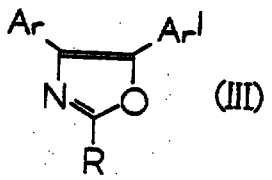
wherein Ar and Ar¹ are the same or different aryl radicals and R represents a carboxyethyl or carboxypropyl residue, with a nitrogen-donating cyclisation agent, for example, ammonia or an ammonium salt. In practice the ester is obtained by esterification of an aroylarylcarbonol having the formula



(II)

(wherein Ar and Ar¹ are as defined above) with a reactive derivative of a butanedioic or pentanedioic acid and recovering and purifying the ester. The purified ester is cyclised preferably by reaction in the presence of ammonium acetate and acetic acid and the oxazole obtained is isolated and purified.

We have now found that it is possible to obtain the oxazole in a form of good purity without separation and purification of the esterification product. The invention provides a method of preparation of a 4,5 - diaryloxazol 2 - ylalkanoic acid having the formula



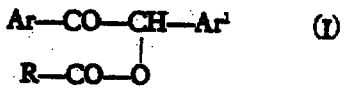
(III)

wherein Ar and Ar¹ represent the same or different aryl radicals and R represents carboxyethyl or carboxypropyl, or a non-toxic salt thereof, wherein an aroylarylcarbinol having the formula



(II)

wherein Ar and Ar¹ are as defined above is esterified with a reactive derivative of a butanedioic or pentanedioic acid to form a keto ester having the formula



(I)

(where Ar, Ar¹ and R are as defined above) in the reaction mixture, a nitrogen-donating cyclising agent is added to the reaction mixture and the keto ester is cyclised with the nitrogen-donating cyclising agent to form an oxazole, and, if desired, an acid product is converted into a non-toxic salt thereof.

Ar and Ar¹ represents the same or different aryl radicals. The term "aryl" as used herein includes heteroaryl groups, for example, thienyl or furyl. Any of the aryl groups may be substituted on the aromatic ring, but for simplicity all such aromatic radicals are referred to herein as aryl radicals. The aryl radicals contemplated include phenyl, naphthyl, thienyl and furyl radicals. Examples are unsubstituted phenyl, phenyl substituted by halogen (e.g. fluorine, chlorine, or bromine), by lower alkyl (e.g. methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl and *iso*-butyl), by lower alkoxy (e.g. methoxy or ethoxy), by trifluoromethyl, by nitro or by di(lower alkyl) amino (e.g. dimethylamino) or substituted or unsubstituted naphthyl, thienyl or furyl radicals (e.g. 1- or 2-naphthyl, 2- or 3-thienyl or 2-

or 3-furyl). The radicals Ar and Ar¹ are preferably selected from unsubstituted phenyl, monohalophenyl, mono (lower alkyl) phenyl and mono (lower alkoxy) phenyl. R represents a carboxyethyl or carboxy propyl radical, preferably carboxyethyl. The terms "lower alkyl" and "lower alkoxy" as used herein mean that the alkyl or alkoxy radical contains up to 6, preferably up to 4, carbon atoms.

The preferred esterifying agents used in the process of the invention are succinic anhydride and glutaric anhydride, advantageously succinic anhydride. We prefer to incorporate pyridine in the reaction mixture since it is advantageous as a catalyst for the ester formation and may facilitate handling at a convenient temperature. For best results we prefer to carry out the ester formation reaction under a dry inert atmosphere, e.g. nitrogen.

The cylisation is carried out without isolation of the keto ester of formula I from the reaction mixture in which it is formed. The cyclisation is carried out directly in the said reaction mixture by adjusting the reaction mixture to the conditions used for the cyclisation step and incorporating the cyclising agent into the reaction mixture. The cyclisation works under acidic conditions and thus we prefer to add the cyclising agent in conjunction with an acid. However the acid may be added before or after the addition of the cyclising agent. As cyclising agent there may be used urea or an ammonium salt. We prefer to use ammonium acetate as cyclising agent with acetic acid as solvent.

The invention may be carried out as follows:

Succinic anhydride or glutaric anhydride and the keto alcohol are added to a suitable organic solvent such as pyridine and the mixture is heated to a temperature ranging from 90—120°C with stirring under a nitrogen atmosphere. The esterification may take from one to several hours. It is important that the hemisuccinate or hemiglutarate obtained as esterification product should remain in the reaction mixture before processing with the cyclisation step. Ammonium acetate and glacial acetic acid, preferably in the form of a solution of the ammonium acetate in the glacial acetic acid, are added to the reaction mixture and the temperature is maintained to allow the cyclisation to proceed. The cyclisation reaction may take from 1 to several hours. The product is filtered and washed with acetic acid and water to obtain the crude oxazole product. An advantage of the invention is that the crude product obtained without recrystallisation from an organic solvent may itself be of high purity.

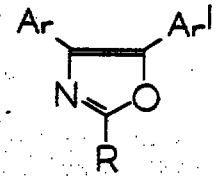
The invention is illustrated by the following Example:—

Example

A 5 litre flask was set up and equipped with stirrer, thermometer, reflux condenser and nitrogen inlet. Succinic anhydride (373 grams), benzoin (531 grams) and pyridine (300 millilitres; 296 grams) were introduced. The flask was purged with nitrogen and the reaction mixture heated to 90—95°C. The mixture was stirred for one and a half hours at this temperature. Glacial acetic acid (1300 millilitres) and ammonium acetate (385 grams) were added to the reaction mixture and the mixture reheated to 90—95°C. Stirring was continued and this temperature was maintained for a further 2 hours. The mixture was filtered, rinsing through with glacial acetic acid (150 millilitres). Distilled water (750 millilitres) is added and the mixture reheated to 90—95°C before gradual cooling with stirring to 15°C over 1 hour. After filtering and washing with a mixture of acetic acid and distilled water in a ratio of 2:1 (600 millilitres), the product was slurried with distilled water (1000 millilitres). After filtering and washing with distilled water (2×400 millilitres), the product is dried at 90—100°C under vacuum. 702 Grams (67% yield) of β - (4,5 - diphenyloxazole - 2 - yl)-propionic acid were obtained as a white crystalline powder, m.p. 163—5°C. The material was investigated for quality by TLC. The produnct had high purity and merely showed a number of very faint trace impurities.

WHAT WE CLAIM IS:—

1. A method of preparation of a 4,5-diaryl-oxazol-2-ylalkanoic acid having the formula

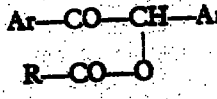


(III)

wherein Ar and Ar¹ represent the same or different aryl radicals and R represents carboxyethyl or carboxypropyl or a non-toxic salt thereof, wherein an aroylarylcarbinol having the formula

Ar—CO—CH(OH)—Ar¹ (II)

(wherein Ar and Ar¹ are as defined above) is esterified with a reactive derivative of a butanedioic or pentanedioic acid to form a keto ester having the formula



(I)

(where Ar, Ar¹ and R are as defined above) in the reaction mixture, a nitrogen-donating cyclising agent is added to the reaction mixture and the keto ester is cyclised with the

or 3-furyl). The radicals Ar and Ar¹ are preferably selected from unsubstituted phenyl, monohalophenyl, mono (lower alkyl) phenyl and mono (lower alkoxy) phenyl. R represents a carboxyethyl or carboxy propyl radical, preferably carboxyethyl. The terms "lower alkyl" and "lower alkoxy" as used herein mean that the alkyl or alkoxy radical contains up to 6, preferably up to 4, carbon atoms.

The preferred esterifying agents used in the process of the invention are succinic anhydride and glutaric anhydride, advantageously succinic anhydride. We prefer to incorporate pyridine in the reaction mixture since it is advantageous as a catalyst for the ester formation and may facilitate handling at a convenient temperature. For best results we prefer to carry out the ester formation reaction under a dry inert atmosphere, e.g. nitrogen.

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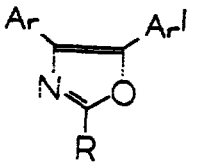
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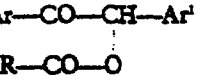


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(I)

(where Ar, Ar¹ and R are as defined above) in the reaction mixture, a nitrogen-donating cyclising agent is added to the reaction mixture and the keto ester is cyclised with the

nitrogen-donating cyclising agent to form an oxazole and, if desired, an acid product is converted into a non-toxic salt thereof.

2. A method as claimed in Claim 1, wherein Ar and Ar^1 are independently selected from phenyl, monohalophenyl, mono(lower alkyl)-phenyl and mono(lower alkoxy)phenyl.

3. A method as claimed in Claim 1 or Claim 2, wherein R represents carboxyethyl.

4. A method as claimed in Claim 1 or 2, wherein succinic anhydride or glutaric anhydride is used as esterifying agent.

5. A method as claimed in Claim 3, wherein succinic anhydride is used as esterifying agent.

6. A method as claimed in any one of Claims 1 to 5, wherein pyridine is incorporated into the reaction mixture for the esterification.

7. A method as claimed in any one of Claims 1 to 6, wherein the ester formation is carried out under dry nitrogen.

8. A method as claimed in any one of Claims 1 to 7, wherein the cyclising agent used is urea or an ammonium salt.

9. A method as claimed in any one of Claims 1 to 7, wherein the cyclisation is carried out with ammonium acetate and acetic acid.

10. A method as claimed in Claim 1, carried out substantially as described herein with reference to the Example.

11. A 4,5 - diaryloxazol - 2 - ylalkanoic acid or non-toxic salt thereof, whenever prepared by a method as claimed in any one of Claims 1 to 10.

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Chartered Patent Agent.

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