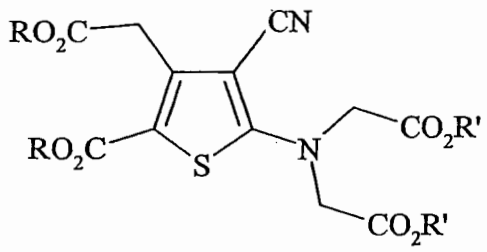
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New process for the industrial synthesis of tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid, and application to the synthesis of bivalent salts of ranelic acid and their hydrates

The present invention relates to a process for the industrial synthesis of tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and to the application thereof in the industrial production of bivalent salts of ranelic acid and their hydrates.

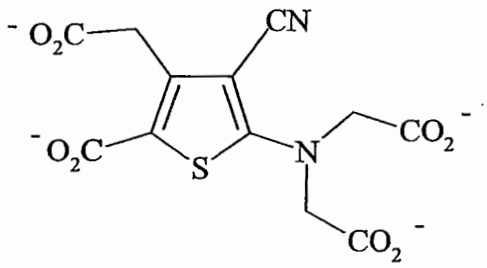
More specifically, the present invention relates to a new process for the industrial synthesis of compounds of formula (I) :



(I)

wherein R and R', which are the same or different, each represent a linear or branched (C_1-C_6)alkyl group.

The compounds of formula (I) obtained according to the process of the invention are useful in the synthesis of ranelic acid, its strontium, calcium or magnesium salts of formula (II) :



, 2 M^{2+} (II),

wherein M represents strontium, calcium or magnesium,

and hydrates of the said salts.

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The bivalent salts of ranelic acid have very valuable pharmacological and therapeutic properties, especially pronounced anti-osteoporotic properties, making these compounds useful in the treatment of bone diseases.

The bivalent salts of ranelic acid, and more especially strontium ranelate, the preparation thereof and the therapeutic use thereof have been described in the European Patent Specification EP 0 415 850.

In view of the pharmaceutical interest of that compound, it has been important to be able to synthesise the intermediate of formula (I) by using an effective industrial synthesis process, allowing the compound of formula (I) to be obtained in a good yield and with excellent purity, but which is also readily transferable to the industrial scale.

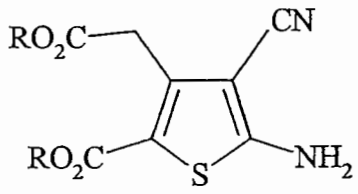
The journal Bull. Soc. Chim. France 1975, pp. 1786-1792, describes obtaining a compound of formula (I) (R = R' = ethyl) by reacting 5-amino-3-(carboxymethyl)-4-cyano-2-thiophenecarboxylic acid with ethyl bromoacetate, in the presence of potassium carbonate, followed by isolation in a highly dilute aqueous-organic medium.

However, the low yield of that reaction (65 %), the large amount of aqueous saline waste generated by that reaction and, above all, the very long reaction time (5 days) have completely precluded use of that reaction on an industrial scale.

The Applicant has now developed a simple industrial synthesis process which allows the compound of formula (I) to be obtained in a very good yield, with a considerably shorter reaction time and excellent purity and in which the aqueous saline waste is completely avoided.

More specifically, the present invention relates to a process for the industrial synthesis of compounds of formula (I),

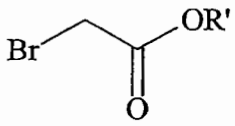
which process is characterised in that a compound of formula (III) :



(III),

wherein R represents a linear or branched (C_1-C_6)alkyl group,

is reacted with a compound of formula (IV) :



(IV),

wherein R' represents a linear or branched (C_1-C_6)alkyl group,

in the presence of a catalytic amount of a C_8-C_{10}-type quaternary ammonium compound,
and in the presence of potassium carbonate,
at the reflux of an organic solvent;
the reaction mixture is subsequently filtered;
the mixture is then concentrated by distillation;
a co-solvent is then added,
and the reaction mixture is cooled and filtered
to yield, after drying of the powder thereby obtained, the compound of formula (I).

A C_8-C_{10}-type quaternary ammonium compound is understood to be a compound of formula (A) or a mixture of compounds of formula (A) :

$$R_1 R_2 R_3 R_4\text{-}N^{+}\,^{-}X \qquad (A)$$

wherein R_1 represents a (C_1-C_6)alkyl group, R_2, R_3 and R_4, which are the same or different, each represent a (C_8-C_{10})alkyl group, and X represents a halogen atom.
C_8-C_{10}-type quaternary ammonium compounds to which preference is given are the catalysts Adogen 464® and Aliquat 336®.

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Surprisingly, only the use of a C_8-C_{10}-type quaternary ammonium compound allows the compound of formula (I) to be obtained both with a greatly reduced reaction time and with very good selectivity, in contrast to other types of quaternary ammoniums, as the following Table shows :

Catalyst	Duration of reaction	Content of reaction mixture
Tetrabutylammonium hydrogen sulphate (TBAHS)	12 hours	92 %
N,N-bis(2-hydroxyethyl)-N-methyl 1-dodecanaminium bromide	18 hours	82 %
Adogen 464®	5 hours	96 %
Aliquat 336®	4 hours	95 %

Furthermore, the somewhat simplified isolation (the precipitation step followed by filtration has been replaced by simple filtration of the reaction mixture) allows, by virtue of the particular conditions developed, the compound of formula (I) to be obtained not only in a very good yield (89 %) but also with excellent purity (greater than 98 %), whilst avoiding the burden on the environment that the aqueous saline waste represented.

- The amount of potassium carbonate is preferably from 2 to 3 mol per mol of compound of formula (III).

- The amount of compound of formula (IV) is preferably from 2 to 3 mol per mol of compound of formula (III).

- The initial volume of organic solvent is preferably from 6 to 12 ml per gram of compound of formula (III).

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- Organic solvents that are preferred for the reaction are acetone and acetonitrile.

- A co-solvent that is preferred for isolation is methanol.

Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate and methyl 5-[bis(2-ethoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate, particular and preferred cases of the compounds of formula (I), are new compounds which are useful as synthesis intermediates in the chemical or pharmaceutical industry, especially in the synthesis of strontium ranelate and accordingly form an integral part of the present invention.

The Examples hereinbelow illustrate the invention but do not limit it in any way.

EXAMPLE 1 **: *Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate***

Introduce into a reactor 400 kg of 5-amino-3-(carboxymethyl)-4-cyano-2-thiophenecarboxylic acid, 478 kg of potassium carbonate, 2810 litres of acetone, 16 kg of Adogen 464® and 529.6 kg of methyl bromoacetate.

Bring the temperature to 60°C. After refluxing for 5 hours, cool the reaction mixture and then filter it. Concentrate the filtrate obtained.

Add methanol; cool and filter the suspension obtained, and then dry the powder.

Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is thereby obtained in a yield greater than 85 % and with a chemical purity greater than 98 %.

EXAMPLE 2 **:** ***Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate***

Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is obtained in the same manner as Example 1, but replacing Adogen 464® by Aliquat 336®.

EXAMPLE 3 **:** ***Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate***

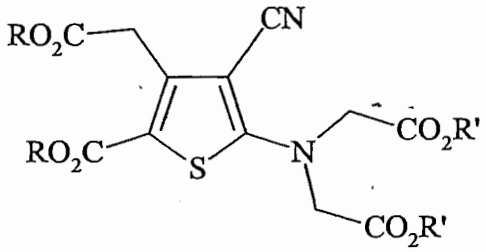
Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is obtained in the same manner as Example 1, but replacing the acetone by acetonitrile.

EXAMPLE 4 **:** ***Methyl 5-[bis(2-ethoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate***

Methyl 5-[bis(2-ethoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is obtained in the same manner as Example 1, but replacing the 529.6 kg of methyl bromoacetate by 578.1 kg of ethyl bromoacetate.

CLAIMS

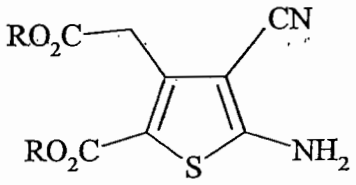
1. Process for the industrial synthesis of compounds of formula (I) :



(I),

wherein R and R', which are the same or different, each represent a linear or branched (C_1-C_6)alkyl group,

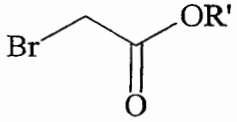
characterised in that a compound of formula (III) :



(III),

wherein R is as defined hereinbefore,

is reacted with a compound of formula (IV) :



(IV),

wherein R' is as defined hereinbefore,

in the presence of a catalytic amount of a C_8-C_{10}-type quaternary ammonium compound,
and in the presence of potassium carbonate,
at the reflux of an organic solvent;
the reaction mixture is subsequently filtered;
the mixture is then concentrated by distillation;
a co-solvent is then added,
and the reaction mixture is cooled and filtered
to yield, after drying of the powder thereby obtained, the compound of formula (I),

it being understood that a C_8-C_{10}-type quaternary ammonium compound is a compound of formula (A) or a mixture of compounds of formula (A) :

$$R_1R_2R_3R_4\text{-}N^+\,^-X \qquad (A)$$

wherein R_1 represents a (C_1-C_6)alkyl group, R_2, R_3 and R_4, which are the same or different, each represent a (C_8-C_{10})alkyl group, and X represents a halogen atom.

2. Synthesis process according to claim 1 allowing the compound of formula (I), wherein R represents a methyl group and R' represents an ethyl group, to be obtained.

3. Synthesis process according to claim 1 allowing the compound of formula (I), wherein R and R' each represent a methyl group, to be obtained.

4. Process according to any one of claims 1 to 3, characterised in that the C_8-C_{10}-type quaternary ammonium compound is Adogen 464® or Aliquat 336®.

5. Synthesis process according to any one of claims 1 to 4, characterised in that the amount of potassium carbonate is from 2 to 3 mol per mol of compound of formula (III).

6. Synthesis process according to any one of claims 1 to 5, characterised in that the amount of compound of formula (IV) is from 2 to 3 mol per mol of compound of formula (III).

7. Synthesis process according to any one of claims 1 to 6, characterised in that the initial volume of organic solvent is from 6 to 12 ml per gram of compound of formula (III).

8. Synthesis process according to any one of claims 1 to 7, characterised in that the organic solvent used for the reaction is acetone or acetonitrile.

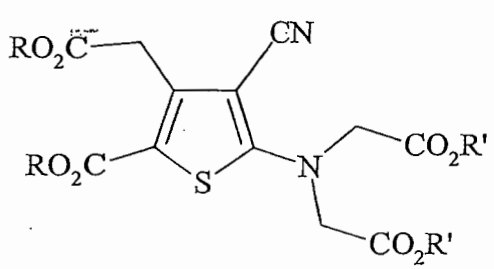
9. Synthesis process according to any one of claims 1 to 8, characterised in that the co-solvent used during isolation is methanol.

10. Synthesis process according to any one of claims 1 to 9, characterised in that the compound of formula (I) obtained has a chemical purity greater than 98 %.

11. Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate.

12. Methyl 5-[bis(2-ethoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate.

13. Process for the synthesis of ranelic acid, its strontium, calcium or magnesium salts and hydrates of the said salts, starting from a compound of formula (I) :



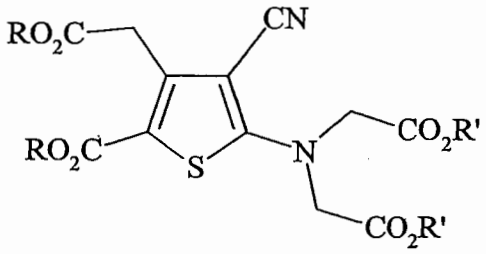
(I),

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wherein R and R', which are the same or different, each represent a linear or branched (C_1-C_6)alkyl group,

characterised in that the compound of formula (I) is obtained by the synthesis process according to any one of claims 1 to 10.

14. Process for the synthesis of strontium ranelate and its hydrates, starting from a compound of formula (I) :



(I),

wherein R and R', which are the same or different, each represent a linear or branched (C_1-C_6)alkyl group,

characterised in that the compound of formula (I) is obtained by the synthesis process according to any one of claims 1 to 10.