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(54) Titre : FABRICATION D'UN ACIDE CYCLIQUE
(54) Title: MANUFACTURE OF A CYCLIC ACID

(57) Abrégé/Abstract:
A process for the production of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid and, respectively, of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride starting from a meso-2,3-bis(benzylamino)succinic acid dialkali metal salt comprises reacting the meso-2,3-bis(benzylamino)succinic acid dialkali metal salt with phenyl chloroformate in a monophasic solvent system consisting of an about 2:1 to 1:1 mixture of a water-miscible ether and aqueous alkali metal hydroxide solution at a temperature not exceeding about 40°C, and converting the resulting 2-oxo-1,3-dibenzyl-cis-4,5- imidazolidinedicarboxylic acid dialkali metal salt by acidification into the desired 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid and isolating this or converting this by heating with acetic anhydride in an aromatic hydrocarbon as the organic solvent into the desired 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid anhydride and isolating this. Each product is an important intermediate in the multi-stage process for the manufacture of biotin (vitamin H).

Case 20593

Abstract

A process for the production of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid and, respectively, of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride starting from a meso-2,3-bis(benzylamino)succinic acid dialkali metal salt comprises reacting the meso-2,3-bis(benzylamino)succinic acid dialkali metal salt with phenyl chloroformate in a monophasic solvent system consisting of an about 2:1 to 1:1 mixture of a water-miscible ether and aqueous alkali metal hydroxide solution at a temperature not exceeding about 40°C, and converting the resulting 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid dialkali metal salt by acidification into the desired 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid and isolating this or converting this by heating with acetic anhydride in an aromatic hydrocarbon as the organic solvent into the desired 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid anhydride and isolating this. Each product is an important intermediate in the multi-stage process for the manufacture of biotin (vitamin H).

Case 20593

The present invention is concerned with a process for the production of a cyclo acid, namely of 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid, and, respectively, of the corresponding anhydride, which are important intermediates in the multi-stage process for the manufacture of biotin (vitamin H) described, for example, in the review article of Pierre J. de Clercq in Chem. Rev. 97, 1755-1792 (1997).

The production of the aforementioned cyclo acid starting from meso-2,3-bis(benzylamino)succinic acid in the form of its dialkali metal salt is known. Thus, for example, US Patent No. 5,151,525 from the year 1992 describes such a process in which phosgene is used as the reagent in an alkaline-aqueous/organic two-phase solvent system for the linkage of the two secondary nitrogen atoms via a carbonyl group with resulting ring formation. In this case, anisole is employed as the essentially water-immiscible solvent for the reaction.

As is known, the reagent phosgene is, however, highly toxic and, moreover, potentially explosive under the influence of other gases or certain reaction liquids, so that its use is extremely dangerous when it is carelessly handled or supervised, and special precautions are required in its transport, storage and use, e.g. the employment of safety devices in the apparatus.

A process for the production of the aforementioned cyclo acid which also starts from meso-2,3-bis(benzylamino)succinic acid in the form of its dialkali metal salt, but using an alkyl, haloalkyl or aryl chloroformate in place of phosgene for the ring formation, has already been described in the substantially older Japanese Patent Publication (Kokai) No. 8270/1976. Although thereby the disadvantages of phosgene outlined above can indeed be avoided, this process still has other likewise serious disadvantages, which may be the reason why the use of chloroformates has hitherto not been adopted. Thus, the cyclo acid can be produced in the desired yield only with the reagent which is most preferred according to the Examples, phenyl chloroformate. However, the use of phenyl chloroformate has other disadvantages apart from the high costs. Thus, on the one hand, diphenyl carbonate and phenol occur as unavoidable byproducts and on the other hand the diphenyl carbonate separates as a viscous mass from the aqueous reaction solution and clogs up the reactor components as well as the pH probe. For this reason, the pH value cannot be conveyed back accurately, which is of critical significance for the controlled performance of the reaction.

The phenyl chloroformate forms in a first reaction step with the meso-2,3-bis-(benzylamino)succinic acid dialkali metal salt with the cleavage of hydrochloric acid a monourethane intermediate, which then reacts further to the cyclo acid. The alkali phenolate which results reacts in turn with phenyl chloroformate to form the byproduct diphenyl carbonate. The hydrochloric acid which results can be neutralized by the addition of alkali metal hydroxide solution, whereby the pH value should be neither too low nor too high. If the pH is too low, the meso-2,3-bis(benzylamino)succinic acid precipitates out and cannot be reacted. Moreover, the meso-2,3-bis(benzylamino)succinic acid combines with the separated diphenyl carbonate to a viscous mass, which leads to further clogging of the reactor components including the stirrer. At too high pH values the phenyl chloroformate hydrolyzes too rapidly, which leads to unnecessary consumption.

Moreover, the precipitation of the cyclo acid by the addition of a strong acid is difficult to accomplish, since this often separates as a viscous mass, which is in agreement with the details in the aforementioned Japanese Patent Publication and which can result in a further clogging of the reactor components including the stirrer.

The object of the present invention is to provide a process for the production of 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid which likewise starts from meso-2,3-bis(benzylamino)succinic acid in the form of its dialkali metal salt, while on the one hand avoiding the use of phosgene as the reagent for the ring formation explained in more detail above and on the other hand avoiding the considerable disadvantages of performing the process according to the aforementioned Japanese Patent Publication.

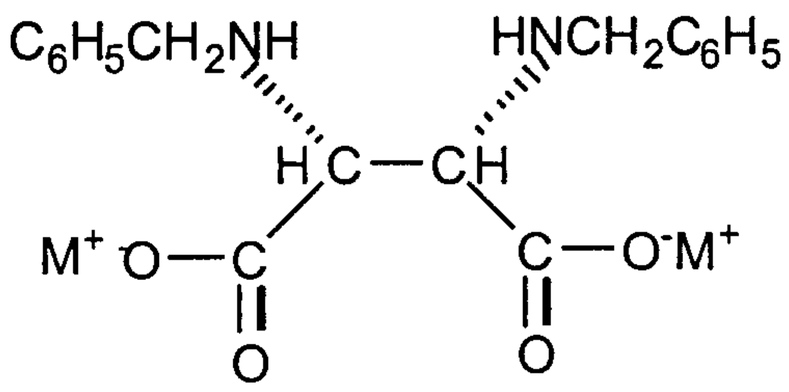
This object is achieved surprisingly simply and well by carrying out the reaction of meso-2,3-bis(benzylamino)succinic acid in the form of its dialkali metal salt with phenyl chloroformate in a mixture of a water-miscible ether and water under alkaline conditions, by which means it is possible to keep in solution the diphenyl carbonate formed in the reaction. Accordingly, the reaction can be performed in a monophasic solvent system which is free from solid byproducts, whereby, furthermore, a clogging of the reactor components including the stirrer can be avoided.

The process in accordance with the invention is accordingly a process for the production of 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid starting from a meso-2,3-bis(benzylamino)succinic acid dialkali metal salt, which process comprises

reacting the meso-2,3-bis(benzylamino)succinic acid dialkali metal salt with phenyl chloroformate in a monophasic solvent system consisting of an about 2:1 to 1:1 mixture (parts by volume) of a water-miscible ether and aqueous alkali metal hydroxide solution at a temperature not exceeding about 40°C, and converting the resulting 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid dialkali metal salt by acidification into the desired 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid and isolating this.

Examples of water-miscible ethers are tetrahydrofuran and ethylene glycol ethers, e.g. glyme and diglyme, preferably tetrahydrofuran.

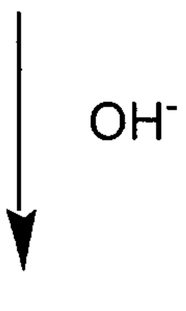
The following Reaction Scheme is a structural representation of the process in accordance with the invention:

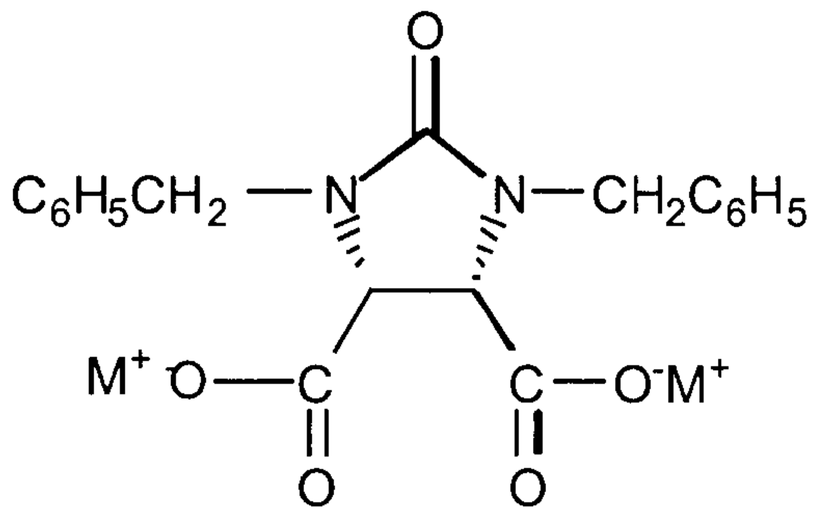


meso-2,3-Bis(benzylamino)-
succinic acid dialkali metal salt

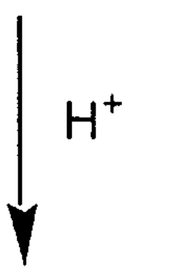
+

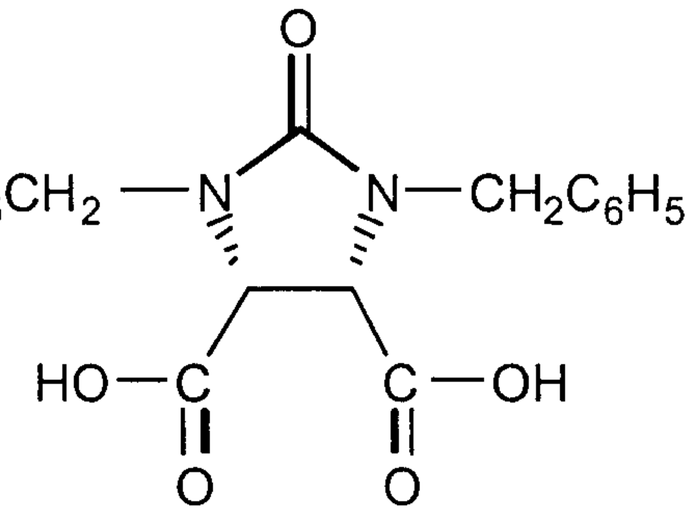
Phenyl chloroformate





2-Oxo-1,3-dibenzyl-cis-4,5-
imidazolidinedicarboxylic acid
dialkali metal salt





2-Oxo-1,3-dibenzyl-cis-4,5-
imidazolidinedicarboxylic acid

In the above Reaction Scheme the alkali metal ion M^+ is conveniently the lithium, sodium or potassium ion, preferably the potassium ion, so that the dilithium, disodium or

dipotassium salt, preferably the last-named, is conveniently used as the starting material for the process in accordance with the invention.

For the production of the meso-2,3-bis(benzylamino)succinic acid dialkali metal salt, the acid itself is conveniently suspended in water, preferably deionized water, and the resulting suspension is treated with alkali metal hydroxide solution, i.e. conveniently lithium, sodium or potassium hydroxide solution, preferably potassium hydroxide solution, generally at a pH value of about 9 to about 14, preferably at a pH value of about 12 to about 13. This gives an alkaline-aqueous solution of the desired dialkali metal salt. The concentration of the alkali metal hydroxide solution to be added is not critical, although it amounts to about 40-50 weight percent when a commercial alkali metal hydroxide solution, e.g. potassium hydroxide solution, is used. Suitable amounts of water and alkali metal hydroxide solution are used in order to ensure that the concentration of the meso-2,3-bis(benzylamino)succinic acid dialkali metal salt formed conveniently amounts to about 5 to about 20 weight percent, preferably about 10 to about 15 weight percent, based on the total weight of the resulting clear alkaline-aqueous solution at pH about 9 to about 14. The water-miscible ether can, if desired, already be in the suspension of the meso-2,3-bis(benzylamino)succinic acid, so that the acid is effectively suspended in aqueous ether, or can be added for the first time after preparation of the aqueous dialkali metal salt solution in order ultimately to produce the alkaline-aqueous ether solution required in the process in accordance with the invention.

The combination of the alkaline-aqueous ether solution of the meso-2,3-bis-(benzylamino)succinic acid dialkali metal salt with the phenyl chloroformate can be effected in the desired sequence, but preferably the dialkali metal salt solution is provided and the phenyl chloroformate is added thereto. In this case it has been found to be advantageous to add the phenyl chloroformate slowly and continuously, i.e. in a stream. During the addition the pH value of the reaction mixture is held constant as far as possible by the addition of alkali metal hydroxide solution. In order to achieve a good intermixing during the addition the mixture is conveniently stirred or otherwise intermixed. Moreover, the combination is conveniently effected at about room temperature. However, if desired, not only the solution, but also the phenyl chloroformate can be previously warmed to a slightly elevated temperature of about 30-35°C.

As regards the relative amounts of meso-2,3-bis(benzylamino)succinic acid dialkali metal salt and phenyl chloroformate, the dialkali metal salt : phenyl chloroformate molar ratio suitably amounts to about 1 : 1 to about 1 : 4, preferably about 1 : 2 to about 1 : 3.

During the reaction of the phenyl chloroformate with the meso-2,3-bis(benzyl-amino)succinic acid dialkali metal salt the pH value of the reaction mixture is conveniently held in the range of about 8 to about 14, preferably in the range of about 9 to about 11. As already mentioned, in order to maintain this pH range, aqueous lithium, sodium or potassium hydroxide solution is added at the same time as the reactants are combined. The concentration of the lithium, sodium or potassium hydroxide solution to be added is not critical, although suitably it amounts to about 20 to about 50 weight percent. For this purpose it is especially suitable to use the same lithium, sodium or potassium hydroxide solution as that which was used for the production of the meso-2,3-bis(benzylamino)-succinic acid dialkali metal salt.

The reaction is effected at a temperature not exceeding about 40°C, generally at temperatures in the range of about 25°C to about 35°C, preferably at about 30°C. The pressure is not critical; the reaction is normally carried out under atmospheric pressure or slightly elevated pressure.

The performance of the process in accordance with the invention is conveniently effected under an inert gas atmosphere. When an inert gas atmosphere is used, there is suitably used as the inert gas is nitrogen or argon, nitrogen being preferred on an industrial scale.

After the addition has been effected, which usually takes about 2 to 5 hours, the reaction has normally also finished. The resulting monophasic mixture, which contains the 2-oxo-1,3-dibenzyl-cis-4,5-imiazolidinedicarboxylic acid dialkali metal salt as the product, can then be worked up by rendering the reaction mixture slightly alkaline by the addition of acid, especially to pH about 7-8, and extracting with an aromatic hydrocarbon, preferably toluene or xylene. A mineral acid, e.g. hydrochloric acid, hydrobromic acid or sulphuric acid, preferably hydrochloric acid, is especially suitable as the acid used for the acidification. The desired product, still as the dialkali metal salt, is present in the aqueous phase. Tetrahydrofuran is then suitably added to the separated aqueous phase and the dialkali metal salt is converted by acidification into the free acid and taken up as such in the organic phase. As the acid for the acidification there is conveniently used a mineral acid, especially hydrochloric acid, hydrobromic acid or sulphuric acid, preferably hydrochloric acid, the respective concentration and amount being conveniently so chosen that the aqueous phase finally has a pH value of < 3, preferably about 1. The organic phase containing the desired product as the free acid and separated from the aqueous phase can

then after the addition of an aromatic hydrocarbon, e.g. toluene or xylene, as a solvent be subjected to a distillation under reduced pressure in order to remove mainly the tetrahydrofuran, a small amount of aromatic solvent as well as residual water. The 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid then precipitates as crystals from the resulting super-saturated solution of the desired product in the anhydrous aromatic solvent, optionally by seeding and/or by cooling.

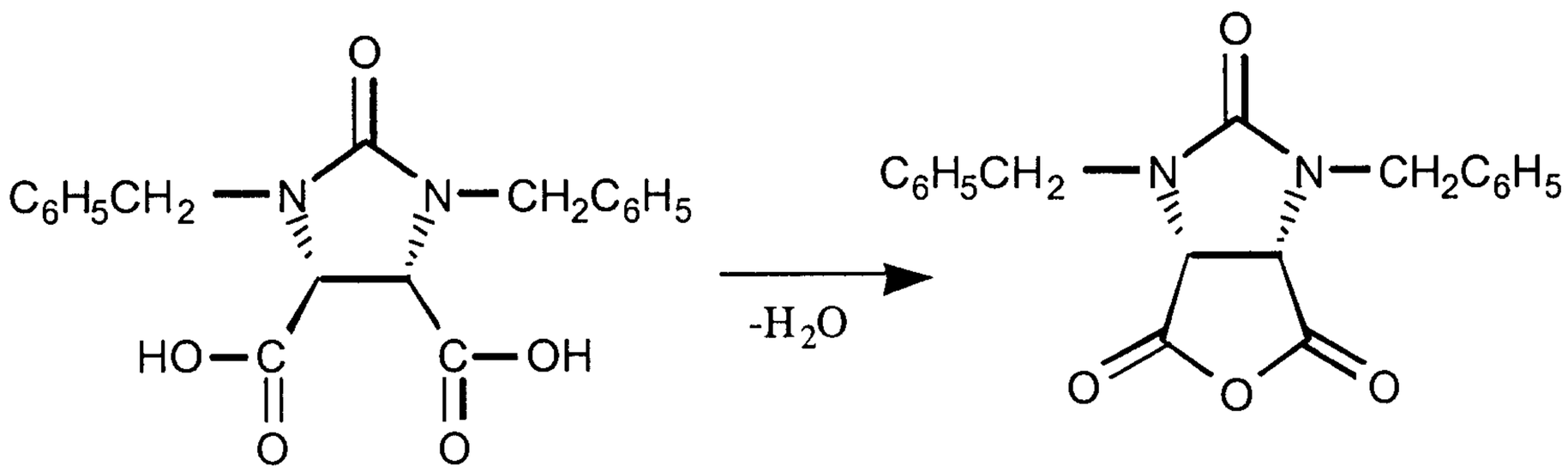
The thus-isolated 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid can in a manner known per se be washed, conveniently with water, dried and, if desired, purified further.

The performance of the reaction in a monophasic system and the crystallization from an aromatic hydrocarbon offer the following advantages:

- Safer performance of the reaction without precipitations of diphenyl carbonate or meso-2,3-bis(benzylamino)succinic acid
- No clogging of the reactor components including the stirrer
- Adequate control of the pH value during the duration of the reaction
- Reduction of the amount of phenyl chloroformate in comparison to the standard process
- Reproducible precipitation of the 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinecarboxylic acid as a fine particulate solid
- Improved yield

In the scope of the present invention it has been established that by a simple modification of the procedure towards the end of the working up described above it is possible for the first time to proceed without isolation of the 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid to 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride, the product of the next step in the synthesis of biotin.

Whereas towards the end of the working up described above, i.e. immediately after the distillation of the organic solvents, the 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidine-dicarboxylic acid crystallizes out and at the same time is isolated, the modified process embodiment involves the addition of additional aromatic solvent, preferably toluene, and acetic anhydride. For this purpose there is suitably used at least one mol of acetic anhydride per mol of meso-2,3-bis(benzylamino)succinic acid dialkali metal salt which was used as the starting material, preferably about 1.05 mol to about 1.3 mol, of acetic anhydride per mol of starting material. Upon subsequent heating to 70°C to 130°C, preferably about 75°C to about 95°C, especially about 80°C, the 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid reacts in accordance with the Formula Scheme set forth below to give 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride, which precipitates from the solution and can be isolated according to methods known per se, e.g. by filtration.



2-Oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid

2-Oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid anhydride

Accordingly, the present invention also includes a process for the production of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride in which after carrying out the process defined above for the production of 2-oxo-1,3-dibenzyl-4,5-imidazolidine-dicarboxylic acid starting from a meso-2,3-bis(benzylamino)succinic acid dialkali metal salt and before isolation of the resulting 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid this is converted by heating with acetic anhydride in an aromatic hydrocarbon as the organic solvent, preferably toluene, into the desired 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride, and this is isolated.

The isolated 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride can be washed in a manner known per se, conveniently with toluene, dried and, if desired, purified further.

The conversion into 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride in, for example, toluene as the solvent is thus exactly the same as the dehydration of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid to the anhydride in a mixture of acetic acid and acetic anhydride, a method which has hitherto been used.

The advantages of the process embodiment without isolation of the 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid are:

- No isolation of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid
- Complete and simple crystallization of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride
- Cleaner product
- Reduced expense with respect to apparatus and personnel
- Replacement of acetic acid by toluene
- 2-Oxo-1,3-dibenzylamino-4,5-imidazolidinedicarboxylic acid need not be dried, discharged and again charged
- No necessity to adjust and distill mixtures of acetic acid/acetic anhydride
- Reduction of the amount of acetic anhydride by at least 30%
- Improved yield compared with the yield resulting after completion of the two individual steps

The process in accordance with the invention is illustrated by the following Examples:

Example 1

220 g (0.67 mol) of meso-2,3-bis(benzylamino)succinic acid were placed under a nitrogen atmosphere in a 2 l flask fitted with two dropping funnels, a pH electrode and a stirrer. The meso-2,3-bis(benzylamino)succinic acid was then suspended while stirring in 800 ml of tetrahydrofuran and 400 ml of deionized water and brought into solution by the addition of 108 ml of 50% potassium hydroxide solution. 200 ml of 2.4 mol eq. phenyl chloroformate were added dropwise to the solution obtained within 3.5 hours. The pH was held between 9 and 11 during the addition of phenyl chloroformate by the successive addition of 50% potassium hydroxide solution, and the internal temperature was held between 30°C and 35°C. After completion of the addition the mixture was stirred at about 30°C for a further 2 hours and then adjusted to a pH value of about 7-8 with concentrated hydrochloric acid. The aqueous solution was extracted twice with toluene. 500 ml of tetrahydrofuran were added to the entire aqueous phase. Then, the mixture was adjusted to a pH value of 1.0 with 37% hydrochloric acid and the aqueous phase was separated off. 400 ml of toluene were added to the tetrahydrofuran phase and the tetrahydrofuran was distilled off under reduced pressure. Thereafter, water which still remained was removed azeotropically with toluene. The residual brownish, oily solution was seeded and the crystalline solid was filtered off and washed twice with toluene. After drying under reduced pressure to constant weight there were obtained 181.5 g (76% yield) of 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid, m.p. 172.8°C.

Example 2

220 g (0.67 mol) of meso-2,3-bis(benzylamino)succinic acid were placed under a nitrogen atmosphere in a 2 l flask fitted with two dropping funnels, a pH electrode and a stirrer. The meso-2,3-bis(benzylamino)succinic acid was then suspended while stirring in 800 ml of tetrahydrofuran and 400 ml of deionized water and brought into solution by the addition of 108 ml of 50% potassium hydroxide solution. 200 ml of 2.4 mol eq. phenyl chloroformate were added dropwise to the solution obtained within 3.5 hours. The pH was held between 9 and 11 during the addition of phenyl chloroformate by the successive addition of 50% potassium hydroxide solution and the internal temperature was held between 30°C and 35°C. After completion of the addition the mixture was stirred at about 30°C for a further 2 hours and then adjusted to a pH value of about 7-8 with concentrated hydrochloric acid. The aqueous solution was extracted twice with toluene. 500 ml of tetrahydrofuran were added to the entire aqueous phase. Then, the mixture was adjusted to a pH value of 1.0 with 37% hydrochloric acid and the aqueous phase was separated off.

400 ml of toluene were added to the tetrahydrofuran phase and the tetrahydrofuran was distilled off under reduced pressure. Thereafter, water which still remained was removed azeotropically with toluene. After the addition of 700 ml of toluene and 130 ml of acetic anhydride the mixture was heated to 80°C. After the 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride had crystallized out the suspension obtained was cooled to 10°C within 2 hours for completion of the crystallization and thereafter the crystalline 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride was filtered off and washed twice with toluene. After drying under reduced pressure to constant weight there were obtained 173.6 g (78% yield) of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride in the form of an analytically pure, colourless solid, m.p. 240.2°C. A further 3.0 g of crystals of 2-oxo-1,3-dibenzylamino-4,5-imidazolidinedicarboxylic acid anhydride were obtained on evaporation of the mother liquor.

Claims:

1. A process for the production of 2-oxo-1,3-dibenzyl-4,5-imidazolidine-dicarboxylic acid and, respectively, of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride starting from a meso-2,3-bis(benzylamino)succinic acid dialkali metal salt, which process comprises reacting the meso-2,3-bis(benzylamino)succinic acid dialkali metal salt with phenyl chloroformate in a monophasic solvent system consisting of an about 2:1 to 1:1 mixture of a water-miscible ether and aqueous alkali metal hydroxide solution at a temperature not exceeding about 40°C and converting the resulting 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid dialkali metal salt by acidification into the desired 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid and isolating this or converting this by heating with acetic anhydride in an aromatic hydrocarbon as the organic solvent into the desired 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid anhydride and isolating this.

2. A process according to claim 1, wherein toluene is used as the aromatic hydrocarbon in the production of 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid anhydride.

3. A process according to claim 1 or 2, wherein tetrahydrofuran or an ethylene glycol ether, such as glyme or diglyme, preferably tetrahydrofuran, is used as the water-miscible ether.

4. A process according to any one of claims 1 to 3, wherein the dilithium salt, disodium salt or dipotassium salt of meso-2,3-bis(benzylamino)succinic acid, preferably the last-named, is used as the starting material.

5. A process according to any one of claims 1 to 4, wherein the meso-2,3-bis-(benzylamino)succinic acid dialkali metal salt is produced by suspending the acid itself in water and treating the resulting suspension with alkali metal hydroxide solution, preferably potassium hydroxide solution, in order to obtain an alkaline-aqueous solution of the desired dialkali metal salt.

6. A process according to any one of claims 1 to 5, wherein the water-miscible ether is added before or after the production of the aqueous dialkali metal salt solution.

7. A process according to any one of claims 1 to 6, wherein the alkaline-aqueous ether solution and/or the phenyl chloroformate is/are warmed to an elevated temperature of about 30-40°C before the reaction.

8. A process according to any one of claims 1 to 7, wherein the meso-2,3-bis(benzylamino)succinic acid dialkali metal salt : phenyl chloroformate molar ratio is about 1 : 1 to about 1 : 4, preferably about 1 : 2 to about 1 : 3.

9. A process according to any one of claims 1 to 8, wherein the pH value of the reaction mixture is held in the range of about 8 to about 14, preferably in the range of about 9 to about 11, during the reaction of the meso-2,3-bis(benzylamino)succinic acid dialkali metal salt with the phenyl chloroformate.

10. A process according to any one of claims 1 to 9, wherein the reaction is carried out at a temperature in the range of about 25°C to about 35°C, preferably at about 30°C.

11. A process according to any one of claims 1 to 10, wherein a mineral acid, especially hydrochloric acid, hydrobromic acid or sulphuric acid, preferably hydrochloric acid, is used for the acidification of the 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidine-dicarboxylic dialkali metal salt obtained.

12. A process according to any one of claims 1 to 11, wherein the 2-oxo-1,3-dibenzyl-cis-4,5-imidazolidinedicarboxylic acid obtained is treated without isolation with an aromatic hydrocarbon, preferably toluene, and acetic anhydride and the reaction mixture is heated to about 70°C to about 130°C, preferably about 75°C to about 95°C, especially about 80°C.

13. A process according to any one of claims 1 to 12, wherein the 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid or the 2-oxo-1,3-dibenzyl-4,5-imidazolidine-dicarboxylic acid anhydride is isolated by crystallization from a solution in an aromatic hydrocarbon.

14. The use of 2-oxo-1,3-dibenzyl-4,5-imidazolidinedicarboxylic acid anhydride produced in accordance with any one of claims 1 to 12 for the manufacture of biotin.