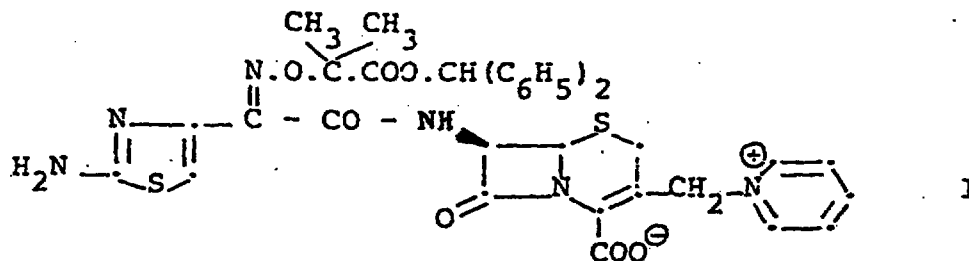


Description

The present invention provides a new crystalline, highly pure and stable form of the syn-isomer of the cephalosporin derivative of formula

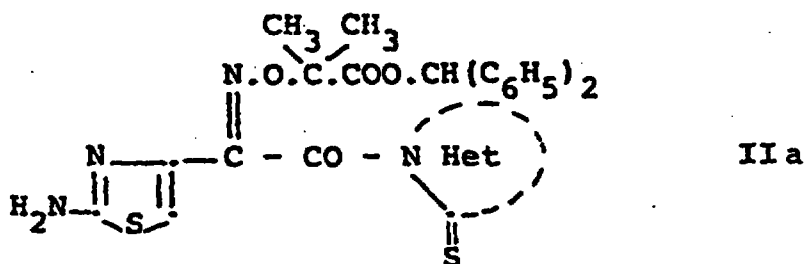
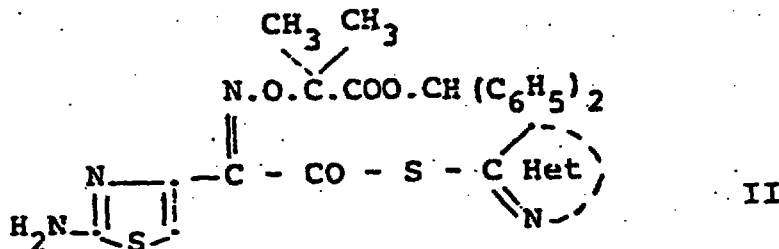


as well as a process for its production.

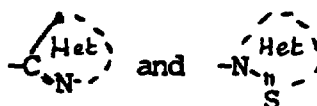
The cephalosporin derivative of formula I is useful as an intermediate for the production of highly active cephalosporin antibiotics which can be administered parenterally and show a very broad spectrum of activity against pathogenic microorganisms, particularly in the gram negative area.

The syn-isomer compound of formula I has usually been isolated in the form of a salt, such as the dihydrochloride or chloride hydrochloride (WO 85/04659). Hitherto, the free betaine form has only been isolated from complex solvent mixtures which has resulted in a product, in particular a solvate, with less than optimal purity and stability (WO 85/04659). It has now surprisingly been found that the syn-isomer of the compound of formula I can be isolated in free betaine form, and free of acid or solvent adducts, in excellent yield and purity ($\geq 97\%$) as a stable highly crystalline product, direct from the reaction mixture used to produce it. The product has the physical characteristics set out in the Example hereinafter.

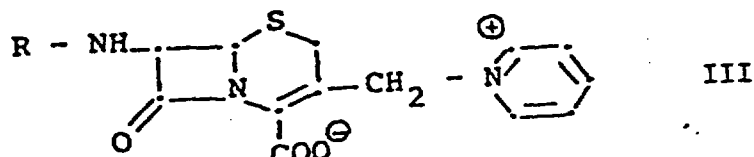
The present invention provides more particularly a process for the production of the syn-isomer of compound of formula I in crystalline form, comprising reacting the syn-isomer of a compound of formula II and/or IIa



in which



signify a 5-or 6-membered heterocyclic ring which may contain in addition to the nitrogen atom one or two further hetero atoms for example oxygen, nitrogen or sulphur, and which may be substituted, and which may be fused to a benzene ring which may itself be substituted,
with a compound of formula III,



in which R is hydrogen or an amino protecting group, or a salt thereof, e.g. the hydrochloride, mixing the resulting reaction mixture with a mixture of an acetic acid C₂₋₄ alkyl ester and a C₁₋₂ alkanol in a ratio of 2-3:1:1 by volume at a temperature of from 0 to 40°C, preferably 15° to 25°, and recovering the precipitated product. In this manner, the product crystallises out in a matter of a few minutes to a few hours in practically quantitative yield and high purity (≥97% yield and purity). Acetic acid esters include ethyl, propyl and butyl acetate. The preferred alkanol is methanol.

The nature of the "Het" ring in the compounds II and IIa is not critical, the preferred compounds being determined by such factors as availability of starting materials and ease of production. The preferred rings are 2-pyridyl and, in particular 2-benzthiazolyl or less preferably pyrimidinyl, triazolyl or thiazolyl, and the corresponding thiones as in compounds IIa.

The compounds of formula II, IIa and III are known and may be produced in conventional manner.

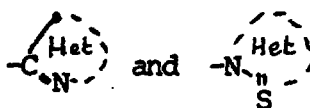
In the following Example, which illustrates the invention of all temperatures are in °C.

Example: (6R, 7R)-7-[[2-(2-Amino-4-thiazolyl)-(Z)-2-(1-diphenylmethoxycarbonyl-1-methylethoxy)imino]-acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate

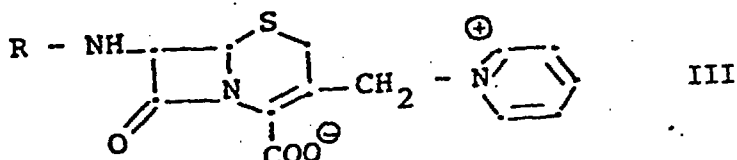
212g of 2-(2-Amino-4-thiazolyl)-(Z)-2-(1-diphenylmethoxycarbonyl-1-methylethoxy)iminoacetic acid are suspended together with 138g of triphenylphosphine in 800 ml of methylene dichloride, the mixture is cooled to 0° and 175 g of mercaptobenzthiazole disulphide are added. After 2 hours stirring at 0°, the formation of the thioester II or the corresponding compound IIa is complete (as determined by DC) and 260 g of 7-amino-3-pyridiniummethylcephalosporanic acid hydrochloride and 61 g of triethylamine are added at 0°. The mixture is stirred for 15 hours at 0° until the reaction is complete (as determined by HPLC) and the reaction mixture (yellow-brown) (ca. 1400 ml) is introduced into a mixture of 1400 ml of methanol and 3.5 litres of butylacetate at about 20°. The resulting clear solution is stirred at room temperature for 2 hours and then at 0° for a further 2 hours. The resulting highly crystalline precipitate is filtered off, washed with cold methanol and dried in vacuo. The highly pure (≥97%) by weight, free-flowing heading compound results.

Claims

1. Crystalline (6R, 7R)-7-[[2-(2-Amino-4-thiazolyl)-(Z)-2-(1-diphenylmethoxycarbonyl-1-methylethoxy)-imino]acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate.
2. The product of claim 1 in a purity of at least 97%.
3. A process for the production of the product of claim 1 comprising reacting a compound of formula II or IIa



signify a 5- or 6-membered heterocyclic ring which may contain in addition to the nitrogen atom one or two further hetero atoms for example oxygen, nitrogen or sulphur, and which may be substituted, and which may be fused to a benzene ring which may itself be substituted,
with a compound of formula III,



in which R is hydrogen or an amino protecting group, or a salt thereof, e.g. the hydrochloride, mixing the resulting reaction mixture with a mixture of an acetic acid C₂₋₄ alkyl ester and a C₁₋₂ alkanol in a ratio of 2-3:1:1 by volume at a temperature of from 0 to 40°C, preferably 15° to 25°, and recovering the precipitated product. In this manner, the product crystallises out in a matter of a few minutes to a few hours in practically quantitative yield and high purity (≥97% yield and purity). Acetic acid esters include ethyl, propyl and butyl acetate. The preferred alkanol is methanol.

The nature of the "Het" ring in the compounds II and III is not critical, the preferred compounds being determined by such factors as availability of starting materials and ease of production. The preferred rings are 2-pyridyl and, in particular 2-benzthiazolyl or less preferably pyrimidinyl, triazolyl or thiazolyl, and the corresponding thiones as in compounds IIa.

The compounds of formula II, III and IIIa are known and may be produced in conventional manner.

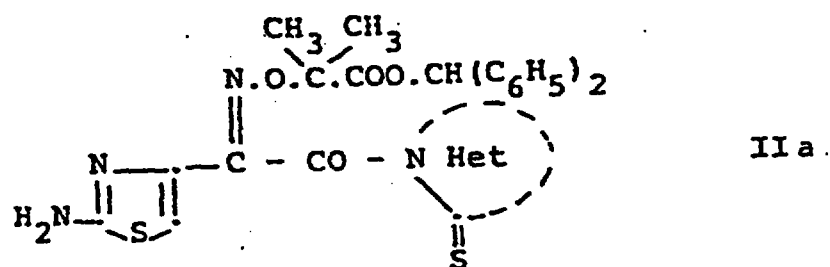
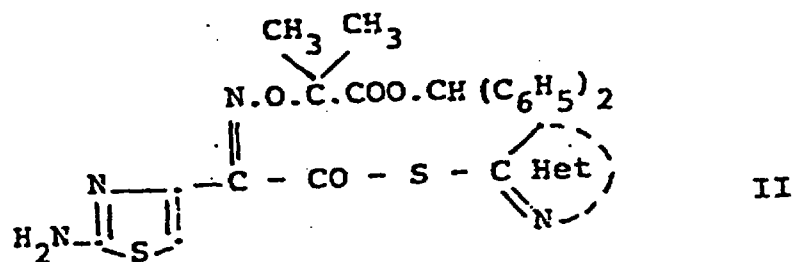
In the following Example, which illustrates the invention of all temperatures are in °C.

Example: (6R, 7R)-7-[[2-(2-Amino-4-thiazolyl)-(Z)-2-(1-diphenylmethoxycarbonyl-1-methylethoxy)imino]-acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate

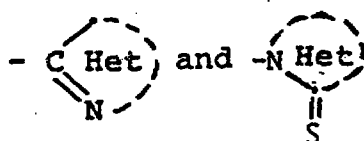
212g of 2-(2-Amino-4-thiazolyl)-(Z)-2-(1-diphenylmethoxycarbonyl-1-methylethoxy)iminoacetic acid are suspended together with 138g of triphenylphosphine in 800 ml of methylene dichloride, the mixture is cooled to 0° and 175 g of mercaptobenzthiazole disulphide are added. After 2 hours stirring at 0°, the formation of the thioester II or the corresponding compound IIIa is complete (as determined by DC) and 260 g of 7-amino-3-pyridiniummethylcephalosporanic acid hydrochloride and 61 g of triethylamine are added at 0°. The mixture is stirred for 15 hours at 0° until the reaction is complete (as determined by HPLC) and the reaction mixture (yellow-brown) (ca. 1400 ml) is introduced into a mixture of 1400 ml of methanol and 3.5 litres of butylacetate at about 20°. The resulting clear solution is stirred at room temperature for 2 hours and then at 0° for a further 2 hours. The resulting highly crystalline precipitate is filtered off, washed with cold methanol and dried in vacuo. The highly pure (≥97%) by weight, free-flowing heading compound results.

Claims

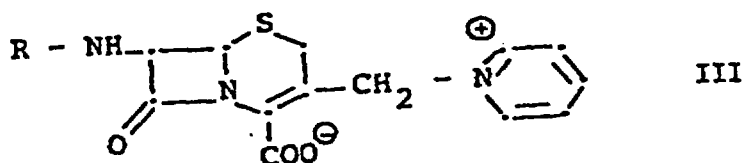
1. Crystalline (6R, 7R)-7-[[2-(2-Amino-4-thiazolyl)-(Z)-2-(1-diphenylmethoxycarbonyl-1-methylethoxy)-imino]acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate.
2. The product of claim 1 in a purity of at least 97%.
3. A process for the production of the product of claim 1 comprising reacting a compound of formula II or IIIa



in which



signify a 5- or 6-membered heterocyclic ring which may contain in addition to the nitrogen atom one or two further hetero atoms, and which may be substituted, and which may be fused to a benzene ring which may itself be substituted, with compound of formula III,



in which R is hydrogen or an amino protecting group, or a salt thereof, characterised by mixing the resulting reaction mixture with a mixture of an acetic acid C₂₋₄ alkyl ester and a C₁₋₂ alkanol in a ratio of 2-3:1 by volume at a temperature of from 0 to 40 °C, recovering the precipitated product.

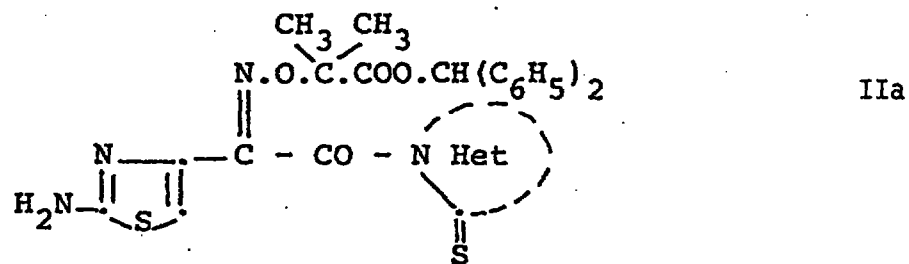
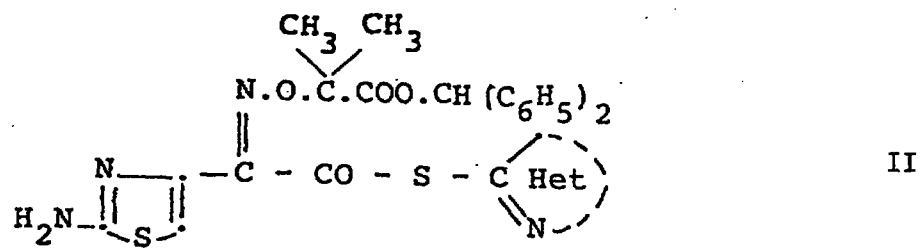
4. A process according to claim 3, in which the alkanol is methanol.

Patentansprüche

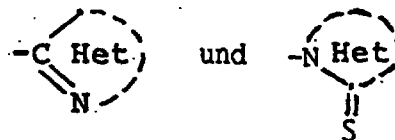
1. Kristallines (6R,7R)-7-[(2-(2-Amino-4-thiazolyl)-(Z)-2-(1-diphenylmethoxycarbonyl-1-methylethoxy)imino]-acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylat.
2. Das Produkt gemäss Anspruch 1 in einer Reinheit von mindestens 97%.



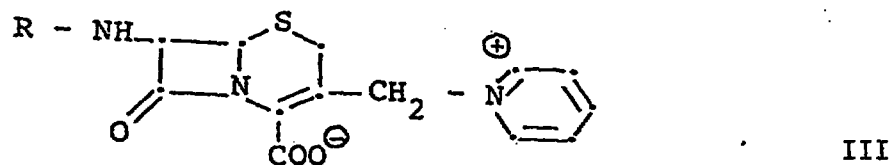
3. Verfahren zur Herstellung des Produktes gemäss Anspruch 1, umfassend die Umsetzung einer Verbindung der Formel II oder IIa



worin



für einen 5- oder 6-gliedrigen heterocyclischen Ring, der zusätzlich zu dem Stickstoffatom ein oder zwei weitere Heteroatome enthalten kann, und der substituiert sein kann und der mit einem gegebenenfalls substituierten Benzolring kondensiert sein kann, stehen, mit Verbindung der Formel III



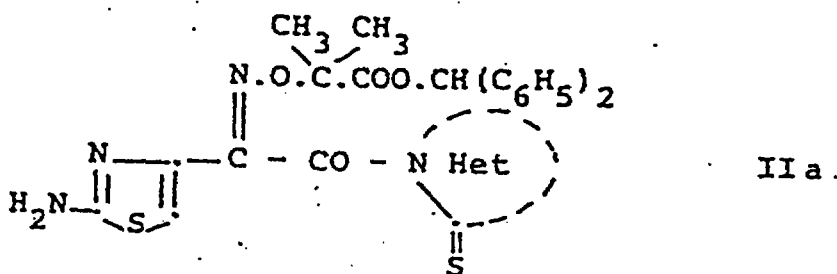
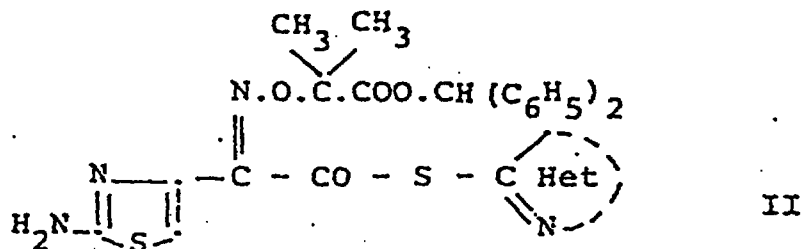
50 worin R für Wasserstoff oder eine Aminoschutzgruppe steht, oder dessen Salz, dadurch gekennzeichnet, dass man das erhaltene Reaktionsgemisch mit einem Gemisch von einem Essigsäure-C₂₋₄alkylester und einem C₁₋₂Alkanol in einem Verhältnis von 2-3:1:1 nach Volumen bei einer Temperatur von 0 bis 40 °C vermischt, das ausgefallene Produkt gewinnt.

- 55 4. Verfahren nach Anspruch 3, worin der Alkanol Methanol ist.

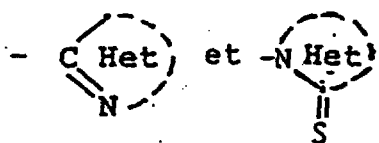
Revendications



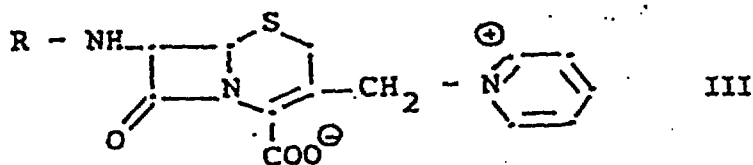
1. Le (6R,7R)-7-[[2-(2-amino-4-thiazolyl)-(Z)-2-(1-diphényl-méthoxycarbonyl-1-méthyléthoxy)imino]-acétamido]-3-(1-pyridinométhyl)-3-céphème-4-carboxylate cristallin.
2. Le produit selon la revendication 1 ayant une pureté d'au moins 97%.
3. Un procédé de préparation du produit selon la revendication 1, comprenant la réaction d'un composé de formule II ou IIa



où



signifient un hétérocycle à 5 ou 6 chaînons qui, en plus de l'atome d'azote, peut contenir un ou deux autres hétéroatomes et qui peut être substitué et peut être condensé à un cycle benzénique qui peut lui-même être substitué, avec un composé de formule III



dans laquelle R signifie l'hydrogène ou un groupe protecteur du groupe amino, ou un sel de ce composé, caractérisé en ce qu'on mélange le mélange réactionnel résultant avec un mélange d'un ester alkylique en C₂-C₄ de l'acide acétique et d'un alcool en C₁-C₂ dans un rapport de 2-3:1:1 en volume à une température comprise entre 0 et 40 °C, et on récupère le produit qui a précipité.

4. Un procédé selon la revendication 3, dans lequel l'alcool est le méthanol.