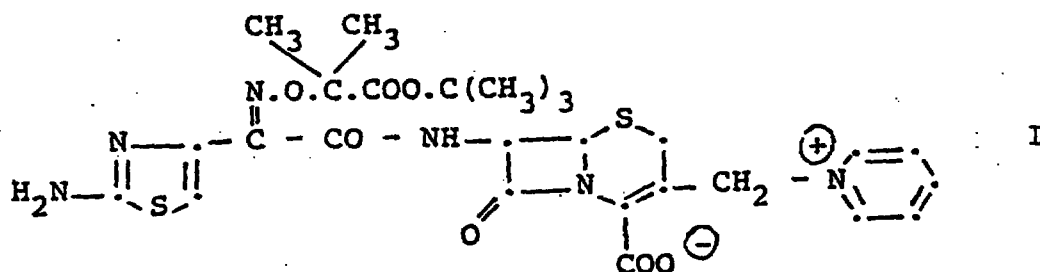


Stable crystalline form of an intermediate product of
cephalosporine

The invention relates to a new stable, crystalline form of (6R,7R)-7-[[2-(2-amino-4-thiazolyl)-(Z)-2-(1-tert.butoxycarbonyl-1-methylethoxy)imino]acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate (ceftazidime-t-butylester) of formula

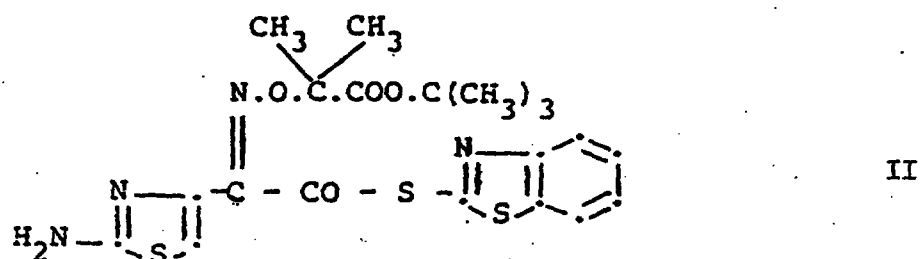


and processes for the production thereof.

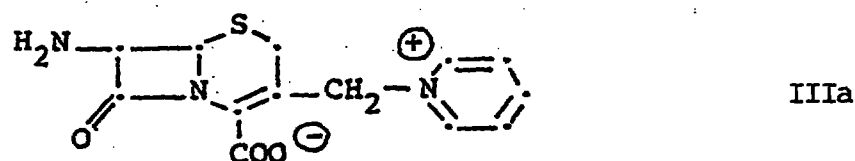
The compound of formula I is an important intermediate product in the production of ceftazidime. Ceftazidime is a highly active antibiotic, which has attained exceptional significance due to its broad spectrum activity against micro-organisms, especially in the gram-negative range, and is used as a parenteral pharmaceutical, in particular in hospitals, whereby its activity against problem bacteria, such as *Pseudomonas*, is also of importance.

Production of ceftazidime is usually effected via intermediate products which contain protecting groups on the amino group of the thiazole ring, on the carboxyl group in the side chain and sometimes also on the carboxyl group of the thiazolidine ring. These protecting groups are split off in one or several reaction steps.

Amongst these protected ceftazidime intermediate products the compound of formula I is especially noteworthy, since by its further processing to ceftazidime, e.g. by acid hydrolysis as a by-product only isobutene is obtained and ceftazidime may be isolated in high purity and a good yield. In WO 85/4659 is described an especially simple method of producing the compound of formula I by reacting the activated thiol ester of formula



in syn-form with the compound of formula



However, using the process of this application, the compound of formula I is only obtained in amorphous form which is difficult to isolate.

It has now been found that when using suitable solvents, the compound of formula I may be isolated from the reaction mixture in crystalline form and in good yield and purity, by means of simple filtration, whereby the by-products and impurities remain in solution.

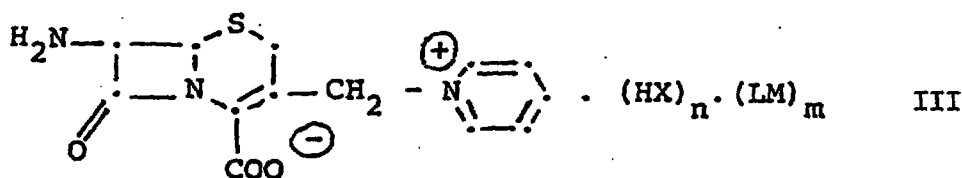
Suitable solvents are halogenated aliphatic hydrocarbons, e.g. dichloromethane or chloroform, lower aliphatic alcohols, e.g. methanol to n-butanol, lower aliphatic carboxylic acid esters, e.g. ethyl acetate or butyl acetate, dimethylformamide or dimethyl sulfoxide and mixtures of these solvents. Mixtures of lower alcohols, dimethylformamide or dimethyl sulfoxide on the one hand and aromatic hydrocarbons, e.g. benzene, toluene, chlorobenzene, or acetone or acetonitrile on the other hand may also be used as solvents. Preferred solvents are mixtures of dichloromethane, chloroform, butyl acetate, ethyl acetate or toluene on the one hand and methanol or dimethyl sulfoxide on the other hand. The ratios of the mixtures are normally between 20:1 and 1:20, and depend on the solubility of the end product.

The activated thiol ester of formula II is produced in known manner, e.g. by reacting the corresponding acid with bis-(benzothiazol-2-yl)disulfide and triphenylphosphine, whereby the reaction mixture may be used for the reaction with the compound of formula IIIa without isolating the thiol ester. The use of isolated thiol ester however gives better yields and purer products.

The compound of formula IIIa may be used as an inner salt or as the addition salt of an organic or inorganic acid. Solvates of these compounds may also be used. Examples of the employed forms of the compound of formula IIIa are dihydrate, monohydrochloride.monohydrate, dihydrochloride.dihydrate, hydriodide.monohydrate and oxalate. When using acid addition salts, an amount of a base (e.g. triethylamine), which is equivalent to the acid, must be added at latest prior to filtration of the product.

The compound of formula IIIa may therefore be defined in general

as follows:



whereby HX signifies an organic or inorganic acid, LM signifies water or an organic solvent and n and m are 0, 1 or 2.

The reaction temperatures are preferably between 0°C and room temperature. The reaction may however be carried out at lower or higher temperatures, whereby longer reaction times or increased secondary reactions would have to be taken into account.

Filtration of the product is normally carried out at the same temperature as the reaction; to raise the yield or to improve purity of the product, filtration may also be effected at a lower or higher temperature. For the same reasons (yield, purity), the reaction mixture may be diluted prior to filtration with a solvent which has already been used or with an additional solvent, or part of the solvent used may be distilled off.

As already mentioned, the ceftazidime-t-butylester is obtained in crystalline form in the form of small needles which are double refracting under the polarizing microscope. The crystallinity of the product was confirmed by measuring X-ray diffraction of a powder sample:

<u>d (Å)</u>	<u>I</u>
17.0	w
15.5	m
5.9	w
5.0	w
4.15	w
3.84	w
3.3	w

w = weak

m = medium

This crystalline form is referred to in the following as α -form. In the process according to the invention, this α -form is obtained in high yield but has relatively low storage stability. For example, if this product is stored for a few days at room temperature ($\sim 25^{\circ}\text{C}$), disintegration is observed. This ability to disintegrate (accompanied by the odour of pyridine) is undesirable, and leads apart from the problems of drying also to problems relating to increased expenditure during storage and further processing.

It has now also been found that the compound of formula I may also be obtained in another, more stable form and highest purity ($\geq 97\%$). This new crystalline modification, called the β -form in the following, may be produced from the amorphous form or also by modifying the isolation of the process for producing the α -form, without or with intermediate isolation of the α -form. The new modification exists as a crystalline powder, which under the polarisation microscope appears as small double refracting needles, and whose X-ray spectrum differs characteristically from that of the α -form:

<u>d (Å)</u>	<u>I</u>
22.0	m
10.0	w
8.5	m
7.3	w
6.7	m
5.9	md
5.6	m
5.3	wd
4.2	w
3.94	w
3.82	w
3.7	w
3.3	w

w = weak

m = medium

d = diffuse

This new β -form of the compound of formula I, is according to the present process of the invention, recovered from aqueous phase, whereby the aqueous phase may also contain solvents miscible with water.

The process according to the invention is characterised by transferring the compound of formula I, which is in the reaction mixture in amorphous form or in α -form, by extraction with water or with a mixture of water and a solvent which is miscible with water, whereby at least 50% water are used, at a pH value of less than 3, especially pH 1.0 to 2.0, into an aqueous phase which may also contain solvents miscible with water and crystallising the compound of formula I in β -form from this aqueous phase by adjusting the pH value to the region of the isoelectric point of the compound of formula I or above this value, that is to the

region of 3.5 to 7.5, especially to 4.2 to 5.2. The compound of formula I is thereby obtained in the form of a highly-crystalline, colourless deposit, which may be easily isolated by filtration. However, the isolated compound in amorphous form or in α -form may also be dissolved in water or in a mixture of water and one or several solvents which are miscible with water - advantageously in highly concentrated solution - optionally adding an acid up to about pH 2.0 or below this value, then the new crystalline β -form of the invention may be crystallised out by adjusting the pH value to 3.5 - 7.5, especially to 4.2 - 5.2, thereby obtaining a colourless crystalline deposit which may be easily isolated and represents the β -form of the compound of formula I of the invention in a highly pure form ($\geq 98\%$).

If, as described, the procedure starts with the amorphous or the isolated α -form, then it is not absolutely necessary to set the pH value to below 3.0, since the α -form also dissolves well in water or mixtures of water with solvents which are miscible with water in a neutral range or at pH values of between 3.5 and 7.5, but it may occur that the new β -form of the compound of formula I of the invention already begins to crystallise before all the α -form has gone into solution. This happens in particular when working in highly concentrated solutions ($> 10\%$) using pure water without adding solvents. In principle, it is not necessary for all the α -form to be brought into solution before the new β -form of the invention precipitates, since even when a intermediately clear solution has not been obtained, the starting material completely dissolves in the existing suspension (already-precipitated new β -form present) and is converted into the new β -form of the invention. For the sake of better control, especially on a larger scale, and in order to obtain a stable, clear solution (for possible filtration of foreign bodies or after adding adjuvants such as active charcoal etc. for

purification purposes), the preparation of a clear, stable solution (without having to expect the new β -form to crystallise out) is desirable. This may be achieved by adding an acid, whereby it is favourable to use at least 1 equivalent of acid, so that the compound of formula I is kept in solution as an acid adduct (salt). In order to obtain the desired new crystalline β -form of the invention, that amount of base which is required to neutralise the previously added acid is then added, whereby the new β -form of the compound of formula I may be crystallised from the aqueous solution and isolated.

As an acid, which is employed both during isolation from the reaction mixture, and for producing the new β -form by means of conversion from the isolated α -form, all conventional inorganic and organic acids, in particular sulfuric acid and hydrochloric acid, may be used. Hydrochloric acid is especially suitable.

As solvents which are miscible with water alcohols, acetone, acetonitrile and those in which the β -form of the compound of formula I of the invention does not dissolve or only dissolves poorly may be employed. As alcohols are therefore ethanol, isopropanol, n-propanol and also n-butanol suitable, while methanol is only suitable in small concentrations, since in higher concentrations, it increases the solubility of the new β -form of the compound of formula I too much. In general, the addition of solvents which are miscible with water is not necessary, and it is advantageous to use only water as the medium for extraction or reprecipitation, since the solubility of the new β -form of the compound of formula I of the invention is thus at its lowest, and thus the highest yields are obtained.

In the following examples, which illustrate the invention more fully, but in no way limit its scope, all temperatures are given

in degrees celsius. The specific optical rotation $[\alpha]_D^{20}$ was measured in water/methanol 1:1 at a concentration of 1 g/100 ml.

The identity of the products was checked by NMR: $^1\text{H-NMR}$ (90 MHz, $\text{DMSO-D}_6/\text{D}_2\text{O}/\text{DCL}$): 8.1 to 9.1 (5H, pyridinium); 7.15 (1H, s, thiazole); 5.92 (1H, d, $J = 5 \text{ Hz}$, H_7); 5.6 (2H, $\text{CH}_2\text{-N}$); 5.32 (1H, d, $J = 5 \text{ Hz}$, H_6); 3.6 (2H, S-CH_2); 1.55 (6H, s, $\text{C}(\text{CH}_3)_2$); 1.40 (9H, $\text{C}(\text{CH}_3)_3$).

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

12 g of 2-(2-Amino-4-thiazolyl)-(Z)-2-[(1-tert.butoxycarbonyl-1-methylethoxy) imino]thioacetic acid-S-benzothiazol-2-yl-ester, 7.7 g of (6R, 7R)-7-amino-3-(1-pyridiniummethyl)-3-cephem-4-carboxylic acid.chloride.monohydrate and 3.8 ml of triethylamine are stirred for 10 hours at 0° in a mixture of 75 ml of dichloromethane and 5 ml of methanol. The solid substance is filtered off, washed with dichloromethane and dried in vacuum at room temperature. 10.5 g of the title compound are obtained in the form of a colourless crystal powder (=78% of theory). Purity: 97%, $[\alpha]_D^{20} = -36.4^\circ$.

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

A preparation as in example 1 is stirred for 4 hours at room temperature in 80 ml of dichloromethane. The reaction suspension is heated to 40° and the solid substance filtered off. 10 g of the title compound are obtained (= 75% of theory) in crystalline

form. Purity: 95%; $[\alpha]_D^{20} = -36.2^\circ$.

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

A preparation as in example 1 is stirred in 50 ml of methanol for 20 hours at 0° and then for 2 hours at -20° . The solid substance is isolated as in example 1. 9 g of the title compound are obtained (67% of theory) in crystalline form. Purity: 98%; $[\alpha]_D^{20} = -35.6^\circ$.

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

The reaction is carried out as in example 1, but in a mixture of 70 ml of dichloromethane and 10 ml of dimethyl sulfoxide. 8 g of the title compound are obtained (60% of theory) as crystals. Purity: 95%; $[\alpha]_D^{20} = -35.8^\circ$.

Example 5: (6R,7R)-7-[[2-(2-Amino-4-thiazolyl)-(Z)-2-(1-tert.-butoxycarbonyl-1-methylethoxy) imino]acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate (α -form):

2.4 g of 2-(2-Amino-4-thiazolyl)-(Z)-2-[(1-tert.butoxycarbonyl-1-methylethoxy) imino]thioacetic acid-S-benzothiazol-2-yl-ester and 1.3 g of (6R,7R)-7-amino-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate.monohydrate are stirred for 6 hours at 0° in a mixture of 15 ml of dichloromethane and 5 ml of methanol. The solid substance is isolated as in example 1. 1.9 g of the title

compound are obtained (75% of theory) in crystalline form.

Purity: 98%; $[\alpha]_D^{20} = -36.5^\circ$.

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

19.1 g of 2-(2-Amino-4-thiazolyl)-(Z)-2-[(1-tert.butoxycarbonyl-1-methylethoxy)imino]thioacetic acid-S-benzothiazol-2-yl-ester, 14.6 g of (6R,7R)-7-amino-3-(1-pyridiniummethyl)-3-cephem-4-carboxylic acid.iodide.monohydrate and 5.6 ml of triethylamine are stirred for 24 hours at 0° in a mixture of 142.5 ml of dichloromethane and 7.5 ml of methanol. The solid substance is filtered off, washed with dichloromethane and dried in vacuum at room temperature. 16.0 g of the title compound are obtained (=79.6% of theory) in crystalline form.

Purity: 97%; $[\alpha]_D^{20} = -36.7^\circ$.

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

40 g of (6R,7R)-7-[[2-(2-Amino-4-thiazolyl)-(Z)-2-(1-tert.-butoxycarbonyl-1-methylethoxy)imino]acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate (α -form) are dissolved in 400 ml of water. This solution is seeded with crystals of the β -form, whereby a colourless crystalline deposit is formed. After cooling to about $+4^\circ$, the crystals are isolated, and after washing with water and drying, 27 g of the β -form are obtained.

Example 8: (6R,7R)-7-[[2-(2-Amino-4-thiazolyl)-(Z)-2-(1-tert.-butoxycarbonyl-1-methylethoxy)imino]acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate (β -form)

24 g of 2-(2-Amino-4-thiazolyl)-(Z)-2-[(1-tert.butoxycarbonyl-1-methylethoxy)imino]thioacetic acid-S-benzothiazol-2-yl-ester, 15.4 g of (6R,7R)-7-amino-3-(1-pyridiniummethyl)-3-cephem-4-carboxylic acid.chloride and 7.6 ml of triethylamine are stirred for 20 hours at 0° in a mixture of 150 ml of dichloromethane and 5 ml of methanol. Then, 100 ml of water and 20 ml of conc. HCl are added to the reaction mixture, and the phases are separated. The cold aqueous phase is filtered, and then the pH value of the solution is adjusted to 4.8 - 5.0 with 3N NaOH, whereby the temperature rises to 20 - 22° and the title compound crystallises out. After cooling to about 4° for 2 hours, the crystals are filtered off, washed with a little cold water, and after drying in vaccum, 16 g of the title compound are obtained in β -form.

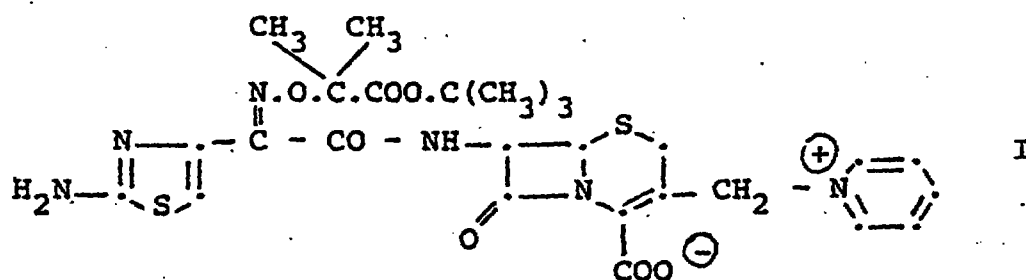
Example 9: (6R,7R)-7-[[2-(2-Amino-4-thiazolyl)-(Z)-2-(1-tert.-butoxycarbonyl-1-methylethoxy)imino]acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate (β -form):

70 g of (6R,7R)-7-[[2-(2-Amino-4-thiazolyl)-(Z)-2-(1-tert.-butoxycarbonyl-1-methylethoxy)imino]acetamido]-3-(1-pyridinium-methyl)-3-cephem-4-carboxylate (α -form; 85%) are added to a mixture of 25 ml of conc. HCl and 500 ml of ice water. A clear solution of about pH 1.5 is obtained. The pH value is then adjusted to 4.8 - 5.0 with 2 N NaOH, and the temperature thereby rises to 18-22°. The title compound crystallises in the form of a colourless deposit. Cooling is subsequently effected for 2 hours to +4°, and then the crystals are isolated, washed with cold

water (100 ml) and the water moist cake is dried on a fluidised bed with air of 45 - 50°. In this way, 52 g of highly pure ($\geq 98\%$) title compound of the β -form are obtained with a H₂O content of 8.6%.

Claims:

1. New crystalline, stable form of (6R,7R)-7-[[2-(2-amino-4-thiazolyl)-(Z)-2-(1-tert.butoxycarbonyl-1-methylethoxy)imino]acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate (ceftazidime-t-butylester) of formula



having the X-ray spectrum

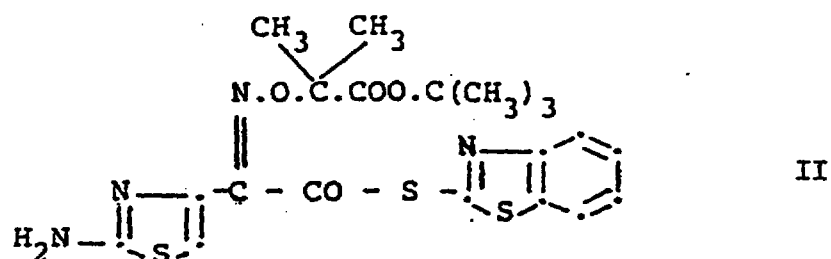
d (Å)	I	
17.0	w	
15.5	m	w = weak
5.9	w	m = medium
5.0	w	
4.15	w	
3.84	w	
3.3	w	

(α -form).

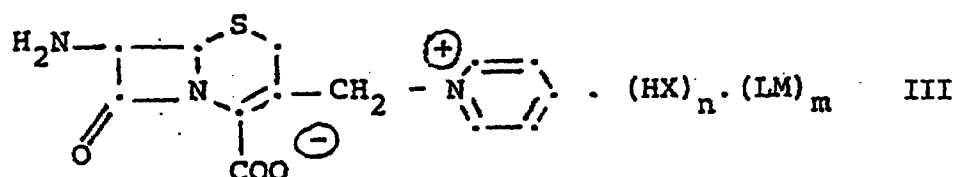
2. Process for the production of a new crystalline, stable form of (6R,7R)-7-[[2-(2-amino-4-thiazolyl)-(Z)-2-(1-tert.butoxycarbonyl-1-methylethoxy)imino]acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate (α -form) according to claim 1,



by reacting the compound of formula



in syn-form with a compound of formula



whereby HX signifies an inorganic or organic acid, LM denotes water or an organic solvent, and n and m are 0, 1 or 2, optionally adding a base, characterised in that the reaction is carried out in a solvent or solvent mixture in which the compound of formula I is poorly soluble, for example halogenated hydrocarbons, lower aliphatic carboxylic acid esters, lower aliphatic alcohols, dimethylformamide or dimethyl sulfoxide or mixtures of these solvents, and the compound of formula I is filtered off from the reaction mixture directly after the reaction.

3. Process according to claim 2, characterised in that as solvents mixtures of lower aliphatic alcohols, dimethylformamide or dimethyl sulphoxide on the one hand and



aromatic hydrocarbons, acetone or acetonitrile on the other hand are used.

4. Process according to claim 2, characterised in that mixtures of dichloromethane and methanol are used.
5. New crystalline, stable form of (6R,7R)-7-[[2-(2-amino-4-thiazolyl)-(Z)-2-(1-tert.butoxycarbonyl-1-methylethoxy)imino]-acetamido]-3-(1-pyridiniummethyl)-3-cephem-4-carboxylate (ceftazidime-t-butylester) of formula I, as defined in claim 1, having the X-ray spectrum

<u>d (Å)</u>	<u>I</u>	
22.0	m	
10.0	w	w = weak
8.5	m	m = medium
7.3	w	d = diffuse
6.7	m	
5.9	md	
5.6	m	
5.3	wd	
4.2	w	
3.94	w	
3.82	w	
3.7	w	
3.3	w	

(β -form).

6. Process for the production of the new crystalline, stable form of the compound of formula I (β -form) according to claim 5, characterised in that the compound of formula I is crystallised from an aqueous solution at pH 3.5 - 7.5.



7. Compound of formula I according to claim 1 or 5 for use as intermediate product for the production of ceftazidime.

