

Case 970-9731/PCT/II

Cephalosporins are valuable antibiotics used in human medicine. A group of these compounds (e.g. Cefalotin, Cefotaxime) is derived from the basic structure 7-aminocephalosporanic acid (7-ACA). 7-ACA may easily be prepared by fermentation of Cephalosporin C, subsequent isolation of the natural product and splitting off of the side chain, and is a readily obtainable commercial product.

A further, substantially larger group of the cephalosporins therapeutically used today is, however, derived from 7-aminocephalosporanic acids having a different substituent in position 3 than 7-ACA (e.g. Cefaloridin, Cefamandole, Cefazolin, Cefoperazone, Ceftazidime, Ceftriaxone, Cefmenoxime, Cefonicid). For the production of such compounds, generally an exchange of the substituents in the 3-position of 7-ACA is to be carried out initially and the 3-substituted 7-ACA must be isolated. A further step results in the acylation of position 7 and isolation of the desired cephalosporin antibiotic.

The reaction may also be carried out in reverse, namely the 7-ACA is first acylated with the desired group in position 7 and subsequently the acyl derivative of 7-ACA is isolated. Subsequent exchange in aqueous buffer systems usually results in the desired cephalosporin end-product.

Both reactions have limitations, namely they do not allow random execution with every combination of desired substituents in the 3- or 7-position. In any case the acylation/exchange and/or isolation is to be carried out in protic medium. If the side chain in the 7-position itself contains an acylatable or activatable function, this group is first to be protected by a selected protecting group and after isolation of the desired cephalosporin end-product, these protecting groups must again be split off.

The prior art concerning the production of such compounds describes essentially three processes, which, however, all have certain disadvantages. Thus DOS 2,804,896 (TOYAMA) describes the reaction of 7-aminocephem(3)-4-carboxylic acids with Lewis

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acids or protonic acids in excess, whereby preferably boron trifluoride is used. It is known that such reagents are extremely toxic and cause environmental problems and further that β -lactams are unstable under strongly acidic conditions in protic media.

A second process describes the exchange reaction in position 3 in aqueous buffer systems (USP 3,516,997). This process gives low yields because under the conditions used (7-ACA + heterocyclic thiole) cephalosporins are decomposed to a substantial extent in buffer solutions between pH 5 and 9 and therefore the title compounds are obtained in insufficient purity.

A third process describes splitting off the acyl groups of the side chain in position 7 of a cephalosporin which already has the correct substituent in position 3 (e.g. USP 4,369,313). For the production of the starting materials used in this patent, 7-ACA must, however, firstly be acylated in position 7, then the exchange in position 3 is to be undertaken, and finally the side chain in position 7 must be split off. Seen overall, this reaction series must be considered uneconomic on the yield from 7-ACA.

In DE-A-3 316 798, Hoechst AG, there is described a process for the preparation of 7-aminocephalosporanic acid which is substituted in position 3 by a base, by addition of the corresponding base to 7-aminocephalosporanic acid and thereafter adding trimethyliodosilane in a diluent and refluxing, or by refluxing of the base with trimethyliodosilane in a diluent, addition of 7-aminocephalosporanic acid and further refluxing. The yields of this process are, however, in many cases unsatisfying.

In EP-A-0 154 417, Yamanouchi Pharmaceutical Co. Ltd., which is a publication under Art. 54(3) EPC for the contracting states Germany, France, Great Britain and Italy, it is disclosed that 7-aminocephalosporanic acid firstly might be iodinated in position 3 and thereafter silylated in positions 7 and 3 by use of a silylation agent. According to the description it is assumed, that 7-trimethylamino-3-iodomethylcephem(3)-4-carboxylic acid trimethylsilylester is obtained as intermediate. It was, however, found that in this kind of reaction process mixtures of the mono- and bissilylated compound are obtained, which are practically inseparable and which contain the bissilylated compound to an extent of



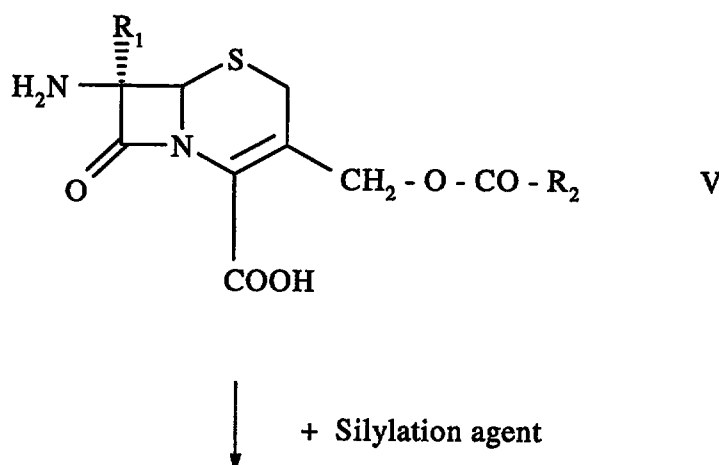
approximately 64% only.

It was now unexpectedly found that a pure 7-trialkylamino-3-iodomethylcephem(3)-4-carboxylic acid trialkylsilyl ester is a particular useful intermediate in the production of 7-aminocephalosporanic acids which are substituted in position 3 by a base and that high yields in the substitution reaction of the iodo atom of 7-trimethylamino-3-iodomethylcephem(3)-4-carboxylic acid trimethylsilyl ester in position 3 by a base is essentially dependent on the purity of the ester and that 7-trialkylamino-3-iodomethylcephem(3)-4-carboxylic acid trialkylsilyl ester may be obtained by iodination of 7-trialkylsilylaminocephalosporanic acid trialkylsilyl ester with trialkyliodosilane in high purity.

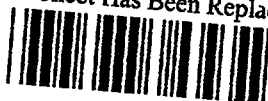
According to the present process, 7-ACA or a derivative thereof is converted in its N,O-bissilylated derivative, which is reacted with a trialkyliodosilane to give the 3-iodomethyl derivative. This derivative is converted into the desired 3-substituted derivative of the N,O-bissilylated 7-ACA by addition of a nucleophilic reagent. The 3-substituted derivative is either deprotected or reacted with an acylating agent, thus introducing the desired acyl group in position 7, and deprotected, thus terminating the reaction.

The complete process may be carried out without isolating any of the intermediates.

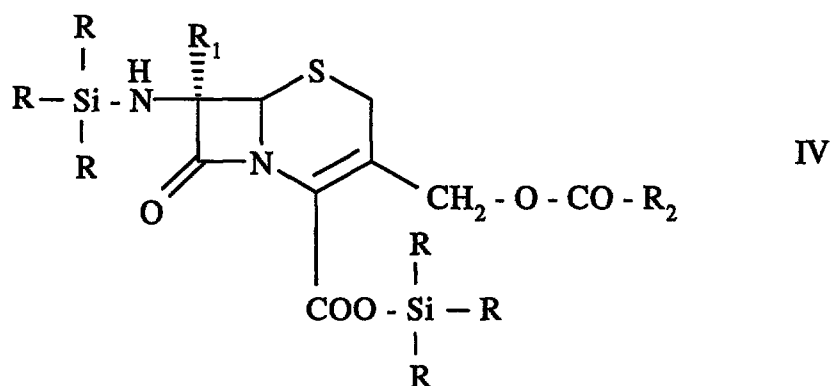
The process may be described by the following general reaction scheme:



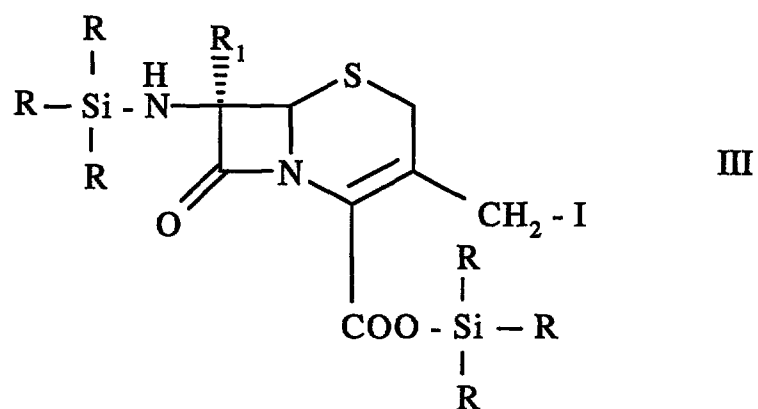
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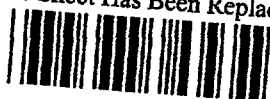


+ iodination agent

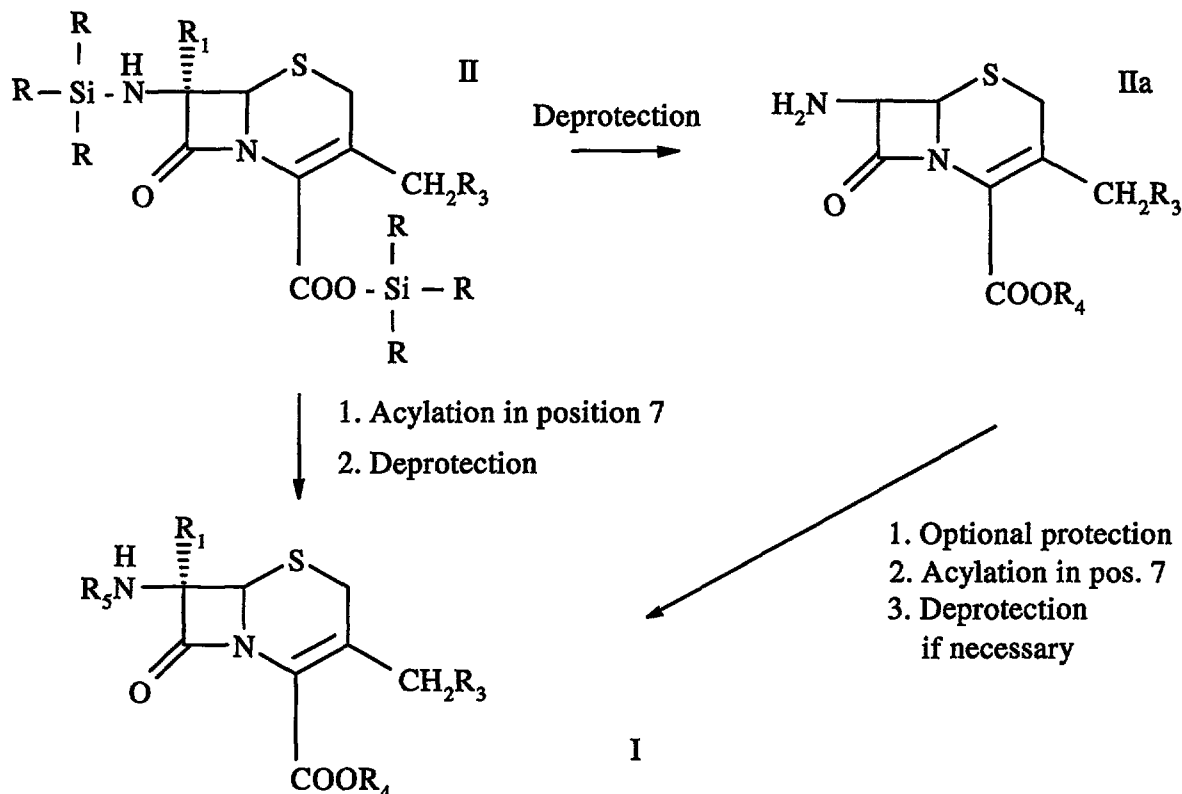


nucleophilic exchange
in position 3

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In formulae I to V, R_1 denotes hydrogen or the methoxy group, R_2 the methyl or amino group, R a lower alkyl group and R_4 hydrogen, alkali or a negative charge, or OR_4 denotes halogen. R_5 signifies an acyl group conventional in cephalosporin chemistry. R_3 denotes the residue of a nucleophile. The invention relates particularly to steps III to II; and the series III to II to IIa; III to II/IIa $\rightarrow$ I.

This process may for example be carried out as follows:

A 7-aminocephem(3)-4-carboxylic acid of formula V, preferably 7-ACA, is suspended in a solvent which is inert under the reaction conditions and refluxed in the presence of an excess of a silylating agent. Halogenated hydrocarbons, such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2-trichloroethane and tetrachloroethylene, organic nitriles, such as acetonitrile, propionitrile, nitroalkanes as nitromethane, or sulfones, such as sulfolan, come into question as the solvent for this silylation reaction. The silylation



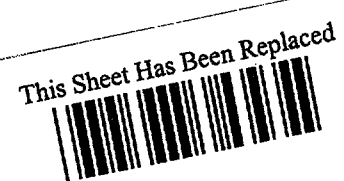
reaction may either be carried out with high-boiling solvents, by heating to the appropriate temperatures or with low-boiling solvents using a special catalysis of an organic oxygen acid, e.g. squaric acid, trifluoroacetic acid or mixtures thereof. Conventional silylating agents, such as hexamethyldisilazane, trimethylchlorosilane, bis-trimethylsilurea, N-trimethylsilyldialkylamine, or bis- or monosilylated acetamides, or mixtures of these reagents may be used in this reaction. It is preferred that the bis-silylation proceeds to 100 %, because small amounts of the monosilyl derivative may disturb the further reaction substantially. The reaction of the resulting compound of formula IV is for example undertaken in a manner such that 1.1 to 1.5 equivalents of trialkyliodosilane, e.g. trimethyliodosilane are added to the obtained reaction mixture and the reaction is carried out at temperatures of from -20 to +50 °C, preferably at 0 to 45 °C. It is surprising that a compound of the structure of 3-iodomethyl-N,O-bis-trialkylsilyl-7-aminocephalosporanic acid is stable. With certain similar structures, which are described in literature, excessive self-alkylation on the nitrogen occurs. (DOS 3,212,900 YAMANOUCHI). The fact that the N,O-bis-trialkylsilyl-3-iodomethyl-7-aminocephalosporanic acids of the invention are stable may be attributed to steric hindrance of the trialkylsilyl group on the nitrogen. It is therefore essential that pure bis-silyl compound is present, because the presence of monosilyl compounds results in excessive decomposition and polymerisation.

Bis-trimethylsilyl-3-iodomethyl-7-aminocephem(3)-4-carboxylic acids of formula III may be isolated, by removal of the excess solvent and trialkyliodosilane *in vacuo*, in pure form and characterised by means of the NMR spectrum.

The cephalosporin derivatives of formula III may easily be converted into 3-substituted 7-aminocephem(3)-4-carboxylic acids of formulae II or IIa, whereby the compounds of formula III need not to be isolated, namely by a reaction with a nucleophile such as

- a) a tertiary (nitrogen) heterocycle (e.g. pyridine, quinoline) or a tertiary aliphatic or cycloaliphatic amine, e.g. N-ethylpiperidine or N-methylpyrrolidine, or
- b) a thiolate anion of a mercapto-substituted heterocycle or the free mercapto heterocycle and an acid binding agent, or

- c) a secondary nitrogen-bearing heterocycle,
and optionally simultaneous or subsequent deprotection.



As reaction partners for the compounds of formula III, the following come into question in particular:

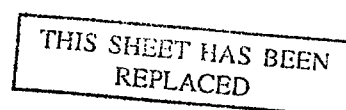
- a) aromatic nitrogen bases, such as pyridine, quinoline, which may be further substituted by one or more substituents; aliphatic trialkylamines, whereby alkyl preferably means C_1-C_4 , and carbocyclic, saturated or unsaturated tertiary amines, e.g. N-ethylpiperidine, N-methylpyrrolidine, quinuclidine, etc.
- b) Salts of mercapto-substituted heterocycles or the free mercapto compounds in the presence of acid binding agents,
- c) Heterocycles which have a secondary alkylated nitrogen, e.g. triazoles, tetrazoles, pyrazoles, pyrrolidines, imidazoles.

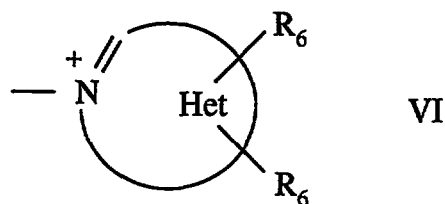
These reactions with the above reaction partners can be carried out in the above mentioned solvents at temperatures of from -78 to $+70$ °C, preferably -50 to $+40$ °C. In the case of difficult solubility of a reaction partner in the above mentioned solvents, an absolutely dry aprotic polar solvent, e.g. DMF, HMPT, may be added as required.

Finally, for the production of compounds of formula I, the desired acyl group in position 7 may be introduced, and, if present, the silyl groups split off, in the same reaction mixture, by methods known *per se*.

For the acylation, compounds of formula II or IIa, in which R_1 is as defined above and R_3 has the following significance are preferably prepared in the reaction mixture:

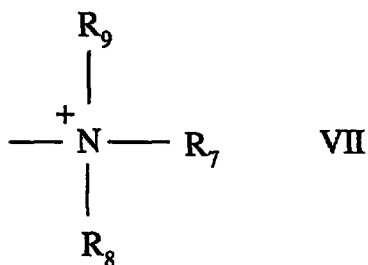
- a) an aromatic nitrogen base of formula





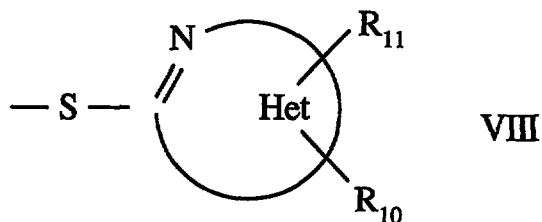
in which Het denotes pyridine, quinoline, pyrimidine or thiazole and R_6 denotes carboxy, carbamido, a sulfonic acid residue or a substituent conventional in β -lactam chemistry, or, both R_6 form an optionally substituted carbocyclic ring, or

b) an aliphatic or cycloaliphatic nitrogen base of formula



wherein the substituents R_7 , R_8 and R_9 may be the same or different and each denote a lower alkyl or lower alkenyl group, or R_7 and R_8 together with the nitrogen atom denote a five- or six-membered saturated or unsaturated carbocyclic ring substituted by R_9 , which may additionally denote a 1,3- or 1,4-alkylene or vinylene bridge, or

c) an optionally substituted heterocyclic thiole group of formula



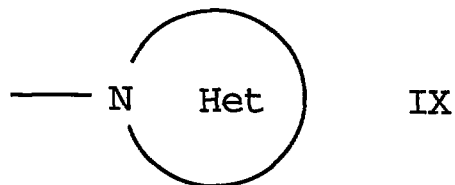
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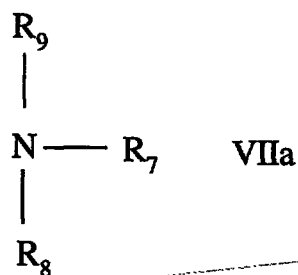
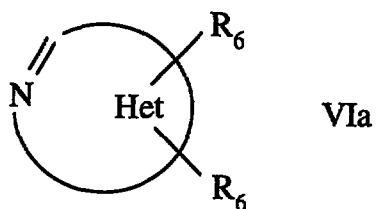
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wherein Het denotes a five- or six-membered heterocycle, and R_{10} and R_{11} denote alkyl, halogen or alkenyl, in which an alkyl group may be further substituted by sulfonic acid groups, acylamino, dialkylamino, oxo or hydroxy or

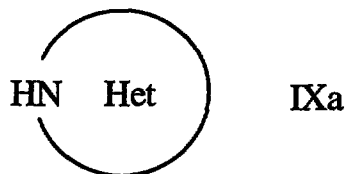
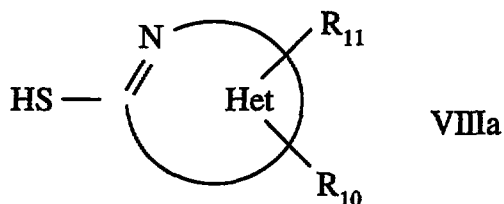
d) a group of formula



in which Het signifies tetrazole, triazole, imidazole, pyrrolidine or pyrazole, which may be substituted by a lower alkyl group. These compounds may be obtained by addition of a compound of formula:



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in which R_6 to R_{11} and Het are as defined above, to the reaction mixture which contains a compound of formula II or IIa.

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In the following Examples which should illustrate the invention without, however, limiting its scope, all temperatures are given in degree Celsius.

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Example 1: 7-Trimethylsilylamino-3-iodomethylcephem(3)-4-carboxylic acid trimethylsilyl ester (compound of formula III)

a) 7-Trimethylsilylamino-3-acetoxymethylcephem(3)-4-carboxylic acid trimethylsilyl ester (Formula IV):

To a boiling suspension of 2.5 g of 7-aminocephalosporanic acid, 1.75 ml trichlorosilane and 7.56 ml hexamethyldisilazane in 100 ml of dry chloroform are added 45 mg of squaric acid and the mixture is boiled under a nitrogen atmosphere overnight under reflux. The clear solution is evaporated to dryness *in vacuo*, whereupon the 7-trimethylsilyl-aminocephalosporanic acid trimethylsilylester is obtained in solid form. Because of extreme hydrolysability, no melting point determination may be carried out; characterisation is effected by NMR-spectroscopy.

^1H NMR: 0.15 (9H, N-Si $\equiv$); 0.36 (s, 9H -CO₂Si $\equiv$); 1.43 (d, J = 12 Hz, 1H, NH); 2.09 (s, 3H, O-C-CH₃); 3.46 (AB, J = 18 Hz, 2H, C₂-H); 4.60 - 5.28 (m, 4H, CH₂-I, C₆-H, C₇-H).

b) 7-Trimethylsilylamino-3-iodomethylcephem(3)-4-carboxylic acid trimethylsilyl ester (Formula III):

N,O-bissilylated 7-ACA [prepared as described under a)] is dissolved in 125 ml of dry dichloromethane, the solution is cooled to 0 ° and 1.87 ml of trimethyliodosilane are added dropwise. The solution is allowed to cool to room temperature and is stirred for 2 hours. After evaporation of the solvent *in vacuo*, the title compound is obtained in solid form, which because of high hydrolysis sensivity is characterised only by NMR-spectroscopy.

^1H NMR (CDCl₃): 0.125 (b, 9H, N-Si $\equiv$); 0.38 (s, 9H, -CO₂Si $\equiv$); 1.55 (d, J = 12 Hz, 1H, NH); 3.50 (AB, J = 18 Hz, 2H, C₂H); 4.39 (AB, J = 9 Hz, 2H, -CH₂-I); 4.58 (d, d, J = 12 Hz, 4,5 Hz, 1H, C₇-H); 4.71 (d, J = 4,5 Hz, 1H, C₆-H).

The following 3-substituted derivatives may for example be prepared from the 7-

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trimethylsilylamino-3-iodomethylcephem(3)-4-carboxylic acid trimethylsilyl ester:

**Example 2: 7-Amino-3-pyridiniummethylcephem(3)-4-carboxylic acid hydroiodide
(Formula IIa):**

To the solution of the title compound of example 1 are added under ice-cooling 1.47 ml of pyridine, and the solution is stirred thereafter for 2 hours at room temperature. By addition of 1.7 ml of methanol to the solution, the crude 7-amino-3-pyridiniummethylcephem(3)-4-carboxylic acid is precipitated as the hydroiodide. Treatment of the solid material in water yields the pure title compound. M.p. 145 ° (decomp.).

¹HNMR (D₂O, K₂CO₃): 3.38 (AB, J = 18 Hz, 2H, C₂-H); 4.80 (d, J = 5.8 Hz, 1H, C₇-H); 5.10 (d, J = 5.8 Hz, 1H, C₆-H); 5.43 (AB, J = 17 Hz, 2H, CH₂-N⁺≡); 8.0 - 8.2 (m, 2H, pyridine 3H's); 8.41 - 8.63 (m, 1H, pyridine-C₄-H); 8.93 (d, J = 6.3 Hz, 2H, pyridine-2H's).

**Example 3: 7-Amino-3-[5-(1,2,3-triazolyl)thiomethyl] cephem(3)-4-carboxylic acid
(Formula IIa):**

To the solution of the title compound of example 1 in dichloromethane are added at 0° 5 ml of N,N-dimethylformamide and 2.26 g of 5-mercapto-1,2,3-triazole/Na-salt and the solution is stirred for 2 hours at room temperature. 5 ml of methanol are added under ice-cooling whereupon the title compound precipitates. This is dissolved in 6 N HCl and the pH is adjusted to 1 with conc. NaOH whereupon the title compound again precipitates out. Decomp. point > 190°.

NMR (DMSO; CF₃CO₂H): 3.28 (AB, J = 18 Hz, 2H); 3.95 (AB, J = 12.6 Hz, 2H); 4.76 (d, J = 5.7 Hz, 1H); 4.97 (d, J = 5.7 Hz, 1H); 7.9 (s, 1H).

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Example 4: 7- β -Amino-3-(2-dehydroquinuclidinium)methylcephem(3)-4-carboxylate dihydrochloride (Formula IIa):

2.22 g of 7-aminocephalosporanic acid are, as described in example 1, reacted to 7-trimethylsilylamino-3-iodomethylcephem(3)-4-carboxylic acid trimethylsilyl ester. To this solution in dichloromethane are added under ice-cooling 1 g of 1-aza-bicyclo[2.2.2]oct-2-ene and the mixture is stirred for 2 hours at room temperature. The crude product is precipitated by addition of 2 ml of saturated etheric HCl. The crude product is dissolved in dilute aqueous HCl and precipitated with isopropanol. A colourless powder results. Decomp. from 140°.

¹HNMR (D₂O): 1.70 - 2.50 (m, 4H); 3.0 - 5.2 (m); 3.76 and 4.10 (AB, J = 19 Hz, 2H); 5.34 (d, J = 6 Hz, 1H); 5.53 (d, J = 6 Hz, 1H); 6.70 - 7.3 (m, 2H).

Example 5: 7- β -Amino-3-(N-methylpyrrolidinium)methylcephem(3)-4-carboxylate. hydrochloride (Formula IIa):

10.88 g of 7-aminocephalosporanic acid are converted as described to 7-trimethylsilylamino-3-iodomethylcephem(3)-4-carboxylic acid trimethylsilyl ester. To the solution of this compound in 120 ml of dichloromethane are added slowly at -60° 4.15 ml of N-methylpyrrolidine, and the mixture is stirred for 90 minutes at this temperature. The reaction mixture is poured onto 100 ml of ethanol, mixed with some HCl gas. Subsequently, the pH of the suspension is adjusted to 2.5. After standing overnight, the solid residue is isolated. It is suspended in 20 ml of water and the pH is adjusted to 0 with concentrated HCl. 5 g of activated charcoal are added, the mixture is stirred for 5 minutes and the insolubles and activated charcoal are filtered off. The pH of the colourless aqueous solution is adjusted to 2.5 with 5 N NaOH and 200 ml of acetone are slowly added to the solution. After standing for 2 hours in a refrigerator, the precipitate is isolated over a suction filter and washed with acetone and ether. After drying in the drying chamber, a colourless powder is obtained. Decomp. point 115 °. Yield: 5.6 g (42 % of theory).

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^1H NMR ($\text{CF}_3\text{CO}_2\text{D}+\text{D}_2\text{O}$): 5.48 (1H, d, $J = 5.2$ Hz, $\text{C}_7\text{-H}$); 5.31 (1H, d, $J = 5.2$ Hz, $\text{C}_6\text{-H}$); 4.73 (2H, AB, $J = 13$ Hz; $\text{CH}_2\text{-N-}$); 4.1-3.47 (6H, m, $\text{C}_2\text{-H}$ and N-methyl-pyrrolidine-H); 3.15 (3H, s, $\text{CH}_3\text{-N-}$); 2.37 (4H, b, N-methyl-pyrrolidine-H).

Compounds of formula I may be obtained as follows:

Example 6: (6R,7R)-7-[2-(2-Amino-4-thiazolyl)]-(Z)-2-[(1-diphenylmethoxycarbonyl-1-methylethoxy)imino] acetamido-3-(1-pyridiniummethyl)cephem(3)-4-carboxylic acid chloride. hydrochloride (Formula I):

To a boiling suspension of 2.5 g of 7-ACA, 1.75 ml of trichlorosilane and 7.65 ml of hexamethyldisilazane in 100 ml of dry chloroform are added 45 mg of squaric acid and the mixture is boiled under a nitrogen atmosphere overnight under reflux. The clear solution is then evaporated to dryness, whereupon the 7-trimethylsilylaminocephalosporanic acid trimethylsilyl ester precipitates in solid form. This is dissolved in 125 ml of dry dichloromethane, the mixture is cooled to 0° and 1.87 ml of iodotrimethylsilane are added dropwise. The solution is allowed to cool to room temperature and is stirred for 2 hours. To the resulting 7-trimethylsilylamino-3-iodomethylcephem(3)-4-carboxylic acid trimethylsilyl ester are added 1.47 ml of dry pyridine and the mixture is stirred for 2 hours at room temperature. To this solution are then added 5.41 g of 2-(2-amino-4-thiazolyl)-(Z)-2-[(1-diphenylmethoxycarbonyl-1-methylethoxy)imino]-thioacetic acid-S-benzothiazol-2-yl ester and the mixture is stirred for 2 days at room temperature. The reaction mixture is then transferred into a 50° solution of 4.5 ml of concentrated hydrochloric acid in 500 ml of isopropanol, whereupon the title compound precipitates. This is filtered off by a suction and washed with isopropanol. After drying and recrystallisation from aqueous HCl/isopropanol, the title compound is obtained as a yellowish product. m.p (decomp.) from 160° .

^1H NMR (DMSO-d_6): 9.84 (1H, d, -N-H, $J = 8$ Hz); 9.20, 8.67 and 8.23 (5H, pyridinium-H); 7.28 (10H, phenyl-H); 6.98 (1H, s, thiazolyl-H); 6.79 (1H, s, CH-Ph_2); 5.95 (1H, dd, H_7 , $J = 8$ Hz, $J = 5$ Hz); 5.72 (2H, $\text{CH}_2\text{-pyridine}$); 5.27 (1H, d, H_6 , $J = 5$ Hz); 3.57 (2H, H_2 and H_2'); 1.63 (6H, $-\text{C}(\text{CH}_3)_2$).

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Example 7: 7-[α -(Ethoxycarbonylmethoxy)imino-1H-pyrazol-3-yl]acetamido-3-[(1-methyl-1H-tetrazol-5-yl)thiomethyl]cephem(3)-4-carboxylic acid. ethanol-solvate (Formula I):

To a solution of 3.82 g of 7-trimethylsilylamino-3-iodomethyl-3-cephem-4-carboxylic acid trimethylsilyl ester (prepared as described in examples 1 or 6) in 125 ml of dry dichloromethane are added 5 ml of dimethylformamide and 1.4 g of 1-methyl-5-mercapto-1,2,3,4-tetrazole sodium salt and the solution is stirred for 2 hours at room temperature. 4.16 g of crystalline (methoxycarbonylmethoximino)-1H-pyrazol-3-yl-acetic acid-mercaptobenzthiazolyl ester are then added and the reaction mixture is stirred overnight at room temperature. The charge is stirred into 350 ml of ethanol pre-warmed to 55° and is slowly cooled to 30°. By seeding with the title compound, the title compound precipitates in crystalline form and is filtered off and dried.
m.p 119 - 121°.

Example 8 : 7- β -(2-Thienylacetamido)-3-pyridiniummethylcephem(3)-4-carboxylic acid nitrate (Formula I):

To a solution of 3.82 g of 7-trimethylsilylamino-3-iodomethylcephem(3)-4-carboxylic acid trimethylsilyl ester (prepared as described in examples 1 or 6) in 125 ml of dry dichloromethane are added 1.47 ml of dry pyridine, and the mixture is stirred for 2 hours at room temperature. A solution of 3.2 g of thienylacetic acid-S-mercapto-benzthiazolyl ester in 20 ml of dichloromethane (prepared *in situ* from 1.56 g of thiophenacetic acid, 4.47 g of bis(benzothiazol-2-yl)disulfide and 3.53 g of triphenylphosphine in dichloromethane) is added to this solution and the mixture is stirred for 30 hours at room temperature. By addition of 5 ml of methanol the crude title compound precipitates as the hydroiodide. This is dissolved in 5 % bicarbonate solution, filtered from insolubles, and by addition of dilute nitric acid, the title compound crystallises at a pH of 1.8 as the nitrate.
m.p 151 - 152° (decomp.).

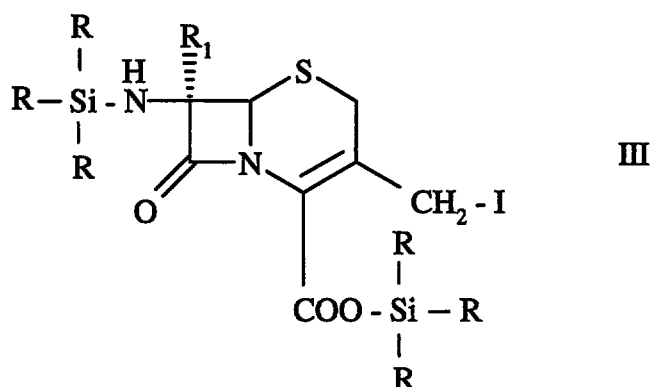
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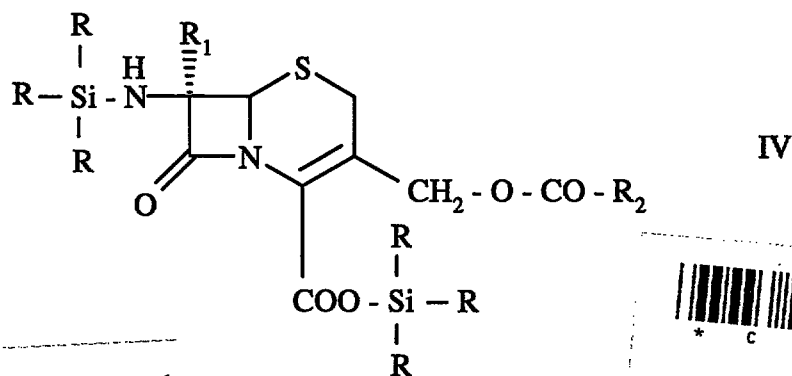
Patent Claims

1. A cephalosporin derivative of formula



wherein R denotes a lower alkyl group and R₁ denotes hydrogen or the methoxy group.

2. Use of a cephalosporin derivative of formula III according to claim 1 as an intermediate in the production of a cephalosporin derivative.
3. Use according to claim 2, characterized in, that the cephalosporin derivative of formula III is obtained by reaction of a compound of formula



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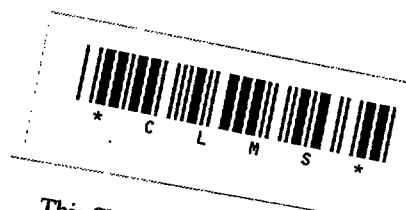


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wherein R and R₁ are as defined in claim 1 and R₂ denotes the methyl or the amine group with a trialkyliodosilane.

4. Use according to claim 3, characterized in that the trialkyliodosilane is trimethyliodosilane.
5. Use according to anyone of claims 3 or 4, characterized in that 1.1 to 1.5 equivalents of trialkyliodosilane per equivalent cephalosporin derivative of formula IV are used.
6. Process for the production of a cephalosporin derivative, characterized in that a cephalosporin derivative of formula III according to claim 1 is reacted with the desired nucleophile and the derivative obtained which is substituted in position 3 by the residue of the nucleophile is either deprotected by splitting off the silyl protecting groups or acylated with an acylating agent in position 7 and deprotected by splitting off the silyl protection groups.
7. Process according to claim 6, characterized in that the cephalosporin derivative of formula III is obtained according to anyone of claims 3 to 5.

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