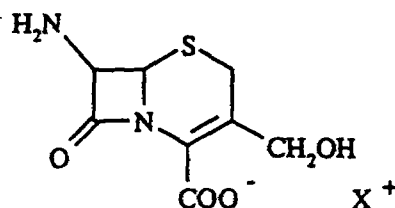


This invention relates to intermediates in the synthesis of cephalosporins. It provides in one aspect novel amidine salts of 7-Amino-3-hydroxymethyl-3-cephem-4-carboxylic acid (= HACA) which include guanidine and diaza-bicyclo-alkylene salts.

Particularly the invention provides a compound of formula

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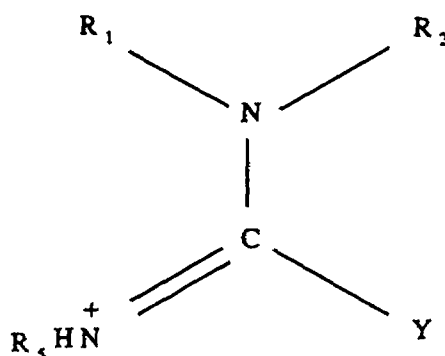


I

15 wherein X^+ denotes a compound of formula

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II

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wherein Y

(i) denotes a group of formula $-NR_3R_4$ and

a) R_1 to R_5 are the same or different and denote independently of one another hydrogen, optionally substituted alkyl or aryl or

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b) two of the substituents R_1 to R_5 , which are bonded to different nitrogen atoms, together form a $-(CH_2)_2-$ or $-(CH_2)_3-$ group and the other substituents R_1 to R_5 are as defined above

(ii) denotes together with R_2 a $-(CH_2)_3-$ or $-(CH_2)_5-$ group and R_1 and R_5 denote together a $-(CH_2)_3-$ group.

HACA is of great interest as a starting material for highly effective cephalosporins. Position 7 thereof may be acylated to form the corresponding 7-acylamino-3-hydroxymethyl-3-cephem-4-carboxylic acid, and likewise, the hydroxy function in position 3 and optionally the carboxylic function in position 4 may be changed to form a series of highly effective derivatives. For example, the active substances

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RO 23-9424

Nc1cc(NC(=O)C2C(=O)N(C2)C3C(S3)C(C(=O)O)COC(=O)C4=C(C(=O)N5C=CC=C5S4)C6=C(C(=O)O)C7=C(C(F)=C8C(=C(C(F)=C8)N9CCN(C)CC9)C6=O)N(C)CC

x 2HCl

Particularly useful are guanidines of formula II in which R₁ to R₅ independently of one another denote hydrogen, methyl, ethyl, benzyl or phenyl, for example tetramethyl guanidine, pentamethyl guanidine or



methylphenyl guanidine, preferably tetramethyl guanidine.

Salts of HACA are known: The Na salt (Journal of Antibiotics 45/5, page 721 ff, 1992) and the triethylammonium salt (ES 403 523). In the Journal of Antibiotics, the acylation of the sodium salt of HACA with 2-(2-chloroacetamidothiazol-4-yl)-2(Z)-methoximino-acetyl chloride hydrochloride is described. In this, the HACA is acylated as the sodium salt in a mixture of THF/water and the protecting group is subsequently removed. The yield is only 50 % and derivitisation of the hydroxy function then takes place in a separate step. Moreover, water is a most unfavorable solvent for such a sensitive derivitisation reaction. In example 3 of ES 403 523, the triethylammonium salt of HACA is acylated without stating the solvent system, but undesired lactonisation simultaneously takes place. We have found that HACA may not be dissolved using triethyl amine in, for example, dichloromethane or methanol.

Salts of certain 7-amino-3-cephem-4-carboxylic acid derivatives with amidines and guanidines are known for example from EP 127 541, but all the β -lactam nuclei mentioned have non-reactive substituents in position 3, for example the substituent in position 3 may be a simple methyl group or a sulphur heterocycle. In contrast, HACA with its hydroxy function possesses a reactive functional group in position 3. It is known, that β -lactams are not inert towards alcohols. In addition, in the case of 3-hydroxymethyl-3-cephem-4-carboxylic acids, there is a great risk of lactonisation.

Surprisingly, the salts of HACA according to the invention are stable in solution, and in practice there is neither decomposition in the presence of the strong bases through inter-molecular nucleophilic ring opening of the β -lactam ring due to the alcohol function, nor intra-molecular lactonisation.

The salts according to the invention may be produced by e.g. bringing into contact the HACA with the corresponding amidine or guanidine preferably in a solvent. In an aprotic solvent preferably an approximately stoichiometric quantity of the amidine or the guanidine, preferably 1.0 to 1.2 equivalents are used based on the HACA employed. In protic solvents, e.g. in methanol, in order to obtain a solution, the quantity should be increased to ca. 1.5 to 2.0, e.g. to 1.8 equivalents. The salts according to the invention may be isolated by adding a non-solvent to the solution. Thus for example, the tetramethylguanidinium salt of HACA may be precipitated as a syrup from a solution in dichloromethane by adding methyl tert.butyl ether or by adding acetone to a methanolic solution. The 1,5-diaza-bicyclo[4.3.0]non-5-ene (=DBN) salt may be crystallized from chloroform, the tetramethylguanidinium salt also from dichloromethane.

Suitable solvents are e.g. the chlorinated hydrocarbons such as dichloromethane, ethers such as tetrahydrofuran, alcohols such as methanol, amides such as dimethylformamide, sulfoxides or sulphones such as sulfolane, ketones such as acetone, methyl isobutyl ketone, acetonitrile or mixtures of such solvents. Preferred solvents are dichloromethane, methanol, dimethylformamide, acetone or acetonitrile, particularly preferred are dichloromethane, methanol or acetonitrile.

In another aspect the invention provides a process for the production of cephalosporins which comprises acylating an amidine salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid in the 7-position and if necessary converting the product into other cephalosporins, particularly converting the product into a derivative from the 3-hydroxymethyl group.

In another aspect the invention provides the use of an amidine salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid in the production of cephalosporins.

The salts according to the invention may be acylated on the amino group in excellent yields. The reaction may be carried out using any conventional method for acylation, e.g. in analogous manner to that described in the Examples thereafter. Preferably the carboxylic acid used for acylating is in activated form. Suitable activated forms of carboxylic acids are the acid chlorides, (mixed) anhydrides, activated esters or a carboxylic acid-carbodiimide system. If required, in order to bind the acid being released, a base may be added, preferably an organic nitrogen base.

When the reaction has taken place, the corresponding acyl derivatives of HACA may be in situ further converted into other cephalosporins, e.g. on the hydroxy function in position 3, e.g. to produce the compounds S1108 or RO 23-9424, as necessary temporarily protecting reactive group; if desired the acyl derivatives may be isolated before. Reactions at position 3 are conventional derivitisation reactions of alcohols, e.g. ester formation with activated carboxylic acid derivatives, carbamate formation with isocyanates or nucleophilic substitution by means of an activated derivative of the alcohol and may be carried out using any suitable conventional method.

As a result of the surprising stability and solubility of the salts according to the invention in organic solvents, on the one hand there is freedom of choice of the acylation agent in order to produce the most varied N-acyl derivatives of HACA in good yields and good purity and on the other hand, if desired, the solvent (system) may be selected such that the second reaction sequence, i. e. the further derivitisation on the hydroxy function, may be carried out in the same solvent (system) as the acylation reaction in situ with sensitive reagents.



In the following Examples, which illustrate the invention more fully, but in no way limit its scope, the temperatures are given in degree celsius.

The following abbreviations are used:

- 5 HACA = 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid
 THF = tetrahydrofuran
 DBN = 1,5-diaza-bicyclo-[4.3.0]non-5-ene
 DBU = 1,8-diaza-bicyclo[5.4.0]undec-7-ene

Example 1: Salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid with tetramethylguanidine

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1 g of HACA are suspended in 3 ml of dichloromethane. After addition of 1.2 equivalents of tetramethyl guanidine a solution is obtained within 5 minutes at room temperature. To this solution ca. 5 ml of methyl tert.butyl ether are added, whereby a sirupy deposit is formed. The supernatant solution is decanted off, the residue digested with methyl tert.butyl ether and dried. The title compound is obtained as a syrup.

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Example 2: Salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid with tetramethylguanidine

23 g of HACA are suspended in 130 ml of dichloromethane. After addition of 1.2 equivalents of tetramethyl guanidine a solution is obtained within ca. 30 minutes at 0°. This solution is cooled to -25° and inoculated. The title compound crystallizes and is filtered off. The crystals are washed with cold dichloromethane and dried.

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Melting point: 150-154° (Decomposition).

In analogous manner to that described in the preceding Examples, as appropriate, the following HACA salts are obtained:

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Example	Salt	
3	DBU	syrup
4	DBN	M.p.: 143-146° (decomp.)

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The salts according to the invention may be used to produce cephalosporin end products, e.g. the following of which are produced:

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Example 5: Production of 7 β -((Z)-(2-amino-1,3-thiazol-4-yl)-2-methoximinoacetamido)-3-hydroxymethyl-3-cephem-4-carboxylic acid

a) Production using the salt of HACA with tetramethylguanidine

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18.4 g of HACA are suspended in 120 ml of methanol and the suspension is cooled to 0°. After addition of 10.6 ml of tetramethylguanidine a clear solution is obtained within ca. 5 minutes. To this solution 30.8 g of (Z)-2-aminothiazol-4-yl-methoximinoacetic acid-2-mercaptobenzthiazylester are added in portions and the mixture is stirred for 4 hours at 0°. 120 ml of water are added dropwise. The mercaptobenzthiazole which is released slowly precipitates. After filtration the mother liquor is slowly adjusted to pH 3.5. The suspension formed is stirred for 1 hour in an ice bath. The product crystallizes, is filtered off, washed with cold methanol and dried.

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b) Production using the salt of HACA with DBU

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23.0 g of HACA are suspended in 250 ml of dichloromethane. After addition of 15 ml of DBU and of 25 ml of methanol whilst stirring and cooling with ice, and within ca. 15 minutes a practically clear solution is obtained. After addition of 38.6 g of (Z)-2-aminothiazol-4-yl-methoximinoacetic acid-2-mercaptobenzthiazylester the suspension is stirred for 2.5 hours. HPLC analysis shows that the starting material is completely reacted. The reaction mixture is diluted with 100 ml of water, the phases are separated and the dichloromethane phase is washed with 25 ml of saturated bicarbonate solution. The combined aqueous solutions are re-extracted with dichloromethane. The pH of the aqueous phase is adjusted to 3 with aqueous hydrochloric acid. The title compound precipitates as a raw product. The raw product is suspended in 170 ml of water, dissolved with 2 N NaOH at pH 7 and the mixture is treated with 7 g of active carbon. After

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filtration, the aqueous phase is mixed with its half volume of ethanol, and the pH of the solution is adjusted to pH 3 with hydrochloric acid. The title compound precipitates, is filtered off, washed with 50 ml of water and dried.

- 5 Example 6: Production of 7 β -((Z)-2-(2-tert-butoxycarbonylaminothiazol-4-yl)-2-pentenoyl)-amino-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid diisopropylamine salt

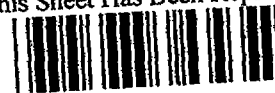
a) Production using the salt of HACA with tetramethylguanidine

- 10 13.8 g of HACA are suspended in 90 ml of dichloromethane. After addition of 9.1 ml of tetramethylguanidine a practically clear solution is obtained within ca. 5 minutes which is cooled to -20°. This solution is added to the mixed anhydride of (Z)-2-(2-tert-butoxy-carbonylaminothiazol-4-yl)-2-pentenecarboxylic acid and methanesulphonic acid, produced by reacting 19.3 g of (Z)-2-(2-tert-butoxy-carbonylaminothiazol-4-yl)-2-pentenoic acid and 5.55 ml of methanesulphonic acid chloride in 195 ml of methylene chloride in the
15 presence of 11.8 ml of diisopropylamine at -15°. The temperature is held at about -10°. Simultaneously 5.1 ml of diisopropylamine are added in order to neutralize the methanesulphonic acid being released. After addition, the reaction mixture is stirred for a further 30 minutes at a temperature of less than -10°. The mixture is cooled to about -40° and 3.2 ml of methanesulphonic acid in 30 ml of dichloromethane are added over the course of 10 minutes, followed by 7.3 ml of chlorosulphonyl isocyanate. The temperature is
20 kept below -40°C. The mixture is subsequently stirred for 30 minutes at the above temperature. The reaction mixture is mixed with a mixture of 90 ml of dimethylformamide and 250 ml of water and the emulsion is heated for ca. 3 hours to 30°. After phase separation the organic phase is extracted with 200 ml of water. To the methylene chloride phase 8.4 ml of diisopropylamine are added. The title compound precipitates. The product suspension is stirred for another 30 minutes, the product is isolated through a
25 suction filter, washed with methylene chloride and dried.

b) Production using the salt of HACA with DBU

- 2.3 g of HACA are suspended in 30 ml of dichloromethane. After addition of 3.0 ml of DBU a practically
30 clear solution is obtained within 5 minutes. This solution is cooled to -20° and added slowly to a solution of the mixed anhydride of (Z)-2-(2-tert. butoxycarbonylaminothiazol-4-yl)-2-pentenecarboxylic acid (BAPA) and methanesulphonic acid, produced by reacting 3.43 g of BAPA and 0.98 ml of methanesulphonic acid chloride in 68 ml of dichloromethane in the presence of 2.1 ml of diisopropylamine. The temperature is held at about -10°. The mixture is stirred for a further 30 minutes at a temperature of less than -10°. HPLC
35 analysis shows that the reaction is practically completed. The mixture is cooled to -50° and 0.62 ml of methanesulphonic acid, followed by 1.4 ml of chlorosulphonyl isocyanate are added. After 15 minutes HPLC analysis shows that the reaction is practically completed.

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¹ H-NMR Spectra (300 MHz, CDCl ₃)	
Example	Spectrum:
1, 2	4.90 (d, J = 5.0 Hz, 1 H, H-6), 4.78 (d, J = 5.0 Hz, 1 H, H-7), 4.45 (d, J = 12.3 Hz, 1 H, CHH'-OH), 3.77 (d, J = 12.3 Hz, 1 H, CHH'-OH), 3.51 and 3.46 (AB, J = 17.8 Hz, 2 H, CH ₂ -S), 2.99 (s, 12 H, 4 x CH ₃ -N)
3	4.90 (d, J = 5.0 Hz, 1 H, H-6), 4.78 (s broad, 1 H, H-7), 4.45 (d, J = 12.3 Hz, 1 H, CHH'-OH), 3.72 (d, J = 12.3 Hz, 1 H, CHH'-OH), 3.60 to 3.35 (m, 8 H, CH ₂ -S, 3 x CH ₂ -N), 2.85 (s broad, 2 H, CH ₂ -C=), 2.10 (qt, J = 5.7 Hz, 2 H, -CH ₂ -), 1.9 to 1.5 (m, 8 H, 3 x -CH ₂ -, -NH ₂)
4	4.90 (d, J = 5.0 Hz, 1 H, H-6), 4.78 (d, J = 5.0 Hz, 1 H, H-7), 4.40 (d, J = 12.3 Hz, 1 H, CHH'-OH), 3.71 (d, J = 12.3 Hz, 1 H, CHH'-OH), 3.64 to 3.42 (m, 6 H, CH ₂ -S, 2 x CH ₂ -N), 3.37 (t, J = 6.0 Hz, 2 H, CH ₂ -N), 3.20 (m, 2 H, CH ₂ -C=), 2.16 (qt, J = 7.9 Hz, 2 H, -CH ₂ -), 2.04 (qt, J = 5.9 Hz, 2 H, -CH ₂ -)

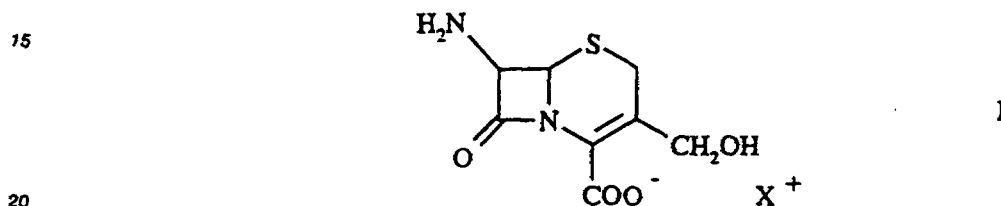
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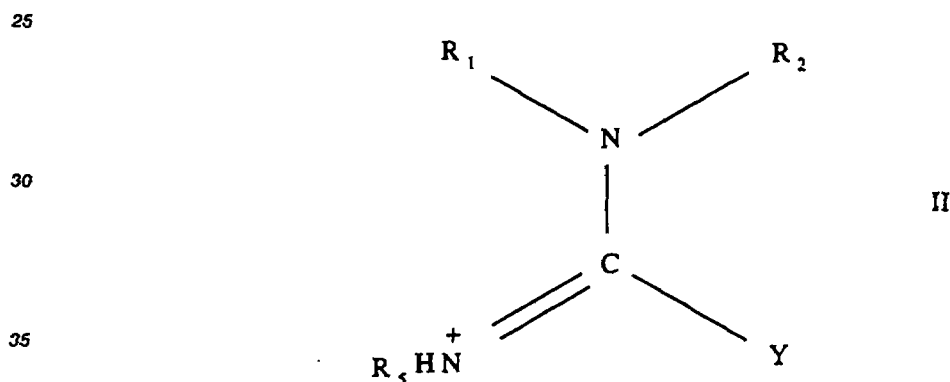


Claims

- 5 1. An amidine salt of 7-Amino-3-hydroxymethyl-3-cephem-4-carboxylic acid.
2. A salt according to claim 1 which is a guanidine salt.
3. A salt according to claim 1 which is a diaza-bicyclo-alkylene salt.
- 10 4. A compound of formula



wherein X^+ denotes a compound of formula



wherein Y

- 40 (i) denotes a group of formula $-NR_3R_4$ and
 - a) R_1 to R_5 are the same or different and denote independently of one another hydrogen, optionally substituted alkyl or aryl or
 - b) two of the substituents R_1 to R_5 , which are bonded to different nitrogen atoms, together form a $-(CH_2)_2-$ or $-(CH_2)_3-$ group and the other substituents R_1 to R_5 are as defined above
 - 45 (ii) denotes together with R_2 a $-(CH_2)_3-$ or $-(CH_2)_5-$ group and R_1 and R_5 denote together a $-(CH_2)_3-$ group.
5. A compound of formula I as defined in claim 4, wherein Y denotes a group of formula $-NR_3R_4$ and R_1 to R_5 are the same or different and denote independently of one another hydrogen, (C_1-C_8) alkyl, benzyl or phenyl.
 - 50 6. A compound of formula I as defined in anyone of claims 1 to 5 which is the salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid with
 - (a) tetramethylguanidine
 - 55 (b) 1,8-diaza-bicyclo-(5.4.0)undec-7-ene
 - (c) 1,5-diaza-bicyclo-(4.3.0)non-5-ene.

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7. A process for the production of cephalosporins which comprises acylating an amidine salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid in the 7-position and if necessary converting the product into other cephalosporins.
- 5 8. A process for the production of cephalosporins according to claim 7 which comprises converting the product into a derivative from the 3-hydroxymethylgroup.
9. Use of an amidine salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid in the production of cephalosporins.

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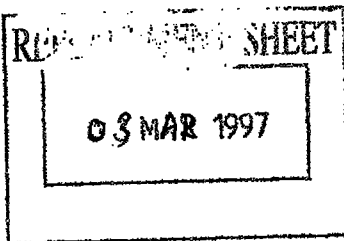
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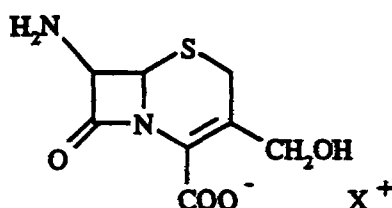
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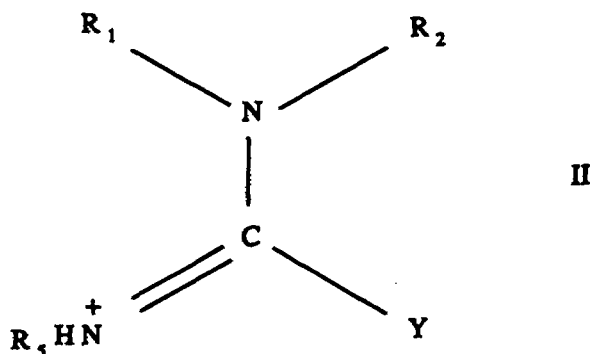
Intermediates in the synthesis of cephalosporins

This invention relates to intermediates in the synthesis of cephalosporins. It provides in one aspect novel amidine salts of 7-Amino-3-hydroxymethyl-3-cephem-4-carboxylic acid (= HACA) which include guanidine and diaza-bicyclo-alkylene salts.

Particularly the invention provides a compound of formula



wherein X^+ denotes a compound of formula



wherein Y

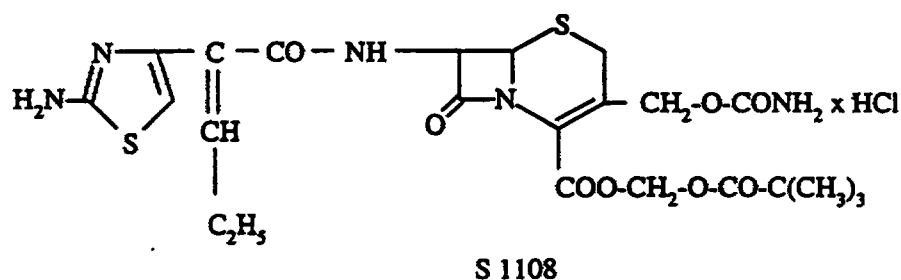
(i) denotes a group of formula $-NR_3R_4$ and

- a) R_1 to R_5 are the same or different and denote independently of one another hydrogen, optionally substituted alkyl or aryl or
- b) two of the substituents R_1 to R_5 , which are bonded to different nitrogen atoms, together form a $-(CH_2)_2-$ or $-(CH_2)_3-$ group and the other substituents R_1 to R_5 are as defined above

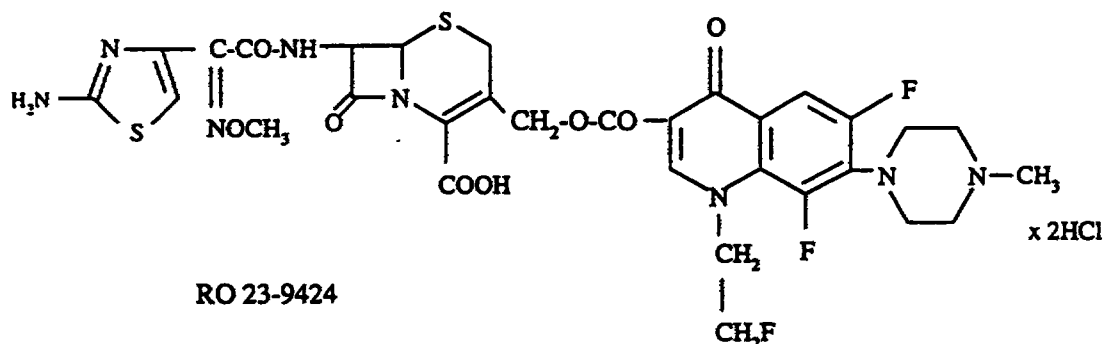
(ii) denotes together with R_2 a $-(CH_2)_3-$ or $-(CH_2)_5-$ group and R_1 and R_3 denote together a $-(CH_2)_3-$ group.

03 MAR 1997

HACA is of great interest as a starting material for highly effective cephalosporins. Position 7 thereof may be acylated to form the corresponding 7-acylamino-3-hydroxymethyl-3-cephem-4-carboxylic acid, and likewise, the hydroxy function in position 3 and optionally the carboxylic function in position 4 may be changed to form a series of highly effective derivatives. For example, the active substances



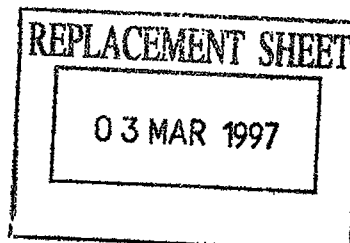
and



may be produced.

We have found particular forms of HACA which are particularly useful for economical synthesis in the production of such cephalosporins. These are stable soluble forms of HACA in a solvent or solvent mixture which allows derivation to take place in position 7 and, if desired, subsequently in position 3, without either having to change a solvent or having to isolate the intermediate stage, for reasons of reactivity of the derivitisation reagents.

Surprisingly, soluble forms of HACA have been found in the form of its amidine salts, which on the one hand are stable despite the high basicity of the corresponding bases, and on the



other hand are soluble in a number of solvents or solvent mixtures, and thus create many options in the synthesis of cephalosporin end products or intermediate products, depending on the reactivity and solubility of the derivitisation reagents.

Amidine means also a guanidine which has a further amine group at the carbon atom of the $\text{N}=\text{C}-\text{N}-$ group thus being an amino-amidine. Suitable guanidines are for example compounds of formula II, wherein Y denotes a group of formula $-\text{NR}_3\text{R}_4$ and

- a) R_1 to R_5 are the same or different and denote independently of one another hydrogen, optionally substituted alkyl or aryl or
- b) two of the substituents R_1 to R_5 , which are bonded to different nitrogen atoms, together form a $-(\text{CH}_2)_2-$ or $-(\text{CH}_2)_3-$ group and the other substituents R_1 to R_5 are as defined above.

Any carbon containing group except where otherwise stated herein preferably contains up to 20 carbon atoms.

Preferably R_1 to R_5 denote independently of one another hydrogen, unsubstituted alkyl or alkyl substituted by a phenyl group, for example benzyl, or unsubstituted aryl.

Alkyl means preferably (C_1-C_8) alkyl, more preferably (C_1-C_6) alkyl. Aryl means preferably a group having an aryl structure such as phenyl, naphthyl or an aromatic heterocyclic radical. More preferably aryl means a phenyl group.

Alkyl and aryl may optionally be substituted by groups which are inert under the reaction conditions of the following reaction steps such as acylation and further derivitisation. Such groups are in the case of alkyl for example: aryl, as for example phenyl, nitro groups, protected hydroxy or thio groups, protected amine groups and in the case of aryl for example: alkyl, aryl, protected hydroxy or thio groups, halogen, nitro groups, protected amino groups. Protection groups are such which do not disturb the acylation reaction and further derivitisation reactions.

Particularly useful are guanidines of formula II in which R_1 to R_5 independently of one

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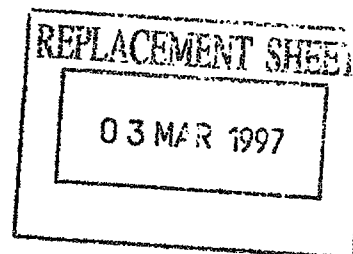
another denote hydrogen, methyl, ethyl, benzyl or phenyl, for example tetramethyl guanidine, pentamethyl guanidine or methylphenyl guanidine, preferably tetramethyl guanidine.

Salts of HACA are known: The Na salt (Journal of Antibiotics 45/5, page 721 ff, 1992) and the triethylammonium salt (ES 403 523). In the Journal of Antibiotics, the acylation of the sodium salt of HACA with 2-(2-chloroacetamidothiazol-4-yl)-2(Z)-methoximino-acetyl chloride hydrochloride is described. In this, the HACA is acylated as the sodium salt in a mixture of THF/water and the protecting group is subsequently removed. The yield is only 50 % and derivitisation of the hydroxy function then takes place in a separate step. Moreover, water is a most unfavorable solvent for such a sensitive derivitisation reaction. In example 3 of ES 403 523, the triethylammonium salt of HACA is acylated without stating the solvent system, but undesired lactonisation simultaneously takes place. We have found that HACA may not be dissolved using triethyl amine in, for example, dichloromethane or methanol.

Salts of certain 7-amino-3-cephem-4-carboxylic acid derivatives with amidines and guanidines are known for example from EP 127 541, but all the β -lactam nuclei mentioned have non-reactive substituents in position 3, for example the substituent in position 3 may be a simple methyl group or a sulphur heterocycle. In contrast, HACA with its hydroxy function possesses a reactive functional group in position 3. It is known, that β -lactams are not inert towards alcohols. In addition, in the case of 3-hydroxymethyl-3-cephem-4-carboxylic acids, there is a great risk of lactonisation.

Surprisingly, the salts of HACA according to the invention are stable in solution, and in practice there is neither decomposition in the presence of the strong bases through inter-molecular nucleophilic ring opening of the β -lactam ring due to the alcohol function, nor intra-molecular lactonisation.

The salts according to the invention may be produced by e.g. bringing into contact the HACA with the corresponding amidine or guanidine preferably in a solvent. In an aprotic solvent preferably an approximately stoichiometric quantity of the amidine or the guanidine, preferably 1.0 to 1.2 equivalents are used based on the HACA employed. In protic solvents,



e.g. in methanol, in order to obtain a solution, the quantity should be increased to ca. 1.5 to 2.0, e.g. to 1.8 equivalents. The salts according to the invention may be isolated by adding a non-solvent to the solution. Thus for example, the tetramethylguanidinium salt of HACA may be precipitated as a syrup from a solution in dichloromethane by adding methyl tert.butyl ether or by adding acetone to a methanolic solution. The 1,5-diaza-bicyclo[4.3.0]non-5-ene (=DBN) salt may be crystallized from chloroform, the tetramethylguanidinium salt also from dichloromethane.

Suitable solvents are e. g. the chlorinated hydrocarbons such as dichloromethane, ethers such as tetrahydrofuran, alcohols such as methanol, amides such as dimethylformamide, sulfoxides or sulphones such as sulfolane, ketones such as acetone, methyl isobutyl ketone, acetonitrile or mixtures of such solvents. Preferred solvents are dichloromethane, methanol, dimethylformamide, acetone or acetonitrile, particularly preferred are dichloromethane, methanol or acetonitrile.

In another aspect the invention provides a process for the production of cephalosporins which comprises acylating an amidine salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid in the 7-position and if necessary converting the product into other cephalosporins, particularly converting the product into a derivative from the 3-hydroxymethyl group.

In another aspect the invention provides the use of an amidine salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid in the production of cephalosporins.

The salts according to the invention may be acylated on the amino group in excellent yields. The reaction may be carried out using any conventional method for acylation, e.g. in analogous manner to that described in the Examples thereafter. Preferably the carboxylic acid used for acylating is in activated form. Suitable activated forms of carboxylic acids are the acid chlorides, (mixed) anhydrides, activated esters or a carboxylic acid-carbodiimide system. If required, in order to bind the acid being released, a base may be added, preferably an organic nitrogen base.

When the reaction has taken place, the corresponding acyl derivatives of HACA may be in

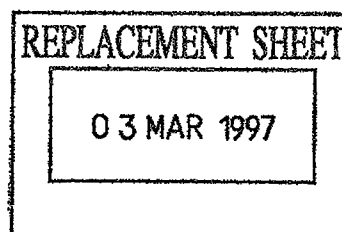
situ further converted into other cephalosporins, e.g. on the hydroxy function in position 3, e.g. to produce the compounds S1108 or RO 23-9424, as necessary temporarily protecting reactive group; if desired the acyl derivatives may be isolated before. Reactions at position 3 are conventional derivitisation reactions of alcohols, e.g. ester formation with activated carboxylic acid derivatives, carbamate formation with isocyanates or nucleophilic substitution by means of an activated derivative of the alcohol and may be carried out using any suitable conventional method.

As a result of the surprising stability and solubility of the salts according to the invention in organic solvents, on the one hand there is freedom of choice of the acylation agent in order to produce the most varied N-acyl derivatives of HACA in good yields and good purity and on the other hand, if desired, the solvent (system) may be selected such that the second reaction sequence, i. e. the further derivitisation on the hydroxy function, may be carried out in the same solvent (system) as the acylation reaction in situ with sensitive reagents.

In the following Examples, which illustrate the invention more fully, but in no way limit its scope, the temperatures are given in degree celsius.

The following abbreviations are used:

HACA	= 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid
THF	= tetrahydrofuran
DBN	= 1,5-diaza-bicyclo[4.3.0]non-5-ene
DBU	= 1,8-diaza-bicyclo[5.4.0]undec-7-ene



Example 1: Salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid with tetramethyl-guanidine

1 g of HACA are suspended in 3 ml of dichloromethane. After addition of 1.2 equivalents of tetramethyl guanidine a solution is obtained within 5 minutes at room temperature. To this solution ca. 5 ml of methyl tert.butyl ether are added, whereby a sirupy deposit is formed. The supernatant solution is decanted off, the residue digested with methyl tert.butyl ether and dried. The title compound is obtained as a syrup.

Example 2: Salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid with tetramethyl-guanidine

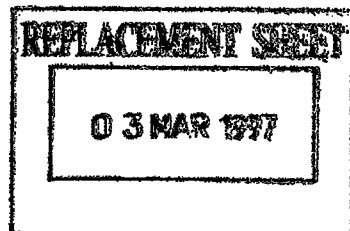
23 g of HACA are suspended in 130 ml of dichloromethane. After addition of 1.2 equivalents of tetramethyl guanidine a solution is obtained within ca. 30 minutes at 0°. This solution is cooled to -25° and inoculated. The title compound crystallizes and is filtered off. The crystals are washed with cold dichloromethane and dried.

Melting point: 150-154° (Decomposition).

In analogous manner to that described in the preceding Examples, as appropriate, the following HACA salts are obtained:

Example	Salt	
3	DBU	syrup
4	DBN	M.p.: 143-146° (decomp.)

The salts according to the invention may be used to produce cephalosporin end products, e.g. the following of which are produced:



Example 5: Production of 7B-((Z)-(2-amino-1,3-thiazol-4-yl)-2-methoximinoacetamido)-3-hydroxymethyl-3-cephem-4-carboxylic acid

a) Production using the salt of HACA with tetramethylguanidine

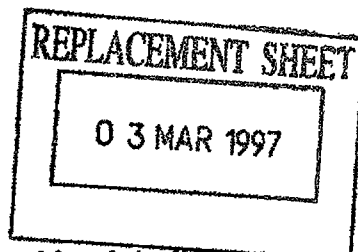
18.4 g of HACA are suspended in 120 ml of methanol and the suspension is cooled to 0°. After addition of 10.6 ml of tetramethylguanidine a clear solution is obtained within ca. 5 minutes. To this solution 30.8 g of (Z)-2-aminothiazol-4-yl-methoximinoacetic acid-2-mercaptobenzthiazolylester are added in portions and the mixture is stirred for 4 hours at 0°. 120 ml of water are added dropwise. The mercaptobenzthiazole which is released slowly precipitates. After filtration the mother liquor is slowly adjusted to pH 3.5. The suspension formed is stirred for 1 hour in an ice bath. The product crystallizes, is filtered off, washed with cold methanol and dried.

b) Production using the salt of HACA with DBU

23.0 g of HACA are suspended in 250 ml of dichloromethane. After addition of 15 ml of DBU and of 25 ml of methanol whilst stirring and cooling with ice, and within ca. 15 minutes a practically clear solution is obtained. After addition of 38.6 g of (Z)-2-aminothiazol-4-yl-methoximinoacetic acid-2-mercaptobenzthiazolylester the suspension is stirred for 2.5 hours. HPLC analysis shows that the starting material is completely reacted. The reaction mixture is diluted with 100 ml of water, the phases are separated and the dichloromethane phase is washed with 25 ml of saturated bicarbonate solution. The combined aqueous solutions are re-extracted with dichloromethane. The pH of the aqueous phase is adjusted to 3 with aqueous hydrochloric acid. The title compound precipitates as a raw product. The raw product is suspended in 170 ml of water, dissolved with 2 N NaOH at pH 7 and the mixture is treated with 7 g of active carbon. After filtration, the aqueous phase is mixed with its half volume of ethanol, and the pH of the solution is adjusted to pH 3 with hydrochloric acid. The title compound precipitates, is filtered off, washed with 50 ml of water and dried.

REPLACEMENT SHEET

03 MAR 1997



Example 6: Production of 7B-((Z)-2-(2-tert-butoxycarbonylaminothiazol-4-yl)-2-pentenoyl)-amino-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid diisopropylamine salt

a) Production using the salt of HACA with tetramethylguanidine

13.8 g of HACA are suspended in 90 ml of dichloromethane. After addition of 9.1 ml of tetramethylguanidine a practically clear solution is obtained within ca. 5 minutes which is cooled to -20° . This solution is added to the mixed anhydride of (Z)-2-(2-tert-butoxycarbonylaminothiazol-4-yl)-2-pentenecarboxylic acid and methanesulphonic acid, produced by reacting 19.3 g of (Z)-2-(2-tert-butoxy-carbonylaminothiazol-4-yl)-2-pentenoic acid and 5.55 ml of methanesulphonic acid chloride in 195 ml of methylene chloride in the presence of 11.8 ml of diisopropylamine at -15° . The temperature is held at about -10° . Simultaneously 5.1 ml of diisopropylamine are added in order to neutralize the methanesulphonic acid being released. After addition, the reaction mixture is stirred for a further 30 minutes at a temperature of less than -10° . The mixture is cooled to about -40° and 3.2 ml of methanesulphonic acid in 30 ml of dichloromethane are added over the course of 10 minutes, followed by 7.3 ml of chlorsulphonyl isocyanate. The temperature is kept below -40°C . The mixture is subsequently stirred for 30 minutes at the above temperature. The reaction mixture is mixed with a mixture of 90 ml of dimethylformamide and 250 ml of water and the emulsion is heated for ca. 3 hours to 30° . After phase separation the organic phase is extracted with 200 ml of water. To the methylene chloride phase 8.4 ml of diisopropylamine are added. The title compound precipitates. The product suspension is stirred for another 30 minutes, the product is isolated through a suction filter, washed with methylene chloride and dried.

b) Production using the salt of HACA with DBU

2.3 g of HACA are suspended in 30 ml of dichloromethane. After addition of 3.0 ml of DBU a practically clear solution is obtained within 5 minutes. This solution is cooled to -20° and added slowly to a solution of the mixed anhydride of (Z)-2-(2-tert-butoxycarbonylaminothiazol-4-yl)-2-pentenecarboxylic acid (BAPA) and methanesulphonic

acid, produced by reacting 3.43 g of BAPA and 0.98 ml of methanesulphonic acid chloride in 68 ml of dichloromethane in the presence of 2.1 ml of diisopropylamine. The temperature is held at about -10° . The mixture is stirred for a further 30 minutes at a temperature of less than -10° . HPLC analysis shows that the reaction is practically completed. The mixture is cooled to -50° and 0.62 ml of methanesulphonic acid, followed by 1.4 ml of chlorosulphonyl isocyanate are added. After 15 minutes HPLC analysis shows that the reaction is practically completed.

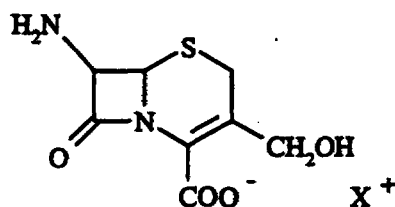
^1H -NMR Spectra
(300 MHz, CDCl_3)

Example	Spectrum:
1, 2	4.90 (d, $J = 5.0$ Hz, 1 H, H-6), 4.78 (d, $J = 5.0$ Hz, 1 H, H-7), 4.45 (d, $J = 12.3$ Hz, 1 H, $\text{CHH}'\text{-OH}$), 3.77 (d, $J = 12.3$ Hz, 1 H, $\text{CHH}'\text{-OH}$), 3.51 and 3.46 (AB, $J = 17.8$ Hz, 2 H, $\text{CH}_2\text{-S}$), 2.99 (s, 12 H, 4 x $\text{CH}_3\text{-N}$)
3	4.90 (d, $J = 5.0$ Hz, 1 H, H-6), 4.78 (s broad, 1 H, H-7), 4.45 (d, $J = 12.3$ Hz, 1 H, $\text{CHH}'\text{-OH}$), 3.72 (d, $J = 12.3$ Hz, 1 H, $\text{CHH}'\text{-OH}$), 3.60 to 3.35 (m, 8 H, $\text{CH}_2\text{-S}$, 3 x $\text{CH}_2\text{-N}$), 2.85 (s broad, 2 H, $\text{CH}_2\text{-C=}$), 2.10 (qi, $J = 57$ Hz, 2 H, $-\text{CH}_2-$), 1.9 to 1.5 (m, 8 H, 3 x $-\text{CH}_2-$, $-\text{NH}_2$)
4	4.90 (d, $J = 5.0$ Hz, 1 H, H-6), 4.78 (d, $J = 5.0$ Hz, 1 H, H-7), 4.40 (d, $J = 12.3$ Hz, 1 H, $\text{CHH}'\text{-OH}$), 3.71 (d, $J = 12.3$ Hz, 1 H, $\text{CHH}'\text{-OH}$), 3.64 to 3.42 (m, 6 H, $\text{CH}_2\text{-S}$, 2 x $\text{CH}_2\text{-N}$), 3.37 (t, $J = 6.0$ Hz, 2 H, $\text{CH}_2\text{-N}$), 3.20 (m, 2 H, $\text{CH}_2\text{-C=}$), 2.16 (qi, $J = 7.9$ Hz, 2 H, $-\text{CH}_2-$), 2.04 (qi, $J = 5.9$ Hz, 2 H, $-\text{CH}_2-$)

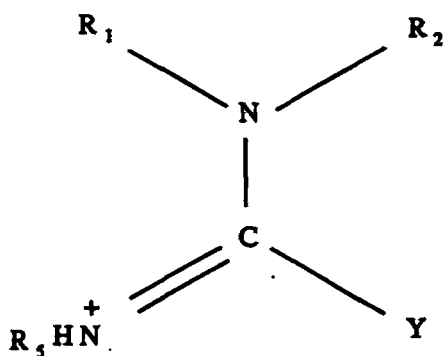


Patent claims:

1. An amidine salt of 7-Amino-3-hydroxymethyl-3-cephem-4-carboxylic acid.
2. A salt according to claim 1 which is a guanidine salt.
3. A salt according to claim 1 which is a diaza-bicyclo-alkylene salt.
4. A compound of formula



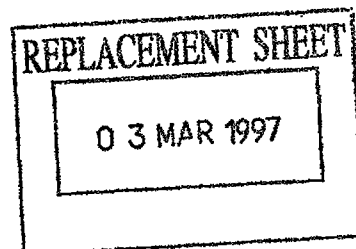
wherein X^+ denotes a compound of formula



wherein Y

(i) denotes a group of formula $-NR_3R_4$ and

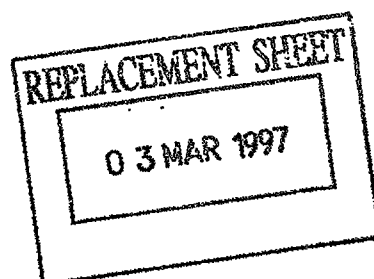
- a) R_1 to R_3 are the same or different and denote independently of one another hydrogen, optionally substituted alkyl or aryl or
- b) two of the substituents R_1 to R_3 , which are bonded to different nitrogen atoms, together form a $-(CH_2)_2-$ or $-(CH_2)_3-$ group and the other substituents R_1 to R_3





are as defined above

- (ii) denotes together with R_2 a $-(CH_2)_3-$ or $-(CH_2)_5-$ group and R_1 and R_5 denote together a $-(CH_2)_3-$ group.
5. A compound of formula I as defined in claim 4, wherein Y denotes a group of formula $-NR_3R_4$ and R_1 to R_5 are the same or different and denote independently of one another hydrogen, (C_1-C_6) alkyl, benzyl or phenyl.
6. A compound of formula I as defined in anyone of claims 1 to 5 which is the salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid with
- (a) tetramethylguanidine
 - (b) 1,8-diaza-bicyclo-(5.4.0)undec-7-ene
 - (c) 1,5-diaza-bicyclo-(4.3.0)non-5-ene.
7. A process for the production of cephalosporins which comprises acylating an amidine salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid in the 7-position and if necessary converting the product into other cephalosporins.
8. A process for the production of cephalosporins according to claim 7 which comprises converting the product into a derivative from the 3-hydroxymethylgroup.
9. Use of an amidine salt of 7-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid in the production of cephalosporins.





INTERMEDIATES IN THE SYNTHESIS OF CEPHALOSPORINS

Novel amidine salts of 7-Amino-3-hydroxymethyl-3-cephem-4-carboxylic acid (= HACA), particular guanidine and diaza-bicyclo-alkylene salts, are useful as intermediates in the synthesis of cephalosporins.

