IMPROVEMENTS IN OR RELATING TO BETA LACTAM PRODUCTION

This invention relates to a process for the production of a highly pure 7-alpha-aminoacyl-cephalosporins other than 7-alpha-aminoacyl-desacetoxycephalosporins, hereinafter referred to as compounds of the invention which on the industrial scale is economical to operate, and is environmentally acceptable, avoiding the use of halogen-containing solvents such as methylene chloride.

Many processes have been investigated for the industrial production of the compounds of the invention. Such processes must meet the necessary criteria for adoption on a commercial scale e.g. high yield, economy and ease of operation, including easy and effective purification of the end product, and few reaction steps. Processes which have been operated commercially on a large scale have required the use of halogen-containing solvents such as methylene chloride, despite the fact that these solvents are difficult to recycle or dispose of in an environmentally acceptable manner. The compounds of the invention produced also inevitably contain trace amounts of solvents and in the case of halogen-containing solvents such as methylene chloride, this is undesirable since there are fears that these could be carcinogenic.

In the literature there is no general or clear teaching of how varying reaction conditions, reactants, solvents or other factors in the synthesis of the compounds of the invention and their solvates affect yields, purity etc. This may be due to the fact that the cephalosporin nucleus is very labile, several reactive moieties are present. The art is thus very empirical.

In USP 4073902 cefroxadine is prepared in methylene chloride by reacting a mixed anhydride of an amino protected α-amino-α-(1,4-cyclohexadienyl)acetic acid with 7-amino-3-methoxy-3-cephem-4-carboxylic acid diphenylmethyl ester and subsequent removal of the protecting groups.

In USP 3422103 cephaloglycin is prepared by reacting a mixed anhydride of a lower alkanoic acid and a N-trityl amino acid with 7-aminocephalosporanic acid in chloroform (yield 29,5%) and thereafter removing the trityl group by hydrolysis with acetic acid (yield 37,8%) or by hydrogenolysis with palladium on carbon (yield 7,1%).

USP 3925372 describes the synthesis of cefaclor in toxic acetonitrile. The cephem nucleus is first silylated and reacted then with a mixed anhydride formed from chloroformic acid ester and a Dane salt. The yield is low, 44%.

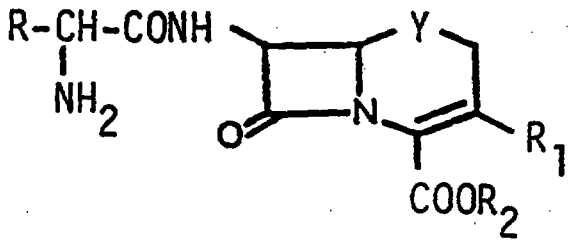
Methylene chloride is a widely used solvent because of its physical properties e.g. low boiling point, thus easy removal. Despite these advantages the use of methylene chloride and other halogen containing solvents have been criticised for years. Environmental problems arise in its use since methylene chloride is not biologically degradable. Emission controls on manufacturing plants using chlorinated hydrocarbons are contemplated. Various Pharmacopeia Commissions are considering the possibility of reducing methylene chloride residues in pharmaceuticals. The problem is especially acute for antibiotics since the proposed limits of 100-500 ppm residual methylene chloride is far exceeded in the case of antibiotics (usual values 1000 to 3000 ppm).

There was thus a clear need to find alternative industrially viable syntheses of the compounds of the invention. After exhaustive testing we have found a new synthesis for the production of these compounds which possesses a number of significant practical and economic

advantages in industrial use. We have surprisingly found that it is suitable for a very wide variety of cephems with a wide variety of 3-substituents. It uses only solvents which do not contain halogen atoms and are environmentally acceptable, gives high yields of at least 80 to 85 per cent or, in some cases, even over 90 per cent and produces highly pure products. It also obviates the need for equipment for generating vacuum, sealing and safety problems, which result from the use of e.g. acetonitrile or acetone as solvent. Furthermore it is economical in operation and yet complicated purification techniques are avoided. The process is applicable to the synthesis of a wide variety of 7-alpha-aminoacyl-cephalosporins.

Accordingly in another aspect the invention provides a process for the production of a compound of the invention without the use of a halogen-containing solvent which comprises the steps of (i) producing a mixed carboxylic acid anhydride by reacting an N-substituted vinyl alpha-amino acid with an appropriate acylating agent in a solvent which does not contain halogen atoms and which is water-immiscible or sparingly soluble in water, and (ii) further reacting the resultant mixed carboxylic acid anhydride with a 7-amino-ceph-3-em-4-carboxylic acid or a derivative thereof in a solvent which does not contain halogen atoms.

In particular the present invention provides a process for the production of a cephem of formula I



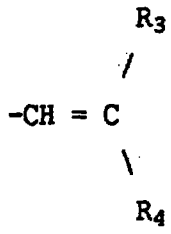
I

wherein

R is phenyl, 4-hydroxyphenyl or 1,4-cyclohexadien-1-yl

Y is oxygen, sulphur or methylene,

R_1 is hydrogen, halogen, alkoxy, ethyl, a group of formula



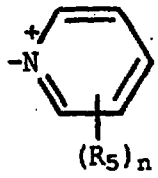
wherein

R_3 and R_4, which may be the same or different, are hydrogen, a (C_{1-6})aliphatic, (C_{3-7})cycloaliphatic, (C_{7-10})araliphatic, (C_{6-12})aromatic, cyano or lower alkoxycarbonyl;

or a group of formula $-CH_2Z$,

wherein Z has of the following meanings

a) a group of formula



wherein

n is 0 or an integer from 1 to 5 and R_5, which when n is from 2 to 5, may be the same or different, is an aliphatic, an aryl, an araliphatic, alkoxymethyl, formyl, acyloxy, acyloxymethyl, esterified carboxyl; alkoxy, aryloxy, aralkoxy, alkylthio, arylthio; aralkylthio; cyano, hydroxy, carbamoyl, N-monoloweralkylcarbamoyl, N,N-diloweralkylcarbamoyl,

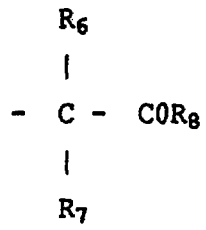
N-(hydroxyloweralkyl)carbamoyl or carbamoylloweralkyl group;

b) azido;

c) amino or acylamido;

d) a derivative of a residue of a nucleophile obtained by reacting a compound, wherein Z is azido with a acetylenic, ethylenic or cyano dipolarophile (e.g. as disclosed in USP 4,024,133, the contents of which are incorporated herein by reference),

e) a group of formula

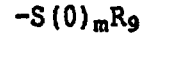


wherein

R_6 and R_7, which may be the same or different, are selected from hydrogen, cyano, lower alkyl, phenyl, substituted phenyl, lower alkoxycarbonyl, mono- or diaryl lower alkoxycarbonyl, lower alkylcarbonyl, aryl lower alkyl and C_5 or C_6 cycloalkyl and

R_8 is hydrogen, lower alkyl, phenyl, substituted phenyl, aryl lower alkyl and C_5 or C_6 cycloalkyl;

f) a group of formula



wherein

R_9 is an aliphatic, araliphatic, alicyclic, aromatic or heterocyclic group, and m is 0, 1 or 2;

g) a group of formula

$$-OR_{10}$$

wherein

R_{10} is hydrogen, lower alkyl, lower alkenyl, lower alkinyl, lower cycloalkyl, lower cycloalkyl lower alkyl, aryl, aryl lower alkyl, a heterocyclic group or a heterocyclyl lower alkyl, which may be optionally substituted by one or more lower alkoxy, lower alkylthio, halogen, lower alkyl, nitro, hydroxy, acyloxy, carboxy, carbalkoxy, lower alkylcarbonyl, lower alkylsulfonyl, lower alkoxysulfonyl, amino lower alkyl amino or acylamido groups,

h) acetoxy;

i) a group $-OCOR_{11}$, wherein R_{11} is

ia) a straight or branched chain alkyl group of 1 to 7 carbon atoms, which may be interrupted by oxygen, sulfur or imino, and substituted by cyano, carboxyl, alkoxycarbonyl, hydroxy, carboxycarbonyl, halogen or amino;

ib) a straight or branched chain alkenyl group of 2 to 7 carbon atoms, which may be interrupted by oxygen, sulfur or imino;

ic) optionally substituted aryl or heterocyclyl or cycloalkyl;

id) arylalkyl, heterocyclyl-alkyl or cycloalkylalkyl, which may be substituted in the ring;

j) a group of formula

$$-O-COAR_{12}$$

wherein
A is oxygen, sulfur or imino and
R_{12} is hydrogen, methyl or R_{11};

k) a group of formula

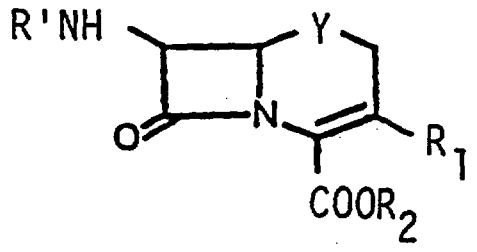
$$-OCONH(CH_2)_mQ$$

wherein Q is fluorine, chlorine, bromine or iodine and m is an integer of 1 to 4,

and

R_2 represents hydrogen, a cation, a carboxy-protecting group or $COOR_2$ is COO^-, when R_1 is a positive charged group,

without the use of halogen-containing solvent which comprises the steps of (i) producing a mixed carboxylic acid anhydride by reacting a N-substituted vinyl alpha-amino acid with an appropriate acylating agent in a solvent which does not contain halogen atoms and which is water-immiscible or sparingly soluble in water, and (ii) further reacting the resultant mixed carboxylic acid anhydride with a compound of formula II



II

wherein Y, R_1 and R_2 are as defined above and R′ is hydrogen or an

amino protecting group in a solvent which does not contain halogen atoms.

Preferred values for R_1 are hydrogen, halogen, alkoxy, a group of formula

$-CH=CHR_3$

wherein R_3 is hydrogen, (C_{1-6})alkyl or a (C_{6-12})aromatic or R_1 is a group of formula

$-CH_2Z$

wherein Z is a group of formula

$-SR_9$

in which R_9 is a heterocyclic group or Z is acetoxy.

In the definition of R_9, the term "heterocycle" includes single or fused rings comprising up to four hetero atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted up to three (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen, trihalo-(C_{1-4})alkyl, hydroxy, oxo, mercapto, amino, carboxyl, carbamoyl, di-(C_{1-4})alkyl-amino, carboxymethyl, carbamoylmethyl, sulfomethyl and methoxy-carbonylamino.

Examples of heterocycle include unsubstituted and substituted imidazolyl, diazolyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, thiatriazolyl, oxazolyl, oxadiazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, triazolylpyridyl, purinyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazolyl and triazinyl.

Suitable heterocycles include unsubstituted and substituted

1,2,3-triazolyl; 1,2,4-triazolyl; tetrazolyl; oxazolyl; thiazolyl; 1,3,4-oxadiazolyl; 1,3,4-thiadiazolyl or 1,2,4-thiadiazolyl. Preferably the heterocycle is 1-methyl-1H-tetrazol-5-yl, 2-methyl-1,3,4-thiadiazol-5-yl, 1-carboxymethyl-1H-tetrazol-5-yl, 6-hydroxy-2-methyl-5-oxo-2H-1,2,4-triazin-3-yl and 1,2,3-triazol-5-yl.

Particularly preferred values for R_9 are 1-methyl-1H-tetrazol-5-yl and 1,2,3-triazol-5-yl.

As used herein "aryl" or "aromatic" is preferably phenyl, and alkyl preferably is (C_{1-4})alkyl.

In the definition of R_2 a cation includes an alkali metal, an alkaline earth metal, ammonium or substituted ammonium. The term "carboxy protecting group" includes conventional silyl protecting groups, e.g. trialkylsilyl.

The process of the invention is useful for the preparation of a wide variety of 7-alpha-aminoacyl-cephalosporins, e.g. cefaclor, cephaloglycin, cefatrizine, cefroxadine, cefprozil or loracarbef.

Examples of a N-substituted vinyl alpha-amino acid are alpha-amino acids, wherein the amino group bears a protecting group as e.g. 1-methoxycarbonyl-propen-2-yl, 1-ethoxycarbonyl-propen-2-yl, 1-acetyl-propen-2-yl, 1-benzoyl-propen-2-yl, 1-(4-methoxy-benzoyl)-propen-2-yl or 1-(2,6-dimethoxy-benzoyl)-propen-2-yl.

The N-substituted vinyl alpha-amino acid can be employed as its salt. Examples of a salt are potassium, sodium, dicyclohexylammonium, N-methylpiperidinium or N-methylmorpholinium salts. Preferably salts are employed, more preferably Dane salts.

Examples of Dane salts suitable for the production of cefaclor, cephaloglycine, cefatrizine or cefroxadine include sodium or potassium

D-N-(1-methoxycarbonylpropen-2-yl)-α-aminophenylacetate, sodium or potassium D-N-(1-ethoxycarbonyl-propen-2-yl)-α-aminophenylacetate, sodium or potassium D-N-(1- methoxycarbonylpropen-2-yl)-α-amino-p-hydroxyphenylacetate, or sodium or potassium D-N-(1-ethoxycarbonyl-propen-2-yl)-α-amino-p-hydroxyphenylacetate, sodium or potassium D-N-(1-methoxycarbonylpropen-2-yl)-α-amino-2-(1,4-cyclohexadien-1-yl)-acetate.

The acylating agent is for example a reactive acid derivative of a C_4 - C_9 acid. Suitable reactive derivatives include acid halides, e.g. an acid chloride. The acid may be an aliphatic, alicyclic, or aromatic acid. The acid may be for example an alkanoic acid such as pivalic acid or 2-ethylhexanoic acid. If desired the acid may contain an aromatic ring, e.g. benzoic acid. Preferred acylating agents are pivaloyl chloride, 2-ethyl-hexanoyl chloride and benzoyl chloride. Alternatively the acylating agent may be a chloroformic acid alkyl ester, e.g. ethyl chloroformate.

The formula of the mixed anhydride is preferably as follows:

$$R\text{-}CH(CO\text{-}O\text{-}CO\text{-}R_{16})\text{-}NH\text{-}CR_{13}{=}CR_{14}\text{-}COR_{15} \qquad I$$

wherein R is as defined above,

R_{13} is a (C_{1-3})alkyl group, preferably methyl,

R_{14} is hydrogen or (C_{1-3})alkyl group, preferably hydrogen,

R_{15} is a (C_{1-4})alkyl group, preferably methyl or ethyl; a (C_{1-4})alkoxy group, preferably methoxy or ethoxy; phenyl optionally substituted by alkoxy,

R_{16} is an aliphatic, alicyclic, or aromatic group, e.g. a (C_{3-8})alkyl group, or preferably phenyl or 1-ethylpentyl, or especially tert-butyl,

and preferably wherein the amino group and the carbonyl group

attached to the double bond have the cis configuration.

A small amount of a free C_4 - C_9 acid may also be present in the production of the mixed anhydride. The acid is for example a C_4-C_9 acid. The acid may be for example an alkanoic acid such as pivalic acid or 2-ethylhexanoic acid. If desired the acid may contain an aromatic ring, e.g. benzoic acid.

The side chain of the free acid may be the same or different to that of the acylating agent. The preferred free acid is 2-ethylhexanoic acid or pivalic acid.

As indicated above in step i) there are used solvents which do not contain any halogen atoms. The term "sparingly soluble" includes solvents which are insoluble or slightly soluble in water. Examples of such solvents which are water-immiscible or sparingly soluble in water include those of low dielectric constant, e.g. appropriate ketones, esters and aromatic hydrocarbons. Examples include methyl-(C_{2-4})alkyl-ketones, such as methyl isobutyl ketone (hereinafter MIBK), di-(C_{2-4})alkyl-ketones, (C_{1-3})alkanoic acid butyl esters such as n-butyl acetate (hereinafter NBA), (C_{1-3})alkanoic acid propyl esters such as isopropylacetate and toluene. Preferred solvents include MIBK, NBA and isopropylacetate.

Naturally the solvent system used in step i) may contain more than one solvent, provided that halogen-containing solvents are not used.

The solvent used in the formation of the mixed anhydride step may comprise one or more solvents, provided that the system as a whole is water-immiscible or sparingly soluble in water.

Thus if desired a small amount of a co-solvent may be present in step i) which improves or activates the reaction of a Dane salt with the acid halide or other acylating agent.

We prefer to use as a co-solvent an organic amide such as a formamide or an acetamide, or their N-mono or N,N-dimethyl derivatives, e.g. dimethyl formamide, or preferably N-methylacetamide, N,N-dimethylacetamide, or N-methylpyrrolidine or tetramethylurea. Also a branched chain alcohol such as isopropanol is suitable.

Preferably a base, e.g. a tertiary amine base, is present as a catalyst for mixed carboxylic acid anhydride formation. Preferred catalysts include pyridines, for example a picoline, e.g. 3- or 4-picoline, or a lutidine.

The formation of the mixed carboxylic acid anhydride may be effected, e.g. at temperatures, from -50 to 50°C, and preferably from -40° to 0°C.

The product of step i) is generally a solution or a suspension of the mixed carboxylic acid anhydride which can be used further as such. If desired this anhydride may be maintained between step i) and step ii) at from ca. -60° to -20°C.

The step ii) is an acylation reaction of a 7-amino-ceph-3-em-4--carboxylic acid, in particular of a compound of formula II which is preferably in salt form.

Conveniently a solution of the salt of a 7-amino-ceph-3-em-4-carboxylic acid, in particular of a compound of formula II is added to the reaction mixture resulting from the mixed carboxylic acid anhydride formation. Alternatively a N-silylated 7-amino-ceph-3-em-4-carboxylic acid, in particular a N-silylated compound of formula II may be employed (R′ is a silyl protecting group e.g. trialkyl(C_{1-4})silyl).

Thus the solvents indicated above as preferably used for the mixed carboxylic acid anhydride formation are also conveniently present in the acylation step.

The salt of a 7-amino-ceph-3-em-4-carboxylic acid, in particular of a compound of formula II is preferably in a solution or suspension in an organic solvent miscible with the solvent system used in the mixed carboxylic acid anhydride step and not containing halogen atoms.

The solvent system used for dissolving or suspending the salt of a compound of formula II is preferably an alkanol, e.g. (C_1-C_4)alkanol, e.g. ethanol, and preferably a (C_{3-4})alkanol, e.g. butanol or especially isopropanol, optionally in combination with a solvent used in step i).

If desired a small amount of water may be present.

If desired small amounts of a (C_{4-9})alkanoic acid e.g. 2-ethylhexanoic acid may be added to the mixture of the salt of a 7-amino-ceph-3-em-4--carboxylic acid, in particular of a compound of formula II, and solvent.

Preferred salts include secondary or tertiary amine salts e.g. 1,8-diazabicyclo[5,4,0]undec-7-ene or tetramethylguanidine.

Suitable reaction temperatures for the acylation step may be from about -60°C to room temperature, preferably at or under -15°C.

The reaction mixture of the acylation step may be worked up in conventional manner. The protected 7-alpha-aminoacyl-cephem may be deprotected using known methods. The substituted vinyl group may be split by hydrolysis in aqueous acid.

The final product may be isolated in conventional manner, by adjusting pH. Purity may be very high, e.g. above 98%. The isolated product may contain traces of solvent residues, but is free from halogen-containing solvent.

In a preferred embodiment the invention provides a process for the production of a compound of the invention without the use of a halogen-containing solvent which comprises the steps of i) producing a mixed acid anhydride by reacting a N-substituted vinyl alpha-amino acid with an appropriate acylating agent in a solvent which does not contain halogen atoms and which is water-immiscible or sparingly soluble in water, and (ii) further reacting the resultant mixed acid anhydride with a salt of a 7-amino-ceph-3-em-4-carboxylic acid or derivative thereof in a solvent which does not contain halogen atoms.

Insofar as the production of any starting material used in the process of the invention, e.g. the Dane salt, is not particularly described herein this is known or may be made in analogous manner to known processes.

The following non-limitative examples illustrate the invention. All temperatures are in degrees Centigrade and are uncorrected.

In the examples the following abbreviations are used:

NBA	=	n-butyl acetate
IPA	=	isopropanol
Dane salt A	=	Potassium D-N-(1-ethoxycarbonylpropen-2-yl)-α-aminophenylacetate
Dane salt B	=	Potassium D-N-(1-ethoxycarbonylpropen-2-yl)-α-amino-p-hydroxyphenylacetate
DBU	=	1,8-diazabicyclo[5,4,0]undec-7-ene
TMG	=	tetramethylguanidine
TEA	=	triethylamine
7-ACA	=	7-aminocephalosporanic acid
7-ACCA	=	3-chloro-7-amino-3-cephem-4-carboxylic acid
TET-ACA	=	3-[(1-methyl-1H-tetrazol-5-yl)thiomethyl]-7-amino-3-cephem-4-carboxylic acid

The yield given is based on the 7-amino-ceph-3-em-4-carboxylic acid derivative used as starting material.
Purity is measured by HPLC on anhydrous basis.

The examples illustrate in step i) the mixed carboxylic acid anhydride formation, in step ii) the acylation of the beta-lactam using the mixture obtained in step i) without isolation, and in step iii) working up, including deprotection, to give the product.

EXAMPLE 1: **3-[(Acetyloxy)methyl]-7-[(aminophenylacetyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (Cephaloglycin)**

i) 4.6×10^{-3} ml 4-picoline are added to a suspension of 10.014 g Dane salt A in 46 ml NBA. The resultant mixture is stirred for 5 minutes at room temperature and cooled to -15°C; 3.8 ml benzoylchloride are added. The resultant suspension is stirred at -10°C for 60 minutes, 15 ml NBA are added and then cooled to -55°C giving a mixture containing the mixed carboxylic acid anhydride.

ii) 7.62 g 7-ACA are added to a mixture of 12 ml IPA and 12 ml NBA. The resulting suspension is cooled to 10°C and 3.69 ml TMG are added. The mixture is stirred for 15 minutes to give a yellow solution. This solution is added dropwise to the mixture obtained in step i) at a temperature of -55°C to -50°C over 20 minutes and the reaction mixture is stirred for a further 15 minutes at the same temperature and then for 3 hours at a temperature of -30° to -40°C. HPLC gives a cephaloglycin yield of 93%.

iii) The resultant crude protected cephaloglycin mixture is worked up by treating with a mixture of 27 ml ice-water and 6 ml concentrated HCl and stirred for 15 minutes while cooling with ice. The aqueous phase is separted off and the organic phase is back-extracted with 2 ml ice-water. The combined aqueous phases are heated to 25°C and TEA is added until a pH value of 4.5/4.7 is reached. The title compound is obtained in the dihydrate form by standing the mixture 30 minutes, filtering the crystals and washing then with 30 ml ice-water and 30 ml 80% acetone, followed by drying. Yield 84.2%.

EXAMPLE 2: **7-[(aminophenylacetyl)amino]-3-[[(1-methyl-1h-tetrazol)-5-yl) thio]methyl]-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid**

i) 4.6×10^{-3} ml 4-picoline are added to a suspension of 10.014 g Dane salt A in 25 ml NBA and 28 ml dimethylformamide. The resultant mixture is stirred for 5 minutes at room temperature and cooled to -15°C, 3.8 ml benzoylchloride are added. The solid is dissolved giving a fluid solution which is stirred at -10°C for 60 minutes and then cooled to -55°C giving a mixture containing the mixed carboxylic acid anhydride.

ii) 9.194 g of TET-ACA are added to a mixture of 10 ml IPA and 5 ml dimethylformamide. The resulting suspension is cooled to 10°C and 3.69 ml TMG are added. The mixture is stirred for 15 minutes to give a pale brownish solution. This solution is added dropwise to the mixture obtained in step i) at a temperature of -55°C to -50°C over 30 minutes and the reaction mixture is stirred for 1 hour at a temperature of -50 to -40°C and for 2 hours at a temperature of -40°C to -30°C. HPLC shows the formation of the title compound with a yield of 94%.

iii) The mixture of step ii) is worked up by adding a mixture of 27 ml ice-water and 5 ml concentrated HCl and stirred for 15 minutes while cooling with ice. The phases are divided and the acidic aqueous phase is diluted with 50 ml water and treated slowly with triethylamine to bring the pH to 4.5.

The title compound separates out, is collected by filtering and washing followed by drying as in Example 1.

EXAMPLE 3: **7-[[amino(4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1H-tetrazol)-5-yl)thio] methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (PRECEFOPERAZONE)**

i) 0.096 ml 4-picoline are added to a suspension of 10.47 g Dane Salt B in 25 ml NBA and 28 ml dimethylacetamide. The resultant mixture is stirred for 5 minutes at room temperature and cooled to -15°C; 3.77 ml benzoylchloride are added. The resultant suspension is stirred at -10°C for 60 minutes and then cooled to -55°C giving a mixture containing the mixed carboxylic acid anhydride.

ii) 9.194 g of TET-ACA are added to a mixture of 7.5 ml IPA and 7.5 ml dimethylacetamide. The resulting suspension is cooled to 10°C and 3.69 ml TMG are added. The mixture is stirred for 15 minutes to give a pale brownish solution. This solution is added dropwise to the mixture obtained in step i) at a temperature of -55°C to -50°C over 30 minutes and the raction mixture is stirred for 1 hour at a temperature of -50° to -40°C and for 2 hours at a temperature of -40°C to -30°C.HPLC shows the formation of the title compound with a yield of 87%.

iii) The mixture is worked up in analogous manner to Example 3.

EXAMPLE 4: **7-[(aminophenylacetyl)amino]-3-[chloro]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (CEFACLOR)**

i) 2.3×10^{-3} ml 4-picoline are added to a suspension of 5.02 g Dane Salt A in 23 ml NBA. The resultant mixture is stirred for 5 minutes at room temperature and cooled to -15°C, 1.93 ml benzoyl chloride are added. The resultant suspension is stirred at -10°C for 60 minutes and then cooled to -55°C giving a mixture containing the mixed carboxylic acid anhydride.

ii) 3.287 g 7-ACCA are added to a mixture of 5.5 ml IPA and 5.5 ml NBA. The resulting suspension is cooled to 10°C and 2.2 ml DBU are added. The resulting mixture is stirred for 15 minutes to give a pale brownish solution, which is added dropwise to the mixture obtained in step i) at a temperature of -55°C to -50°C over 30 minutes. The reaction mixture is stirred at a temperature of -55°C to -50°C for 15 minutes and then for 1 hour at a temperature of -30°C to -40°C. HPLC gives a Cefaclor yield of 87%.

iii) The resultant crude protected Cefaclor mixture is worked up by treating with a mixture of 13.5 ml ice-water and 2.0 ml concentrated HCl and stirred for 25 minutes while cooling with ice. The aqueous phase is separated off and the organic phase is back-extracted with 1.25 ml ice-water. The combined aqueous phases are mixed with 30 ml dimethylformamide, and the resulting suspension is cooled to 15°C, filtered and the solid washed with 8 ml dimethylformamide, which are added to the filtrate. The final solution is treated slowly with concentrated aqueous ammonia to bring the pH to 6.8. The cristalline suspension is stirred at 20°C for 1 hour, filtered and the crystals washed with 16 ml acetone. After drying, 5.86 g of the title compound were obtained as dimethylformamide solvate.

EXAMPLE 5: **Cefaclor**

i) 2.3×10^{-3} ml 4-picoline are added to a suspension of 5.02 g Dane Salt A in 23 ml isopropylacetate. The resultant mixture is stirred for 5 minutes at room temperature and cooled to -15°C, 1.93 ml benzoylchloride are added. The resultant suspension is stirred at -10°C for 60 minutes and then cooled to -55°C giving a mixture containing the mixed carboxylic acid anhydride.

ii) 3.287 g 7-ACCA are added to 11 ml IPA. To the resulting suspension 1.84 ml TMG are added. After stirring for 15 minutes, a pale brownish solution is obtained. This solution is added dropwise to the mixture obtained in step i) at a temperature of -55°C to -50°C over 30 minutes. The reaction mixture is stirred at a temperature of -55°C to -50°C over 30 minutes. The reaction mixture is stirred at a temperature of -55°C to -50°C for 15 minutes and then for 1 hour at a temperature of -30°C to -40°C. HPLC analysis of the mixture gives a Cefaclor yield of 84%.

iii) the mixture is worked up in analogous manner to Example 4 step iii)

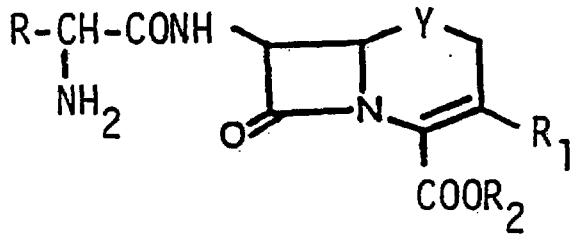
Example 5 is repeated with the following changes:

a) the same quantity of isobutylacetate is used instead of isopropyl acetate in step i). HPLC yield in Cefaclor: 84%.

WHAT WE CLAIM IS:

1. A process for the production of an 7-alpha-aminoacyl-cephalosporin, other than an 7-alpha-aminoacyl-desacetoxycephalosporin, without the use of halogen-containing solvent which comprises the steps of (i) producing a mixed carboxylic acid anhydride by reacting a N-substituted vinyl alpha-amino acid with an appropriate acylating agent in a solvent which does not contain halogen atoms and which is water-immiscible or sparingly soluble in water, optionally containing a co-solvent and (ii) further reacting the resultant mixed carboxylic acid anhydride with a 7-amino-ceph-3-em-4-carboxylic acid or derivative thereof in a solvent which does not contain halogen atoms, optionally containing a co-solvent.

2. A process for the production of a compound of formula I,



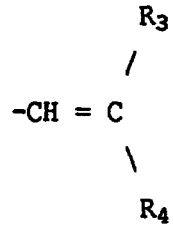
I

wherein

R is phenyl, 4-hydroxyphenyl or 1,4-cyclohexadien-1-yl,

Y is oxygen, sulphur or methylene,

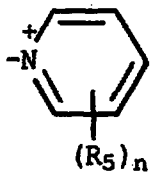
R_1 is hydrogen, halogen, alkoxy, ethyl, a group of formula



wherein R_3 and R_4, which may be the same or different, are hydrogen, a (C_{1-6})aliphatic, (C_{3-7})cycloaliphatic, (C_{7-10})araliphatic, (C_{6-12})aromatic, cyano or lower alkoxycarbonyl;

or a group of formula $-CH_2Z$,
wherein Z has the following meanings

a) a group of formula



wherein
n is 0 or an integer from 1 to 5 and R_5, which when n is from 2 to 5 may be the same or different, is an aliphatic, an aryl, an araliphatic, alkoxymethyl, formyl, acyloxy, acyloxymethyl, esterified carboxyl, alkoxy, aryloxy, aralkoxy, alkylthio, arylthio, aralkylthio; cyano, hydroxy, carbamoyl, N-monoloweralkylcarbamoyl, N,N-diloweralkylcarbamoyl, N-(hydroxyloweralkyl)carbamoyl or carbamoylloweralkyl group;

b) azido,

c) amino or acylamido;

d) a derivative of a residue of a nucleophile obtained by reacting a compound, wherein Z is azido with a acetylenic, ethylenic or cyano dipolarophile,

e) a group of formula



$$-\underset{\displaystyle R_7}{\overset{\displaystyle R_6}{\overset{|}{\underset{|}{C}}}}-COR_8$$

wherein
R_6 and R_7, which may be the same or different, are selected from hydrogen, cyano, lower alkyl, phenyl, substituted phenyl, lower alkoxycarbonyl, mono- or diaryl lower alkoxycarbonyl, lower alkylcarbonyl, aryl lower alkyl and C_5 or C_6 cycloalkyl and

R_8 is hydrogen, lower alkyl, phenyl, substituted phenyl, aryl lower alkyl and C_5 or C_6 cycloalkyl;

f) a group of formula

$$-S(O)_mR_9$$

wherein
R_9 is an aliphatic, araliphatic, alicyclic, aromatic or heterocyclic group, and m is 0, 1 or 2;

g) a group of formula

$$-OR_{10}$$

wherein
R_{10} is hydrogen, lower alkyl, lower alkenyl, lower alkinyl, lower cycloalkyl, lower cycloalkyl lower alkyl, aryl, aryl lower alkyl, a heterocyclic group or a heterocyclyl lower alkyl, which may be optionally substituted by one or more lower alkoxy, lower alkylthio, halogen, lower alkyl, nitro, hydroxy, acyloxy, carboxy, carbalkoxy, lower alkylcarbonyl, lower alkylsulfonyl, lower

alkoxysulfonyl, amino lower alkyl amino or acylamido groups,

h) acetoxy;

i) a group $-OCOR_{11}$, wherein R_{11} is

ia) a straight or branched chain alkyl group of 1 to 7 carbon atoms, which may be interrupted by oxygen, sulfur or imino, and substituted by cyano, carboxyl, alkoxycarbonyl, hydroxy, carboxycarbonyl, halogen or amino;

ib) a straight or branched chain alkenyl group of 2 to 7 carbon atoms, which may be interrupted by oxygen, sulfur or imino;

ic) optionally substituted aryl, heterocyclyl or cycloalkyl; or

id) arylalkyl, heterocyclyl-alkyl or cycloalkylalkyl, which may be substituted in the ring;

j) a group of formula

$$-O-COAR_{12}$$

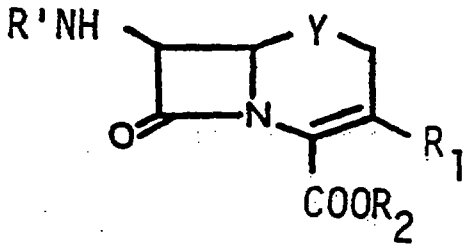
wherein
A is oxygen, sulfur or imino and
R_{12} is hydrogen, methyl or R_{11};

k) a group of formula

$$-OCONH(CH_2)_mQ$$

wherein Q is fluorine, chlorine, bromine or iodine and m is an integer of 1 to 4,
and

R_2 represents hydrogen, a cation, a carboxy-protecting group or $COOR_2$ is COO^-, when R_1 is a positive charged group, without the use of halogen-containing solvent which comprises the steps of (i) producing a mixed carboxylic acid anhydride by reacting a N-substituted vinyl alpha-amino acid with an appropriate acylating agent in a solvent which does not contain halogen atoms and which is water-immiscible or sparingly soluble in water, optionally containing a co-solvent, and (ii) further reacting the resultant mixed carboxylic acid anhydride with a compound of formula II



II

wherein Y, R_1 and R_2 are as defined above and R' is hydrogen or an amino protecting group in a solvent which does not contain halogen atoms, optionally containing a co-solvent.

3. A process according to claim 1 wherein step (ii) is effected by mixing a solution or suspension of a salt of a 7-amino-ceph-3-em-4-carboxylic acid in an (C_{3-4})alkanol, e.g. isopropanol, with the mixed carboxylic acid anhydride.

4. A process according to claim 1, 2 or 3 wherein the mixed anhydride is produced in the presence of a pyridine, especially a picoline.

* C L M S *

5. A process according to any preceding claim wherein the mixed carboxylic acid anhydride is of formula

$R\text{-}CH(CO\text{-}O\text{-}CO\text{-}R_{16})\text{-}NH\text{-}CR_{13}=CR_{14}\text{-}COR_{15}$ I

wherein R is phenyl, 4-hydroxyphenyl or 1,4-cyclohexadien-1-yl,
R_{13} is a (C_{1-3})alkyl group,
R_{14} is hydrogen or (C_{1-3})alkyl group,
R_{15} is a (C_{1-4})alkyl group, a (C_{1-4})alkoxy group, phenyl optionally substituted by alkoxy,
R_{16} is an aliphatic, alicyclic or aromatic group.

6. A process according to any preceding claim wherein the mixed anhydride is produced from an acylating agent which is a reactive acid derivative of a C_4-C_9 alkanoic acid or benzoic acid.

7. A process according to claim 6 wherein the acylating agent is pivaloyl chloride, 2-ethylhexanoyl chloride or benzoyl chloride, and the acylation is optionally effected in the presence of a free (C_{4-9}) carboxylic acid.

8. A process according to any preceding claim wherein the mixed anhydride is produced in solvent which comprises an ester or a ketone.

9. A process according to claim 8 wherein the solvent is n-butyl acetate.

10. A process according to claim 8 wherein the solvent is methyl isobutyl ketone.

11. A process according to claim 8 wherein the solvent is isopropylacetate.

* C L M S *

12. A process according to any preceding claim wherein the co-solvent is selected from formamide, acetamide, N,N-dimethyl formamide, N-methylacetamide, N,N-dimethylacetamide, N-methylpyrrolidine, tetramethylurea and isopropanol.