

Description

This invention relates to a chemical process for the preparation of β -lactam compounds, and in particular for the introduction of a substituent into a β -lactam having an acylamino side chain containing an α -acidic group the substituent being introduced onto the carbon atom carrying the acylamino side chain. Certain of the substituted β -lactam compounds produced by this process are antibacterial agents; others are useful as intermediates for producing such agents.

One method that has been described for the introduction of substituents into β -lactam compounds at the carbon atom carrying the acylamino side chain, that is to say, for example, for the introduction of a 6 α -substituent into a penicillin or of a 7 α -substituent into a cephalosporin, is the so-called 'acyl-imine procedure'. That procedure has been described both by Koppel and Koehler (*J. Amer. Chem. Soc.*, 95, 2403 (1973); GB 1 412 886, Eli Lilly) and also by Firestone and Christensen (*J. Org. Chem.*, 38, 1436 (1973); GB 1 401 059, Merck). It involves the reaction of the corresponding unsubstituted β -lactam compound with a halogenating agent and a nucleophilic reagent providing the desired substituent, under strongly basic conditions, and it proceeds via the formation of an imine anion.

Subsequently, Lunn and Mason report (*Tetrahedron Letters* No. 14, 1311 (1974)) that that procedure is not satisfactory "when the acyl side residue itself formed an anion". Taylor and Burton reported (*Tetrahedron Letters* No. 43, 3831 (1977)) that one example of such a situation arises with 6 β -2'-carboxyacetamidopenicillin diesters, such as the diesters of carbenicillin and ticarcillin. Their attempts to introduce a 6 α -methoxy substituent into those diesters by the acyl-imine procedure produced a mixture of diesters of the corresponding 6 β -2'-carboxy-2'-chloro-acetamidopenicillin with no 6 α -substitution.

It has now surprisingly been found that, although, as shown by Taylor and Burton, the acyl-imine procedure cannot be used with diesters of 6 β -2'-carboxyacetamidopenicillins, it can be used with corresponding compounds containing a free 2'-acidic group.

Accordingly, the present invention provides a process for the preparation of a β -lactam compound of partial structure (I):



wherein

A represents alkoxy or alkylthio, and

X represents an acidic group;

which process comprises reacting a β -lactam compound of partial structure (II):



wherein X is as defined above;

with an halogenating agent and with a nucleophilic reagent constituting a source of an alkoxy or alkylthio radical, in the presence of a strong base (which may be the nucleophilic reagent itself).

The acidic group X may be, for example a carboxy group, CO_2H , or another group which can carry a negative charge such sulpho, SO_3H .

The acidic group X is attached to the carbon atom adjacent the carbonyl group of the acylamino side chain, which is usually referred to as the α - or 2'- position of the side chain.

Suitable alkyl groups in the alkoxy and alkylthio moieties A include straight and branched chain alkyl groups containing from 1 to 6 carbon atoms, such as methyl, ethyl, propyl and butyl. A particular alkyl group is methyl.

Preferably A represents alkoxy, suitably C_{1-6} alkoxy.

The partial structures (I) and (II) preferably represent a penam, bisnorpenam, cephem or oxacephem structure.

Thus, in a preferred aspect, the present invention provides a process for the preparation of an antibacterially active β -lactam compound of formula (III):

0 112 049



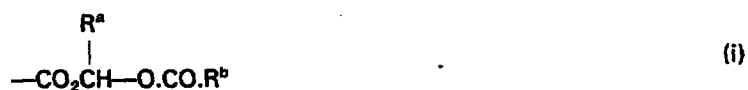
wherein

- R represents C₁₋₆ alkyl,
 R¹ represents a hydrocarbon or heterocyclyl group,
 R² represents hydrogen or a pharmaceutically acceptable salt or ester group,
 R³ represents hydrogen or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester group,
 Y represents —S—C(CH₃)₂—, —S—CH₂—, or —Y¹—CH₂—C(Z)=,
 Y¹ represents oxygen, sulphur or —CH₂—,
 Z represents hydrogen, halogen, C₁₋₆ alkoxy, —CH₂Q or —CH=CH—Q, and
 Q represents hydrogen, halogen, hydroxy, mercapto, cyano, pyridinium, carboxy, carboxy ester, C₁₋₆ alkoxy, acyloxy, aryl, heterocyclyl or heterocyclylthio;
 which process comprises reacting a compound of formula (IV):



wherein

- R¹ and Y are as defined above, and
 R^x represents hydrogen or a carboxyl blocking group;
 with a halogenating agent and with a nucleophilic reagent constituting a source of the ion RO⁻, in the presence of a strong base (which may be the nucleophilic reagent itself); and
 optionally thereafter converting the product to a salt or ester.
 The term 'hydrocarbon' as used herein includes groups having up to 18 carbon atoms, suitably up to 10 carbon atoms, conveniently up to 6 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl, aryl, and aryl(C₁₋₆)alkyl.
 The term 'aryl' as used herein includes phenyl and naphthyl, optionally substituted with up to five, preferably up to three, groups selected from halogen, C₁₋₆ alkyl, phenyl, C₁₋₆ alkoxy, halo(C₁₋₆)alkyl, hydroxy, amino, nitro, carboxy, C₁₋₆ alkoxycarbonyl, (C₁₋₆)alkoxycarbonyl(C₁₋₆)alkyl, C₁₋₆ alkylcarbonyloxy, and C₁₋₆ alkylcarbonyl groups.
 The term 'heterocyclyl' as used herein includes single or fused rings comprising up to four hetero atoms in the ring selected from oxygen, nitrogen and sulphur, and optionally substituted with up to three substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo(C₁₋₆)alkyl, hydroxy, optionally substituted amino, optionally substituted amino(C₁₋₆)alkyl, carboxy, C₁₋₆ alkoxycarbonyl, (C₁₋₆)alkoxycarbonyl(C₁₋₆)alkyl, carboxy(C₁₋₆)alkyl, sulphy(C₁₋₆)alkyl, aryl, and oxo groups.
 Suitably the heterocyclic ring comprises from 4 to 7 ring atoms, preferably 5 or 6 ring atoms.
 Preferred values for Y in the compounds of formulae (III) and (IV) are —S—C(CH₃)₂— and —S—CH₂—C(CH₂Q)=; that is to say, the compound of formulae (III) and (IV) are preferably derivatives of a penicillin or cephalosporin.
 A particularly preferred value for Y is —S—C(CH₃)₂—.
 Preferably R¹ represents phenyl, *p*-hydroxyphenyl, 3,4-dihydroxyphenyl, 2-thienyl, or 3-thienyl.
 Preferably R represents methyl.
 Examples of suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. Suitable ester groups of this type include those of part formula (i), (ii) and (iii):





(iii)

wherein

R^a represents hydrogen, methyl, or phenyl;

R^b represents C_{1-6} alkyl, C_{1-6} alkoxy, or phenyl; or

R^a and R^b together represent a 1,2-phenylene group optionally substituted by one or two methoxy groups;

R^c represents C_{1-6} alkylene optionally substituted with a methyl or ethyl group;

each of R^d and R^e independently represents C_{1-6} alkyl; and

R^f represents C_{1-6} alkyl.

Examples of suitable *in vivo* hydrolysable ester groups include for example acyloxyalkyl groups such as acetoxymethyl, pivaloyloxy-methyl, α -acetoxylethyl and α -pivaloyloxyethyl groups; alkoxycarbonyloxy-alkyl groups, such as ethoxycarbonyloxymethyl and α -ethoxycarbonyloxyethyl; dialkylaminoalkyl, especially di-loweralkyl-aminoalkyl groups, such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; lactone groups, such as phthalidyl and dimethoxyphthalidyl; and esters linked to a second β -lactam antibiotic or to a β -lactamase inhibitor.

Suitable pharmaceutically acceptable salts of the compounds of formula (III) include metal salts, for example aluminium, alkali metal salts, such as sodium or potassium, alkaline earth metal salts, such as calcium or magnesium; and also ammonium or substituted ammonium salts, for example those with lower alkylamines, such as triethylamine; hydroxy-lower alkyl-amines, such as 2-hydroxyethylamine, bis(2-hydroxyethyl)amine or tris(2-hydroxyethyl)amine; cycloalkylamines, such as dicyclohexylamine; procaine, dibenzyl-piperidine, *N*-benzyl- β -phenethylamine, dehydroabietylamine, *N,N'*-bisdehydroabietylamine, ethylenediamine, or bases of the pyridine type, such as pyridine, collidine or quinoline.

Suitable carboxyl-blocking derivatives for the group $-\text{CO}_2\text{R}^x$ in formula (IV) include salts and ester derivatives of the carboxylic acid. The derivative is preferably one which may readily be cleaved at a later stage of the reaction.

Suitable salts include metal salts, such as those with sodium, potassium and lithium, and tertiary amine salts, such as those with tri-lower alkyl-amines, *N*-ethylpiperidine, 2,6-lutidine, pyridine, *N*-methylpyrrolidine, dimethylpiperazine. Preferred salts are the sodium and triethylamine salts.

Suitable ester-forming carboxyl-blocking groups are those which may be removed under conventional conditions. Such groups for R^x include benzyl, *p*-methoxybenzyl, 2,4,6-trimethylbenzyl, 3,5-di-*t*-butyl-4-hydroxybenzyl, benzoylmethyl, *p*-bromobenzoylmethyl, *p*-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, *t*-butyl, allyl, acetonyl, *t*-amyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, *p*-toluenesulphonyl, methoxymethyl, a silyl group, a stannyl group, a phosphorus-containing group, an oxime radical of formula $-\text{N}=\text{CHR}^o$ where R^o is aryl or heterocyclyl, or an *in vivo* hydrolysable ester radical such as defined above.

The carboxyl group may be regenerated from any of the above esters by usual methods appropriate to the particular R^x group, for example, by acid-catalysed, base-catalysed, or enzymically-catalysed hydrolysis, or by hydrogenation.

Suitable halogenating agents for the process of the present invention include hypohalite, *N*-haloamide, *N*-haloimide, *N*-halosulphonamide, 1-halobenzotriazole, and halotriazine compounds. Specific examples include methyl hypochlorite, ethyl hypochlorite, isopropyl hypochlorite, *t*-butyl hypochlorite, *t*-butyl-hypoiodite, *N*-chloroacetamide, *N*-chlorosuccinimide, *N*-bromosuccinimide, *N*-bromophthalimide, *N*-chlorobenzenesulphonamide, *N*-chloro-*p*-toluenesulphonamide, 1-bromobenzotriazole. A preferred agent is *t*-butyl hypochlorite. When *t*-butyl hypochlorite is employed, it is preferred that the agent be as pure as possible, preferably distilled or freshly prepared.

The function of the halogenating agent employed in the process of the present invention is to halogenate the nitrogen atom attached to the β -lactam ring. The halogenation reaction is facilitated by a base, and the halogenating agent is therefore employed in the presence of a strong base. Suitable strong bases include sodium hydride, lithium di-isopropylamide, phenyl lithium and butyl lithium. Alternatively, it may be convenient to employ as the strong base, a compound which is also the desired nucleophilic reagent for the process, such as an alkali metal alkoxide, for example lithium methoxide.

As the halogenation step of the present process to produce an intermediate compound occurs prior to the nucleophilic addition to such intermediate, the order of addition of the reagents to the β -lactam starting material of formula (I) may be the halogenating agent followed by the nucleophilic reagent. However, in order to avoid or reduce unwanted side reactions of the halogenating agent, the nucleophilic reagent may be added first, so that as the halogenating agent is added, the intermediate is produced and reacts *in situ* with the nucleophilic reagent present. This mode of carrying out the reaction is particularly advantageous when the nucleophilic reagent is itself the strong base and can be used as the base to facilitate the action of the halogenating agent.

The solvent employed in the process of this invention should suitably be an anhydrous solvent in which the starting materials are soluble. Suitable solvents for the process include methanol, ethanol, methylene dichloride, dimethylformamide, dimethacetamide, dimethoxyethane, tetrahydrofuran, dioxan, methyl acetate, ethyl acetate and isopropyl acetate, as well as mixtures of any such solvents.

The process is conveniently carried out at low temperature, suitably less than 0°C. The preferred temperature for a particular reaction will depend on the nature of the β -lactam starting material and the reagents employed.

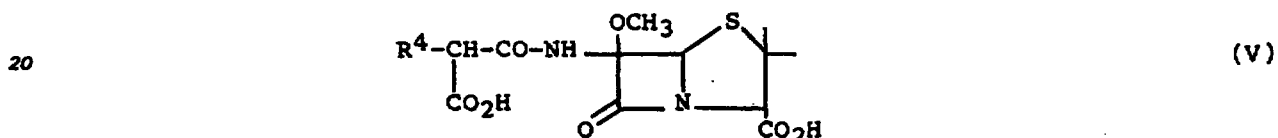
The reaction requires only a short period, for example up to 60 minutes, conveniently less than 30 minutes, suitably from 3 to 10 minutes. The reaction mixture may then conveniently be quenched by acidification.

Suitable acids which may be used to quench the reaction are concentrated mineral acids such as concentrated sulphuric acid, and low molecular weight alkyl carboxylic acids such as formic acid, acetic acid or propionic acid, optionally in the presence of a trialkylphosphite.

The product of the process may be isolated by conventional methods, such as solvent extraction, chromatographic separation, in particular ion-exchange chromatography, precipitation, freeze-drying and spray-drying techniques.

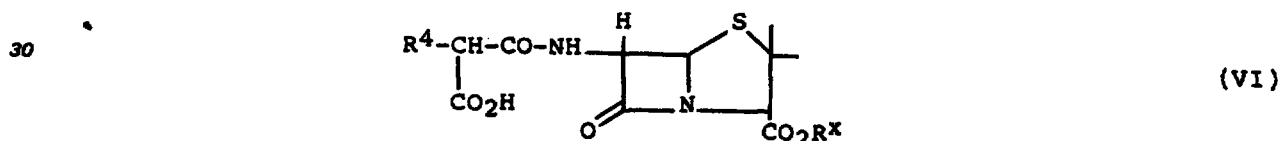
Suitable solvents for the precipitation of the product include non-polar solvents, such as methyl isobutyl ketone, isopropyl ether, methylene dichloride, and diethyl ether.

In a further preferred aspect of this invention, there is provided a process for the preparation of an anti-bacterially active β -lactam compound of formula (V) or a pharmaceutically acceptable salt thereof:



25 wherein

R^4 represents phenyl, p-hydroxyphenyl, 2-thienyl, or 3-thienyl; which process comprises reacting a salt of a compound of formula (VI):



35 wherein

R^x represents hydrogen or a carboxy-blocking group; with a halogenating agent and with a nucleophilic reagent constituting a source of methoxide ions, CH_3O^- , in the presence of a strong base (which may be the nucleophilic reagent itself); and if R^x is other than hydrogen or a salt, converting the group $-\text{CO}_2\text{R}^x$ to a free acid or salt.

40 The group R^4 in formula (V) and (VI) is preferably phenyl or thienyl, especially 3-thienyl.

In this aspect of the invention, a preferred halogenating agent is again t-butyl hypochlorite. Preferably the methoxide ions are present prior to, or at the same time as, the halogenating agent so that they can act as a base to remove a proton and thereby facilitate the halogenation. Preferably therefore an additional equivalent of methoxide is employed so that it can act as a base and as a nucleophilic reagent.

45 Suitably the source of methoxide ions is an alkali metal alkoxide, such as sodium or lithium methoxide. Alternatively, methanol may be employed in the presence of a strong base, such as sodium hydride or lithium di-isopropylamide.

A preferred source of methoxide ions is lithium methoxide. If sodium methoxide is employed, it is also advantageous to employ a small amount of lithium chloride.

50 The compound of formula (VI) may be present in the form of a disalt, i.e. R^x represents a salting ion. Suitable salting ions include sodium, potassium, lithium, calcium, aluminium, magnesium, and dicyclohexylamine, preferably the di-sodium salt. Alternatively the di-acid corresponding to compound (VI), i.e. $\text{R}^x=\text{H}$, may be employed, or a mono salt thereof together with an additional 2 or 1 equivalent respectively of methoxide, as that amount is initially consumed as a base to produce the disalt of the compound of formula (VI).

55 In the methoxylation aspect of this invention, i.e. the formation of compound (V) from (VI), it is convenient to employ methanol as a solvent. Preferred solvents for this aspect of the invention include dimethylformamide and methanol, in particular a mixture of the two, optionally in the presence of tetrahydrofuran or methyl acetate. A preferred solvent system is dimethylformamide/methanol/methyl acetate. Preferred proportions of dimethylformamide to methanol are from 3:1 to 6:1, preferably 5:1.

60 The starting material of formula (VI) is preferably present at a concentration of 5–7% of this reaction solution.

For the preparation of compounds of formula (V), a suitable temperature is from -100°C to -50°C , advantageously from -80°C to -60°C .

65 When such low temperature reactions are carried out, it is preferable to pre-cool the solutions of

reagents before they are added to the reaction mixture. A preferred reaction time is from 5 to 15 minutes. The following examples illustrate the process of this invention.

Example 1

5 Preparation of disodium 6 β -[2-carboxy-2-(thien-3-yl)acetamido]-6 α -methoxy penicillanate (temocillin) from disodium 6 β -[2-carboxy-2-(thien-3-yl)acetamido]penicillinate (ticarcillin)

0.03 Moles of ticarcillin disodium salt were dissolved in a mixture of dimethylformamide and methanol (160 ml:25 ml) maintained at 3 to 5°C. The solution was then cooled to -75°C.

10 0.045 Moles of lithium methoxide were dissolved in 20 ml of methanol. The solution was then cooled to -75°C.

The solution of lithium methoxide was added quickly to the solution of ticarcillin with stirring. The vessel having contained the lithium methoxide solution was washed with 5 ml of methanol and transferred to the reaction vessel.

15 The reaction mixture was stirred for 1 minute and then 5.5 ml of t-butylhypochlorite, precooled at -75°C were added. The reaction mixture was allowed to stir for about 5 minutes. The reaction was then quenched by the addition of 0.8 ml of concentrated sulfuric acid. The solution temperature was allowed to raise to ambient temperature.

1 litre of methylisobutylketone was added.

20 The reaction mixture was stirred for about 20 minutes and then filtered under vacuum. The crude product was washed with 50 ml of methylisobutylketone followed by 50 ml of diisopropylether. The crude product was redissolved in 50 ml of distilled water. The organic layer was separated and discarded, and the aqueous solution acidified to pH 2 with 5N hydrochloric acid in the presence of 50 ml of methylisobutylketone. The aqueous layer was separated and discarded. The organic layer was extracted with 25 ml water and 5N sodium carbonate solution to pH 6.5. The organic layer was separated and the carbonate 25 extract washed with 50 ml of isopropylether. The aqueous solution was degassed and freeze-dried to provide about 9 g of powder containing 81% of temocillin as free acid.

Example 2

Preparation of temocillin from disodium ticarcillin

30 173 g of ticarcillin disodium salt (100% as free acid) was dissolved in a mixture of 375 ml of methyl acetate, 1200 ml of dimethylformamide and 400 ml methanol.

7.5 g lithium chloride were added to the solution. The mixture was cooled to -75°C.

825 ml of methyl acetate, pre-cooled at -75°C, were added. A solution of 36.45 g sodium methoxide in 300 ml methanol was cooled to -75°C and added. After 1 minute, 95 ml of t-butyl hypochlorite were added 35 over a period of 7 minutes. The mixture was stirred for 2.5 hours, maintaining a constant temperature of -75°C.

The reaction was quenched by addition of 15 ml of glacial acetic acid and then 60 ml of triethylphosphite. The product was isolated as described in Example 1 to give 95.5 g temocillin at 82% 40 purity (as free acid).

Example 3

Preparation of disodium 6 β [2-carboxy-2-(thien-3-yl)acetamido]-6 α -methoxy penicillanate (temocillin) from monosodium 6 β -[2-carboxy-2-(thien-3-yl)acetamido] penicillanate

45 0.03 Moles of ticarcillin monosodium salt were dissolved in a mixture of dimethylformamide and methanol (50 ml : 25 ml) maintained at 3° to 5°C. 0.5 g lithium chloride were added to the solution. The solution was then cooled to -75°C. 100 ml of methylacetate at -70°C were added to the solution. 0.075 Moles of sodium methoxide were dissolved in 25 ml of methanol. 75 ml of dimethylformamide were added to the solution of sodium methoxide, this solution was cooled to -75°C and quickly added to the solution of ticarcillin with stirring.

50 The reaction mixture was stirred for 1 minute and 5.5 ml of precooled (at -75°) t-butylhypochlorite in 75 ml dimethylformamide were added in 5 minutes with good stirring. The reaction mixture was allowed to stir for about 15 minutes and then quenched by the addition of 1 ml of glacial acetic acid. The solution temperature was allowed to raise to ambient temperature. The product was isolated as described in Example 1.

55

Example 4

Preparation of temocillin from monosodium ticarcillin

11.5 g of monosodium ticarcillin (100% as pfa) was dissolved in a mixture of 38 ml dimethyl formamide and 30 ml methanol. To this solution was added 0.5 g of lithium chloride, the solution cooled to -75°C and 60 then 115 ml of methyl acetate, precooled to -75°C, were added. Then a solution of 4.75 g of sodium methoxide in 25 ml methanol was prepared and when dissolved 85 ml of DMF, precooled to -75°C, is added thereto. This solution was then added to the ticarcillin solution. Immediately thereafter a solution of 4.95 ml of t-butyl hypochlorite diluted with 75 ml of dimethylformamide pre cooled to -75°, was added. After 15 mins, 1.6 ml of glacial acetic acid were added, and after 1 minute, 2 ml of triethyl phosphite.

65 The product was isolated as described in Example 1, to give 8 g product (purity 82% as pfa).

Example 5

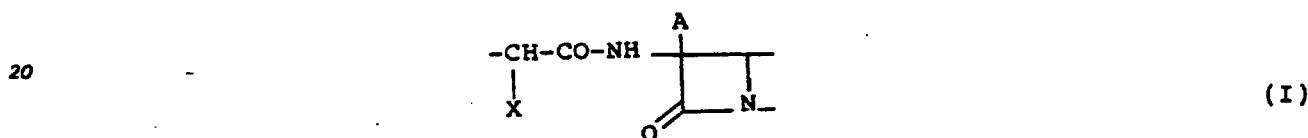
Preparation of disodium 6β[2-carboxy-2-phenylacetamido] 6α-methoxy penicillanate from disodium 6β-[2-carboxy-2-phenylacetamido]penicillanate (carbenicillin)

5 0.06 Moles of carbencillin disodium salt were dissolved in a mixture of dimethylformamide and methanol (100 ml: 50 ml) maintained at 3 to 5°C. The solution was then cooled to -75°C and additional quantity of dimethylformamide (220 ml) was then added. 0.09 Moles of lithium methoxide were added quickly to the solution of carbencillin with stirring. The vessel having contained the lithium methoxide solution was washed with 5 ml of methanol and transferred to the reaction vessel.

The reaction mixture was stirred for 1 minute and then 11 ml of precooled (at -75°C) *t*-butylhypochlorite (0.092 moles) were added. The reaction mixture was allowed to stir for about 15 minutes, and then quenched by the addition of 1.6 ml of concentrated sulfuric acid. The solution temperature was allowed to raise to ambient temperature. The product was isolated as described in example 1.

Claims

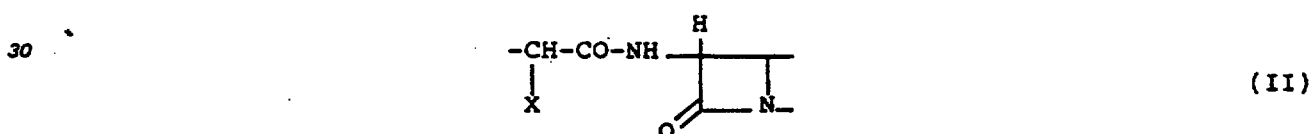
- 1. A process for the preparation of a β -lactam compound of partial structure (I):**



wherein

25 A represents alkoxy or alkylthio, and
X represents an acidic group;

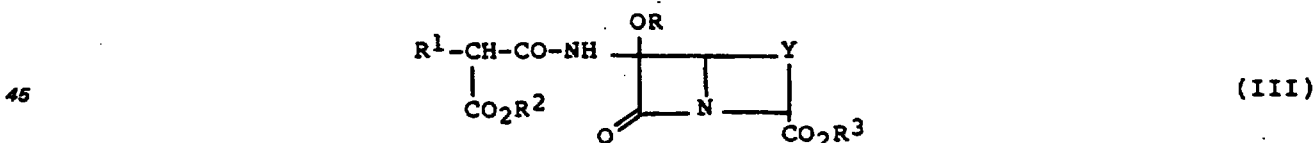
which process comprises reacting a β -lactam compound of partial structure (II):



35 wherein X is as defined above;

wherein X is as defined above, with an halogenating agent and with a nucleophilic reagent constituting a source of an alkoxy or alkylthio radical, in the presence of a strong base (which may be the nucleophilic reagent itself).

2. A process as claimed in claim 1, wherein A represents C₁₋₆ alkoxy.
3. A process as claimed in claim 1 or claim 2, wherein X represents carboxy.
4. A process for the preparation of an antibacterially active β -lactam compound of formula (III):



wherein

R represents C₁₋₆ alkyl,

50 R¹ represents a hydrocarbon or heterocyclyl group,

R² represents hydrogen or a pharmaceutically acceptable salt or ester group,

R³ represents hydrogen or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester group,

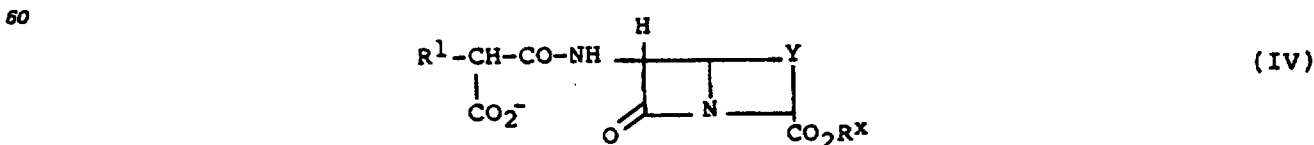
Y represents $-\text{S}-\text{C}(\text{CH}_3)_2-$, $-\text{S}-\text{CH}_2-$, or $-\text{Y}'-\text{CH}_2-\text{C}(\text{Z})=$,

Y' represents oxygen, sulphur or $-\text{CH}_2-$,

55 Z represents hydrogen, halogen, C₁₋₆ alkoxy, —CH₂Q or —CH=CH—Q, and

Q represents hydrogen, halogen, hydroxy, mercapto, cyano, pyridinium, carboxy, carboxy ester, C₁₋₆ alkoxy, acyloxy, aryl, heterocyclyl or heterocyclylthio;

which process comprises reacting a compound of formula (IV):





0 112 049

Example 5

Preparation of disodium 6 β [2-carboxy-2-phenylacetamido]6 α -methoxy penicillanate from disodium 6 β -[2-carboxy-2-phenylacetamido]penicillanate (carbenicillin)

0.06 Moles of carbenicillin disodium salt were dissolved in a mixture of dimethylformamide and methanol (100 ml: 50 ml) maintained at 3 to 5°C. The solution was then cooled to -75°C and additional quantity of dimethylformamide (220 ml) was then added. 0.09 Moles of lithium methoxide were added quickly to the solution of carbencillin with stirring. The vessel having contained the lithium methoxide solution was washed with 5 ml of methanol and transferred to the reaction vessel.

The reaction mixture was stirred for 1 minute and then 11 ml of precooled (at -75°C) t-butylhypochlorite (0.092 moles) were added. The reaction mixture was allowed to stir for about 15 minutes, and then quenched by the addition of 1.6 ml of concentrated sulfuric acid. The solution temperature was allowed to raise to ambient temperature. The product was isolated as described in example 1.

Claims

1. A process for the preparation of a β -lactam compound of partial structure (I):



wherein

A represents alkoxy or alkylthio, and

X represents an acidic group;

which process comprises reacting a β -lactam compound of partial structure (II):



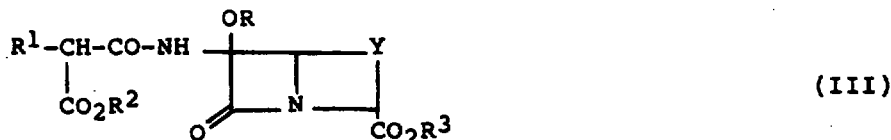
wherein X is as defined above;

with an halogenating agent and with a nucleophilic reagent constituting a source of an alkoxy or alkylthio radical, in the presence of a strong base (which may be the nucleophilic reagent itself).

2. A process as claimed in claim 1, wherein A represents C_{1-6} alkoxy.

3. A process as claimed in claim 1 or claim 2, wherein X represents carboxy.

4. A process for the preparation of an antibacterially active β -lactam compound of formula (III):



wherein

R represents C_{1-6} alkyl,

R^1 represents a hydrocarbon or heterocyclyl group,

R^2 represents hydrogen or a pharmaceutically acceptable salt or ester group,

R^3 represents hydrogen or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester group,

Y represents $-\text{S}-\text{C}(\text{CH}_3)_2-$, $-\text{S}-\text{CH}_2-$, or $-\text{Y}^1-\text{CH}_2-\text{C}(\text{Z})-$,

Y^1 represents oxygen, sulphur or $-\text{CH}_2-$,

Z represents hydrogen, halogen, C_{1-6} alkoxy, $-\text{CH}_2\text{Q}$ or $-\text{CH}=\text{CH}-\text{Q}$, and

Q represents hydrogen, halogen, hydroxy, mercapto, cyano, pyridinium, carboxy, carboxy ester, C_{1-6} alkoxy, acyloxy, aryl, heterocyclyl or heterocyclylthio;

which process comprises reacting a compound of formula (IV):





0 112 049

wherein

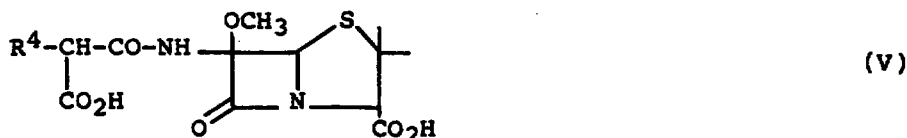
R¹ and Y are as defined above, and

R^x represents hydrogen or a carboxyl blocking group;

with a halogenating agent and with a nucleophilic reagent constituting a source of the ion RO⁻, in the presence of a strong base (which may be the nucleophilic reagent itself); and optionally thereafter converting the product to a salt or ester.

5. A process as claimed in claim 4, wherein Y represents —S—C(CH₃)₂—.

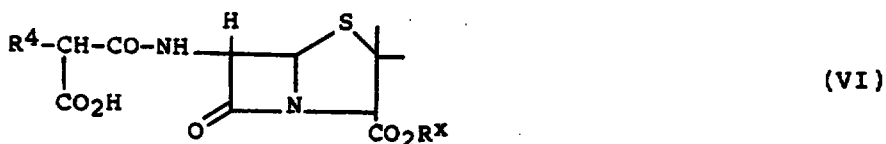
6. A process for the preparation of an antibacterially active β-lactam compound of formula (V) or a pharmaceutically acceptable salt thereof:



wherein

R⁴ represents phenyl, p-hydroxyphenyl, 2-thienyl, or 3-thienyl;

which process comprises reacting a salt of a compound of formula (VI):



wherein

R⁴ is as defined above, and

R^x represents hydrogen or a carboxy-blocking group;

with a halogenating agent and with a nucleophilic reagent constituting a source of methoxide ions, CH₃O⁻, in the presence of a strong base (which may be the nucleophilic reagent itself); and if R^x is other than hydrogen or a salt, converting the group —CO₂R^x to a free acid or salt.

7. A process as claimed in claim 8, wherein the nucleophilic reagent and strong base are lithium methoxide.

8. A process as claimed in claim 6, wherein the compound of formula (VI) is in the form of a (mono or di)-alkali metal salt.

9. A process as claimed in any one of claims 1 to 8, wherein the halogenating agent is t-butyl hypochlorite.

Patentansprüche

1. Ein Verfahren zur Herstellung einer β-Lactamverbindung mit nachstehender Teilstruktur (I):



in welcher A Alkoxy oder Alkylthio bedeutet und X eine saure Gruppe darstellt, welches Verfahren das Umsetzen einer β-Lactamverbindung mit der nachstehenden Teilstruktur (II)

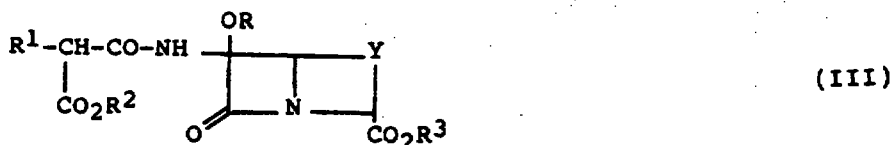


in welcher X die vorstehend angegebene Bedeutung hat, mit einem halogenierend wirkenden Mittel und mit einem nukleophilen Reaktanten, welcher als Lieferant für einen Alkoxy- oder Alkylthioest dient, in Gegenwart einer starken Base umfaßt (wobei diese starke Base auch der nukleophile Reaktant selbst sein kann).



0 112 049

2. Ein Verfahren, wie in Anspruch 1 beansprucht, in welchem A C₁₋₆-Alkoxy bedeutet.
3. Ein Verfahren, wie in Anspruch 1 oder 2 beansprucht, in welchem X Carboxy bedeutet.
4. Ein Verfahren zur Herstellung einer antibakteriell aktiven β -Lactamverbindung der nachstehenden Formel (III):



in welcher R C₁₋₆-Alkyl bedeutet,

R¹ eine Kohlenwasserstoff- oder heterocyclische Gruppe darstellt,

R² Wasserstoff oder eine pharmakologisch annehmbare Salz- oder Estergruppe ist,

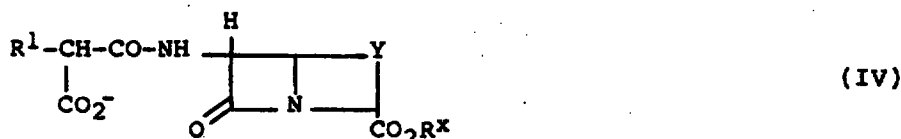
R³ Wasserstoff oder eine pharmakologisch annehmbare Salz- gruppe oder eine in vivo hydrolysierbare Estergruppe bedeutet,

Y eine der nachstehenden Gruppen ist —S—C(CH₃)₂—, —S—CH₂— oder —Y¹—CH₂—C(Z)=,

Y¹ Sauerstoff, Schwefel oder die Gruppe —CH₂— ist,

Z Wasserstoff, Halogen, C₁₋₆-Alkoxy, —CH₂Q oder —CH=CH—Q bedeutet und

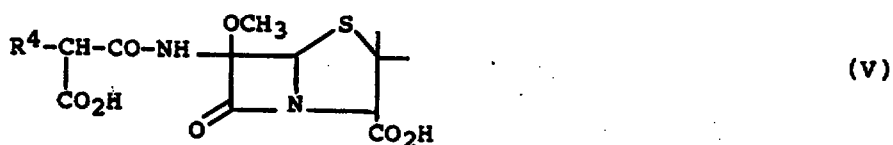
Q Wasserstoff, Halogen, Hydroxy, Mercapto, Cyan, Pyridinium, Carboxy, eine Carboxyestergruppe, C₁₋₆-Alkoxy, Acyloxy, Aryl, eine heterocyclische Gruppe oder eine heterocyclische Thiogruppe darstellt, welches Verfahren die Umsetzung einer Verbindung der nachstehenden Formel (IV):



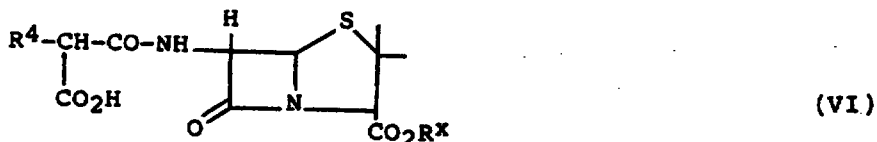
in welcher R¹ und Y die vorstehend definierte Bedeutung haben und R^x Wasserstoff oder eine die Carboxylgruppe blockierende Gruppe darstellt, mit einem halogenierend wirkenden Mittel und mit einem nukleophilen Reaktanten, welcher als Lieferant für das Ion RO⁻ dient, in Anwesenheit einer starken Base (wobei es sich auch um den nukleophilen Reaktanten selbst handeln kann) und gegebenenfalls die anschließende Umwandlung des so erhaltenen Produkts in ein Salz oder einen Ester umfaßt.

5. Ein Verfahren, wie in Anspruch 4 beansprucht, in welchem Y die Gruppe —S—C(CH₃)₂— bedeutet.

6. Ein Verfahren zur Herstellung einer antibakteriell aktiven β -Lactamverbindung der Formel (V) oder eines pharmakologisch annehmbaren Salzes derselben



in welcher R⁴ Phenyl, p-Hydroxyphenyl, 2-Thienyl oder 3-Thienyl bedeutet, welches Verfahren das Umsetzen eines Salzes einer Verbindung der nachstehenden Formel (VI)



in welcher R⁴ die vorstehend angegebene Bedeutung hat und R^x Wasserstoff oder eine die Carboxygruppe blockierende Gruppe darstellt, mit einem halogenierend wirkenden Mittel und mit einem nukleophilen Reaktanten, welcher als Lieferant für Methoxidionen CH₃O⁻ dient, in Gegenwart einer starken Base (bei welcher es sich auch um den nukleophilen Reaktanten selbst handeln kann) und, falls R^x weder Wasserstoff noch eine Salzgruppe ist, das Umwandeln der Gruppe —CO₂R^x in eine freie Säure oder ein Salz umfaßt.

7. Ein Verfahren, wie in Anspruch 8 beansprucht, in welchem der nukleophile Reaktant und sogleich die starke Base Lithiummethoxid ist.

8. Ein Verfahren, wie in Anspruch 6 beansprucht, in welchem die Verbindung der Formel (VI) in Form eines Mono- oder Dialkalimetallsalzes vorliegt.

9. Ein Verfahren, wie in irgendeinem der Ansprüche 1 bis 8 beansprucht, in welchem das halogenierend wirkende Mittel t-Butylhypochlorit ist.



0 112 049

Revendications

1. Procédé pour la préparation d'un composé à cycle β -lactame ayant une structure partielle (I):



10 dans laquelle

A est un groupe alcoxy ou alcoylthio; et

X est un groupe acide;

lequel procédé comprend la réaction d'un composé à cycle β -lactame de structure partielle (II):



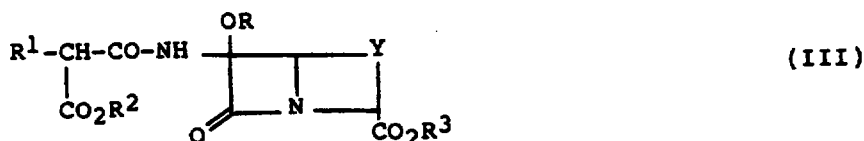
20 dans laquelle X est tel que défini plus haut;

avec un agent halogénant et avec un réactif nucléophile constituant une source de radical alcoxy ou alcoylthio, en présence d'une base forte (qui peut être le réactif nucléophile lui-même).

2. Procédé suivant la revendication 1, dans lequel A représente un groupe alcoxy en C_{1-6} .

3. Procédé suivant la revendication 1 ou la revendication 2, dans lequel X représente un groupe carboxy.

4. Procédé pour la préparation d'un composé à cycle β -lactame actif du point de vue antibactérien et ayant une formule (III):



35 dans laquelle

R est un groupe alcoyle en C_{1-6} ;

R^1 est un groupe hydrocarboné ou hétérocyclyle,

R^2 est un atome d'hydrogène ou un groupe sel ou ester acceptable du point de vue pharmaceutique,

R^3 est un atome d'hydrogène ou un groupe ester hydrolysable in-vivo ou un sel acceptable du point de vue pharmaceutique,

Y est un groupe $-\text{S}-\text{C}(\text{CH}_3)_2-$, $-\text{S}-\text{CH}_2-$ ou $-\text{Y}'-\text{CH}_2-\text{C}(\text{Z})=$,

Y' est un atome d'oxygène, de soufre ou un radical $-\text{CH}_2-$,

Z est un atome d'hydrogène, d'halogène, un groupe alcoxy en C_{1-6} , $-\text{CH}_2\text{O}$ ou $-\text{CH}=\text{CH}-\text{O}$, et

45 Q est un atome d'hydrogène, d'halogène, un groupe hydroxy, mercapto, cyano, pyridinium, carboxy, ester de fonction carboxy, alcoxy en C_{1-6} , acyloxy, aryle, hétérocyclyle ou hétérocyclylthio;

lequel procédé comprend la réaction d'un composé de formule (IV)



55 dans laquelle

R^1 et Y sont tels que définis plus haut, et

R^x est un atome d'hydrogène ou un groupe bloquant la fonction carboxy;

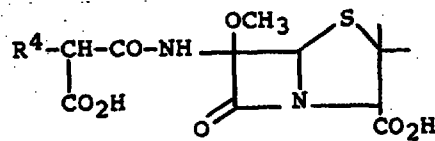
avec un agent halogénant et avec un réactif nucléophile constituant une source de l'ion RO^- , en présence d'une base forte (qui peut être le réactif nucléophile lui-même); et

60 la conversion ultérieure éventuelle du produit en un sel ou en un ester.

5. Procédé suivant la revendication 4, dans lequel Y représente un groupe $-\text{S}-\text{C}(\text{CH}_3)_2-$.

6. Procédé pour la préparation d'un composé à cycle β -lactame actif du point de vue antibactérien et de formule (V) ou d'un sel de celui-ci acceptable du point de vue pharmaceutique:

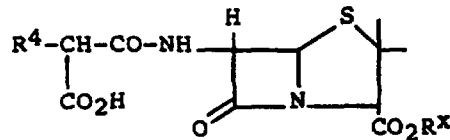
0 112 049



(V)

dans laquelle

R^4 représente un groupe phényle, p-hydroxyphényle, 2-thiènyle ou 3-thiènyle;
lequel procédé comprend la réaction d'un sel d'un composé de formule (VI):



(VI)

dans laquelle:

R^4 est tel que défini plus haut; et

R^x est un atome d'hydrogène ou un groupe bloquant la fonction carboxy;
avec un agent halogénant et avec un réactif nucléophile constituant une source d'ions méthylate, CH_3O^- ,
en présence d'une base forte (qui peut être le réactif nucléophile lui-même); et
si R^x est autre qu'un atome d'hydrogène ou un sel, la conversion du groupe $-\text{CO}_2\text{R}^x$ en un acide libre
ou un sel.

7. Procédé suivant la revendication 6, dans lequel le réactif nucléophile et la base forte sont du
méthylate de lithium.

8. Procédé suivant la revendication 6, dans lequel le composé de formule (VI) est sous la forme d'un
mono-sel ou d'un disel de métal alcalin.

9. Procédé suivant l'une quelconque des revendications 1 à 8, dans lequel l'agent halogénant est
l'hypochlorite de t-butyle.

