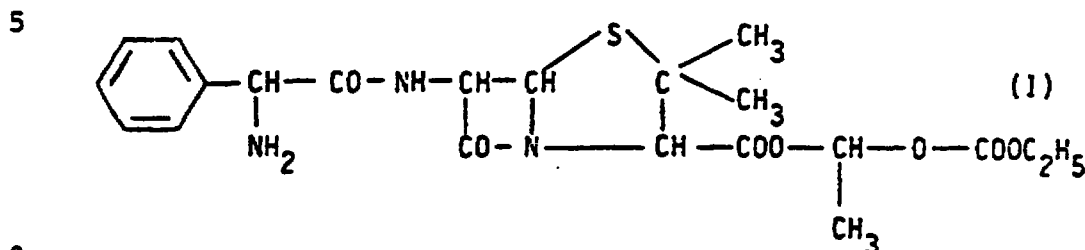


PROCESS FOR THE PRODUCTION OF 1-ETHOXYCARBONYLOXYETHYL ESTER
OF 6-(D-(-)- α -AMINO- α -PHENYLACETAMIDO) PENICILLANIC ACID

This invention relates to a novel method of manufacturing the 1-ethoxycarbonyloxyethyl ester of the 6-(D-(-)- α -amino- α -phenylacetamido) penicillanic acid of formula I:



This application is divided from Application No. 17346/83 (Publication No. 2123821) which relates to a process for producing the ethoxycarbonyloxyethyl ester of 6-aminopenicillanic acid, penicillins and cephalosporins using a quaternary ammonium catalyst.

Application No. 22826/85, also divided from No. 17346/83 is directed to the novel compound α -bromodiethylcarbonate, methods for its preparation and the use of α -bromodiethylcarbonate in the preparation of the ethoxycarbonyloxyethyl ester of 6-(D-(-)- α -amino- α -phenyl acetamido) penicillanic acid.

Application No. 20344/86, divided from No. 22826/85 is directed to processes for producing the ethoxycarbonyloxyethyl ester of penicillins such as penicillin G, penicillin V and ampicillin and cephalosporins using alpha-bromodiethylcarbonate.

The substance I concerned is an ampicillin ester which is extremely important from the therapeutic point of view since it is well absorbed when administered orally and gives much higher blood levels of ampicillin than ampicillin itself.

12
This ester is isolated in the form of a hydrochloride and is known as bacampicillin hydrochloride.

5

On the basis of previous known processes (cf. Belgian patent No. 772723), bacampicillin hydrochloride can be synthesized by the two following methods:

- 10 A) Reaction of potassium benzylpenicillin with α -chlorodiethylcarbonate in organic solvents or in an aqueous solution of 70% dioxane in the presence of sodium bicarbonate. The 1-ethoxycarbonyloxyethyl ester of benzylpenicillin which is obtained is subjected to the reaction of removing the phenylacetic chain, via the iminochloride-iminoether, in order
15 to obtain the 1-ethoxycarbonyloxyethyl ester of the 6-aminopenicillanic acid, which is isolated as the hydrochloride.

By subsequent condensation of the latter intermediate with D-(-)- α -phenylglycine, the compound according to formula I is obtained.

20

- B) Esterification reaction of the 6-(D-(-)- α -azido- α -phenylacetamido)-pencillanic acid with α -chlorodiethylcarbonate in a polar solvent.

- Subsequently, by catalytic hydrogenation of the 1-ethoxycarbonyloxyethyl ester of the 6-(D-(-)- α -azido- α -phenylacetamido)penicillanic acid the
25 compound according to formula I is obtained.

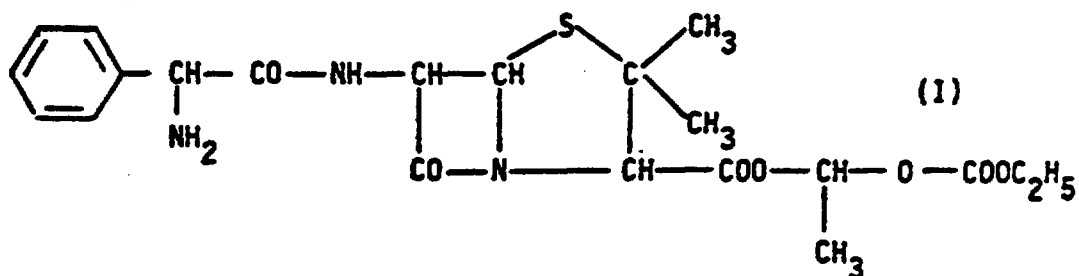
As one can see, these methods are rather complex since they involve the use of numerous raw materials and lengthy processing times.

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- A prime object of this invention is to provide a method of preparing the active substance concerned which is easier to carry out and industrially more advantageous. A more specific object of this invention is
35 to provide a method of preparing bacampicillin using ampicillin as starting material, with considerable simplification of the said method and obtaining a high degree of purity of the desired product.

It is possible to achieve the said prime object of preparing the 1-ethoxycarbonyloxyethyl ester of the 6-(D-(-)- α -amino- α -phenylacetamido) penicillanic acid having the following formula:

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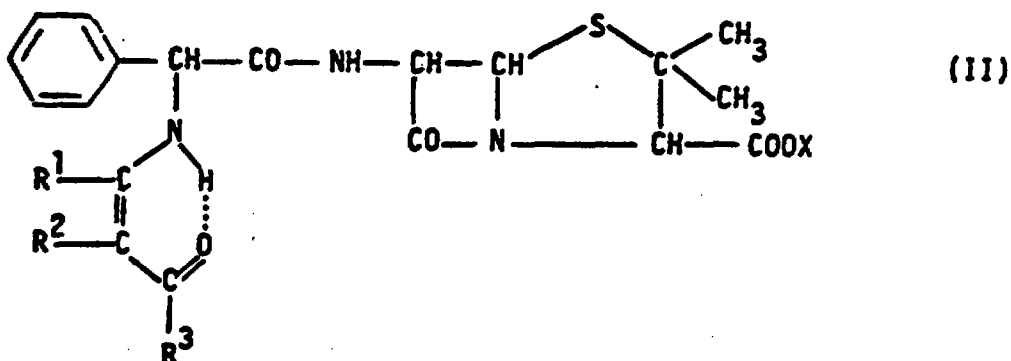
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characterized by the following stages:

15

a) reacting ampicillin or an alkali metal, alkaline earth metal or organic base salt thereof with a reactive derivative of acetoacetic acid to form the corresponding enamine having the following formula:

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25

where:

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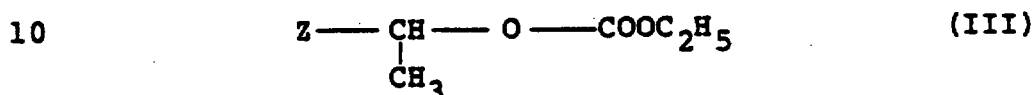
R^1 represents an alkyl group containing 1 to 4 carbon atoms, a substituted or unsubstituted aryl group or an aralkyl group;

R^2 represents hydrogen, an alkyl group containing 1 to 4 carbon atoms, a substituted or unsubstituted aryl group or an aralkyl group;

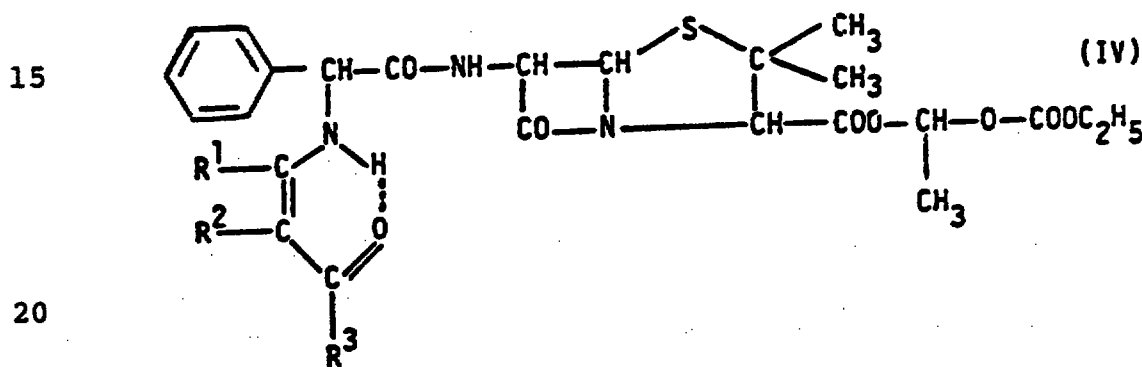
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- (2)
- R^3 represents an alkyl group containing 1 to 4 carbon atoms, a substituted or unsubstituted aryl group, an arylalkyl group, an alkoxy group containing 1 to 4 carbon atoms, an aryloxy group or an amino group, and
- 5 X represents hydrogen, an alkali metal, an alkaline-earth metal or an organic base;

b) reaction of the resulting intermediate with an ~~α-bromo~~^{halo} diethylcarbonate having the following formula:



wherein Z is Cl or I in the presence of a catalyst to form the corresponding ester having the following formula:



where R^1 , R^2 and R^3 have the same significance as above and

- c) subjecting ester IV to mild hydrolysis in an acid medium,
- 25 obtaining the compound according to formula (I).

The esterification reaction between the compounds II and III is carried out with an esterification catalyst present.

- 30 The addition of a catalyst at this stage considerably shortens the reaction times and provides higher yields of the product with a greater degree of purity.

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For this purpose the following substances can be used as catalysts: quaternary ammonium salts, for example tetrabutylammonium bromide, the bromides or iodides of alkali metals and cyclic ethers.

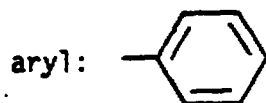
- 5 The catalyst may be used in an amount which varies from 0.005 to 0.10 moles per mole of compound III to amounts which are equimolar with the compound III. In a preferred embodiment tetrabutylammonium bromide is used in an amount of from 0.01 to 0.10 moles per mole of compound III.

- 10 Illustrative examples of the radicals R^1 , R^2 and R^3 are:

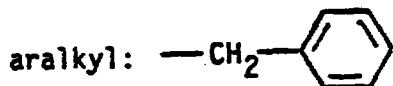
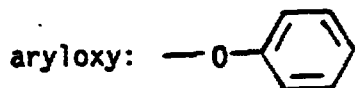
alkyl: CH_3 , C_2H_5 , $n\text{-C}_3\text{H}_7$, $i\text{-C}_3\text{H}_7$, $n\text{-C}_4\text{H}_9$

alkoxy (R^3 only): OCH_3 , OC_2H_5 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{O}(\text{CH}_2)_3\text{CH}_3$

15



substituted aryl: phenyl substituted with halogen such as Cl and Br



16 The radical X is selected among groups which are well known in the art, for example

alkali metal: Na, K

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alkaline earth metals: Ca, Mg

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organic base: organic bases which are known in the synthesis of penicillins, e.g. tertiary ammonium groups, triethylamine, ethylpiperidine and methymorpholine.

15

In the preferred embodiment of the invention, the group protecting the amino group of the ampicillin is a 1-methoxy-carbonyl-propen-2-yl group or a 1-ethoxy-carbonyl-propen-2-yl group for which the preferred intermediate is the sodium or potassium salt of the N-(1-methoxy-carbonyl-propen-2-yl) penicillanic acid respectively N-(1-ethoxy-carbonylpropen-2-yl) penicillanic acid according to formula II (R^1 = methyl; R^2 = methyl; R^3 = methoxy or ethoxy and X = Na or K).

20

The intermediate IV is stable in a neutral or alkaline medium, whereas in an acid medium it is possible to remove the group protecting the amino group simply, quickly and selectively.

25

The group protecting the amino group of the ampicillin can be selected e.g. from the groups mentioned in the British patent specification 991586, and from other groups which are known in the art.

30

More specifically, therefore, the process method according to a preferred embodiment of this invention, comprises the following stages:

- transformation of ampicillin trihydrate in a polar solvent, for example N,N-dimethylformamide, into a salt thereof, for example potassium,



and subsequent formation of the corresponding enamine (II) by reaction with a derivative of acetoacetic acid, for example methyl acetoacetate.

5 - addition of an esterification catalyst, preferably tetrabutylammonium bromide

10 - addition of α -chloro or α -iodo-diethylcarbonate to the reaction mixture to form the 1-ethoxycarbonyloxyethyl ester of the ampicillin in the form of the enamine (IV).

- hydrolysis of the protective group with HCl diluted in an organic solvent, for example n-butyl acetate/water.

15 - recovery of the bacampicillin hydrochloride by saturation in the aqueous phase, for example with sodium chloride and extraction with a suitable solvent, for example n-butyl acetate.

20 - concentration of the solution at low pressure in n-butyl acetate in order to crystallize the product to a high level of purity, the product then being isolated by filtration.

25 Among the main advantages of the process according to the invention, the principal one is that, by this process, it is possible to obtain bacampicillin hydrochloride practically in one operation and with a high degree of purity.

30 In fact the impurities which are present in the product obtained by the process according to the present invention are negligible as compared with the known processes of the previous state of the art.

Another equally important advantage is that ampicillin trihydrate is used as the starting material, this being a known antibiotic which is easily obtainable in pure form and at low cost.

35 The intermediate (II) can be easily prepared as described for example in British patent specification 991586 with a yield of over 95% by reaction of ampicillin trihydrate with methyl or ethyl acetoacetate,

10 to 50% more than the stoichiometric ratio, in the presence of an organic base or an alkali metal carbonate, for example potassium carbonate.

- 5 The intermediate (II) can be isolated and added to the esterification reaction in solid form. Or, without isolation of the intermediate (II), the esterification reaction can be effected in the same solvent in which the reaction for the formation of enamine (II) took place.
- 10 The reaction for the formation of ampicillin enamine (II) is conducted in an aprotic polar solvent, such as N,N-dimethylacetamide, N,N-dimethylformamide, dimethoxyethane, dimethylsulphoxide, tetrahydrofuran or dioxane.
- 15 To complete the reaction, it is sufficient to leave the components of the mixture in contact at a temperature between 0°C and 60°C, preferably between 20°C and 30°C, for 2 to 8 hours, preferably 3 hours.

- 20 The compound II can be prepared via acylation of 6-aminopenicillanic acid with a corresponding enamine derivative of phenylglycine to the formation of the compound II which thereafter can be esterified directly and converted to bacampicillin with isolation of the compound II.

- 25 The esterification reaction after the addition of the α -halodiethylcarbonate to the said mixture, takes place at a temperature between 15°C and 80°C, preferably between 45°C and 55°C, for a period of time from 1 hour to 24 hours, preferably from 5 to 10 hours.

- 30 The esterification reaction is suitably carried out in an organic solvent such as methylene chloride or acetone, dimethylacetamide, dimethylformamide and dimethylsulfoxide, or in a mixture of organic solvents. It is possible to use also organic solvent containing water.

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In the easiest and most suitable conditions for industrial purposes, the esterified enamine (IV) is isolated by dilution of the reaction mixture with water and subsequent extraction with a suitable solvent which is immiscible with water, for example n-butyl acetate.

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The acetate phase is agitated with a dilute solution (0.2 - 0.3N) of HCl until the protective group is completely hydrolysed, which requires a contact time of 2 to 8 hours, preferably 4-5 hours, at ordinary temperatures.

10

By addition of sodium chloride, compound (I) separates out from the aqueous phase in the form of the hydrochloride, which is extracted with a suitable solvent, for example n-butyl acetate.

15 By concentrating the organic phase at low pressure at a temperature of 40°C until a small volume remains, crystallization of the product according to formula (I) takes place.

The crystalline product is isolated by filtration, washing and vacuum drying.

20

The following examples illustrate the present aspects of the invention without limiting it in any way.

25 Example 1

36.4 g (0.075 m) of potassium N-(1-methoxycarbonyl-propen-2-yl)-6-[D(-)- α -amino- α -phenylacetamido] penicillate are added to a solution of 17.8 g (0.116 m) of α -chlorodiethylcarbonate and 3 g (0.01 m) of tetrabutylammonium bromide in 150 ml of N,N-dimethylformamide. Under agitation the temperature is raised to 45°C and maintained at 45°C - 50°C for 5 hours.

30

When heating is completed, the reaction mixture is poured into a mixture comprising 300 ml of a 14% aqueous sodium chloride solution and 600 ml of n-butyl acetate. The mixture is agitated for 10 minutes, then the

35



organic phase is separated and the aqueous phase is extracted with 100 ml of n-butyl acetate. The reunited organic phases, after two washings with 75 ml of 14% sodium chloride aqueous solution, are concentrated at low pressure until an oil is obtained.

5

The oil is mixed with 200 ml of tetrahydrofuran and 100 ml of water; the solution obtained (pH 4.8) is brought under agitation to pH 1.5 by adding, in all, 12 ml of 6N HCl in 1 hour.

10 After leaving the solution to stand for another hour at ordinary temperature, the tetrahydrofuran is removed at low pressure at 40°C, 150 ml of n-butyl acetate are added to the remaining aqueous phase (150 ml) and then 15 g of sodium chloride are added.

15 The organic phase is separated and the aqueous phase is extracted with 100 ml of n-butyl acetate.

The reunited organic phases are concentrated under vacuum at 40°C to a volume of 120 ml.

20

The product is left to crystallize for 15 hours at 5°C.

It is then filtered, washed with n-butyl acetate (50 ml) and ethyl acetate (50 ml).

25

It is vacuum dried at 40°C.

The following is obtained: 25.2 g (66.9%) of the 1-ethoxycarbonyloxy-ethyl ester of the 6-(D-(-)- α -amino- α -phenylacetamido) penicillanic acid hydrochloride with m.p. 160-2°C.

30

Analytical determinations:

Titre: 97.82%

Rotatory power: +166.3° (c=1, EtOH95°)

35

pH: 4.05 (2% aqueous solution)

Moisture content: 0.82%

Residual solvents: ethyl acetate 0.45; n-butyl acetate 0.98%

IR and NMR spectra are standard

Residual ampicillin: 0.06%



Example 2

16.2 ml (0.15 m) of methyl acetoacetate and 30.2 g (0.075 m) of ampicillin trihydrate are added to a suspension of 12.54 g (0.0907 m) of
5 finely pulverized anhydrous potassium carbonate in 100 ml of N,N-dimethylformamide.

It is maintained with agitation at 22°C-23°C for 3 hours and after this time considerable fluidization of the mass can be observed.

10

17.8 g (0.117 m) of α -chloro-diethylcarbonate, 3 g (0.01 m) of tetrabutylammoniumbromide and 50 ml of N,N-dimethylformamide are now added in that order.

15 The mixture is heated under agitation for 5 hours at 45°C - 50°C, then left to stand at +5°C for 15 hours.

The reaction mass is poured into a mixture consisting of 600 ml of water and 200 ml of n-butyl acetate and it is agitated until a complete
20 solution is obtained, the aqueous phase is collected and extracted with another 50 ml of n-butyl acetate.

The reunited organic phases are washed twice with 50 ml of water each time. 75 ml of N HCl and 185 ml of water are added to the organic phase
25 subjected to agitation; it is left under agitation at 22°C -23°C for 4 hours.

The aqueous phase is collected and the organic phase is extracted with 50 ml of water. The reunited aqueous phases are brought to pH4 with a
30 10% aqueous solution of Na_2CO_3 , then bleaching carbon is added to them and they are filtered.

150 ml of n-butyl acetate and 40 g sodium chloride are added to the aqueous filtrate.

35

The organic phase is separated and the aqueous phase is extracted with 100 ml of n-butyl acetate.



The reunited phases in butyl acetate are concentrated at low pressure at 40°C to a volume of approximately 150 ml.

The product is left to crystallize for 15 hours at +5°C.

5

It is filtrated, washed with n-butyl acetate (50 ml) and ethyl acetate (50 ml).

10

It is dried under a vacuum of 10 mm Hg in the presence of moisture at 25°C for 24 hours.

15

Yield: 20.8 g (55%) of the 1-ethoxycarbonyloxyethyl ester of the 6-(D(-)- α -amino- α -phenylacetamido) penicillanic acid hydrochloride with m.p. 159-161°C and characteristics conforming to an authentic sample.

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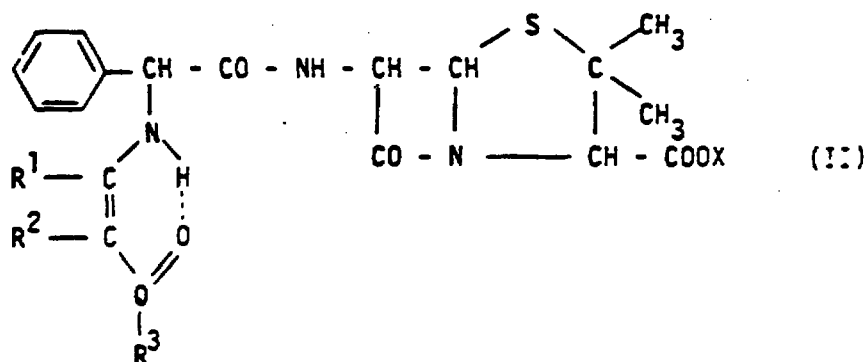
Example 3

The procedure of Example 2 was repeated but using ethyl acetoacetate and ampicillin dane salt. 16.1 g of a white crystalline product was obtained of m.p. 144-148°C (Tottoli apparatus). The IR and TLC analysis conformed to that of a genuine sample, and the product had KF of 0.35%, a pH of 3.55 (2% aqueous solution), an assay TQ of 95.2% and 3.5% total residue solvents.

The procedure was repeated again but with 9 g of
10 alpha-chlorodiethyl carbonate added immediately and the balance added after 2 hours. The reaction mixture was heated for 3 hours at 45°C. 13.7 g. of a crystalline beige product was obtained, m.p. 143-146°C (Tottoli apparatus). The IR and TLC analysis conformed to that of
15 a genuine sample and the product had a KF of 0.2%, a pH of 3.43 (2% aqueous solution), an assay to 94.8% and 2.6% residual solvents.

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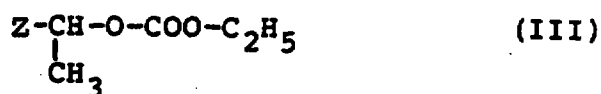
a) reacting ampicillin, or an alkali metal, alkaline earth metal or organic base salt thereof, with a reactive derivative of acetoacetic acid to form the corresponding enamine with the formula:



wherein R¹ represents an alkyl group containing 1-4 carbon atoms, a substituted or non-substituted aryl group or an aralkyl group; R² represents hydrogen, an alkyl group containing 1-4 carbon atoms, a substituted or non-substituted aryl group or an aralkyl group; R³ represents an alkyl group containing 1-4 carbon atoms, a substituted or non-substituted aryl group, an aralkyl group, an alkoxy group containing 1-4 carbon atoms, an aryloxy group or an amine group, and X represents hydrogen or an alkali metal, an alkaline earth metal or an organic base;

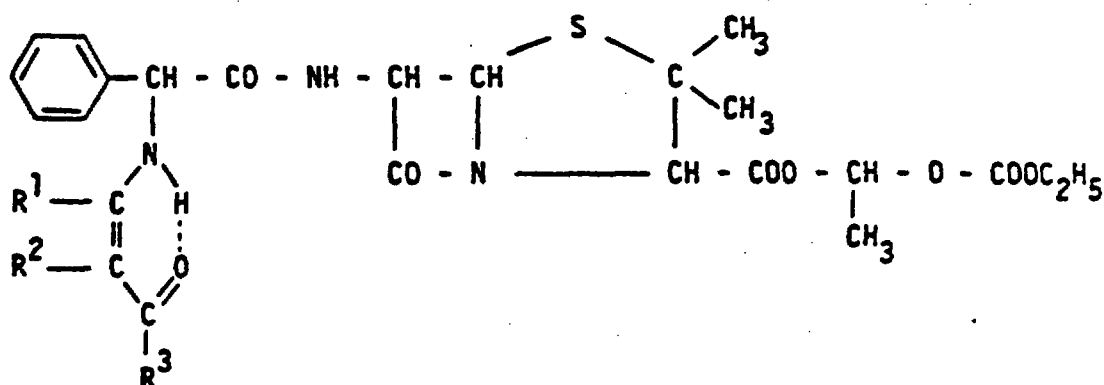


b) reacting an alkali metal, alkaline earth metal or an organic base salt of formula II with a compound of formula:



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wherein Z is Cl or I in the presence of a catalyst to form :
the corresponding ester with the formula:



(IV)

wherein R¹, R² and R³ have the meanings specified above, and

c) subjecting ester IV to mild hydrolysis in an acid medium.

10 2. Process according to claim 1, wherein the ampicillin salt is an alkali metal or alkaline earth metal salt obtained by transforming ampicillin trihydrate by a per se known method in a polar solvent.

15 3. Process according to claim 1 or 2, wherein the formation of the enamine (II) is carried out by reacting the salt of ampicillin with an alkyl acetoacetate in an aprotic polar solvent at a temperature of 0°C to 60°C and for 2 to 8 hours.



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4. Process according to claims 3, wherein the alkyl acetoacetate is methyl or ethyl acetoacetate and is used in an amount 10-50% more than the stoichiometric ratio.
5. Process according to claim 3 or 4, wherein the aprotic polar solvent is selected from N,N-dimethylacetamide, N,N-dimethylformamide, dimethoxyethane, dimethylsulfoxide, tetrahydrofuran and dioxane.
6. Process according to claim 5 in which the polar solvent is N,N-dimethylformamide.
7. Process according to any one of claims 3 to 6, wherein the enamine formation is carried out at a temperature of 20°C to 30°C.
8. Process according to any one of claims 3 to 7, wherein enamine formation is carried out in a time of 3 hours.
9. Process according to any one of the preceding claims, wherein enamine formation is carried out in the presence of an organic base or an alkali metal carbonate or alkaline earth metal carbonate.
10. Process according to any one of the preceding claims wherein the catalyst is selected from quaternary ammonium salts, alkali metal bromides, alkali metal iodides and cyclic ethers.
11. Process according to claim 10, wherein the catalyst is tetrabutylammonium bromide.
12. Process according to any one of the preceding claims, wherein the catalyst is present in an amount of from 0.005



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to 0.10 moles, per mole of the compound III and V,
respectively.

5 13. Processs according to claim 11 wherein the amount of
catalyst present is from 0.01 to 0.1 moles per mole of
compound III and V respectively.

10 14. Process according to any one of the preceding claims,
wherein the esterification reaction temperature is 45°C to
55°C.

15 15. Process according to any one of the preceding claims,
wherein the esterification reaction is carried out in 5-10
hours.

16. Process according to any one of the preceding claims,
wherein the hydrolysis is carried out with dilute
hydrochloric acid after isolating ester (IV).

20 17. A process according to claim 1 substantially as
hereinbefore described with reference to any one of the
Examples.

