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ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ PUBLICATION NUMBER **CY1519**

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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C2C

(54) Improvements in the preparation of ampicillin

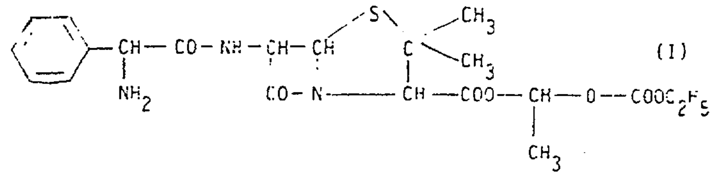
(57) α-Chloro and α-iodo diethylcarbonate are used to prepare the 1-ethylcarbonyloxyethyl ester of 6-(D-(−)-α-amino-α-phenylacetamido)penicillanic acid. The amino group in ampicillin is first protected by reaction with an acetoacetate derivative and the protecting group removed after the esterification step.

SPECIFICATION

Improvements in the preparation of antibiotics

Field of the invention

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


(I)

Furthermore, the invention relates to

- the novel compound α-bromodiethylcarbonate, which with great advantage is used in the said novel method for preparing bacampicillin of the formula I, and which in a more general sense is also used with great advantage in the preparation of the ethoxycarbonyloxyethyl ester of 6-aminopenicillanic acid, penicillins and cefalosporins
- novel methods for the preparation of α-bromodiethylcarbonate
- novel intermediates in the preparation of α-bromodiethylcarbonate
- the use of α-bromodiethylcarbonate in the preparation of the ethoxycarbonyloxyethyl ester of 6-aminopenicillanic acid, penicillins such as penicillin G, penicillin V and ampicillin, and cefalosporins
- improvements in the process for preparing ethoxycarbonyloxyethyl esters of 6-aminopenicillanic acid, penicillins and cefalosporins.

The substance 1 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.

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

Background of the invention

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

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-imineother, in order 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.

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 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.

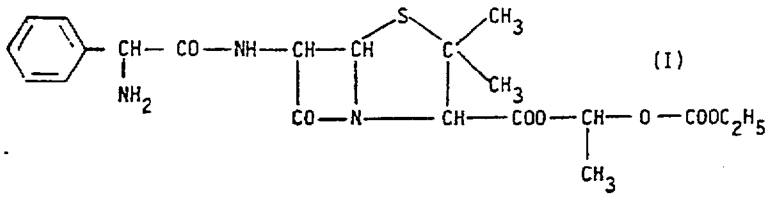
The invention

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 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.

The invention also provides the novel compound α-bromodiethylcarbonate, novel methods for the preparation thereof; novel intermediates in the preparation of α-bromodiethylcarbonate; the use of α-bromodiethylcarbonate in the preparation of the ethoxycarbonyloxyethyl ester of 6-amino-penicillanic acid and penicillins such as penicillin G, penicillin V and ampicillin; and improvements in the process for preparing ethoxycarbonyloxyethyl esters of 6-aminopenicillanic acid, penicillins and cefalosporins.

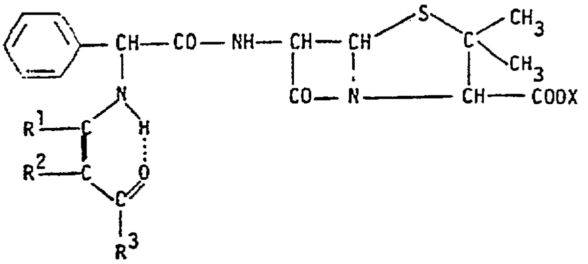
α-Bromodiethylcarbonate is used with great advantage as a reactant in these esterification processes. The use of α-bromodiethylcarbonate leads to particularly high yield and high purity of the final products such as bacampicillin.

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


(I)

characterized by the following stages:

a) reacting of ampicillin, preferably in the form of an alkaline salt, with a reactive derivative of acetoacetic acid to form the corresponding enamine having the following formula:


(II)

where:

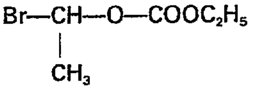
R^1 represents an alkyl group containing 1 to 4 carbon atoms, a substituted or unsubstituted aryl group or an aralkyl group;

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

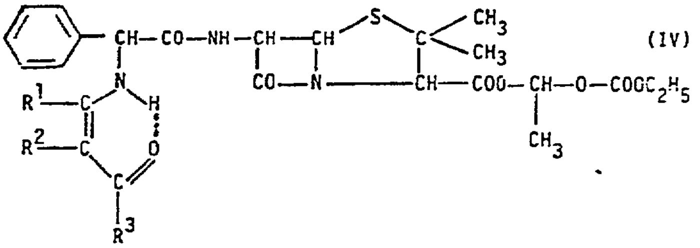
R^3 represents an alkyl group containing 1 to 4 carbon atoms, a substituted or unsubstituted aryl group, an arylkyl group, an alkoxy group containing 1 to 4 carbon atoms, an aryloxy group or an amino group, and

X represents an alkali metal, an alkaline-earth metal or an organic base;

b) reaction of the resulting intermediate with an α-bromo-diethylcarbonate having the following formula:


$$\underset{\displaystyle CH_3}{\underset{|}{Br-CH}}-O-COOC_2H_5 \qquad (III)$$

to form the corresponding ester having the following formula:


(IV)

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

c) hydrolysis in an acid medium, obtaining the compound according to formula (I).

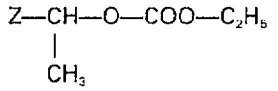
The esterification reaction between the compounds II and III can be carried out with or without an esterification catalyst present.

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.

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.

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.

The invention also includes an embodiment of the process outlined above for the preparation of bacampicillin which comprises reacting a compound of the formula II with a compound of the formula



$$\underset{\displaystyle CH_3}{Z—\underset{|}{CH}}—O—COO—C_2H_5 \qquad (V)$$

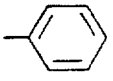
wherein Z is Cl or I, which embodiment is characterized in that the process is carried out in the presence of a catalytic amount of a catalyst as specified above. The catalyst is suitably used in an amount of from 0.005 to 0.10 moles per mole of compound V.

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

alkyl: CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, n-C_4H_9

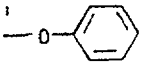
alkoxy (R^3 only): OCH_3, OC_2H_5, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $O(CH_2)_3CH_3$

aryl:

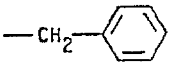


substituted aryl: phenyl substituted with halogen such as Cl and Br

aryloxy:



aralkyl:



The radical X is selected among groups which are well known in the art, for example
alkali metal: Na, K
alkaline earth metals: Ca, Mg
organic base: organic bases which are known in the synthesis of penicillins, e.g. tertiary ammonium groups, triethylamine, ethylpiperidine and methylmorpholine.

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).

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.

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.

The α-bromodiethylcarbonate, compound III, which is a novel compound and as such included in the scope of the invention may be prepared by reacting the corresponding α-chlorodiethylcarbonate with sodium bromide as is exemplified in Example 1 below.

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.
- addition of an esterification catalyst, preferably tetrabutylammonium bromide
- addition of α-bromdiethylcarbonate 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.
- 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.
- 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.

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.

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.

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.

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 enamine (II) took place.

The reaction for the formation of ampicillin enamine (II) is conducted in an aprotic polar solvent, such as N,N-dimethylacetamide, N,N-di-methylformamide, dimethoxyethane, dimethylsulphoxide, tetrahydrofuran or dioxane.

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.

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.

The esterification reaction after the addition of the α-bromdiethylcarbonate 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.

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. The use of esterification catalyst is desirable when acetone is used as solvent for the esterification reaction.

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.

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.

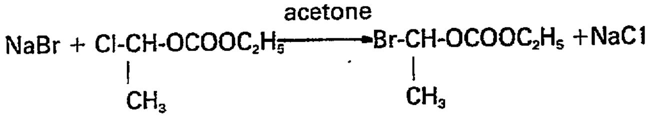
By addition of sodium chloride, compound (I) separates out from the aqueous phase in the form of the hydrochloride, which is extracted with a suitable solvent, for example n-butyl acetate.

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.

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

Example 1 Preparation of α-bromdiethylcarbonate



$$NaBr + \underset{CH_3}{Cl\text{-}CH}\text{-}OCOOC_2H_5 \xrightarrow{\text{acetone}} \underset{CH_3}{Br\text{-}CH}\text{-}OCOOC_2H_5 + NaC1$$

Sodium bromide (102.9 g) dissolved in aceton (600 ml) was reacted for 2-3 hours at ambient temperature (20-25°C) with α-chlorodiethylcarbonate (152.6 g) dissolved in 100 ml of acetone. The mixture was then concentrated under vacuum at low temperature, max. 35°C, until a semi-solid mass was obtained. The reaction mixture was then partitioned with H_2O/ethyl ether. The aqueous phase was separated and was then extracted twice with 400 ml of ethyl ether.

The combined organic phases containing the α-bromdiethylcarbonate were washed with
800 ml of H_2O
1000 ml of 1% sodium metabisulphate aqueous solution
1000 ml of NaCl saturated solution

The organic phase was dried over Mg sulphate, and then concentrated under vacuum at low temperature, max. 35°C to give the title product (60%) in the form of a liquid which initially was colourless or slightly yellow-brown.

It was used directly in the esterification step according to Example 2 below.

Example 2

25.08 g (0.181 m) of finely ground anhydrous potassium carbonate are suspended in 200 ml of N,N-dimethylacetamide and 32.4 ml (0.3 m) of methyl acetoacetate and 60.4 g (0.15 m) pf ampicillin trihydrate are added.

The mixture is maintained under fast agitation for 5 hours at 20°C - 25°C; after this time 46.1 g (0.234 m) of bromdiethylcarbonate, 6 g (0.02 m) of tetrabutyl ammonium bromide and 100 ml of N,N-dimethylacetamide are added.

It is heated under agitation for 10 hours at 40°C - 42°C; the reaction mass is poured into a mixture consisting of 1200 ml of water and 400 ml of n-butyl acetate.

The aqueous phase is collected and extracted with another 100 ml of n-butyl acetate.

The reunited organic phases are washed twice with 100 ml of water each time. 150 ml N HCl and 370 ml of water are added to the organic phase which is 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 100 ml of water.

The reunited aqueous phases are brought to pH 4 with a 10% aqueous solution of Na_2CO_3, then bleaching carbon is added to them and they are filtered.

300 ml of n-butyl acetate and 80 g of sodium chloride are added to the aqueous filtrate.

The organic phase is separated and the aqueous phase is extracted with 200 ml of n-butyl acetate.

The reunited phase in n-butyl acetate are concentrated at low pressure at 40°C to a volume of approximately 300 ml. The product is left to crystallize for 15 hours at +5°C.

It is filtered, washed with n-butyl acetate (100 ml) and ethyl acetate (100 ml). It is vacuum dried at 40°C for 24 hours.

Yield: 54.2 g (72%) of the 1-ethoxycarbonyloxyethyl ester of the 6-(D(-)-α-amino-α-phenylacetamido) penicillanic acid with m.p. 160-2°C. (d) and characteristics conforming to the authentic hydrochloride sample.

Example 3

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.

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 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.

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.

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.

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.

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).

It is vacuum dried at 40°C.

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

Analytical determinations:

Titre: 97.82%
Rotatory power: +166.3° (c=1, EtOH95°)
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 4

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 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.

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.

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 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 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 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.

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.

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

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

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.

Example 5

A mixture of 160 ml acetone, 22.6 g (0.075 mol) of the potassium salt of D(-)-N-methoxycarbonylpropen-2-yl-aminophenylacetic acid, 6.9 ml (0.088 mol) ethyl chloroformate and 3 drops of N-methylmorpholine, is stirred for 15 minutes at a temperature of −20 - −30°C. To this reaction mixture a solution of 16.2 g 6-aminopenicillanic acid, dissolved in 35 ml water through the gentle addition of 7.6 g (0.075 mol) triethylamine with agitation, is added in one portion, after which the mixture is diluted with 90 ml acetone and chilled to −20°C.

After stirring for 45 minutes, without any additional cooling, 23.4 g (0.117 mol) of α-bromodiethylcarbonate, 3 g (0.01 mol) or tetrabutylammonium bromide and 250 ml of N,N-dimethylformamide are added in that order. The mixture is stirred for 18 hours at 25°C. After that time 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 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. 185 ml of water is added to the organic phase and 1 N HCl is added dropwise with agitation to a pH of 1.9. The mixture is left under agitation at 22-23°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 pH 4 with a 10% aqueous solution of Na_2CO_3, active carbon is added to them and they are filtered. 150 ml of n-butyl acetate and 40 g of sodium chloride are added to the aqueous filtrate.

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.

It is filtered, washed with n-butyl acetate (25 ml) and ethyl acetate (25ml). It is dried under a vacuum of 10 mm Hg at 25°C for 24 hours.

Yield: 1.17 g of the 1-ethoxycarbonyloxyethyl ester of 6-(D(-)-α-amino-α-phenylacetamidopenicillanic acid hydrochloride with m.p. 159-161°C and characteristics (NMR, TLC) conforming to an authentic sample.

Example 5a

The procedure of example 5 was repeated with the difference that the 6-aminopenicillanic acid was dissolved in 20 ml water instead of in 35.

Yield: 1.05 g of the ethoxycarbonyloxyethyl ester of 6-(D(-)-α-amino-α-phenylacetamidopenicillanic acid hydrochloride as a white crystalline powder with m.p. 148-151°C, with decomposition, and characteristics (TLC, IR) conforming to an authentic sample.

Example 6

6.25 g (0.045 m) of finely ground anhydrous potassium carbonate are suspended in 50 ml of dimethyl sulphoxide and 8.1 ml (0.075 m) of methyl acetoacetate and 15.1 g (0.0375 m) of ampicillin trihydrate are added.

The mixture is maintained under fast agitation for 5 hours at 20°C - 25°C; after this time 11.5 g (0.059 m) of bromodiethylcarbonate and 25 ml of dimethyl sulphoxide are added.

It is heated under agitation for 17 hours at 35-37°C; the reaction mass is poured into a mixture consisting of 300 ml of water and 100 ml of n-butyl acetate.

The aqueous phase is collected and extracted with another 100 ml of n-butyl acetate.

The reunited organic phases are washed twice with 25 ml of water each time.

92.5 ml of water and NHCl (7.0 ml) to a pH of 1.9 are added to the organic phase which is subjected to agitation; it is left under agitation at 22°C - 23°C for 2,5 hours.

The aqueous phase is collected and the organic phase is extracted with 25 ml of water.

The reunited aqueous phases are brought to pH 4 with 10% aqueous solution of Na_2CO_3, then active carbon is added to them and they are filtered.

75 ml of n-butyl acetate and 37 g of sodium chloride are added to the aqueous filtrate.

The organic phase is separated and the aqueous phase is extracted with 50 ml of n-butyl acetate.

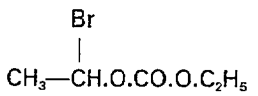
The reunited phases in n-butyl acetate are concentrated at low pressure at 40°C to a volume of approximately 75 ml. The product is left to crystallize for 15 hours at +5°C.

It is filtrated, washed with n-butyl acetate (25 ml) and ethyl acetate (25 ml). It is vacuum dried at 40°C for 3 hours.

Yield: 1.9 g (10%) of the 1-ethoxycarbonyloxyethyl ester of the 6-(D(-)-α-amino-α-phenylacetamido) penicillanic acid with m.p. 160-162°C and characteristics conforming to an authentic sample of the hydrochloride (e.g. IR:V 1790cm^{-1}, β-lactam carbonyl).

The novel compound α-bromdiethylcarbonate of the invention, novel and inventive processes for the preparation thereof and its use in the preparation of the ethoxycarbonyloxyethyl esters of 6-aminopenicillanic acid, penicillins such as penicillin G, penicillin V and ampicillin, and cefalosporins, will now be described and exemplified in more detail.

This aspect of the invention is concerned with improvements in and relating to the preparation of α-bromodiethylcarbonate of the formula:



$$CH_3—\overset{Br}{\overset{|}{C}}H.O.CO.O.C_2H_5 \qquad (III)$$

The alpha--bromo diethylcarbonate of the formula (III) may according to a further aspect of the invention, which is further dealt with later, be used in the synthesis of alpha(ethoxycarbonyloxy)-ethyl esters of 6-amino-penicillanic acid, penicillins and cefalosporins, for example the antibiotic bacampicillin. Alpha-bromodiethylcarbonate may thus advantageously be used in the preparation of the ethoxycarbonyloxyethyl esters of 6-aminopenicillanic acid, penicillin G, penicillin V and ampicillin.

According to the invention two novel and inventive processes, herebelow denoted process A and process B, are provided for the preparation of alpha-bromodiethylcarbonate of the formula III.

A. The first of these processes, process A, comprises the steps of:

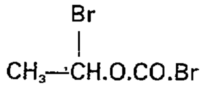
(a) reacting an aldehyde of the formula

$$CH_3CHO \qquad VI$$

with carbonyl bromide

$$COBr_2 \qquad VII$$

to give an alpha-bromo-bromoformate of the formula:

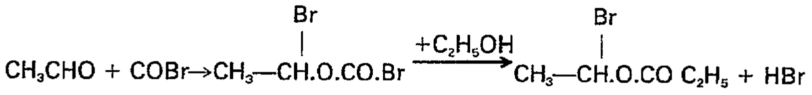


$$CH_3—\overset{Br}{\overset{|}{C}}H.O.CO.Br \qquad VIII$$

and;

(b) reacting the alpha-bromo-bromoformate of formula VIII with an alcohol of the formula C_2H_5-OH to yield the desired alpha-bromo-diethylcarbonate of the formula III.

Thus, the process A in accordance with the invention may be summarised by the reaction scheme:



$$CH_3CHO + COBr \rightarrow CH_3—\overset{Br}{\overset{|}{C}}H.O.CO.Br \xrightarrow{+C_2H_5OH} CH_3—\overset{Br}{\overset{|}{C}}H.O.CO\ C_2H_5 + HBr$$

The alpha-bromo-bromoformate of the formula VIII is in it self a new compound and is provided as a further feature of the invention.

The reaction between the aldehyde, CH_3CHO, and carbonyl bromide is most suitably carried out in the presence of a catalyst which may be, for example, a tertiary amine (for example a tertiary aliphatic amine, a tertiary mixed alkyl/aryl amine or a tertiary aromatic amine), tertiary phosphine, amide, substituted urea or thiurea, phosphoric acid amide, tertiary oxonium or sulphonium salt, or a quaternary ammonium or phosphonium salt. Preferred examples of catalysts for use in the process A according to the invention include pyridine, dimethylformamide, tetra-n-butyl urea, hexamethyl-phosphoric-tri-amide and benzyltrimethyl ammonium bromide.

The catalyst is suitably used in an amount of from 0.05 to 0.5, preferably from 0.05 to 0.15, moles of catalyst per mole of aldehyde.

The reaction between the aldehyde and the carbonyl bromide is suitably carried out in the presence of a solvent which may be, for example, an aromatic hydrocarbon such as toluene or a halogenated hydrocarbon such as dichloromethane, carbon tetrachloride or chlorobenzene. The reaction between the aldehyde and the carbonyl bromide is suitably carried at a temperature of from −40 to 120°C, preferably 0 −40°C. The carbonyl bromide will usually be used in molar excess with respect to the aldehyde, suitably in a molar excess of from 10 to 100%, preferably from 20 to 50%.

The intermediate alpha-bromo-bromoformate of formula VIII produced in step (a) of the process A of the invention need not be isolated prior to reaction with the alcohol C_2H_5OH and, indeed, it is generally preferred not to do so. Thus, in accordance with a preferred embodiment of the invention, the reaction mixture obtained from step (a) is freed of excess carbonyl bromide, for example by warming under reduced pressure or by purging with nitrogen. The crude alpha-bromo-bromoformate-containing reaction mixture is then reacted with an excess of the alcohol. The reaction may conveniently be effected by heating the mixture under reflux until the evolution of hydrogen bromide ceases or by adding a tertiary base to the mixture and, if necessary, warming it. Any residual catalyst from step (a) or its complex with carbonyl bromide does not appear to interfere with the subsequent reaction and, in some cases, appears beneficial.

The resultant crude alpha-bromocarbonate may conveniently be isolated from the reaction mixture by fractional distillation under reduced pressure.

Process A is illustrated in Examples 7 and 8, which are given by way of illustration only.

B. The second process, process B, of the invention for the preparation of α-bromodiethylcarbonate will now be described. Method B is exemplified in Example 9, which is given by way of illustration only.

Process B of the invention is concerned with improvements in and relating to the preparation of α-bromodiethylcarbonate by a modification of the Finkelstein reaction, that is by reaction of an alkyl chloride or arylalkyl chloride (or a compound containing such a group) with an alkali metal bromide or alkali metal iodide to replace the chlorine substituent by a bromine or iodine substituent respectively; or by the reaction of an alkyl bromide or arylalkyl bromide (or a compound containing such a group) with an alkali metal iodide to replace the bromine substituent by an iodine substituent.

The Finkelstein reaction is useful since the resulting iodides are generally more reactive than the bromides which in turn are more reactive than the chlorides. In some cases only catalytic amounts of the alkali metal bromide or iodide are necessary and the resulting more reactive species is allowed to react with the desired substrate regenerating the alkali metal bromide or iodide, thus continuing the reaction.

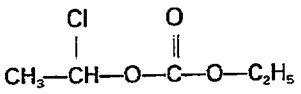
Not all optionally substituted alkyl chlorides or arylalkyl chlorides undergo the reaction and, in particular, it has been found difficult to carry out the reaction with alpha-chloro esters and alpha-chlorocarbonates, that is compounds in which the chlorine atom is attached to a carbon atom which is, in turn, attached to either end of a group -C(O)-O-. An example of such an alpha-chlorocarbonate is α-chlorodiethylcarbonate, which is a known intermediate in the preparation of ethoxycarbonyloxyethyl esters of 6-aminopenicillanic acid and of penicillins as described above.

It has now been found, in accordance with the present invention, that this problem may be overcome by carrying out the reaction using a two-phase solvent system, one phase of which is water and the other is a water-immiscible organic solvent, in the presence of a phase transfer catalyst.

According to process B of the invention, therefore, there is provided a process for the preparation of α-bromodiethylcarbonate by reaction of α-chlorodiethylcarbonate with an alkali metal bromide, which process is characterized in that the reaction is carried out in a two-phase solvent system comprising water and a water-immiscible organic solvent in the presence of a phase transfer catalyst.

Suitable water-immiscible organic solvents for use in accordance with the invention include halogenated hydrocarbons, for example halogenated paraffins such as dichloromethane; and aromatic hydrocarbons such as toluene. Suitable phase transfer catalysts include quaternary ammonium salts, for example tetraalkyl ammonium salts such as cetyltrimethyl ammonium bromide and tetra-n-butyl ammonium hydrogen sulphate. The alkali metal bromide may, for example, be sodium, potassium, or lithium bromide, lithium bromide being preferred.

Thus, in process B of the invention, α-chlorodiethylcarbonate of the formula:

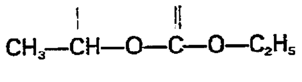


$$CH_3-\overset{\displaystyle Cl}{\overset{|}{CH}}-O-\overset{\displaystyle O}{\overset{\|}{C}}-O-C_2H_5 \qquad IX$$

is reacted in a two-phase solvent system, one phase of which is water and the other is a water-immiscible organic solvent, with an alkali metal bromide of the formula

$$R\text{-}Br \qquad X$$

in which formula R is an alkali metal such as Na, K and Li, to the formation of the compound of the formula:



$$CH_3-\overset{\displaystyle Br}{\overset{|}{CH}}-O-\overset{\displaystyle O}{\overset{\|}{C}}-O-C_2H_5 \qquad III$$

As noted above, the preferred alkali metal R is Li so that LiBr is a preferred reagent of the formula X.

In connection with process B it has been found that lithium bromide may be used with advantage in a conventional Finkelstein reaction (i.e. one employing a single phase organic solvent system), for example to halogenate an alpha-chloro-carbonate. This method is exemplified in Example 10.

Accordingly, the present invention also provides, in accordance with a further embodiment thereof, a process for the preparation of α-bromodiethylcarbonate which comprises reacting α-chlorodiethylcarbonate with lithium bromide.

Suitable solvents for such a process include lower aliphatic alcohols, lower aliphatic ketones, lower aliphatic ethers and lower aliphatic amides of formic acid.

The aspect of the invention which relates to the use of the novel compound α-bromodiethylcarbonate in the preparation of ethoxycarbonyloxyethyl esters of 6-aminopenicillanic acid, penicillins and cefalosporins, will now be described.

In summary, this aspect of the invention comprises

1. the use of α-bromodiethylcarbonate in the preparation of the ethoxycarbonyloxyethyl esters of 6-aminopenicillanic acid, penicillins such as penicillin G, penicillin V and ampicillin, and cefalosporins,
2. a process for the preparation of the ethoxycarbonyloxyethyl ester of 6-aminopenicillanic acid, penicillins and cefalosporins, characterized by reacting 6-aminopenicillanic acid, the penicillin or the cefalosporin, or a salt thereof, with α-bromodiethylcarbonate to the formation of the ethoxycarbonyloxyethyl ester of the 6-aminopenicillanic acid, the penicillin and the cefalosporin, respectively,
3. the improvement in the esterification reaction between an α-halogen-diethylcarbonate and 6-apa, a penicillin or a cefalosporin, which improvement comprises the use of a quaternary ammonium compound at the esterification step, whereby the said quaternary ammonium compound is present in an amount of 1-25, preferably 1-10% of the equimolar amount with respect to the amount of 6-apa, penicillin or cefalosporin.

The ethoxycarbonyloxyethyl ester in particular of 6-apa and of penicillin G are used as in known in the art in the preparation of any desired such semisynthetic penicillin ester by acylating the 6-NH_2 group after removing the side chain in e.g. the penicillin G ester obtained.

This aspect of the invention is concerned with improvements in and relating to the preparation of esters by the reaction of salts of carboxylic acids with α-bromodiethylcarbonate.

The reaction of metal salts of carboxylic acids with alkyl halides or arylalkyl halides to form esters is well known. However, yields are not particularly high and the reaction generally requires forcing conditions such as high temperatures and/or extended reaction times. These forcing conditions limit the synthetic utility of the reaction and its commercial applicability to heat sensitive and labile substances such as pyrethroids, prostaglandins, peptides, penicillins and cephalosporins.

The British patent specification 1443738 discloses the use of a quaternary ammonium salt of penicillins and cefalosporins in place of a metal salt thereof in the preparation of esters of penicillins and cefalosporins.

The preparation of the quaternary ammonium salt of the acid may be time-consuming and expensive. However, as is also disclosed in the British patent specification 1443 738, it is not necessary to first prepare the quaternary ammonium salt of a penicillin or cefalosporin, but the reaction may be carried out by reacting a metal salt of the carboxylic acid, that is the 6-apa, penicillin or cefalosporin with the alkyl or arylalkyl halide in the presence of a quaternary ammonium salt, other than the salt of the carboxylic acid.

It has now been found, according to the present invention, that it is not necessary to employ the said quaternary ammonium salt in a stoichiometric amount with respect to the carboxylic acid, that is 6-apa, the penicillin or the cefalosporin, but that a less than stoichiometric amount with respect to the carboxylic acid, e.g. the 6-apa, penicillin or cefalosporin, will be sufficient.

According to the invention, therefore, there is provided a process for the preparation of an ethoxycarbonyloxyethyl ester of 6-apa, a penicillin or a cefalosporin by reaction of a metal salt or the 6-apa, penicillin or cefalosporin with α-halogendiethylcarbonate in the presence of a quaternary ammonium salt (other than a salt of the said carboxylic acid) whereby the quaternary ammonium compound is present in a less than stoichiometric amount with respect to the 6-apa, penicillin or cefalosporin.

In accordance with the invention, between 1% and 25% of an equivalent of the quaternary ammonium salt is used for each equivalent of the metal salt of the carboxylic acid, and more preferably between 1% and 10% of an equivalent of the quaternary ammonium salt is used.

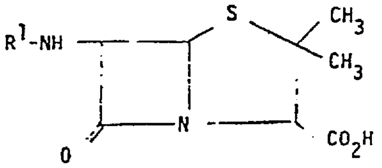
The quaternary ammonium salt of the carboxylic acid is suitably prepared by reaction of a metal of the carboxylic acid with a quaternary ammonium salt of an acid other than said carboxylic acid, typically a mineral acid such as hydrochloric, hydrobromic or sulphuric acid.

Suitable metal salts of carboxylic acids for use in accordance with the present aspect of the invention (either as precursors for the carboxylic acid quaternary ammonium salt or as such) are alkali metal or alkaline earth salts such as sodium, lithium, magnesium and calcium salts. Suitable quaternary ammonium salts of acids other than the carboxylic acid (for use either as precursors for the carboxylic acids quaternary ammonium salts or as such) include for example tetra-alkyl ammonium salts such as tetra-n-butyl ammonium bromide and cetyltrimethyl ammonium bromide and quaternary pyridinium salts such as cetyl-pyridinium bromide. Suitable halides include fluorides, chlorides, bromides and iodides, preferably activated fluorides or activated chlorides or bromides or iodides.

The esterification reaction in accordance with this aspect of the invention may be carried out in the presence or absence of a solvent. Suitable solvents include lower aliphatic alcohols, lower aliphatic ketones, lower aliphatic amides of formic acid and dimethyl sulphoxide. Alternatively, when no solvent is used, an excess of the ester forming halide may be used, particularly if this is a liquid at the temperature, of the reaction.

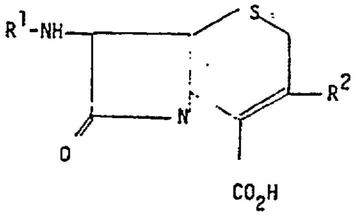
In the previously described aspect of the invention which relates to the use of α-bromodiethylcarbonate in the preparation of ethoxycarbonyloxy ethyl esters of 6-apa, penicillins and cefalosporins, the use of catalyst is optional. Approximately equimolar amounts of the quaternary ammonium salt of the carboxylic acid and the ester forming halide may be used in the reaction. Preferably between 5% and 100% excess of the ester forming halide is used for each equivalent of the salt of the carboxylic acid used and more preferably an excess of between 20% and 60% of the ester forming halide is used.

The improvements in the esterification processes of the invention are particularly suitable for the preparation of the esters of 6-apa, penicillins and cephalosporins and thus, in accordance with a preferred embodiment of the invention the carboxylic acid may be of the formula:



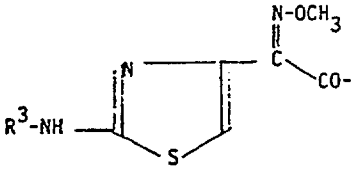
XI

or



XII

in which R¹ is a hydrogen atom or acyl group, particularly a substituted acetyl group such as a phenylacetyl; alpha-aminophenylacetyl; alpha-aminoparahydroxyphenylacetyl; phenoxyacetyl; alpha-carboxyphenylacetyl or alpha-carboxy-3-thienylacetyl group or, when the carboxylic acid is of the formula XII, a group:



XIII

in which R^3 is a hydrogen atom or an amino protecting group such as a benzyloxycarboxyl; trimethylsilyl or *t*-butyloxycarboxylgroup, and

R^2 is a hydrogen atom; an alkyl group (e.g. a methyl group), a substituted alkyl group, e.g. a hydroxymethylene; alkoxy or arylkoxy methylene or acetoxy methylene group) or an acetoxy or substituted acetoxy group (e.g. an alkyl acetoxy, aryl acetoxy, or arylalkyl acetoxy group or the group $C_6H_5.CHOH.CO$-).

In the preparation of esters of penicillins and cephalosporins according to the invention, the ester forming halide is an alpha-halodialkyl carbonate of the formula

CH_3-CH(X)-O-CO-O-CH_2-CH_3,

in which X is a chlorine, bromine or iodine atom, preferably a bromine atom.

In accordance with a preferred embodiment of the invention for the preparation of esters of penicillins and cephalosporins the quaternary ammonium salt employed is tetra-n-butylammonium bromide.

In order that the invention may be well understood the following examples are given by way of illustration.

Example 7

A mixture of acetaldehyde (44 g, 1 mole), carbon tetrachloride (300 ml) and freshly distilled carbonyl bromide (235 g, 1.25 mole) was cooled to 0°C and maintained at this temperature by external cooling during the addition over a period of 1 hour of pyridine (11.9 g, 0.15 mole).

The mixture was allowed to warm up to ambient temperature and then heated to 50°C and maintained at this temperature for a period of 3 hours during which time a precipitate formed.

Evaporation of the reaction mixture under reduced pressure at 50°C gave a semi solid oily mass which readily dissolved in ethanol (92 g, 2 mole) on warming and heating under reflux. After heating under reflux for a further 2 hours, excess ethanol was removed in vacuo and the residue triturated with water (100 ml) and methylene dichloride (200 ml).

Separation of the organic layer and fractional distillation afforded pure ethyl alpha-bromo-ethyl-carbonate (130 g, 66% yield) having a boiling point of 90-92°C at 45 mms of mercury pressure and identical in all respects with an authentic specimen.

Example 8

A mixture of acetaldehyde (44 g, 1 mole), dichloromethane (300 ml) and hexamethylphosphoric-triamide (17.9 g, 0.1 mole) was cooled to −10°C and freshly distilled carbonyl bromide (207 g, 1.1 mole) was gradually added over a period of 4 hours during which time the temperature was allowed to rise to 10°C.

The mixture was then heated under gentle reflux (*ca* 40°C) for 4 hours. While still under reflux, ethanol (69 g, 1.5 mole) was carefully added over a period of 1 hour and heating under reflux continued for a further 1 hour.

Fractional distillation of the resulting mixture afforded pure ethyl alpha-bromoethyl-carbonate directly (114 g, 58% yield).

The authenticity of the ethyl alpha-bronoethyl carbonate formed was confirmed by analysis and independent synthesis as follows.

Diethylcarbonate (118 g, 1.0 mole) was stirred and heated to between 110°C and 112°C and illuminated by a 150 watt tungsten filament lamp. Bromine (96 g, 0.6 mole) was added dropwise over a period of 3 to 4 hours and at such a rate that the mixture did not deepen beyond a pale orange colour.

After addition of bromine was complete, the mixture was cooled to ambient temperature and sodium bicarbonate (20 g) added.

Distillation fractionation of the resulting mixture gave authentic ethyl alpha-bromo-ethyl carbonate (84.2 g, 70% yield) having a boiling point of 87-88°C at 40 mms of mercury pressure.

Example 9

A mixture of lithium bromide (43 g, 0.5 m), ethyl alphachloroethyl carbonate (15.3 g, 0.1 m); water (100 ml), dichloromethane (100 ml) and cetyl trimethyl ammonium bromide (1.5 g) was stirred at ambient temperature for 24 hours. The aqueous layer was removed and replaced by a fresh solution of lithium bromide (26 g, 0.3 m) in water (40 ml) containing cetyl trimethyl ammonium bromide (1 g). After stirring for a further 24 hours during which time the temperature was raised to 35°C, the organic layer was separated, dried and vacuum distilled to afford after repeated fractionation the new compound, ethyl alpha-bromo-ethyl carbonate (15.0 g, 76% yield) having a boiling point of 90-92°C at 35 mms of mercury pressure.

Found:	C 30.7;	H 4.8	Br 40.1%
Calculated:	C 30.5:	H 4.6:	Br 40.6%

The NMR spectrum exhibited peaks as follows:-

1.2 - 1.6 (3H, triplet)	$-CH_2.-\mathit{CH_3}$
2.0 - 2.2 (3H, doublet)	$-CH.\mathit{CH_3}$
4.1 - 4.5 (2H, Quartet)	$-\mathit{CH_2}.CH_3$
6.5 - 6.8 (1H, Quartet)	$-\mathit{CH}.CH_3$

Example 10

Lithium bromide (17.4 g, 0.2 m) was dissolved in dimethyl formamide (150 ml) and the mixture cooled to ambient temperature. Ethyl alphachloroethyl carbonate (30.5 g, 0.2m) was added and the mixture stirred at ambient temperature for 24 hours. The precipitated lithium chloride was filtered off and the filtrate vacuum distilled to afford after careful re-fractionation, ethyl alpha-bromoethyl carbonate in 76% yield based upon recovered ethyl alphachloroethyl carbonate.

Example 11

The authenticity of the foregoing new compound ethyl alpha-bromoethyl carbonate was confirmed by independent synthesis as follows:-

A mixture of diethyl carbonate (35 g, 0.3 m) in carbon tetrachloride (50 ml) and alpha-azo-isobutyronitrile (AIBN) (0.1 g) was heated to gentle reflux and dibromodimethyl hydantoin (28.6 g, 0.1 m) was added in small aliquots over a period of 8 hours together with further additions of AIBN (8×0.05 g): care being taken to ensure that free bromine did not accumulate in the reaction mixture. At the end of the reaction the mixture was subjected to vacuum fractional distillation to afford pure ethyl alpha-bromoethyl carbonate (32.3 g, 82% yield) identical in all respects with the product of Examples 9 and 10.

Example 12 Benzylpenicillin ethoxycarbonyloxyethyl ester

A mixture of potassium penicillin G (7.4 g, 20 mmole), ethyl alpha-chloro-ethyl carbonate (4.6 g, 30 mmole), tetra-n-butyl ammonium bromide (0.8 g, 2.5 mmole) and acetone (80 ml) were stirred and heated under gentle reflux for 4 hours. Excess acetone was removed under partial vacuum and the residue triturated with ice-cold water and methyl isobutylketone. Evaporation of the dried methyl isobutylketone under vacuum gave a semi-crystalline oil (3.8 g) which on trituration with ethanol deposited white crystals (0.9 g) of the alpha-(ethoxycarbonyloxy)-ethyl ester of penicillin G having a purity of 98-99% by HPLC.

Found	C 43.0	H 7.4	N 7.7%
Calculated:	C 43.4	H 7.4	N 8.0%

Example 13 Benzylpenicillin ethoxycarbonyloxyethyl ester

The foregoing experiment of Example 12 was repeated using ethyl alpha-bromo-ethyl carbonate (5.9 g, 30 m mole) instead of ethyl alpha-chloro-ethyl carbonate, whereon there was obtained, on evaporation of the methyl isobutyl ketone, 6.0 g of a semicrystalline oil. Trituration of this oil with warm ethanol and then cooling afforded white crystals (2.5 g, 35% yield) of the alpha-(ethoxycarbonyloxy)-ethyl ester of penicillin G.

Example 14 Benzylpenicillin ethoxycarbonyloxyethyl ester

Potassium benzylpenicillinate (25.08 g, 66.7 mmol) sodium bicarbonate (0.50 g, 6.0 mmol), and tetrabutylammonium bromide (2.15 g, 6.67 mmol) were carefully stirred in methylene chloride (41 ml) and warmed to 40°C. When this temperature was reached α-bromodiethyl carbonate 17.16 g, 86.7 mmol) was added and the slurry was stirred for 4.0 hours. Water (30 ml) was added, followed by a mineral acid to a pH of approx. 5. The mixture was stirred for approx. 4 hours, during which time sodium hydroxide (4%) was added in order to maintain pH between 2.5-3.0. Methylene chloride (50 ml) was then added and the mixture was allowed to separate for a few minutes. The organic phase was washed with water (65 ml) and was then evaporated under reduced pressure. The oily product thus obtained was dissolved in methylene chloride (100 ml) and was evaporated again. The remaining oil was dissolved in methylene chloride to a total volume of 100 ml.

HPLC-analysis of the methylene chloride solution showed a yield of benzylpenicillin ethoxycarbonyloxyethyl ester of 96-97%.

Example 15 Benzylpenicillin ethoxycarbonyloxyethyl ester

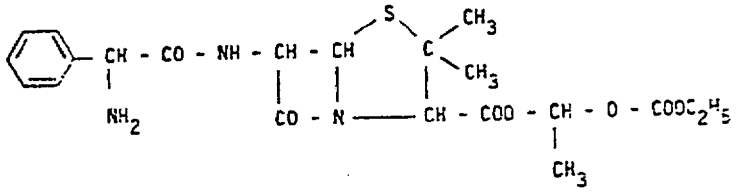
Potassium benzylpenicillinate (5.02 g, 13.3 mmol) and potassium bicarbonate (2.99 g, 38.3 mmol) in dimethyl sulfoxide (13.5 ml) were carefully stirred in an ice-bath. α-bromodiethyl carbonate (3.70 g, 18.6 mmol) was added over a period of 30-40 min using a syringe pump. Stirring was continued while keeping the reaction mixture in the ice-bath. HPLC-analyses showed that a yield of about 70% of the benzylpenicillin ethoxycarbonyloxyethyl ester was obtained within 5-10 min.

Example 16 Benzylpenicillin ethoxycarbonyloxyethyl ester

Potassium benzylpenicillinate (47.03 g, 125 mmol) sodium bicarbonate (0.94 g, 11 mmol), and tetrabutylammonium bromide (2.01 g, 6.25 mmol) were carefully stirred in acetone (77 ml) and warmed to 40°C. When this temperature was reached α-bromodiethyl carbonate (26.06 g, 131 mmol) was added and the slurry was stirred for 4.5 hours. Water (56 ml) was added, followed by a mineral acid to a pH of approx. 5. The mixture was stirred for approx. 3 hours, during which time sodium hydroxide (4%) was added in order to maintain pH between 4.5-4.8. Butyl acetate (100 ml) was then added and the mixture was allowed to separate for a few minutes. The organic phase was washed with water (80 ml) and then evaporated under reduced pressure. The remaining oily product was dissolved in methylene chloride to a total volume of 250 ml. HPLC-analysis of the methylene chloride solution showed a yield of benzylpenicillin ethoxycarbonyloxyethyl ester of 98-99%.

CLAIMS

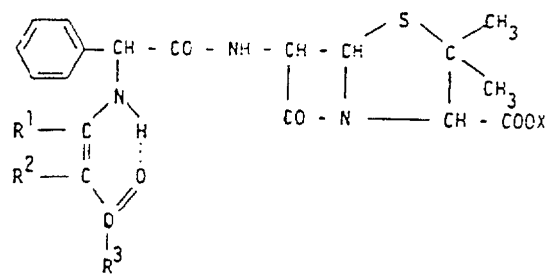
1. Process for the preparation of the 1-ethoxycarbonyloxyethyl ester of the 6-(D-(-)-α-amino-α-phenylacetamido) penicillanic acid with the formula:



(I)

comprising

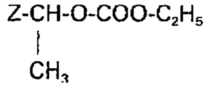
a) reacting ampicillin, or an alkali metal, alkaline earth metal or organic base salt thereof, with a reactive derivative of acetoacetic acid to form the corresponding enamine with the formula:



(II)

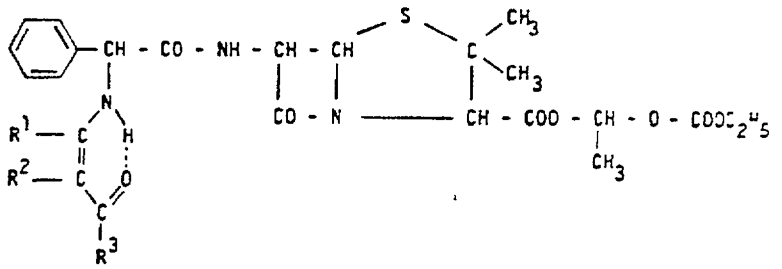
wherein R^1 represents an alkyl group containing 1-4 carbon atoms, a substituted or non-substituted aryl group or an aralkyl group; R^2 represents hydrogen, an alkyl group containing 1-4 carbon atoms, a substituted or non-substituted aryl group or an aralkyl group; R^3 represents an alkyl group containing 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 alkaline 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:



$$\underset{\displaystyle CH_3}{\text{Z-}\underset{|}{\text{CH}}\text{-O-COO-}C_2H_5} \qquad \text{(III)}$$

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



(IV)

wherein R^1, R^2 and R^3 have the meanings specified above, and

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

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, preferably N,N-dimethylformamide.

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.

4. Process according to claim 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, dimethylsulphoxide, tetrahydrofuran and dioxane.

6. Process according to any one of claims 3 to 5, wherein the enamine formation is carried out at a temperature of 20°C to 30°C.

7. Process according to any one of claims 3 to 6, wherein enamine formation is carried out in a time of 3 hours.

8. 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.

9. Process according to any one of the preceding claims, wherein the esterification reaction of the enamine (II) is carried out by addition to the reaction mixture of α-bromo-diethyl carbonate, the reaction being carried out at a temperature of 15-80°C and for a time of 1-24 hours.

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 to 0.10 moles, preferably from 0.01 to 0.10 moles per mole of the compound III and V, respectively.

13. Process according to any one of the preceding claims, wherein the esterification reaction tempera-

ture is 45°C to 55°C.

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

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

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

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