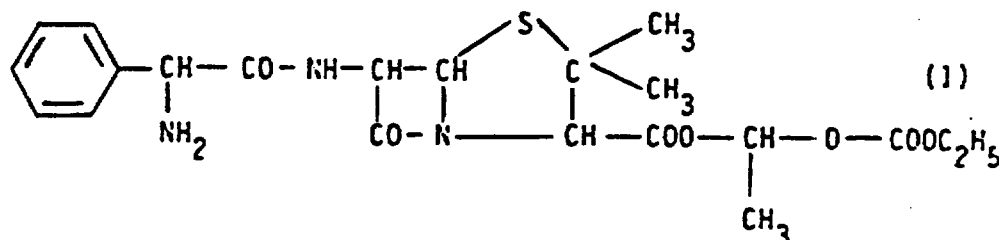


ALPHA-BROMODIETHYLCARBONATE AND ITS USE IN THE PREPARATION
OF ANTIBIOTICS

The present invention relates to α -bromodiethylcarbonate, which with great advantage is used in a method according to the present invention for preparing bacampicillin of the formula I,



The present invention also relates to novel methods for the preparation of α -bromodiethylcarbonate.

15 Application No. 8620344, divided from the present application relates to a method of preparing the ethoxycarbonyloxymethyl ester of 6-aminopenicillanic acid, penicillins and cephalosporins using alpha-dibromoethylcarbonate.

20

The present application is divided from Application No. 17346/83 (Publication No. 2123821) which relates to the use of α -iodo and α -chloro diethyl carbonate, in the presence of a quaternary ammonium salt catalyst, in producing
25 the ethoxycarbonyloxymethyl ester of 6-aminopenicillanic acid, penicillins and cephalosporins.

Application No. 22827/85, also a divisional of 17346/83, relates to the use of α -chloro- or α -iodo-diethylcarbonate in
30 the preparation of the ethoxycarbonyloxymethyl ester of 6-(D,L)- α -amino- β -phenyl acetamido- β -lactam- γ -butyrolidone-2-carboxylic acid in the presence of a catalyst which may be other than a quaternary ammonium salt.

- 1a -

Application No. 28958/85, also a divisional of 17346/83,
relates to novel intermediates in the preparation of
α-bromodiethylcarbonate.

5 The substance I concerned is an ampicillin ester which is
extremely important from the therapeutic 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.

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.

25

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.

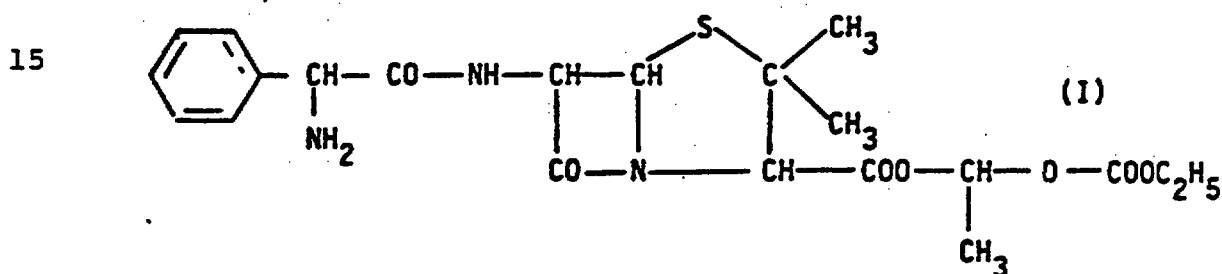
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- A prime object of this invention is to provide a method of preparing the active substance concerned which is easier to carry out and industrially more advantageous. A more specific object of this invention is
35 to provide a method of preparing bacampicillin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

The invention also provides the novel compound α -bromodiethylcarbonate and novel methods for the preparation thereof.

5 α -Bromodiethylcarbonate is used with great advantage as a reactant and leads to particularly high yield and high purity of the final products in an esterification process to produce bacampicillin.

10 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:

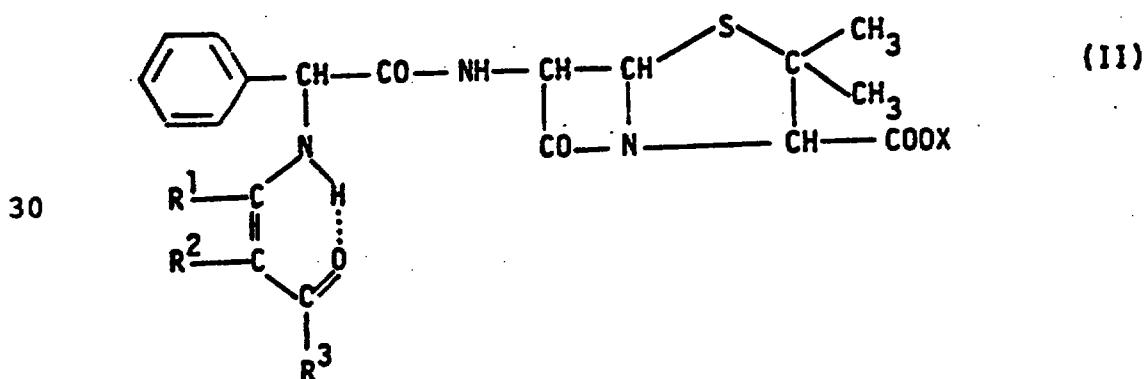


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by

a) reacting ampicillin, preferably in the form of an alkali metal, alkaline earth metal or organic base salt, with a reactive derivative of acetoacetic acid to form

25 the corresponding enamine having the following formula:



35 where:

(15)

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

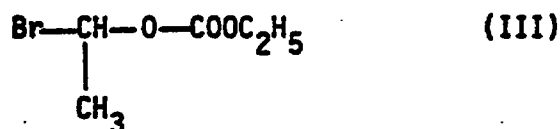
R^2 represents hydrogen, an alkyl group containing 1 to 4 carbon atoms, a substituted or unsubstituted aryl group or an aralkyl group;

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

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

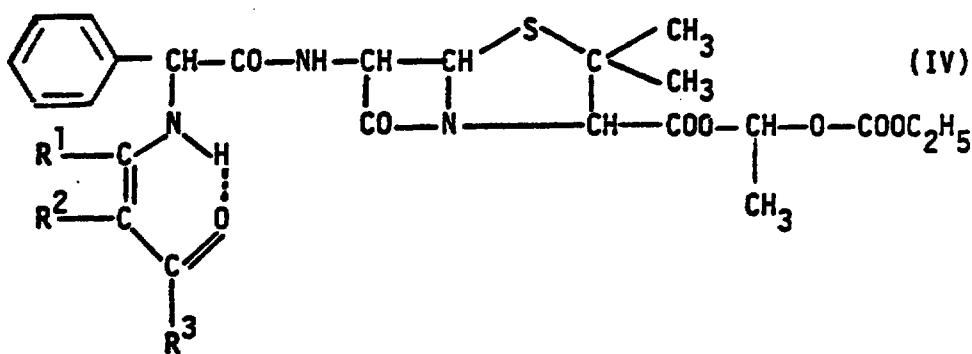
b) reacting the resulting intermediate of formula II with α -bromo-diethylcarbonate having the following formula:

15



to form the corresponding ester having the following formula:

20



25

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

30

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

35

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.

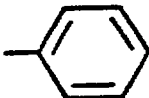
For this purpose the following substances can be used as catalysts: quaternary ammonium salts, for example tetrabutylammonium bromide, the bromides or iodides of alkali metals and, cyclic ethers.

- 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.

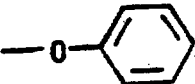
Illustrative examples of the radicals R^1 , R^2 and R^3 are:

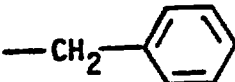
alkyl: CH_3 , C_2H_5 , $n-C_3H_7$, $i-C_3H_7$, $n-C_4H_9$

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

5

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.

10

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).

15

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.

20

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.

25

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.

30

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

35

- 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 -bromodiethylcarbonate 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 -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.

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

3 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 to 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.

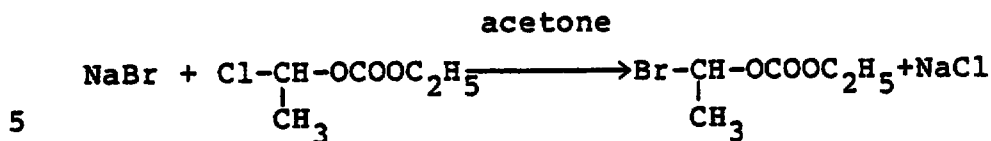
The crystalline product is isolated by filtration, washing and vacuum drying.

25 The following examples illustrate aspects of the present invention.

Examples 1, 5, 6, 7, 8 and 9 illustrate processes for preparing -bromodiethylcarbonate and Examples 2, 3 and 4 illustrate processes using α -bromodiethylcarbonate to produce the 1-ethoxycarbonyloxyethyl ester of 6-apa.

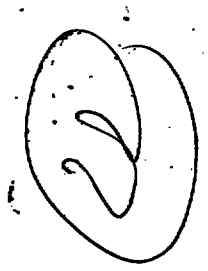
All percentages are by weight unless otherwise stated.

Example 1 Preparation of α -bromodiethylcarbonate



Sodium bromide (102.9 g) dissolved in acetone (600 ml) was reacted for 2-3 hours at ambient temperature (20-25°C) with α -chlorodiethylcarbonate (152.6 g) dissolved in 10 100 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 H₂O/ethyl ether. The aqueous phase was separated and was then extracted twice with 400 ml of 15 ethyl ether.

The combined organic phases containing the α -bromodiethylcarbonate were washed with



800 ml of H₂O
1000 ml of 1% sodium metabisulphate aqueous solution
1000 ml of NaCl saturated solution

- 5 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.

10

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

15 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) of ampicillin trihydrate are added.

20

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.

25

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.

30

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

35

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.

23

The aqueous phase is collected and the organic phase is extracted with 100 ml of water.

5 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.

10

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

15 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.

20

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

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) of 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 (25 ml). 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.

5 Example 3a

The procedure of example 3 was repeated with the difference that the 6-aminopenicillanic acid was dissolved in 20 ml water instead of in 35.

10

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.

15

Example 4

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.

20

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.

25

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.

30

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.

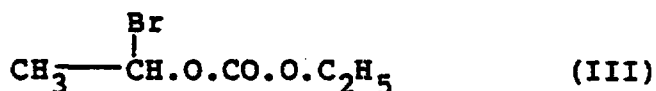
35

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 novel compound α -bromodiethylcarbonate of the invention, novel and inventive processes for the preparation thereof and its use in the preparation of the ethoxycarbonyloxyethyl ester of 6-aminopenicillanic acid, 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:

10



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 the
15 alpha(ethoxycarbonyloxy)-ethyl ester of 6-amino-penicillanic acid.

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

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

25

(a) reacting an aldehyde of the formula



with carbonyl bromide

30



to give an alpha-bromo-bromoformate of the formula

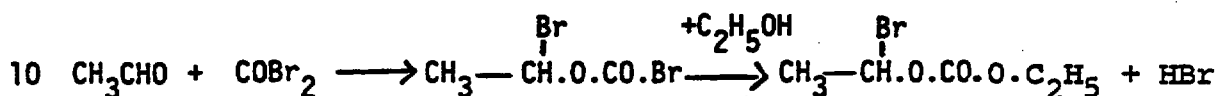




and;

- (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-diethyl-
5 carbonate of the formula III.

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



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.

- 15 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
20 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.

25

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
30 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 $120^\circ C$, preferably $0 - 40^\circ C$.

- 35 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 5 and 6, 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 7, 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
5 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
10 to carry out the reaction with alpha-chloro esters and alpha-chloro-carbonates, 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 alpha-chlorodiethylcarbonate, which is a known intermediate in the preparation of
15 the ethoxycarbonyloxyethyl ester of 6-aminopenicillanic acid.

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-
20 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
25 a process for the preparation of alpha-bromodiethylcarbonate by reaction of alpha-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.

30 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
35 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.

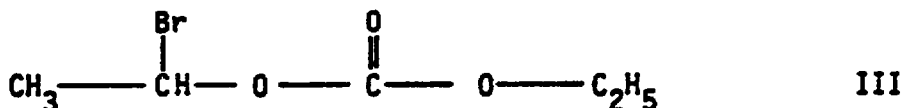
Thus, in process B of the invention, α -chlorodiethylcarbonate of the formula:



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



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



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 α -chloro-carbonate. This method is exemplified in Example 8.

Accordingly, the present invention also provides, in accordance with a further embodiment thereof, a process for the preparation of α -bromo-diethylcarbonate 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.

(31)

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

Example 5

5

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).

10

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.

- 15 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
20 (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
25 in all respects with an authentic specimen.

Example 6

A mixture of acetaldehyde (44 g, 1 mole), dichloromethane (300 ml) and hexamethylphosphoric-tri-amide (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-bromoethyl 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 120°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 and 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 mm of mercury pressure.

Example 7

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-bromoethyl 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) $-\text{CH}_2\text{CH}_3$
 2.0 - 2.2 (3H, doublet) $-\text{CHCH}_3$
 4.1 - 4.5 (2H, Quartet) $-\text{CH}_2\text{CH}_3$
 6.5 - 6.8 (1H, Quartet) $-\text{CHCH}_3$

Example 8

Lithium bromide (17.4 g, 0.2 m) was dissolved in dimethyl formamide (150 ml) and the mixture cooled to ambient temperature. Ethyl alpha-chloroethyl carbonate (30.5 g, 0.2 m) 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 9

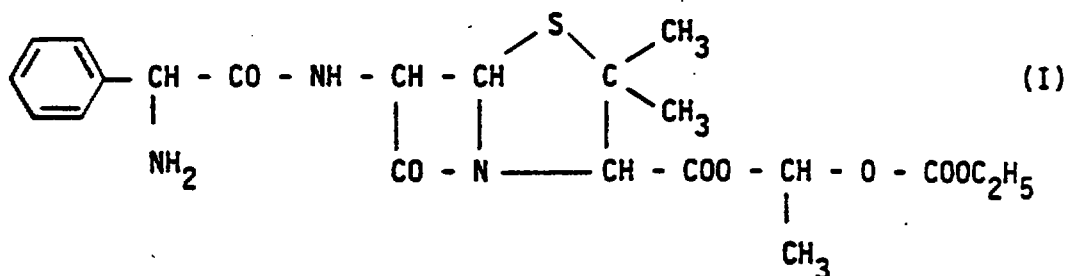
The authenticity of the foregoing new compound ethyl alpha-bromoethyl carbonate was confirmed by independent synthesis as follows:-

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 (8x0.05 g): care being taken to ensure that free bromine did not accumulate in the reaction mixture. At the end of the reaction 5 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 7 and 8.

CLAIMS

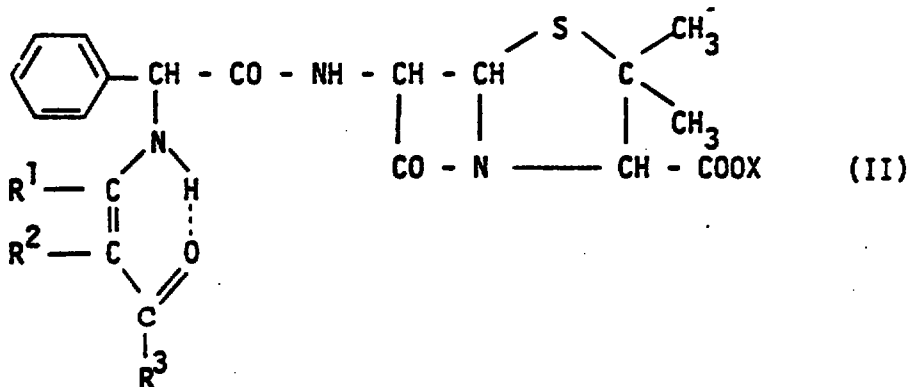
1. Process for the preparation of the 1-ethoxycarbonyloxyethyl ester of the 6-(D-(-)- α -amino- α -phenylacetamido) penicillanic acid with the formula:



5 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:

10

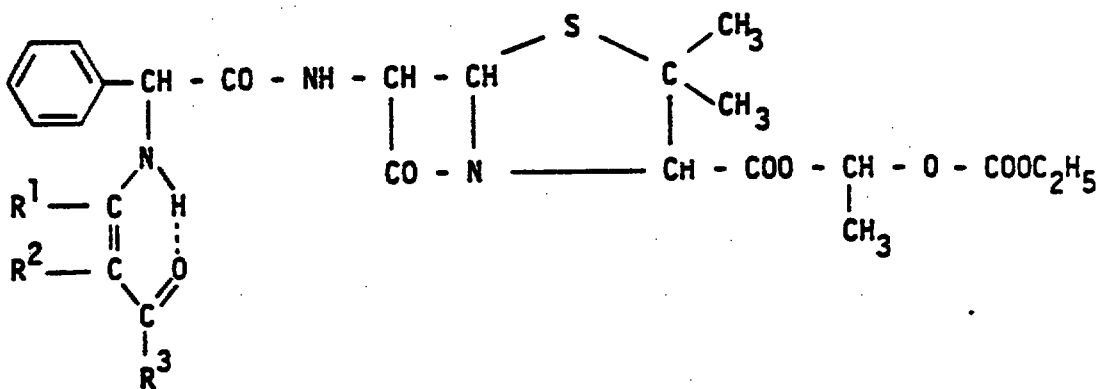


wherein R^1 represents an alkyl group containing 1-4 carbon atoms, a substituted or non-substituted aryl group or an aralkyl group; R^2 represents hydrogen, an alkyl group containing 1-4 carbon atoms, a substituted or non-substituted aryl group or an aralkyl group; R^3 represents an alkyl group containing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





5 to form the corresponding ester with the formula:



(IV)

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

- 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.
3. Process according to claim 2 in which the solvent is N,N-dimethylformamide.
- 15 4. Process according to claim 1, 2 or 3, 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
- 20 for 2 to 8 hours.



5. Process according to claim 4, wherein the alkyl acetoacetate is methyl or ethyl acetoacetate and is used in an amount 10-50% more than the stoichiometric ratio.
- 5 6. Process according to claim 4 or 5, wherein the aprotic polar solvent is selected from N,N-dimethylacetamide, N,N-dimethylformamide, dimethoxyethane, dimethylsulphoxide, tetrahydrofuran and dioxane.
- 10 7. Process according to any one of claims 4 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 4 to 7, wherein enamine formation is carried out in a time of 3 hours.
- 15 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.
- 20 10. 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.
11. Process according to any one of the preceding claims, wherein the esterification is carried out in the presence of a catalyst.



12. Process according to claim 11 wherein the catalyst is selected from quaternary ammonium salts, alkali metal bromides, alkali metal iodides and cyclic ethers.

13. Process according to claim 12, wherein the catalyst is tetrabutylammonium bromide.

14. Process according to any one of claims 11 to 13, wherein the catalyst is present in an amount of from 0.005 to 0.10 moles per mole of the compound III and V, respectively.

15. Process according to claim 14 wherein the catalyst is present in an amount of from 0.01 to 0.10 moles per mole of the compound III and V respectively.

15

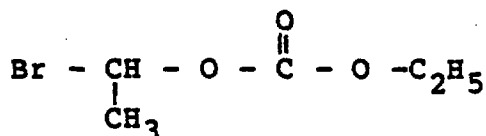
16. Process according to any one of the preceding claims, wherein the esterification reaction temperature is 45°C to 55°C.

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

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

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

20. The compound of the formula:

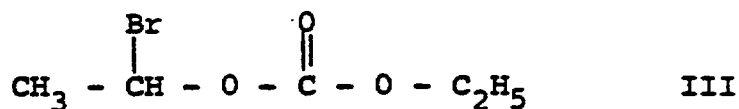


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(39)

21. A process for the preparation of the compound of the formula:



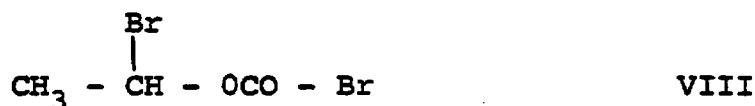
comprising reacting an aldehyde of the formula



with carbonyl bromide



to form a compound of the formula:



10 followed by reacting the compound VIII with $\text{C}_2\text{H}_5\text{OH}$.

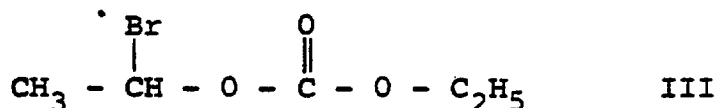
22. A process according to claim 21, carried out in the presence of a catalyst.

23. A process according to claim 22, wherein the catalyst is used in an amount of from 0.05 to 0.5 moles per mole of the compound VI.

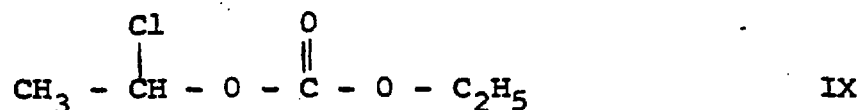
24. A process according to claim 23 wherein the amount of catalyst used per mole of the compound VI is 0.05 to 0.15 moles.

25. A process according to claim 22, 23 or 24 wherein the catalyst is a tertiary amine, a tertiary phosphine, an amide, substituted urea or thiourea, a phosphoric acid amide, a tertiary oxonium or sulphonium salt, or a quaternary ammonium or phosphonium salt.

26. A process for the preparation of a compound of the formula:



by reacting the compound of the formula:



with an alkali bromide of the formula:



- 5 in which formula R is an alkali metal
 wherein 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.
- 10 27. A process according to claim 26 wherein R is lithium.
 28. A process according to claim 27, wherein the organic
 solvent is a halogenated hydrocarbon or an aromatic
 hydrocarbon.
29. A process according to claim 28, wherein the organic
 solvent is dichloromethane.
- 15 30. A process according to any one of claims 26 to 29,
 wherein the phase transfer catalyst is a quaternary
 ammonium salt.
31. A process according to claim 21 or 26 substantially as
 hereinbefore described with reference to any one of the
 20 Examples.

