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(54) Title: A PROCESS FOR THE PREPARATION OF A METAL SALT OF CLAVULANIC ACID

(57) Abstract

A process for the preparation of a metal salt of clavulanic acid which comprises the reaction between an organic amine salt of clavulanic acid and a metal salt precursor compound, the reaction taking place in a liquid medium which comprises a liquid fluorinated and/or chlorinated hydrocarbon.

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A PROCESS FOR THE PREPARATION OF A METAL SALT OF CLAVULANIC ACID

This invention relates to a process for the preparation of salts of clavulanic acid. In particular the invention relates to a process for the preparation of potassium clavulanate from salts of clavulanic acid with organic amines.

Clavulanic acid (3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo [3.2.0] heptane-2-carboxylic acid) is a known beta-lactamase inhibitor, i.e. it and its compounds inhibit the beta-lactamase enzymes by means of which bacteria defend themselves against beta-lactam antibiotics such penicillins. Clavulanic acid, particularly in the form of its salts, can therefore be co-administered with such antibiotics, particularly amoxycillin and ticarcillin to overcome beta-lactamase mediated bacterial resistance.

Clavulanic acid is normally prepared by the fermentation of a microorganism which produces clavulanic acid, such as microorganisms belonging to various Streptomyces strains such as *S. clavuligerus* NRRL 3585, *S. jumoninensis* NRRL 5741, *S. katsurahamanus* IFO 13716 and *Streptomyces sp.* P 6621 FERM P2804 e.g. as described in JP Kokai 80-162993. The resulting aqueous broth may be subjected to conventional purification and concentration processes, for example involving filtration and chromatographic purification, such as disclosed in GB 1508977 and JP Kokai 80-62993, before extraction of the aqueous solution with an organic solvent to yield a solution of crude clavulanic acid in the organic solvent. Alternatively a "whole broth extraction" process of generally known type may be used to yield a solution of crude clavulanic acid in the organic solvent.

To isolate the clavulanic acid from the organic solvent solution one known procedure is to first convert the clavulanic acid into a salt with an organic amine. EP 0026044 discloses the use of the tertiary butylamine ("t-BA") salt of clavulanic acid as a useful intermediate in the isolation of clavulanic acid. This salt may be formed by reaction of the solution of crude clavulanic acid in the organic solvent with tertiary butylamine, resulting in formation of the salt which can be isolated, for example as a crystalline solvate e.g. of acetone. This tertiary butylamine salt of clavulanic acid may be converted to potassium clavulanate by reaction with for example a precursor compound such as potassium 2-ethylhexanoate in a suitable solvent medium such as isopropanol.

Numerous other amines may be used in processes for isolation of clavulanic acid. PT.94.908 describes the use of tri-(lower alkyl)amine, e.g. triethylamine, salts and the dimethylaniline salts of clavulanic acid in a purification process for clavulanic acid in which the triethylamine salt of clavulanic acid is formed and is then converted into a silyl diester of clavulanic acid. EP 0887178A discloses a process for the purification of clavulanic acid in which organic amines may be used

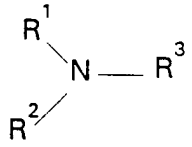
to form an intermediate amine salt with clavulanic acid in an impure solution. WO 93/25557 discloses an extensive series of amines which can be used. WO 96/33197, EP 0562583A, WO 94/21647, EP 0594099A, WO 94/22873, WO 95/23870, GB 2298201A and WO 96/20188 all disclose various other amines which can be used in this way.

Clavulanic acid and its salts such as potassium clavulanate are unstable, moisture sensitive compounds, and known processes for their preparation all suffer to a greater or lesser extent from problems of degradation resulting from such instability and hydrolysis. It is an object of this invention to provide an improved process which to some extent at least overcomes these problems.

According to this invention a process for the preparation of a metal salt of clavulanic acid comprises the reaction between an organic amine salt of clavulanic acid and a metal salt precursor compound, the reaction taking place in a liquid medium which comprises a liquid fluorinated and/or chlorinated hydrocarbon.

In a preferred embodiment of this invention the metal salt of clavulanic acid prepared by this process is potassium clavulanate.

The amine salt may be any amine salt which may be used in a process of the above-described type where clavulanic acid is first isolated as a salt of the amine which is then converted into a metal salt such as potassium clavulanate. In a preferred embodiment the organic amine salt of clavulanic acid is the t-BA salt of clavulanic acid. Other suitable amine salts include the following. (When alkyl groups or substituted alkyl groups are referred to herein unless otherwise defined herein they may suitably contain 1 to 6 carbon atoms in the alkyl system.) Those disclosed in WO 93/25557, i.e an amine of formula (I):



(I)

as an intermediate in a process for the preparation of clavulanic acid or pharmaceutically acceptable salts and esters thereof, wherein R^1, R^2 and R^3 are selected according to the following options:

(1) R^1 being an optionally substituted cyclic group of general formula:

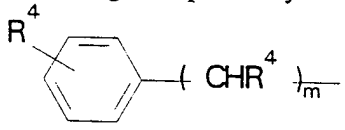
$$R\text{-}(CHR^4)_m\text{-}$$

where m is zero or an integer 1 to 5, R is an optionally substituted aliphatic hydrocarbon ring system containing from 3 to 8 ring carbon atoms, R^4 is hydrogen or alkyl, amino- or hydroxy- substituted alkyl or substituted amino- substituted alkyl, or a group of the same general formula or R^1 above:, R^2 and R^3 may be

selected from the same groups from which R^1 is selected, or from hydrogen, alkyl, alkenyl, amino- or hydroxy-substituted alkyl or alkenyl, or substituted amino-substituted alkyl or alkenyl: or

(2) each of R^1, R^2 and R^3 are the same or different and are independently selected from hydrogen, alkyl, alkenyl, amino - or hydroxy- or alkoxy- substituted alkyl or alkenyl, or substituted amino- substituted alkyl or alkenyl, but with the exception of t-butylamine, s-butylamine, N,N-dimethylethylamine, 1,2-dimethylpropylamine, neopentylamine and 2-amino-3,3-dimethylbutane: or

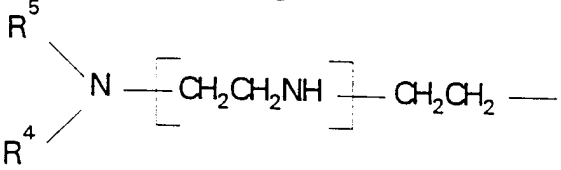
(3) R^1 being an optionally substituted aryl group of general formula:



where R^4 is hydrogen or one or more substituents, and m is zero or an integer 1 to 5, and R^2 and R^3 are independently selected from hydrogen, alkyl, amino- or hydroxy- substituted alkyl or substituted - amino- substituted alkyl or groups of the same general formula as R^1: or

(4) R^1 and R^2, and optionally R^3, together with the nitrogen atom shown being the residue of an optionally substituted heterocyclic ring system including the nitrogen atom as a ring member, and optionally including one or more additional ring hetero atoms, and if R^3 is not part of the ring system it is independently selected from hydrogen, alkyl, amino- or hydroxy- substituted alkyl or substituted amino- substituted alkyl: or

(5) R^1 being a group of general formula:



where R^4 and R^5 are independently hydrogen, alkyl, amino- substituted alkyl or substituted amino- substituted alkyl, and R^2 and R^3 are independently selected from hydrogen, alkyl, amino- or hydroxy- substituted alkyl or substituted amino-substituted alkyl, and m is zero or an integer 1 to 5: or

(6) One or both of R^1 and R^2 are hydrogen and R^3 represents the residue of an amino acid in which the carboxylate group of the amino acid may be esterified or in the form of an amide.

Examples of such amines include cyclopentylamine, cyclohexylamine, cycloheptylamine, NN-dimethylcyclohexylamine, dicyclohexylamine, adamantylamine, NN-diethylcyclohexylamine, N-isopropylcyclohexylamine, N-methylcyclohexylamine, cyclopropylamine, cyclobutylamine, norbornylamine, dehydroabietylamine, t-octylamine, (ie 2-amino-2,4,4-trimethylpentane), t-amylamine, 1-hydroxy-2-methyl-2-propylamine, tri-n-propylamine, tri-n-

octylamine, tri-n-butylamine, dimethylamine, i-propylamine, di-n-hexylamine, di-n-butylamine, diethylamine, 2-aminoethanol, NN-diethylethanolamine, NN-dimethylethanolamine, ethanolamine, n-butylamine, n-hexylamine, n-octadecylamine, N-ethylethanolamine, 1-hydroxyethylamine, diethanolamine, NN-dimethylethanolamine, N-ethyl diethanolamine, 1, 6-diamino hexane, triethanolamine, diisobutylamine, diisopropylamine, 2-methoxyethylamine, hydroxylamine, ammonia, methylamine, ethylamine, n-propylamine, n-butylamine, n-pentylamine, n-hexylamine, n-heptylamine, n-octylamine, n-nonylamine, n-decylamine, n-undecylamine, n-dodecylamine, n-prop-2-ylamine, n-but-2-ylamine, n-pent-2-ylamine, n-hex-2-yl-amine, n-hept-2-ylamine, n-oct-2-ylamine, n-non-2-ylamine, n-dec-2-ylamine, n-undec-2-ylamine, n-dodec-2-ylamine, n-hex-3-ylamine, n-hept-3-ylamine, n-oct-3-ylamine, n-non-3-ylamine, n-dec-3-yl-amine, n-undec-3-ylamine, n-dodec-3-ylamine, n-oct-4-ylamine, n-non-4-ylamine, n-dec-4-ylamine, n-undec-4-ylamine, n-dodec-4-ylamine, n-non-5-ylamine, n-undec-5-ylamine, n-dodec-5-ylamine, and n-octadecylamine, 1-phenylethylamine, p-toluidine, p-aminobenzoic acid, p-bromoaniline, ethyl-4-aminobenzoate (ie benzocaine), benzylamine, diphenylamine, p-methylaminobenzene sulphonamide, m-nitroaniline, N,N'-dibenzylethylenediamine (ie benzathine), diphenylmethylamine, 4-methylbenzylamine, 4-phenylbutylamine, piperidines and optionally substituted piperidines, for example where the substituents are selected from alkyl, hydroxyalkyl, halogen, amino, substituted amino and amino-substituted alkyl, e.g N-ethyl piperidine, 2, 6-dimethyl piperidine, 2-methyl-N-hydroxypropyl piperidine (ie cyclo- methycane), 4-methyl piperazine, 1-methyl-4-phenyl piperazine, N-ethyl morpholamine, hexamethylenimine, pyridine, 2-propylpyridine, 3-chloro-2-aminopyridine, morpholamine, 1, 5-diazabicyclo [4, 3, 0] non-5-ene, 1, 4-diazabicyclo [2, 2, 2] octane, pyrrolidone, quinuclidine, xanthinol, NN-diethylethylene diamine, NN'-diisopropylethylenediamine and triethylene tetramine, naturally occurring amino acids, such as arginine, ornithine, histidine, lysine, benzylglycine, 3-amino-3-methylbutanoic acid, L-ethyl lysinate, L-methyl histidinate, methyl N-carbobenzyloxy-L-lysinate, methyl L-phenylalanate, ethyl glycyl glycinate, ethyl p-hydroxy phenyl glycinate, ethyl p-hydroxy phenyl glycinate, ethyl glycinate, ethyl L-tyrosinate, p-methoxybenzyl α-aminophenylacetate, n-butyl α-aminophenylacetate, methyl arginate, benzylglycine, benzyl phenylglycine, 1-nitrobenzyl phenyl glycine, n-butyl phenylglycine, p-methoxybenzyl phenylglycine, ethyl phenyl glycine, p-nitrobenzyl p-hydroxyphenyl-glycine, p-nitrobenzylserine, n-butyl serine, methyl arginine, dimethyl glutamate, p-nitrobenzyl tyrosinate, p-nitrobenzyl glycinate, benzylglycinate, p-nitrobenzyl α-amino-p-hydroxy-phenyl acetate, p-nitrobenzyl α-aminophenylacetate, ethyl α-amino-p-hydroxy phenyl acetate, ethyl L-tyrosinate.

When the amine (I) contains more than one nitrogen aton the clavulanic acid may form a salt with one or more of the nitrogen atoms, for example as in NN'-diisopropylethylenediamine diclavulanate.

Of the amines last mentioned above, preferred amines are:
phenylethylamine, t-amylamine, t-octylamine, 1-hydroxy-2-methyl-2-propylamine, cyclopentylamine, cycloheptylamine, 1-adamantanamine, N-ethylpiperidine, N'N'-diisopropylethylenediamine and N N-dimethylcyclohexylamine.

Those disclosed in WO 96/33197, i.e having the general formula (II):

$$R^1.R^2N\text{-}CH(R^5)\text{-}(CH_2)_n\text{-}NR^3.R^4 \qquad (II)$$

where the substituents R^1, R^2, R^3 and R^4 are independently hydrogen, $C_{(1-8)}$ straight or branched alkyl, $C_{(2-4)}$ hydroxyalkyl or wherein the groups NR_1R_2 and NR_3R_4 jointly denote a heterocyclic group having 3 to 6 methylene groups optionally substituted with oxygen, sulphur or an imino group; and wherein R_5 denotes hydrogen or methyl, and n is an integer from 1 to 3. Examples of such last mentioned amines include symmetrical N,N'-alkylethylene diamines, such as N,N'-diisopropylethylenediamine, N,N'-diethylenediamine, N,N'-dibenzylethylene-diamine, N,N,N',N'-tetramethylethylenediamine.

Those disclosed in EP 0562583 and WO 94/21647, i.e. of formula (II) with the additional possibilities that R^1, R^2, R^3 and R^4 may independently be an arylalkyl group, for example with the alkyl moiety being methyl or ethyl, and the aryl group, for example phenyl, which may be substituted, particularly in its para- position, with an alkyl e.g methyl, alkoxy e.g methoxy, nitro or halogen; a C_{2-4} hydroxyalkyl group, a C_{2-4} aminoalkyl group, for example substituted by a 1 to 4 carbon atom containing N-alkyl or N,N-dialkyl group; or R^1, R^2, R^3 and R^4 may together form an alkylene ring system with 3 to 6 methylene groups, in which one of these groups may be substituted or replaced by an oxygen or sulphur atom or an imino group.

Those disclosed in WO 94/22873, i.e of formula (III):

$$R^1.R^2N\text{-}(CH_2)_n\text{ - }CHX\text{ -}(CH_2)_m\text{-}NR^3.R^4 \qquad (III)$$

wherein R^1 and R^2 are each C_{1-8} alkyl, C_{3-8} cycloalkyl or C_{3-8} cycloalkyl C1-8 alkyl group, optionally having one or more inert substituents or being interlinked to form a ring of 4-7 ring atoms; R^3 and R^4 are each C_{1-8} alkyl, C_{3-8} cycloalkyl or C_{3-8} cycloalkyl C1-8 alkyl group, optionally having one or more inert substituents or being interlinked to form a ring of 4-7 ring atoms; X is hydrogen or a hydrogen bridge forming group; and m and n are each independently 0-5. Preferred moieties for such substituents are as disclosed in WO 94/22873, and examples of such

amines include N,N,N',N'-tetramethyl-1,2-diaminoethane, 1,3-bis(dimethylamino)-2-propanol, N,N,N',N'-tetramethyl-1,4-diaminobutane, N,N,N',N'-tetramethyl-1,6-diaminohexane, 1,2-dipiperidinoethane and dipiperidinomethane.

Those disclosed in GB2298201A, i.e of formula (IV):

(IV)

wherein each of R^1 and R^2 independently denote hydrogen or a pharmaceutically acceptable substituent, for example lower alkyl, haloalkyl, alkoxyl or acyloxy. An example of such an amine is benzhydrylamine.

Those disclosed in WO 96/20199, i.e of formula (V):

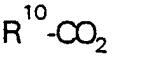
(V)

wherein R1 is an alylene group (the term alkylene encompassing cycloalkylene and alkyl substituted cycloalkylene), optionally having one or more inert substituents; and each of R2 and R3 is a hydrogen atom or an alkyl group (which may be cycloalkyl), optionally having one or more inert substituents. An example of such an amine is bis-(2-dimethylaminoethyleether).

The contents of these forementioned patent publications are included herein in their entirety by way of reference.

Where the amine base contains two or more basic nitrogen atoms, one, or more than one up to all of these basic nitrogen atoms may be combined in the amine salt with a respective clavulanate ion.

The metal salt precursor compound may be a salt or salt-like compound, or a basic compound, of a metal cation with a suitable counter anion. The metal is suitably a pharmaceutically acceptable alkali metal such as sodium or particularly potassium, or an alkaline earth metal. The metal salt precursor compound may be a salt of the metal with an organic carboxylic acid, for example a salt of an alkanoic acid of formula (I):



(I)

wherein R^{10} is an alkyl group, containing for example from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms. Examples of suitable salts include acetate, propionate or ethylhexanoate salts, potassium 2-ethylhexanoate and sodium 2-

ethylhexanoate being preferred. Alternatively the metal salt precursor compound may be a basic compound, for example a carbonate, bicarbonate or hydroxide of the metal.

It is preferred that a stoichiometric excess of the metal salt precursor compound over the organic amine salt of clavulanic acid is used to ensure complete reaction of the organic amine salt of clavulanic acid. For example around a 1.3 : 1 ratio of metal salt precursor compound : organic amine salt of clavulanic acid may be used.

The liquid medium is preferably a gas at ambient temperature but which can be liquefied at ambient temperature by pressure. Suitably the fluorinated and/or chlorinated hydrocarbon is a compound of formula CnHmXpYr where X is fluorine, Y is chlorine n and m are whole numbers, p and r are zero or whole numbers provided both p and r are not zero and (m + p + r) equals 2n + 2. The liquid medium is preferably a fluorinated non-chlorinated hydrocarbon. Preferably the medium is a fluorinated non-chlorinated compound of formula $C_nH_mF_p$ where n, m and p are whole numbers and (m + p) equals 2n + 2.

The lower and upper limits of n are determined more by the practical considerations of achieving a boiling point which is low enough to allow easy evaporation but not so low that high pressures are needed for liquefaction. For example a suitable boiling point for the liquid non-chlorinated fluorinated hydrocarbon is -10 to -50°C at ambient atmospheric pressure, and typically n is between 1 and 10. Preferably in such a compound n is 2 or 3, preferably 2 so that the compound is an ethane, preferably p is 3, 4 or 5, especially 4 so that the compound is a tetrafluoroethane. A preferred fluorinated hydrocarbon is 1,1,1,2 - tetrafluoroethane. Other suitable fluorinated/chlorinated hydrocarbons include fluoroform, methyl chloride, difluorodichloromethane, monofluoromethane, difluoromethane, trifluoromethane, pentafluoroethane, 1,1,1-trifluoroethane, 1,1-difluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2,2,3,3-heptafluoropropane, 1,1,1,3,3,3-hexafluoropropane, 1,1,1,2,2-pentafluoropropane, 1,1,1,2,2,3-hexafluoropropane, 1,1,2,2,3,3-hexafluoropropane, and 1,1,1,2,3,3-hexafluoropropane.

Such fluorinated/chlorinated hydrocarbons, particularly fluorinated non-chlorinated hydrocarbons have the advantages as media for the process of the invention that they are odourless and colourless gases at ambient temperature, liquefy at around 5 bar at ambient temperature, are chemically inert, are non-flammable, are non-toxic, are non-corrosive, have a neutral pH, are non-ozone depleting and are approved for use in food processing by the EEC.

The liquid medium may comprise a mixture of such fluorinated and/or chlorinated hydrocarbons, e.g a mixture of fluorinated non-chlorinated

hydrocarbons, for example to achieve a convenient boiling point. The liquid medium may also include other organic solvents, for example to modify the polarity of the medium, and suitable such organic solvents include alcohols and ethers, for example C_1 - C_5 aliphatic alcohols and ethers. Such organic solvents may be solvents for the metal salt precursor compound. When the metal salt precursor compound is a salt of the metal with an organic carboxylic acid, for example a salt of an alkanoic acid of formula (I) as mentioned above, such as potassium 2- ethyl hexanoate, suitable solvents include C_1 - C_5 aliphatic alcohols such as isopropanol. Typically when a solvent for the metal salt precursor compound is present in the medium this may be present in a volume:volume ratio non-chlorinated fluorinated hydrocarbon : solvent for the metal salt precursor compound of 1 : 0 - 0.5, for example around 1 : 0.1-0.35.

It is preferred that the liquid medium also includes water as the presence of water appears to be desirable to achieve a crystalline product. Preferably water is present in the liquid medium in the range 0.1 - 3.0 % v:v, but excessive amounts of water in the medium should be avoided to minimise aqueous degradation of the clavulanate salt product. Suitably ca. 0.5 - 2.5 % v:v water may be present.

The reaction may be carried out over a broad concentration range of the organic amine salt of clavulanic acid, and the consequent concentration of the metal salt precursor compound as mentioned above. For example the concentration of the amine salt in the medium may lie in the range 0.05-5M.

In one form of the process of the invention the amine salt of clavulanic acid may be dissolved or suspended in an organic solvent, which may be a solvent for the metal salt precursor compound, in a suitable reactor vessel. The reactor vessel may then be charged with the fluorinated hydrocarbon solvent and pressurised to a pressure at which the fluorinated hydrocarbon solvent is a liquid, e.g. typically ca 4-6 bar. With the resulting solution or suspension of the amine salt may then be mixed a solution or suspension of the metal salt precursor compound, for example in a solvent as described above.

As explained above the reaction medium should contain a trace of water, and this may be included in the solution or suspension of the amine salt, or in the solution or suspension of the metal salt precursor compound added thereto, or water may be added to the reaction mixture. Metal salts of clavulanic acid are generally insoluble in the type of liquid medium resulting from this form of the process and the product metal salt of clavulanic acid will normally precipitate out from the reaction medium, so that it can easily be isolated by filtration. In the case of potassium clavulanate such a precipitate may comprise the known needle or rosette crystal forms. The filtered product may then be washed, for example with the fluorinated hydrocarbon. When the fluorinated hydrocarbon is a gas at room

temperature excess fluorinated hydrocarbon may then conveniently be removed by reduction of the pressure in the reactor or filter.

In the above-described form of the process, if the metal salt precursor compound is a salt of an alkanoic acid of an acid of formula (I), for example potassium 2-ethylhexanoate, then the solution of the precursor compound may be made by dissolving the compound in a suitable solvent, or alternatively the precursor compound may be prepared *in situ* by reaction between a suitable metal-containing base such as potassium hydroxide and the parent acid, such as 2-ethyl hexanoic acid in the solvent.

Suitable apparatus for performing the process of the invention will be apparent to those skilled in the art. One suitable apparatus comprises a reaction vessel in which the reaction can take place, which can be charged with the fluorinated hydrocarbon and with the reagents and any other solvents, water etc. from appropriate sources, and which can be pressurised to a pressure at which the fluorinated hydrocarbon is a liquid, a receiver in fluid communication with the reaction vessel and into which liquid medium from the reaction vessel may be transferred after the reaction has taken place, with a filter between and in fluid communication with the reaction vessel and receiver, and which can retain particles of the product metal salt of clavulanic acid. Preferably the reaction vessel and receiver are also capable of evacuation so that the fluorinated hydrocarbon can be easily evaporated off, and the apparatus also preferably includes a compressor to return the fluorinated hydrocarbon to the source or to the reactor. Within such a general description various constructions of apparatus will be apparent to those skilled in the art.

The method of the invention has the advantages that the reaction is simple and rapid, can achieve yield improvements, and reduction in solvent usage.

The invention will now be described by way of example with reference to Fig. 1 which schematically shows a reaction assembly.

Example 1.

Equipment

The equipment used for this work consisted of a 5 L reaction/ extraction vessel (1) and a 5 L receiver/ evaporation vessel (2), both vessels being jacketed, a 1,1,1,2-tetrafluoroethane gas cylinder (3) and compressor (4). The whole was connected together with a system of pipes, pressure gauges (5), thermometers (6), valves (7), condenser (8), etc. to allow a multi task function. The reactor was equipped with a stirrer (9), a pH port (10) and a burette (11) designed to introduce reagents whilst the system was pressurised. After materials were charged into the reaction/ extraction vessel, the whole system could be evacuated then 1,1,1,2-tetrafluoroethane gas charged into the reaction/extraction (1) to a pressure of 5 bar. Reagents could then be introduced via the burette (11). When the reaction or extraction was complete, the mixture could be discharged to the evaporator (2) via a transfer line (12) and an inline filter (13). The 1,1,1,2-tetrafluoroethane gas could be evaporated using the compressor (4) and condensed into liquid form in condenser (8), and could be either charged back into the cylinder (3) or recycled through the reactor/ extractor (1).

Experimental Data

Method: Expts. 1-3

t-BA clavulanate was charged to the reactor followed by isopropanol and water. The vessel was sealed and evacuated then 1,1,1,2-tetrafluoroethane was charged until system pressure equilibrated at 5 bar. Potassium ethyl hexanoate ("KEH") / isopropanol ("IPA") was charged to the burette then added to the reactor whilst stirring over 30 minutes. At the end of a further 20 minute stirring, the contents of the reactor where transferred to the receiver via the in-line filter. 1,1,1,2-tetrafluoroethane gas was compressed back into the reservoir cylinder. The filtered product in the reactor was slurried twice in 1,1,1,2-tetrafluoroethane to remove isopropanol residues and associated impurities. This had the effect of producing dry product with very little solvent and water contamination.

Method: Expts. 4 and 5

2-ethyl hexanoic acid (101g) was charged into a beaker containing isopropanol (300ml). The solution was chilled to 10°C and potassium hydroxide (40.8g) was

added whilst stirring vigorously. When all the potassium hydroxide was dissolved, isopropanol was added to make up a total volume of 420ml. This solution was transferred to the burette vessel of the 1,1,1,2-tetrafluoroethane rig. t-BA clavulanate (154g) and isopropanol (500ml) were charged to the reaction vessel and continued as above.

Results

All products passed on appearance, water content and purity. Stability studies using DVS showed poor results for Expt. 2 suggesting that water presence during the reaction is essential to crystal formation. The stability of the product from Expt. 4 was very good and Expt.5 produced products of exceptional stability.

The following table shows data obtained from reactions using 2.5L 1,1,1,2-tetrafluoroethane and standard potassium ethyl hexanoate/ isopropanol solution (concentration = 2N and water content = 2%)

Expt No	Wt t-BA clav. g	Vol IPA ml	Vol H_2O ml	Wt KEH g	Loss in ML %	Yield %	Purity % pfa
1	250	700	30	191.7	1.2	96.5	81.8
2	150	500	0	116.2	1.2	96.7	81.1
3	150	500	10	116.9	1.4	98.1	81.8

The following data was obtained from reactions using 2.5L 1,1,1,2-tetrafluoroethane and wet potassium ethyl hexanoate/ isopropanol solution which was prepared by mixing equi-molar amounts of potassium hydroxide and 2-ethylhexanoic acid in isopropanol with no azeotropic distillation:

Expt No.	Wt t-BA clav. g	Vol IPA ml	Vol H_2O ml	Wt KEH g	Loss in ML %	Yield %	Purity % pfa
4	150	500	0	117.0	1.2	98%	82.3
5	154	500	4	N/A	1.6	N/A	81.6

Claims:

1. A process for the preparation of a metal salt of clavulanic acid which comprises the reaction between an organic amine salt of clavulanic acid and a metal salt precursor compound, the reaction taking place in a liquid medium which comprises a liquid fluorinated and/or chlorinated hydrocarbon.

2. A process according to claim 1 or 2, *characterised* in that the organic amine salt of clavulanic acid is the salt of clavulanic acid with tertiary-butylamine, a N,N'-substituted diamine, an N,N'- monosubstituted symmetric diamines or N, N'-monosubstituted symmetric alkylethylene diamine or tertiary octylamine.

3. A process according to any one of claims 1 or 2, *characterised* in that the metal salt precursor compound is a salt or salt-like compound, or a basic compound, of a metal cation with a counter anion.

4. A process according to claim 3 characterised in that the metal in the metal salt precursor compound is potassium or sodium.

5. A process according to claim 4 *characterised* in that the metal salt precursor compound is a salt of the metal with an organic carboxylic acid of formula (I):

$$R^{10}\text{-}CO_2 \qquad \text{(I)}$$

wherein R^{10} is an alkyl group containing from 1 to 20 carbon atoms.

6. A process according to claim 5 *characterised* in that the metal salt precursor compound is potassium 2-ethylhexanoate.

7. A process according to any one of claims 1 to 6 *characterised* in that the liquid medium is a gas at ambient temperature which can be liquefied at ambient temperature by pressure.

8. A process according to claim 7 *characterised* in that the boiling point for the liquid fluorinated and/or chlorinated hydrocarbon is -10 to -50°C at ambient atmospheric pressure.

9. A process according to any one of claims 1 to 8 *characterised* in that the fluorinated and/or chlorinated hydrocarbon is a compound of formula CnHmXpYrwhere X is fluorine, Y is chlorine n and m are whole numbers, p and r are zero or whole numbers provided both p and r are not zero and (m + p + r) equals 2n + 2.

10. A process according to any one of claims 1 to 9 *characterised* in that the liquid medium is a fluorinated non-chlorinated hydrocarbon.

11. A process according to claim 9 *characterised* in that the medium is a fluorinated non-chlorinated compound of formula $C_nH_mF_p$ where n, m and p are whole numbers and (m + p) equals 2n + 2.

12. A process according to claim 17 *characterised* in that n is 2 or 3.

13. A process according to claim 1 *characterised* in that the fluorinated and/or chlorinated hydrocarbon is selected from 1,1,1,2 - tetrafluoroethane, fluoroform, methyl chloride, difluorodichloromethane, monofluoromethane, difluoromethane, trifluoromethane, pentafluoroethane, 1,1,1-trifluoroethane, 1,1-difluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2,2,3,3-heptafluoropropane, 1,1,1,3,3,3-hexafluoropropane, 1,1,1,2,2-pentafluoropropane, 1,1,1,2,2,3-hexafluoropropane, 1,1,2,2,3,3-hexafluoropropane, and 1,1,1,2,3,3-hexafluoropropane.

14. A process according to claim 1 *characterised* in that the liquid medium comprises a mixture of fluorinated and/or chlorinated hydrocarbons.

15. A process according to any one of the preceding claims characterised in that the metal salt of clavulanic acid prepared in the reaction is potassium clavulanate.

16. Apparatus for performing a process according to any one of claims 1 to 15, the apparatus comprising;

a reaction vessel in which the reaction can take place, which can be charged with the fluorinated hydrocarbon and reagents, and which can be pressurised to a pressure at which the fluorinated hydrocarbon is a liquid,

a receiver in fluid communication with the reaction vessel and into which liquid medium from the reaction vessel may be transferred after the reaction has taken place.

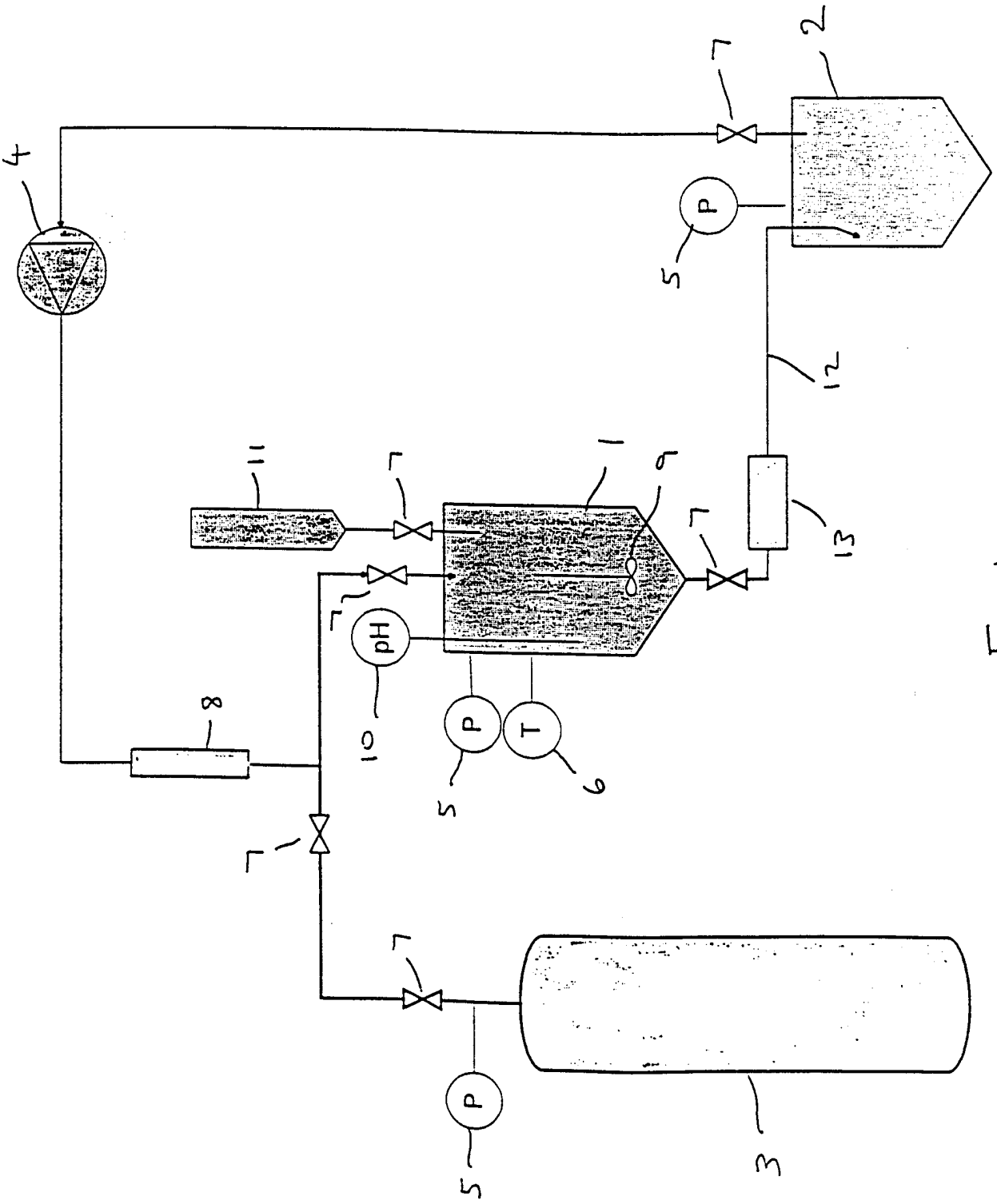


Fig. 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02137

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D503/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 05142 A (SMITHKLINE BEECHAM P. L. C) 13 February 1997 see the whole document ---	1
A	WO 96 28452 A (LEK PHARMACEUTICAL) 19 September 1996 see the whole document ---	1
A	WO 95 34194 A (CHONG KUN DANG CORP.) 21 December 1995 see the whole document ---	1
A	WO 95 21173 A (SMITHKLINE BEECHAM PLC) 10 August 1995 see the whole document -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 1998	24/08/1998

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/EP 98/02137

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