

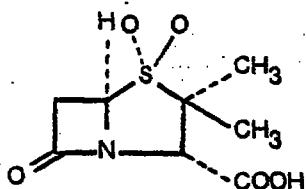
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Description

This invention relates to the chemotherapy of bacterial infections in mammalian subjects. More particularly, it relates to sparingly water-soluble salts of the beta-lactamase inhibitor penicillanic acid 1,1-dioxide, and their use in conjunction with beta-lactam antibiotics in the chemotherapy of bacterial infections in mammals.

One of the most well-known and widely used of the classes of antibacterial agents is the class known as the beta-lactam antibiotics. These compounds are characterized in that they have a nucleus consisting of a 2-azetidinone (beta-lactam) ring fused to either a thiazolidine or a dihydro-1,3-thiazine ring. When the nucleus contains a thiazolidine ring, the compounds are usually referred to generically as penicillins, whereas when the nucleus contains a dihydrothiazine ring, the compounds are referred to as cephalosporins. Typical examples of penicillins which are commonly used in clinical practice are benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), ampicillin and carbenicillin; typical examples of common cephalosporins are cephalothin, cephalexin and cefazolin.

However, despite the wide use and wide acceptance of the beta-lactam antibiotics as valuable chemotherapeutic agents, they suffer from the major drawback that certain members are not active against certain microorganisms. It is thought that in many instances this resistance of a particular microorganism to a given beta-lactam antibiotic results because the microorganism produces a beta-lactamase. The latter substances are enzymes which cleave the beta-lactam ring of penicillins and cephalosporins to give products which are devoid of antibacterial activity. However, certain substances have the ability to inhibit beta-lactamases, and when a beta-lactamase inhibitor is used in combination with a penicillin or cephalosporin it can increase or enhance the antibacterial effectiveness of the penicillin or cephalosporin against certain microorganisms. One useful beta-lactamase inhibitor is penicillanic acid 1,1-dioxide, the compound of the formula I:



(I)

United States patent No. 4,234,579 describes the preparation of penicillanic acid 1,1-dioxide, and methods for its use as a beta-lactamase inhibitor in combination with beta-lactam antibiotics. Additionally, United States patent No. 4,234,579 discloses salts of penicillanic acid 1,1-dioxide, including amine salts. However, the amine salts disclosed in U.S. patent 4,234,579 are relatively soluble in water, and they are rapidly excreted from the mammalian subject after parenteral administration. It has now been found that certain amine salts of penicillanic acid 1,1-dioxide are sparingly soluble in water, and after parenteral administration to a mammalian subject they give prolonged blood levels of penicillanic acid 1,1-dioxide. These sparingly soluble salts of penicillanic acid 1,1-dioxide are the 1:2 *N,N'*-dibenzylethylenediamine salt, the *N*-benzyl-2-phenylamine salt and the dibenzylamine salt.

The 1:2 *N,N'*-dibenzylethylenediamine, the *N*-benzyl-2-phenylethylamine and the dibenzylamine salts of several penicillin antibiotics e.g. benzylpenicillin, have been prepared. See further: United States Patents Nos. 2,627,491 and 2,585,432 and British patent No. 732,559.

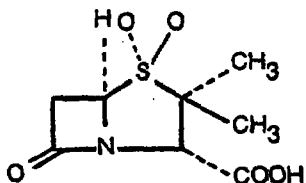
This invention provides the following salts:

- (a) the 1:2 *N,N'*-dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide;
- (b) the *N*-benzyl-2-phenylethylamine salt of penicillanic acid 1,1-dioxide; and
- (c) the dibenzylamine salt of penicillanic acid 1,1-dioxide.

The above salts are sparingly soluble in water, and therefore they are of value as slow-release forms of the well-known beta-lactamase inhibitor, penicillanic acid 1,1-dioxide, in the chemotherapy of bacterial infections in mammals.

The preferred salt of this invention is the 1:2 *N,N'*-dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide.

The compounds of this invention are salts of penicillanic acid 1,1-dioxide, which is the compound of the formula



(I)

The 1:2 *N,N'*-dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide is the salt formed from *N,N'*-

dibenzylethylenediamine and two molar equivalents of penicillanic acid 1,1-dioxide; the *N*-benzyl-2-phenylethylamine salt of penicillanic acid 1,1-dioxide is the salt formed from *N*-benzyl-2-phenylethylamine and one molar equivalent of penicillanic acid 1,1-dioxide; and the dibenzylamine salt of penicillanic acid 1,1-dioxide is the salt formed from dibenzylamine and one molar equivalent of penicillanic acid 1,1-dioxide. *N,N'*-dibenzylethylenediamine is also known as benzathine and as DBED; *N*-benzyl-2-phenylethylamine is also known as benethamine.

The salts of this invention can be prepared by conventional methods, well-known to one skilled in the art. For example, the penicillanic acid 1,1-dioxide and the amine can be contacted in substantially stoichiometric proportions, in an appropriate inert solvent, or a mixture of inert solvents, at a temperature in the range from -20 to 30°C. Salt formation takes place quite rapidly and is complete within a few minutes. Appropriate inert solvents are those which substantially dissolve the penicillanic acid 1,1-dioxide and the amine, and which do not adversely interact with either the penicillanic acid 1,1-dioxide, the amine or the salt.

Typical solvents are lower alkanols, such as methanol and ethanol; low molecular weight ketones, such as acetone and methyl isobutyl ketone; low molecular weight ethers, such as diethyl ether and diisopropyl ether; low molecular weight esters, such as ethyl acetate and butyl acetate; acetonitrile; formamide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethyl sulfoxide; and mixtures thereof. The salt product is recovered simply by filtration, by evaporation of the solvent, or by precipitation followed by filtration, as appropriate, and it can be purified further, if desired, by classical techniques such as recrystallization. Although solvents in which the salt is either freely soluble or sparingly soluble can be used, solvents in which the salt is sparingly soluble are generally preferred.

A variation on the aforesaid method for preparing the salts of this invention involves contacting substantially stoichiometric quantities of a water-soluble salt of penicillanic acid 1,1-dioxide with a water-soluble salt of the amine, in a substantially aqueous solvent system, at a temperature in the range from -20 to 30°C., and at a concentration at which substantially all the salt product precipitates. The product salt can then be recovered by filtration. Salts of the penicillanic acid which can be used for this purpose are alkali metal salts, such as sodium and potassium salts; and low molecular weight amines, such as triethylamine and tributylamine salts. Salts of the amine reactant which can be used are the hydrohalides, such as the hydrochloride and the hydrobromide; and salts with simple aliphatic carboxylic acids, such as acetic acid and propionic acid.

A further variation for preparing the salts of this invention which is possible involves contacting substantially stoichiometric quantities of penicillanic acid 1,1-dioxide with a salt of the amine reactant formed from a weak acid, at a temperature in the range from -20 to 30°C., in a solvent which dissolves the penicillanic acid 1,1-dioxide and the amine salt reactant but in which the salt of the invention is sparingly soluble. Typical salts of the amine reactant which can be used for this purpose are simple aliphatic carboxylic acids, such as acetic acid, propionic acid, butyric acid, isobutyric acid, isocaproic acid, caproic acid and 2-ethylhexanoic acid. Typical solvents which can be used are lower alkanols, such as methanol and ethanol; low molecular weight ketones, such as acetone and methyl ethyl ketone; low molecular weight ethers, such as diethyl ether and diisopropyl ether; low molecular weight esters, such as ethyl acetate and butyl acetate; acetonitrile; and mixtures thereof.

As indicated hereinbefore, the salts of this invention act as slow-release forms of penicillanic acid 1,1-dioxide. Thus administration of a salt of this invention to a mammalian subject gives sustained blood levels of penicillanic acid 1,1-dioxide. Consequently, the salts of this invention are especially useful for co-administration to a mammalian subject with slow-release forms of beta-lactam antibiotics, such as penicillin and cephalosporin compounds which are sparingly soluble in water. Thus, the salts of this invention can conveniently be administered to a mammalian subject as a single dose at approximately the same time as the subject first receives a dose of a sparingly water-soluble penicillin or cephalosporin antibiotic. Subsequent doses can be given as necessary to maintain the desired blood levels of penicillanic acid 1,1-dioxide, while continuing to give the penicillin or cephalosporin compound at appropriate intervals. Alternatively, a salt of this invention can be co-formulated with the penicillin or cephalosporin compound with which it is the co-administered, and the two agents are thereby given simultaneously. The dose is repeated as necessary to sustain the desired blood levels for the required length of time. The weight ratio of the active ingredients will normally be 1:6 to 6:1, and preferably 1:3 to 3:1.

When considering use of a salt of this invention as a slow-release form of penicillanic acid 1,1-dioxide, it is preferably administered intramuscularly or subcutaneously. For this purpose, it is usual to prepare an aqueous or non-aqueous suspension of a salt of this invention in substantially the same manner as that currently used for formulation of a sparingly water-soluble beta-lactam antibiotic such as ampicillin trihydrate or benzathine penicillin G. The proportional ratio of a salt of this invention and the carrier can vary, depending on the dosage contemplated. However, suspensions of a salt of this invention will usually contain from 50 to 200 milligrams of activity of a salt of this invention per milliliter of suspension. In the case of aqueous suspensions, small amounts of other ingredients conventionally used in preparing aqueous suspensions can also be added. For example, it is possible to add emulsifiers, such as lecithin, sorbitan mono-oleate, sorbitan monopalmitate and polyoxyethylene (20) sorbitan mono-oleate; hydrocolloids, such as carboxymethyl cellulose; dispersing agents, such as polyvinylpyrrolidone; and preservatives, such as sodium benzoate, methylparaben and propylparaben. Additionally it is preferable to

buffer the suspension to a pH in the range from 6 to 7, and a sodium citrate/citric acid buffer is convenient for this purpose. Non-aqueous suspensions are commonly made using propylene glycol diester (dicaprylate/caprate) containing a small amount of phenol.

A salt of this invention can be used in conjunction with a sparingly water-soluble penicillin or cephalosporin compound in a human subject, and also in domestic pets (e.g. cats and dogs) and large farm animals (e.g. horses, sheep, cattle and pigs). The prescribing physician or veterinarian will ultimately decide the appropriate dosage, and this will vary according to a variety of factors, such as the weight and response of the individual subject, as well as the nature and severity of the subject's symptoms. However, intramuscular or subcutaneous doses of from about 4 to about 40 mg. per kilogram of body weight will normally be used. The dose will be repeated when the blood level of penicillanic acid 1,1-dioxide has fallen below the desired level. Also, dosing will continue until the desired therapeutic effect has been obtained.

Typical sparingly water-soluble penicillin antibiotics with which a salt of this invention can be co-administered are the 1:2 *N,N'*-dibenzylethylenediamine salts of penicillin G and penicillin V and ampicillin trihydrate.

The following examples are being provided to further illustrate this invention; however they should not be construed as limiting the scope of the invention in any way. Infrared spectra were measured as potassium bromide discs, and major absorptions are reported in wave numbers (cm^{-1}). Proton magnetic resonance spectra were measured as solutions in perdeutero dimethyl sulfoxide, at 100 MHz, and absorptions are reported in parts per million downfield from internal trimethylsilane. The following abbreviations for peak shapes are used: s, singlet; m, multiplet. Proton decoupled ^{13}C magnetic resonance spectra were measured as solutions in perdeutero dimethyl sulfoxide, and absorptions are reported in parts per million downfield from internal tetramethylsilane.

Example 1

1:2 *N,N'*-Dibenzylethylenediamine Salt of Penicillanic Acid 1,1-Dioxide

A solution of 201.7 g. of sodium penicillanate 1,1-dioxide in 1,000 ml. of distilled water, water was cooled to ca. 8°C ., and then a cooled (ca. 10°C .) solution of 156.2 g. of *N,N'*-dibenzylethylenediamine diacetate in 1,400 ml. of distilled water was added dropwise, with vigorous stirring during 12 to 15 minutes. Stirring was continued for a further 20 minutes at $5-8^{\circ}\text{C}$. after the addition ceased, and then the precipitate was recovered by filtration. The solid which was recovered was washed well with cold water and then it was dried at 40°C . under vacuum. This afforded 255.6 g. of the title salt, m.p. $165-66^{\circ}\text{C}$. (dec.). By Karl Fischer titration, this material contained 5.03% of water. The infrared spectrum showed absorptions at 3546, 3333, 2666, 2409, 1769, 1626, 1562, 1398, 1111 and 754 cm^{-1} . The proton magnetic resonance spectrum showed absorptions at 1.31 (s, 6H), 1.38 (s, 6H), 3.04 (s, 4H), 3.08 (m, 2H), 3.26 (m, 2H), 3.90 (s, 2H), 4.04 (s, 4H), 4.93 (m, 2H) and 7.42 (10H) ppm. The proton decoupled ^{13}C magnetic resonance spectrum showed absorptions at 18.4831, 19.9920, 36.9787, 43.6649, 50.6570, 60.6107, 62.6252, 64.7556, 128.599, 129.627, 133.507, 169.961 and 172.023 ppm .

Example 2

N-Benzyl-2-phenylethylamine Salt of Penicillanic Acid 1,1-Dioxide

A solution of 885 mg. of penicillanic acid 1,1-dioxide in 125 ml. of diethyl ether was added, with stirring, during about 20 minutes, to a solution of 828 mg. of *N*-benzyl-2-phenylethylamine in 100 ml. of diethyl ether. The mixture was stirred an additional 20 minutes and the solid was recovered by filtration. The solid was washed with ether and then it was dried under vacuum. This afforded 1.57 g. of the title compound m.p. $161-3^{\circ}\text{C}$. (dec.). By Karl Fischer titration this material contained 1.33% of water. The infrared spectrum showed absorptions at 3067, 2816, 2380, 1785, 1600, 1298, 1111, 784, 751 and 699 cm^{-1} . The proton magnetic resonance spectrum showed absorptions at 1.38 (s, 3H), 1.52 (s, 3H), 3.04 (s, 4H), 3.12 (m, 1H), 3.54 (m, 1H), 3.90 (s, 1H), 4.10 (s, 2H), 4.94 (m, 1H) and 7.28 (m, 10H) ppm. The proton decoupled ^{13}C magnetic resonance spectrum showed absorptions at 18.5835, 20.0678, 31.9754, 36.8485, 47.7418, 50.0436, 60.5537, 62.6515, 65.1919, 126.547, 128.506, 129.710, 133.008, 137.697, 169.570 and 171.986 ppm .

Example 3

Dibenzylamine Salt of Penicillanic Acid 1,1-Dioxide

A solution of 1.275 g. of sodium penicillanate 1,1-dioxide in ca. 3 ml. of water was added to a solution of dibenzylamine hydrochloride in 37 ml. of water, with stirring. Stirring was continued for a further 20 minutes, and the solid was recovered by filtration. The solid was washed with water, and then it was dried at room temperature under vacuum. This afforded 1.102 g. of the title compound, m.p. $159-60^{\circ}\text{C}$. By Karl Fischer titration, the product contained 2.95% of water. The infrared spectrum showed absorptions at 4347, 3333, 2985, 2777, 2597, 2439, 1769, 1587, 1398, 1111, 775 and 669 cm^{-1} . The proton magnetic resonance spectrum showed absorptions at 1.34 (s, 3H), 1.38 (s, 3H), 3.30 (m, 2H), 3.90 (s, 1H), 4.06 (s, 4H), 4.94 (m, 1H) and 7.40 (m, 10H) ppm. The proton decoupled ^{13}C magnetic resonance spectrum showed absorptions at 18.5613, 20.0192, 36.9093, 50.0135, 60.5833, 62.6788, 65.0384, 128.457, 129.703, 133.388, 169.426 and 171.936 ppm .

Example 4

Dibenzylamine Salt of Penicillanic Acid 1,1-Dioxide

A mixture of 38.4 ml. of dibenzylamine, 500 ml. of distilled water and 15 ml. of acetic acid was stirred for 2 hours at room temperature, and the solution so obtained was added dropwise, with rapid stirring, during ca. 20 minutes, to a solution of 62 g. of sodium penicillanate 1,1-dioxide in 300 ml. of distilled water. Stirring was continued for a further 10 minutes, and then the precipitate was collected by filtration. The solid was dried at room temperature overnight, to give 68 g. of the title compound, m.p. 149—51°C. (dec.). By Karl Fischer titration, this material contained 6.11% water.

Example 5

Aqueous Formulation

A typical formulation contains the following ingredients:

Ingredient	Weight (in grams)
Sodium benzoate	0.3
Sodium citrate	0.45
Citric acid	0.05
Lecithin	0.3
Sodium carboxymethyl cellulose	0.5
Polyoxyethylene (20) sorbitan mono-oleate	0.07
1:2 <i>N,N'</i> -Dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide	15.0

The above ingredients are combined and the volume is made up to 100 ml. with deionized water. An appropriate volume is used to provide the dosage required.

Example 6

Non-aqueous Formulation

Ingredient	Amount
1:2 <i>N,N'</i> -Dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide	9.06 g.
Ampicillin trihydrate	13.8 g.
Phenol	0.5 g.
Propyleneglycol diester (dicaprylate/caprate)	80 ml.

The above ingredients are thoroughly mixed. An appropriate volume is used to provide the dosage required.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound selected from the group consisting of:

- the 1:2 *N,N'*-dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide;
- the *N*-benzyl-2-phenylethylamine salt of penicillanic acid 1,1-dioxide; and
- the dibenzylamine salt of penicillanic acid 1,1-dioxide.

2. A pharmaceutical composition comprising a suspension of a compound as claimed in claim 1 in a pharmaceutically acceptable liquid.

3. A composition as claimed in claim 2, which also comprises a beta-lactam antibiotic.

Example 4

Dibenzylamine Salt of Penicillanic Acid 1,1-Dioxide

A mixture of 38.4 ml. of dibenzylamine, 500 ml. of distilled water and 15 ml. of acetic acid was stirred for 2 hours at room temperature, and the solution so obtained was added dropwise, with rapid stirring, during ca. 20 minutes, to a solution of 62 g. of sodium penicillanate 1,1-dioxide in 300 ml. of distilled water. Stirring was continued for a further 10 minutes, and then the precipitate was collected by filtration. The solid was dried at room temperature overnight, to give 68 g. of the title compound, m.p. 149—51°C. (dec.). By Karl Fischer titration, this material contained 6.11% water:

Example 5

Aqueous Formulation

A typical formulation contains the following ingredients:

Ingredient	Weight (in grams)
Sodium benzoate	0.3
Sodium citrate	0.45
Citric acid	0.05
Lecithin	0.3
Sodium carboxymethyl cellulose	0.5
Polyoxyethylene (20) sorbitan mono-oleate	0.07
1:2 <i>N,N'</i> -Dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide	15.0

The above ingredients are combined and the volume is made up to 100 ml. with deionized water. An appropriate volume is used to provide the dosage required.

Example 6

Non-aqueous Formulation

Ingredient	Amount
1:2 <i>N,N'</i> -Dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide	9.06 g.
Ampicillin trihydrate	13.8 g.
Phenol	0.5 g.
Propyleneglycol diester (dicaprylate/caprate)	80 ml.

The above ingredients are thoroughly mixed. An appropriate volume is used to provide the dosage required.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

- A compound selected from the group consisting of:
 - the 1:2 *N,N'*-dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide;
 - the *N*-benzyl-2-phenylethylamine salt of penicillanic acid 1,1-dioxide; and
 - the dibenzylamine salt of penicillanic acid 1,1-dioxide.
- A pharmaceutical composition comprising a suspension of a compound as claimed in claim 1 in a pharmaceutically acceptable liquid.
- A composition as claimed in claim 2, which also comprises a beta-lactam antibiotic.



4. A composition as claimed in claim 3, in which the beta-lactam antibiotic is benzylpenicillin, phenoxymethylpenicillin, carbenicillin or ampicillin.

5. A composition as claimed in claim 4, which comprises a compound as claimed in claim 1 and the 1:2 *N,N'*-dibenzylethylenediamine salt of benzylpenicillin or phenoxymethylpenicillin.

6. A composition as claimed in claim 4, which comprises a compound as claimed in claim 1 and ampicillin trihydrate.

7. The 1:2 *N,N'*-dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide.

8. A pharmaceutical composition comprising a suspension of the 1:2 *N,N'*-dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide and ampicillin trihydrate in a pharmaceutically acceptable liquid.

Claims for the Contracting State: AT

1. A process for the preparation of a salt selected from the 1:2 *N,N'*-dibenzylethylenediamine salt of penicillanic acid 1,1-dioxide, the *N*-benzyl-2-phenylethylamine salt of penicillanic acid 1,1-dioxide and the dibenzylamine salt of penicillanic acid 1,1-dioxide, which comprises either:

(i) contacting substantially stoichiometric quantities of penicillanic acid 1,1-dioxide with either *N,N'*-dibenzylethylenediamine, *N*-benzyl-2-phenylethylamine or dibenzylamine, in an inert solvent; or

(ii) contacting substantially stoichiometric quantities of a water-soluble salt of penicillanic acid 1,1-dioxide with a water-soluble salt of either *N,N'*-dibenzylethylenediamine, *N*-benzyl-2-phenylethylamine or dibenzylamine, in a substantially aqueous solvent system, at a concentration at which substantially all the salt product precipitates; or

(iii) contacting substantially stoichiometric quantities of penicillanic acid 1,1-dioxide with a salt, formed from a weak acid, of either *N,N'*-dibenzylethylenediamine, *N*-benzyl-2-phenylethylamine or dibenzylamine, in a solvent in which the reactants are soluble but the product salt is sparingly soluble.

2. A process according to claim 1, which comprises contacting substantially stoichiometric quantities of penicillanic acid 1,1-dioxide with either *N,N'*-dibenzylethylenediamine, *N*-benzyl-2-phenylethylamine or dibenzylamine, at a temperature in the range from -20 to 30°C ., in a solvent selected from lower alkanols, low molecular weight ketones, low molecular weight ethers, low molecular weight esters, acetonitrile, formamide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and dimethylsulfoxide.

3. A process according to claim 1, which comprises contacting substantially stoichiometric quantities of an alkali metal or a low molecular weight amine salt of penicillanic acid 1,1-dioxide with a hydrohalide or simple aliphatic carboxylic acid salt of either *N,N'*-dibenzylethylenediamine, *N*-benzyl-2-phenylethylamine or dibenzylamine, at a temperature in the range from -20 to 30°C ., in a substantially aqueous solvent system, at a concentration at which substantially all the salt product precipitates.

4. A process according to claim 1, which comprises contacting substantially stoichiometric quantities of penicillanic acid 1,1-dioxide with a simple aliphatic carboxylate salt of either *N,N'*-dibenzylethylenediamine, *N*-benzyl-2-phenylethylamine or dibenzylamine, at a temperature in the range from -20 to 30°C ., in a solvent selected from lower alkanols, low molecular weight ketones, low molecular weight ethers, low molecular weight esters and acetonitrile.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Eine Verbindung ausgewählt aus der Gruppe bestehend aus:

(a) dem 1:2 *N,N'*-Dibenzylethylendiaminsalz von Penicillansäure-1,1-dioxid;

(b) dem *N*-Benzyl-2-phenylethylaminsalz von Penicillansäure-1,1-dioxid; und

(c) dem Dibenzylaminsalz von Penicillansäure-1,1-dioxid.

2. Eine Zusammensetzung aus einer Suspension einer Verbindung gemäß Anspruch 1 in einer pharmazeutisch annehmbaren Flüssigkeit.

3. Eine Zusammensetzung gemäß Anspruch 2, die auch ein beta-Lactam-Antibiotikum enthält.

4. Eine Zusammensetzung gemäß Anspruch 3, in welcher das beta-Lactam-Antibiotikum Benzylpenicillin, Phenoxymethylpenicillin, Carbenicillin oder Ampicillin ist.

5. Eine Zusammensetzung gemäß Anspruch 4, mit einer Verbindung gemäß Anspruch 1 und dem 1:2 *N,N'*-Dibenzylethylendiaminsalz von Benzylpenicillin oder Phenoxymethylpenicillin.

6. Eine Zusammensetzung gemäß Anspruch 4 mit einer Verbindung gemäß Anspruch 1 und Ampicillintrihydrat.

7. Das 1:2-*N,N'*-Dibenzylethylendiaminsalz von Penicillansäure-1,1-dioxid.

8. Eine pharmazeutische Zusammensetzung aus einer Suspension des 1:2-*N,N'*-Dibenzylethylendiaminsalzes von Penicillansäure-1,1-dioxid und Ampicillintrihydrat in einer pharmazeutisch annehmbaren Flüssigkeit.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines Salzes ausgewählt aus dem 1:2-*N,N'*-Dibenzyläthylendiaminsalz von Penicillansäure-1,1-dioxid, dem *N*-Benzyl-2-phenyläthylaminsalz von Penicillansäure-1,1-dioxid und dem Dibenzylaminsalz von Penicillansäure-1,1-dioxid, welches umfaßt entweder



(i) das Inberührungbringen von praktisch stöchiometrischen Anteilen von Penicillansäure-1,1-dioxid mit entweder N,N'-Dibenzyläthylendiamin, N-Benzyl-2-phenyläthylamin oder Dibenzylamin in einem inerten Lösungsmittel oder

(ii) das Inberührungbringen von praktisch stöchiometrischen Anteilen eines wasserlöslichen Salzes von Penicillansäure-1,1-dioxid mit einem wasserlöslichen Salz von entweder N,N'-Dibenzyläthylendiamin, N-Benzyl-2-phenyläthylamin oder Dibenzylamin in einem im wesentlichen wässrigen Lösungsmittelsystem bei einer Konzentration, bei der praktisch das gesamte Salzprodukt ausfällt oder

(iii) das Inberührungbringen von praktisch stöchiometrischen Anteilen von Penicillansäure-1,1-dioxid mit einem Salz, gebildet aus einer schwachen Säure, entweder von N,N'-Dibenzyläthylendiamin, N-Benzyl-2-phenyläthylamin oder Dibenzylamin in einem Lösungsmittel, in dem die Reaktanten löslich sind, aber das Produktsalz gering löslich ist.

2. Verfahren nach Anspruch 1, welches das Inberührungbringen von praktisch stöchiometrischen Anteilen von Penicillansäure-1,1-dioxid mit entweder N,N'-Dibenzyläthylendiamin, N-Benzyl-2-phenyläthylamin oder Dibenzylamin bei einer Temperatur im Bereich von -20 bis 30°C in einem Lösungsmittel ausgewählt aus nied. Alkanolen, Ketonen mit niedrigem Molgewicht, Äthern mit niedrigem Molgewicht, Estern mit niedrigem Molgewicht, Acetonitril, Formamid, N,N-Dimethylformamid, N,N-Dimethylacetamid und Dimethylsulfoxid umfaßt.

3. Verfahren nach Anspruch 1, welches das Inberührungbringen von praktisch stöchiometrischen Anteilen eines Alkalimetall- oder Aminsalzes mit niedrigem Molgewicht von Penicillansäure-1,1-dioxid mit einem Hydrohalogenid oder einem einfachen aliphatischen Carbonsäuresalz entweder von N,N'-Dibenzyläthylendiamin, N-Benzyl-2-phenyläthylamin oder Dibenzylamin bei einer Temperatur im Bereich von -20 bis 30°C in einem im wesentlichen wässrigen Lösungsmittelsystem bei einer Konzentration, bei der praktisch das gesamte Salzprodukt ausfällt, umfaßt.

4. Verfahren nach Anspruch 1, welches das Inberührungbringen von praktisch stöchiometrischen Anteilen von Penicillansäure-1,1-dioxid mit einem einfachen aliphatischen Carboxylatsalz von entweder N,N'-Dibenzyläthylendiamin, N-Benzyl-2-phenyläthylamin oder Dibenzylamin bei einer Temperatur im Bereich von -20 bis 30°C in einem Lösungsmittel ausgewählt aus nied. Alkanolen, Ketonen mit niedrigem Molgewicht, Äthern mit niedrigem Molgewicht, Estern mit niedrigem Molgewicht und Acetonitril umfaßt.

30 Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé choisi dans le groupe comprenant

(a) le sel à 1:2 de la N,N'-dibenzyléthylènediamine et du 1,1-dioxyde de l'acide pénicillanique;

(b) le sel de N-benzyl-2-phényléthylamine du 1,1-dioxyde d'acide pénicillanique et

(c) le sel de dibenzylamine du 1,1-dioxyde d'acide pénicillanique.

2. Composition pharmaceutique, comprenant une suspension d'un composé suivant la revendication 1 dans un liquide pharmaceutiquement acceptable.

3. Composition suivant la revendication 2, qui comprend aussi un antibiotique du type bêta-lactame.

4. Composition suivant la revendication 3, dans laquelle l'antibiotique du type bêta-lactame est la benzylpénicilline, la phénoxyéthylpénicilline et la carbénicilline ou l'ampicilline.

5. Composition suivant la revendication 4, qui comprend un composé suivant la revendication 1 et le sel à 1:2 de N,N'-dibenzyléthylènediamine de la benzylpénicilline ou de la phénoxyéthylpénicilline.

6. Composition suivant la revendication 4, qui comprend un composé suivant la revendication 1 et du trihydrate d'ampicilline.

7. Sel à 1:2 de N,N'-dibenzyléthylènediamine du 1,1-dioxyde de l'acide pénicillanique.

8. Composition pharmaceutique, comprenant une suspension du sel à 1:2 de N,N'-dibenzyléthylènediamine du 1,1-dioxyde de l'acide pénicillanique et de l'ampicilline trihydratée dans un liquide pharmaceutiquement acceptable.

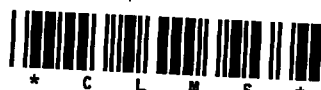
50 Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un sel choisi entre le sel à 1:2 de N,N'-dibenzyléthylènediamine du 1,1-dioxyde de l'acide pénicillanique, le sel de N-benzyl-2-phényléthylamine du 1,1-dioxyde d'acide pénicillanique et le sel de dibenzylamine du 1,1-dioxyde d'acide pénicillanique, qui comprend:

(i) la mise en contact de quantités pratiquement stoechiométriques de 1,1-dioxyde d'acide pénicillanique avec la N,N'-dibenzyléthylènediamine, la N-benzyl-2-phényléthylamine ou la dibenzylamine, dans un solvant inerte; ou

(ii) la mise en contact de quantités pratiquement stoechiométriques d'un sel hydrosoluble du 1,1-dioxyde d'acide pénicillanique avec un sel hydrosoluble de N,N'-dibenzyléthylènediamine, de N-benzyl-2-phényléthylamine ou de dibenzylamine, dans un système de solvants principalement aqueux, à une concentration à laquelle la quasi-totalité du sel obtenu comme produit précipite; ou bien

(iii) la mise en contact de quantités pratiquement stoechiométriques de 1,1-dioxyde d'acide pénicillanique avec un sel, formé à partir d'un acide faible, de N,N'-dibenzyléthylènediamine, de N-benzyl-2-phényléthylamine ou de dibenzylamine, dans un solvant dans lequel les corps réactionnels sont solubles mais le sel formé comme produit est peu soluble.



2. Procédé suivant la revendication 1, qui consiste à faire entrer des quantités pratiquement stoechiométriques de 1,1-dioxyde d'acide pénicillanique en contact avec de la *N,N'*-dibenzyléthylènediamine, de la *N*-benzyl-2-phényléthylamine ou de la dibenzylamine, à une température comprise dans l'intervalle de -20 à 30°C, dans un solvant choisi entre des alcanols inférieurs, des cétones de bas poids moléculaire, des éthers de bas poids moléculaire, des esters de bas poids moléculaire, l'acétonitrile, le formamide, le *N,N*-diméthylformamide, le *N,N*-diméthylacétamide et le diméthylsulfoxyde.

3. Procédé suivant la revendication 1, qui consiste à faire entrer des quantités pratiquement stoechiométriques d'un sel de métal alcalin ou d'un sel d'amine de bas poids moléculaire du 1,1-dioxyde de l'acide pénicillanique en contact avec un halogénhydrate ou un sel simple d'acide carboxylique aliphatique de *N,N'*-dibenzyléthylènediamine, de *N*-benzyl-2-phényléthylamine ou de dibenzylamine, à une température comprise dans l'intervalle de -20 à 30°C, dans un système de solvants principalement aqueux à une concentration à laquelle la quasi-totalité du sel obtenu comme produit précipite.

4. Procédé suivant la revendication 1, qui consiste à faire entrer des quantités pratiquement stoechiométriques de 1,1-dioxyde d'acide pénicillanique en contact avec un sel simple d'acide carboxylique aliphatique de *N,N'*-dibenzyléthylènediamine, de *N*-benzyl-2-phényléthylamine ou de dibenzylamine, à une température comprise dans l'intervalle de -20 à 30°C, dans un solvant choisi entre des alcanols inférieurs, des cétones de bas poids moléculaire, des éthers de bas poids moléculaire, des esters de bas poids moléculaire et l'acétonitrile.

