1 578 739

PATENT SPECIFICATION

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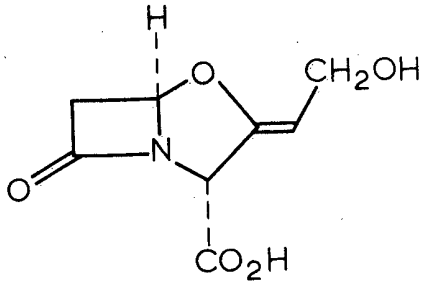
(54) AMINE SALTS OF CLAVULANIC ACID, METHODS FOR THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

(71) We, BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to salts of clavulanic acid, to their preparation and to compositions containing them.

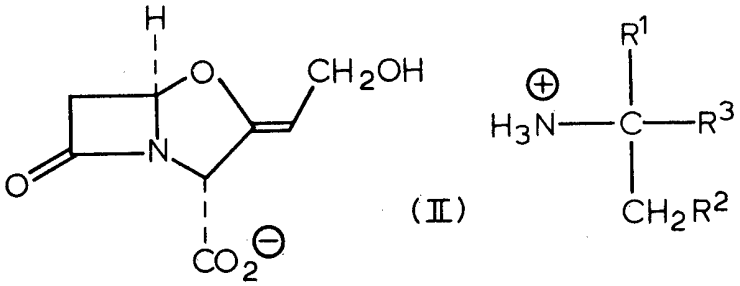
British Patent Specification No. 1508977 (see also Belgian Patent Specification No. 827926) discloses inter alia that clavulanic acid, which has the formula (I):



(I)

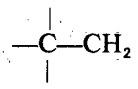
and its pharmaceutically acceptable salts are chemical intermediates and antibacterial agents which are able to enhance the effectiveness of penicillins and cephalosporins against many β-lactamase producing bacteria. British Patent Specification No. 1543563 also relates to clavulanic acid. There has now been discovered a class of salts of clavulanic acid may be obtained containing low levels of moisture. These compounds have favourable storage properties. They may thus be more easily formulated to give stable pharmaceutical compositions than are the previously described salts such as the sodium or potassium salts of clavulanic acid.

Accordingly the present invention provides the salts of the formula (II):



(II)

wherein R^1 is a hydrogen atom or lower alkyl, aralkyl, phenyl or lower alkyl or phenyl inertly substituted by halogen, lower alkoxyl, lower acyloxyl or lower esterified carboxyl; R^2 is a hydrogen atom or lower alkyl, aralkyl, phenyl or lower alkyl or phenyl inertly substituted by halogen, lower alkoxyl, lower acyloxyl or lower esterified carboxyl; and R^3 is lower alkyl, aralkyl, phenyl or lower alkyl or phenyl inertly substituted by halogen, lower alkoxyl, lower acyloxyl or lower esterified carboxyl group and wherein aralkyl refers to lower alkyl substituted by phenyl or inertly substituted phenyl as defined below; or R^1 and R^3 together with the C atom to which they are joined form a carboxylic ring of 5 to 7 atoms and R^2 is as defined above or R^1, R^2 and R^3 together with the

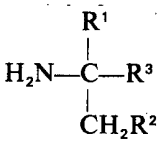


moiety form a polyclic ring of up to 16 C atoms.

When used herein the term 'lower' means that the group contains up to 6 carbon atoms.

The inert substituents are halogen, lower alkoxyl, lower acyloxyl, and lower esterified carboxyl. Suitably 1, 2 or 3 such substituent groups are present, more suitably 1 or 2 and preferably not more than one such substituent group is present.

Normally and preferably the amine of the formula (III):



(III)

from which the salt of the formula (II) is notionally derivable is a pharmaceutically acceptable amine.

Most suitably R^1 is a lower alkyl group; most suitably R^2 is a hydrogen atom or a lower alkyl group: most suitably R^3 is a lower alkyl or aralkyl group.

Most suitably the compound of the formula (III) does not contain a chiral centre.

Suitably the salt of the formula (II) is notionally derivable from an amine of the formula (III) which contains 4—16 carbon atoms, more suitably 4—12 carbon atoms and preferably 4—10 carbon atoms.

Suitably the salt of the formula (II) is notionally derivable from 2 - amino - 2 - methylpropane, 2 - amino - 2 - methylbutane, 2 - amino - 2 - methylpentane, 2 - amino - 2 - methylhexane, 2 - amino - 2 - methylheptane, 2 - amino - 2 - methyloctane, 3 - amino - 3 - methylpentane, 1 - amino - 1 - methylcyclohexane and 1 - amino - adamantane.

Preferred salts of the formula (II) are crystalline.

The present invention also provides a process for the preparation of the salts of formula (II) which process comprises the reaction of clavulanic acid with an amine of the formula (III).

Most suitably this reaction takes place in an organic solvent. Suitable solvents include such conventional non-hydroxylic solvents as tetrahydrofuran, dioxane, ethyl acetate, methyl acetate, acetone and methyl - ethyl - ketone.

The salt forming reaction may take place at any non-extreme temperature but in general temperatures of from 0°C to 35°C are most suitable and temperatures of from 5°C to 25°C are generally most convenient.

The salt of the formula (II) may be recovered from the solution in conventional manner such as evaporation of the solvent under reduced pressure or preferably by crystallisation.

It is frequently convenient to prepare the clavulanic acid in situ, for example by hydrogenation of a hydrogenolysable ester for example the benzyl ester.

The present invention also provides a process for the preparation of a salt of the formula (II) which process comprises the displacement of a cation from a salt of clavulanic acid other than one of the formula (II) by a protonated amine of the formula (III).

The present invention also provides pharmaceutical compositions which comprise a salt of the formula (II) and a pharmaceutically acceptable carrier.

Suitable forms of the compositions of this invention will be similar to those

described in British Patent Specification No. 1508977 (and also see Belgian Patent Specification No. 827926) as suitable for salts of clavulanic acid.

Particularly suitable forms of the compositions of this invention are those which do not contain high levels of residual water. Most suitably such compositions are prepared from dry materials so that the final compositions contain less than 5% moisture, more suitably less than 3% moisture and preferably less than 2% moisture, for example 1% or less of moisture.

Most suitably the compositions of this invention are packaged in moisture-excluding forms such as closed containers or foil lined packs.

The compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of infection in mammals including humans.

Suitable forms of the compositions of this invention include tablets, capsules, reconstitutable powders and sterile forms suitable for injection or infusion. Such compositions may contain conventional pharmaceutically acceptable materials such as diluents, binders, colours, flavours, preservatives, and disintegrants in accordance with conventional pharmaceutical practice in the manner well understood by those skilled in the art of formulating antibiotics.

Injectable or infusable compositions of the salts of formula (II) are particularly suitable as high tissue levels of the compound of clavulanic acid can occur after administration by injection or infusion. Thus, one preferred composition aspect of this invention comprises a salt of the formula (II) in sterile form.

Unit dose compositions comprising a salt of the formula (II) adapted for oral administration form a further preferred composition aspect of this invention.

Suitable β-lactam antibiotics for inclusion in synergistic compositions containing a salt of the formula (II) include not only those known to be highly susceptible to β-lactamases but also those which have a good degree of intrinsic resistance to β-lactamases. Thus, suitable β-lactam antibiotics for inclusion in the compositions of this invention include benzylpenicillin, phenoxymethylpenicillin, carbenicillin, methicillin, propicillin, ampicillin, amoxycillin, epicillin, ticarcillin, cyclacillin, pirbenicillin, cephatrizine, cephaloridine, cephalothih, cefazolin, cephalexin, cefoxitin, cephacetrile, cephamandole, cephapirin, cephradine, cephaloglycine and other well known penicillins and cephalosporins or pro-drugs therefor such as hetacillin, metampicillin, the acetoxymethyl, pivaloyloxymethyl or phthalidyl esters of benzylpenicillin, ampicillin, amoxycillin or cephaloglycine or the phenyl, tolyl or indanyl α-esters of carbenicillin or ticarcillin.

Naturally if the penicillin or cephalosporin present in the composition is not suitable for oral administration then the composition will be adapted for parenteral administration.

When present in a pharmaceutical composition together with a β-lactam antibiotic, the ratio of the salt of formula (II) present to β-lactam antibiotic present may be from, for example, 3:1 to 1:10 and advantageously may be from 1:1 to 1:6, for example from 1:3 to 1:5 by weight.

The total quantity of antibacterial agents present in any unit dosage form will normally be between 50 and 1500 mg and will usually be between 100 and 1000 mg.

Compositions of this invention may be used for the treatment of infections of inter alia, the respiratory tract, the urinary tract and soft tissues in humans.

Compositions of this invention may also be used to treat infections of domestic animals such as mastitis in cattle.

Normally between 50 and 500 mg of the compounds of the invention will be administered each day of treatment.

Particularly favoured compositions of this invention will contain from 150—1000 mg of amoxycillin or ampicillin and from 50—500 mg of a salt of the formula (II) and more suitably from 200—500 mg of amoxycillin or ampicillin and from 50—250 mg of a salt of the formula (II).

Most suitably such compositions comprise amoxycillin trihydrate.

The following Examples illustrate the invention:

Example 1

Clavulanic acid 2 - amino - 2,4,4 - trimethylpentane salt

Benzyl clavulanate (purified by Sephadex chromatography, 20 g, 0.07 moles) ("Sephadex" is a Registered Trade Mark) was dissolved in tetrahydrofuran (distilled from calcium hydride, 400 ml) and 10% palladium on charcoal catalyst (5.7 g) added. The mixture was hydrogenated with stirring at ambient temperature and about 15 psi for 20—30 minutes. The state of reaction was judged by thin layer

chromatography using silica plates developed with ethyl acetate and visualised using triphenyltetrazolium chloride spray reagent. Clavulanic acid Rf 0.0, benzyl ester 0.4.

The reaction mixture was filtered and the filter pad well washed. The combined filtrates (500 ml) containing clavulanic acid were treated with stirring with 2 - amino - 2,4,4 - trimethylpentane (9.0 g, 0.07 moles) in dry tetrahydrofuran (50 ml). Crystallisation was observed within one minute. The mixture was stirred for 0.5 hours at ambient temperature and then 2 hours at 5°. The product was filtered off, washed with dry tetrahydrofuran (100 ml) and dried in vacuo for 12 hours to afford 23.0 g, 100% of the title salt, having m.p. 160—170° (d).

Example 2

Clavulanic acid 1 - aminoadamantane salt

Benzyl clavulanate (3.5 g, 0.012 mole) was hydrogenolysed in tetrahydrofuran (70 ml) as described above. The filtrate plus washings (total 100 ml) was treated with stirring with a solution of 1 - aminoadamantane (1.82 g, 0.012 moles) in dry tetrahydrofuran (25 ml) at ambient temperature. Crystallization was rapid. The suspension was stirred at ambient temperature for 0.5 hours, at 5° for two hours and then filtered. The solid was washed and dried as described above to give 3.5 g, 83% yield of the title salt, having m.p. 190—192 (d) with the following elemental analysis results:

Requires: C, 61.70; H, 7.48; N, 7.99%
Found: C, 61.40; H, 7.31; N, 7.77%

Example 3

Clavulanic acid 2 - amino - 2 - methylpropane salt

The preparation was carried out as in Example 1 using benzyl clavulanate (0.9 g, 0.003 moles) and treating the resulting clavulanic acid solution with 2 - amino - 2 - methylpropane (0.22 g, 0.003 mole) in dry tetrahydrofuran (10 ml). The title salt 0.6 g, 73% yield, had m.p. 150—152° (d).

Example 4

Clavulanic acid D(+) 1 - methylbenzylamine salt

The preparation was carried out as in Example 1 using benzyl clavulanate (0.9 g, 0.003 moles) and treating the resulting clavulanic acid solution with D(+) 1 - methylbenzylamine in dry tetrahydrofuran (10 ml). The mixture was stored at 5° for two days during which time a slow crystallization occurred. Filtration afforded the title salt 0.6 g, 62% yield, having m.p. 125° (d).

Example 5

Hard gelatin capsules may be filled with 50 mg of a compound of any of Examples 1—4.

Example 6

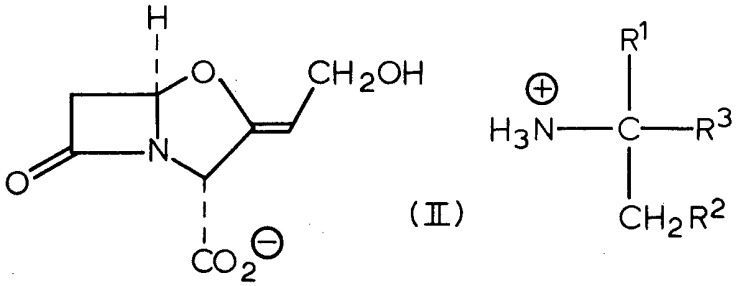
Hard gelatin capsules may be filled with a mixture consisting essentially of 50 mg of a compound of any of Examples 1—4 and 250 mg of amoxycillin trihydrate.

Example 7

When stored for 72 hours at ambient temperature under conditions of 50% humidity the products of Examples 1—7 were found to absorb considerably less moisture than sodium clavulanate or potassium clavulanate maintained under the same conditions. In accelerated storage tests under conditions of 50% humidity the compounds of Examples 1—4 may be shown to be more stable than sodium clavulanate tetrahydrate.

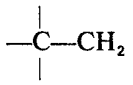
WHAT WE CLAIM IS:—

1. A salt of the formula (II):



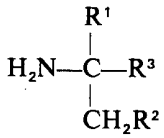
(II)

wherein R^1 is a hydrogen atom or lower alkyl, aralkyl, phenyl or lower alkyl or phenyl inertly substituted by halogen, lower alkoxyl, lower acyloxyl or lower esterified carboxyl, R^2 is a hydrogen atom or lower alkyl, aralkyl, phenyl or alkyl or phenyl inertly substituted by halogen, lower alkoxyl, lower acyloxyl or lower esterified carboxyl and R^3 is a lower alkyl, aralkyl, phenyl or lower alkyl or phenyl inertly substituted by halogen lower alkoxyl, lower acyloxy or lower esterified carboxyl group and wherein aralkyl refers to lower alkyl substituted by phenyl or inertly substituted phenyl as hereinbefore defined; or R^1 and R^3 together with the C atom to which they are joined forms a carboxylic ring of 5 to 7 C atoms and R^2 is as defined above or R^1, R^2 and R^3 together with the



moiety form a polycyclic ring of up to 16 C atoms.

2. A salt as claimed in claim 1 wherein R^1, R^2 and R^3 are such that the compound of the formula (III):



(III)

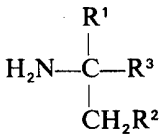
is a pharmaceutically acceptable amine.

3. A salt as claimed in claim 1 or claim 2 wherein R^1 is a lower alkyl group.

4. A salt as claimed in any one of claims 1 to 3 wherein R^2 is a hydrogen atom or a lower alkyl group.

5. A salt as claimed in any one of claims 1 to 4 wherein R^3 is a lower alkyl or aralkyl group.

6. A salt as claimed in any one of claims 1 to 5 wherein R^1, R^2 and R^3 are such that the amine of the formula (III):

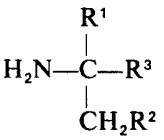


(III)

contains from 4 to 16 carbon atoms.

7. A salt as claimed in claim 6 wherein the amine of the formula (III) contains from 4 to 10 carbon atoms.

8. A process for the preparation of a salt as claimed in claim 1 which process comprises the reaction of clavulanic acid with an amine of the formula (III):



(III)

wherein R^1, R^2 and R^3 are as defined in claim 1.

9. A process as claimed in claim 8 wherein the reaction takes place in a non-hydroxylic solvent.

10. A process as claimed in claim 8 or claim 9 wherein the reaction takes place at from 0°C to 35°C.

11. A process as claimed in any one of claims 8 to 10 wherein the clavulanic acid is generated *in situ*.

12. A process as claimed in claim 11 wherein the clavulanic acid is generated by hydrogenation of a hydrogenolysable ester of clavulanic acid.

13. A process for the preparation of a salt as claimed in any one of claims 1 to 7 which process comprises the displacement of cation from salt of clavulanic acid other than one of the formula (II) by a protonated amine of the formula (III).

14. A pharmaceutical composition comprising a salt of the formula (II) and a pharmaceutically acceptable carrier.

15. A composition as claimed in claim 14 wherein the composition contains less than 5% moisture.

16. A composition as claimed in claim 14 wherein the composition contains less than 3% moisture.

17. A composition as claimed in claim 14 wherein the composition contains less than 2% moisture.

18. An injectable or infusable pharmaceutical composition as claimed in any one of claims 14 to 17 comprising a salt of the formula (II) in sterile form.

19. A pharmaceutical composition as claimed in any one of claims 14 to 17 adapted for oral administration.

20. A pharmaceutical composition as claimed in claim 19 in unit dose form.

21. A pharmaceutical composition as claimed in any one of claims 14 to 20 comprising an additional β-lactam antibiotic.

22. A pharmaceutical composition as claimed in claim 21 wherein the β-lactam antibiotic is selected from benzylpenicillin phenoxymethylpenicillin, carbenicillin, methicillin, propicillin, ampicillin, amoxycillin, epicillin, ticarcillin, cyclacillin, pirbencillin, cephatrizine, cephaloridine, cephalothin, cefazolin, cephalexin, cefoxitin, cephacetrile, cephamandole, cephapirin, cephradine, cephaloglycine, hetacillin, metampicillin, the acetoxymethyl, pivaloyloxymethyl and phthalidyl esters of benzylpenicillin, ampicillin, amoxycillin or cephaloglycine, and the phenyl, tolyl and indanyl α-esters of carbenicillin or ticarcillin.

23. A pharmaceutical composition as claimed in claim 21 or claim 22 wherein the ratio of the salt of the formula (II) to the β-lactam antibiotic is from 3:1 to 1:10 by weight.

24. A pharmaceutical composition as claimed in claim 23 wherein the ratio of the salt of the formula (II) to the β-lactam antibiotic is from 1:1 to 1:6 by weight.

25. A pharmaceutical composition as claimed in claim 23 wherein the ratio of the salt of the formula (II) to the β-lactam antibiotic is from 1:3 to 1:5 by weight.

26. A pharmaceutical composition as claimed in any one of claims 14 to 25 in unit dose form, wherein the total quantity of antibacterial agents present is from 50 to 1500 mg.

27. A pharmaceutical composition as claimed in claim 26 wherein the total quantity of antibacterial agents present is from 100 to 1000 mg.

28. A pharmaceutical composition as claimed in any one of claims 21 to 27 comprising from 150 to 1000 mg of amoxycillin or ampicillin and from 50 to 500 mg of a salt of the formula (II).

29. A pharmaceutical composition as claimed in claim 28 comprising from 200 to 500 mg amoxycillin or ampicillin and from 50 to 500 mg of a salt of the formula II.

30. A pharmaceutical composition as claimed in claim 28 or claim 29 comprising amoxycillin trihydrate.

31. The 2 - amino - 2 - methylpropane salt of clavulanic acid.

32. The 2 - amino - 2 - methylbutane salt of clavulanic acid.

33. The 2 - amino - 2 - methylpentane salt of clavulanic acid.

34. The 2 - amino - 2 - methylhexane salt of clavulanic acid.

35. The 2 - amino - 2 - methylheptane salt of clavulanic acid.

36. The 2 - amino - 2 - methyloctane salt of clavulanic acid.
37. The 3 - amino - 3 - methylpentane salt of clavulanic acid.
38. The 1 - amino - 1 - methylcyclohexane salt of clavulanic acid.
39. The 1 - aminoadamantane salt of clavulanic acid.

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