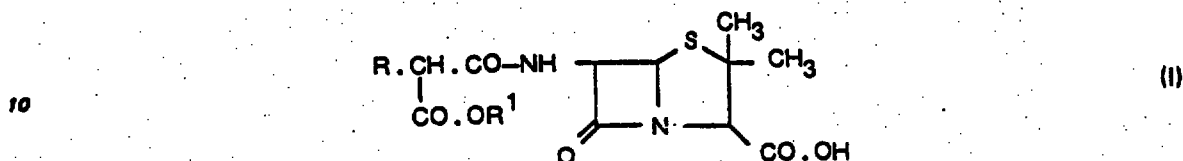


Ortho-tolyl ester of an alpha-carboxy penicillin, process for its preparation and pharmaceutical compositions comprising the penicillin

This invention relates to the o-tolyl ester of an α -carboxy penicillin.

The penicillin and its salts are active against Gram-positive and Gram-negative bacteria which makes them useful as therapeutic and prophylactic agents against bacterial infections in animals, including man and poultry.

US Patent No 3,853,849 claims a penicillin mono-ester of the formula (I):



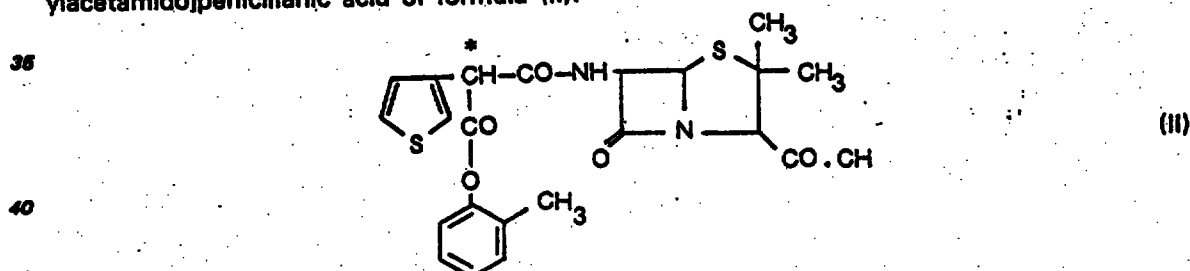
or a non-toxic pharmaceutically acceptable salt thereof, wherein R is phenyl, or 3-thienyl and R¹ is phenyl or methylphenyl. That patent specifically discloses the compound wherein R is 3-thienyl and R¹ is phenyl, ie the α -phenyl ester of α -carboxy-3-thienylmethyl penicillin.

Such mono-esters have the advantage that they are orally absorbed in animal species, including man, where they undergo *in vivo* hydrolysis to produce a degree of blood level antibiotic activity due to the free α -carboxy-penicillin that is not attained when the α -carboxy-penicillin itself is orally administered to the animal species.

British Patent No 1,455,529 claims specifically the α -para-tolyl mono-ester of α -carboxy-3-thienylmethyl penicillin which demonstrates a high degree of oral absorption in man.

The present invention is based on the discovery that the α -ortho-tolyl ester of α -carboxy-3-thienyl-methyl penicillin exhibits considerably higher bioavailability after oral administration in man than either the phenyl or the p-tolyl esters. Although the p-tolyl ester is somewhat better absorbed than the phenyl ester, this improvement is only of the order of 15% at the peak serum level. In contrast, we have now found that the o-tolyl ester produces peak serum levels in man of the order of 150% higher than those produced by the phenyl ester, and the bioavailability as measured by the AUC (area under curve) method for the o-tolyl ester is about 120—220% higher than for the phenyl ester (ie 2—3 times as efficiently absorbed). These dramatic differences could not have been predicted from a knowledge of the esters disclosed in US Patent No 3,853,849 and UK Patent No 1,455,529.

Accordingly, this invention provides 6 β -[2-(2'-methylphenoxyacetyl)-2-thien-3'-ylacetamid]penicillanic acid of formula (II):



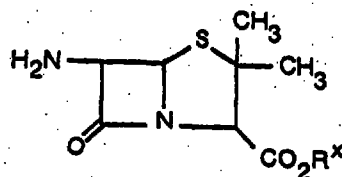
or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

The compounds of the present invention include the pharmaceutically acceptable esters of the 3-carboxylic acid group which hydrolyse readily in the human body to produce the parent acid, for example acyloxyalkyl groups such as acetoxymethyl, pivaloyloxymethyl, α -acetoxylethyl, α -acetoxymethyl and α -pivaloyloxyethyl groups; alkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxyethyl and α -ethoxycarbonyloxyethyl; dialkylaminoalkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; and lactone groups such as phthalidyl or dimethoxyphthalidyl.

Suitable salts of the 3-carboxylic acid group of the compound of formula (I) include metal salts, eg aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium, and ammonium or substituted ammonium salts, for example those with lower alkylamino such as triethylamine, hydroxy-lower alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylamine, N,N-dibenzylethylenediamine, 1-phenamine, N-ethylpiperidine, N-benzyl- β -phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylethylenediamine, or bases of the pyridine type such as pyridine, collidine or quinoline, or other amines which have been used to form salts with known penicillins.

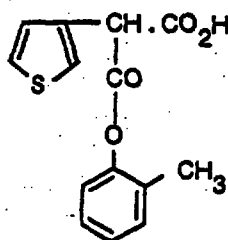
The carbon atom marked * in formula (II) is asymmetric. This invention includes both optically active isomers at that position as well as the D,L-mixture.

The compounds of formula (II) may be prepared by reacting a compound of formula (III):



(III)

wherein the amino group is optionally substituted with a removable group which permits acylation to take place and wherein R^x is hydrogen or a carboxyl blocking group; with an N-acylating derivative of an acid of formula (IV):

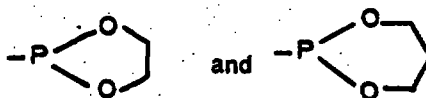


(IV)

and thereafter if necessary carrying out one or more of the following steps:

- (i) removal of any substituent on the amide group;
- (ii) removal of any carboxyl blocking group R^x ;
- (iii) converting the product to a salt or *in vivo* hydrolysable ester thereof.

Suitable groups which permit acylation to take place and which are optionally present on the amino group of the starting material of the formula (III) include N-silyl, N-stannyl and N-phosphorus groups, for example trialkylsilyl groups such as trimethylsilyl, trialkyltin groups such as tri-*n*-butyltin, groups of formula $-P.R^aR^b$ wherein R^a is an alkyl, haloalkyl, aryl, aralkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy or dialkylamino group, R^b is the same as R^a or is halogen or R^a and R^b together form a ring; suitable such phosphorus groups being $-P(OC_2H_5)_2$, $-P(C_2H_5)_2$,



Suitable carboxyl-blocking derivatives for the group $-CO_2R^x$ in formula (II) include salts, ester, and anhydride derivatives of the carboxylic acid. The derivative is preferably one which may readily be cleaved at a later stage of the reaction. Suitable salts include inorganic salts, for example alkali metal salts such as the sodium salt, tertiary amine salts, such as those with tri-lower-alkylamines, N-ethylpiperidine, 2,6-lutidine, pyridine, N-methylpyrrolidine, dimethylpiperazine. A preferred salt is with triethylamine.

Suitable ester-forming carboxyl-blocking groups are those which may be removed under conventional conditions. Such groups for R^x include benzyl, p-methoxybenzyl, 2,4,6-trimethylbenzyl, 3,5-di-*t*-butyl-4-hydroxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, *t*-butyl, *t*-amyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, p-toluenesulphonyl-ethyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, such as described above, an oxime radical of formula $-N=CHR^o$ where R^o is aryl or heterocyclic, or an *in vivo* hydrolysable ester radical such as defined above.

The carboxyl group may be regenerated from any of the above esters by usual methods appropriate to the particular R^x group, for example, acid — and base — catalysed hydrolysis, or by enzymically — catalysed hydrolysis, or by hydrogenation. The hydrolysis must of course be carried out under conditions to which the ortho-tolyl ester group in the side-chain is stable.

A reactive N-acylating derivative of the acid (IV) is employed in the above process. Suitable N-acylating derivatives include an acid halide, preferably the acid chloride or bromide. Acylation with an acid halide may be affected in the presence of an acid binding agent for example tertiary amine (such as triethylamine or dimethylaniline), an inorganic base (such as calcium carbonate or sodium bicarbonate) or an oxirane, which binds hydrogen halide liberated in the acylation reaction. The oxirane is preferably a (C_{1-3}) -1,2-alkylene oxide — such as ethylene oxide or propylene oxide. The acylation reaction using an acid halide may be carried out at a temperature in the range -50°C to $+50^\circ\text{C}$, preferably -20°C to

+20°C, in aqueous or non-aqueous media such as aqueous acetone, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, dichloromethane, 1,2-dichloroethane, or mixtures thereof. Alternatively, the reaction may be carried out in an unstable emulsion of water-immiscible solvent, especially an aliphatic ester or ketone, such as methyl isobutyl ketone or butyl acetate.

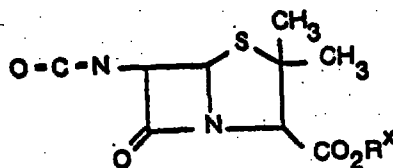
The acid halide may be prepared by reacting the acid (IV) or a salt thereof with a halogenating (eg chlorinating or brominating) agent such as phosphorus pentachloride, thionyl chloride or oxalyl chloride.

Alternatively, the N-acylating derivative of the acid (IV) may be symmetrical or mixed anhydride. Suitable mixed anhydrides are alkoxyformic anhydrides, or anhydrides with, for example carbonic acid monoesters, trimethyl acetic acid, thioacetic acid, diphenylacetic acid, benzoic acid, phosphorus acids (such as phosphoric or phosphorous acids), sulphuric acid or aliphatic or aromatic sulphonic acids (such as *p*-toluenesulphonic acid). The mixed or symmetrical anhydrides may be generated using N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. When a symmetrical anhydride is employed, the reaction may be carried out in the presence of 2,4-lutidine as catalyst.

Alternative N-acylating derivatives of acid (IV) are the acid azide, or activated esters such as esters with 2-mercaptopyridine, cyanomethanol, *p*-nitrophenol, 2,4-dinitrophenol, thioalcohols such as thiophenol, methanethiol, ethanethiol and propanethiol, halophenols, including pentachlorophenol, monomethoxyphenol or 8-hydroxyquinoline, N-hydroxysuccinimide or 1-hydroxybenztriazole; or amides such as N-acylsaccharins or N-acylphthalimides; or an alkylidene iminoester prepared by reaction of the acid (IV) with an oxime.

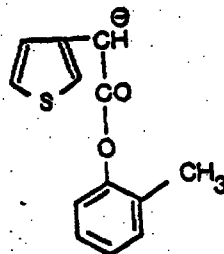
Other reactive N-acylating derivatives of the acid (IV) include the reactive intermediate formed by reaction *in situ* with a condensing agent such as carbodiimide, for example N,N-diethyl-, dipropyl- or diisopropylcarbodiimide, N,N'-di-cyclohexylcarbodiimide, or N-ethyl-N'- γ -dimethylaminopropylcarbodiimide; a suitable carbonyl compound, for example N,N'-carbonyldiimidazole or N,N'-carbonylditriazole; an isoxasolinium salt, for example N-ethyl-5-phenylisoxazolinium-3-sulphonate or N-*t*-butyl-5-methylisoxazolinium perchlorate; or an N-alkoxycarbonyl-2-alkoxy-1,2-dihydroquinoline, such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. Other condensing agents include Lewis acids (for example $\text{BBr}_3 \cdot \text{C}_6\text{H}_6$); or a phosphoric acid condensing agent such as diethylphosphoryl cyanide. The condensation reaction is preferably carried out in an organic reaction medium, for example methylene chloride, dimethylformamide, acetonitrile, alcohol, benzene, dioxan or tetrahydrofuran.

Compounds of formula (II) may also be prepared by reacting a compound of formula (V):



(V)

wherein R^x is as defined above with respect to formula (III) above; with an acid of formula (IV) or a carbocation of formula (IVA):



(IVA)

and thereafter if necessary carrying out one or more of the following steps:

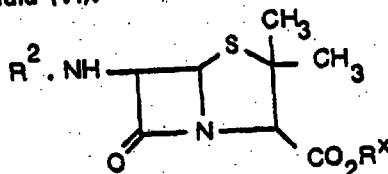
(i) removal of any carboxyl blocking group R^x ;

(ii) converting the product to a salt or *in vivo* hydrolysable ester thereof.

This reaction is preferably carried out at a temperature in the range -10° to $+50^\circ\text{C}$ in an inert organic solvent, such as methylene dichloride, in the presence of a basic catalyst such as triethylamine, pyridine or a nitrogen-containing aromatic mono- or bi-cyclic compound such as 4-methoxy-(dimethylamino)pyridine, 1-methyl(benz)imidazole or imidazo[1,2- α]pyridine.

A third method of preparation of the compounds of formula (II) comprises:

a) treating a compound of formula (VI):



(VI)

wherein R^* is a carboxyl-blocking group, and R^2 is an acyl group, in particular an acyl group derived from the side-chain of a natural penicillin, such as benzyl penicillin or phenoxymethyl penicillin; with an agent forming an imino halide;

- b) treating the imino halide with a compound to introduce a group QR , on the imino carbon atom, wherein Q is oxygen, sulphur or nitrogen and R , is an alkyl group of from 5 to 14 carbon atoms, to form an iminoether, iminothioether, or amidine (when Q is O, S, or N respectively);
- c) reacting with an N-acylating derivative of an acid of formula (IV) above;
- d) treating with water; and
- e) optionally removing the carboxyl-blocking group R^* .

A suitable agent for preparing an imino halide is an acid halide in the presence of an acid binding agent such as a tertiary amine, eg pyridine, triethylamine, or N,N-dimethylaniline. Examples of suitable acid halides are phosphorus pentachloride, phosgene, phosphorous pentabromide, phosphorus oxychloride, oxalyl chloride and p-toluene sulphonic acid chloride. Phosphorus pentachloride and phosphorus oxychloride are preferred. The reaction may be conducted under cooling, preferably at temperatures from 0°C to -30°C when phosphorus pentachloride is employed. The amount of the tertiary amine is preferably 3—5 mols per mol of phosphorus pentachloride. It is also preferable to use the phosphorus halide in an amount slightly in excess of that of the starting material.

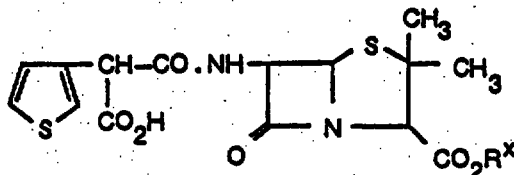
The resulting imino compounds are then treated to introduce a $-QR$ group onto the imino carbon atom. This is preferably effected by reacting the imino halide with a corresponding alcohol. Examples of suitable alcohols for reaction with the imino halide are aliphatic alcohols containing from 1 to 12 carbon atoms, preferably 1 to 5 carbon atoms, such as methanol, ethanol, propanol, isopropyl alcohol, amyl alcohol and butyl alcohol, and aralkyl alcohols such as benzyl alcohol and 2-phenylethanol.

The reaction of the alcohol with the imino halide is preferably effected in the presence of an acid binding agent, such as a tertiary amine, preferably pyridine, and the reaction is usually carried out without isolating the imino halide from the reaction mixture.

Thereafter the imino compound is caused to react with an N-acylating derivative of an acid of formula (IV). The comments made above concerning such N-acylating derivatives, and the conditions for carrying out acylations also apply in this case. In particular, the presence of a tertiary amine such as pyridine or N,N-dimethylaniline in the reaction system is preferred.

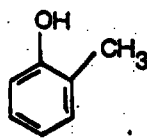
Finally, the product is treated with water. The water treatment may be conducted together with the isolation of the desired material. That is the reaction mixture may be added to water or a saturated aqueous solution of sodium chloride and then the aqueous layer formed is separated from the organic solvent layer.

The compounds of formula (II) may also be prepared by esterification of a compound of formula (VII) or a salt thereof:



(VII)

wherein R^* is hydrogen or a carboxyl blocking group; with compound of formula (VIII):



(VIII)

and thereafter if necessary carrying out one or more of the following steps:

- (i) removal of any carboxyl blocking groups R^* ;
- (ii) converting the product to a salt or *in vivo* hydrolysable ester thereof.

Esterification may be performed by any conventional method, for example by reaction of the free acid with a compound of formula (VIII) in the presence of a catalyst or by reaction of a salt of the free acid:

- a) with the appropriate halide or sulphate derivative of the compound of formula (VIII) in the presence of dimethylsulphoxide and calcium carbonate or with the halide in the presence of hexamethyl phosphoramide; or
- b) by phase transfer catalysis methods with the halide and/or sulphate of the alcohol in aqueous and/or organic solution in the presence of a quaternary ammonium salt such as tetrabutyl ammonium bisulphate or halide, or benzyltrimethylammonium halide.

Alternatively, the mixed anhydride derivative of the compound of formula (VII) may be reacted with the compound of formula (VIII) or an alkali metal or alkaline earth metal salt thereof. Suitable salts include the lithium, sodium or magnesium salts. Suitable mixed anhydrides are alkoxyformic anhydrides, or anhydrides with, for example trimethyl acetic acid, thioacetic acid, diphenylacetic acid, benzoic acid, phosphorus acids (such as phosphoric or phosphorous acids), sulphuric acid or aliphatic or aromatic sulphonic acids (such as p-toluenesulphonic acid). The mixed anhydride may be generated *in situ*. For example, using isobutyl chloroformate or ethyl chloroformate.

Other reactive esterifying derivatives of the acid (VII) include the reactive intermediate formed by reaction *in situ* with a condensing agent such as a carbodiimide, for example N,N-diethyl-, dipropyl- or diisopropylcarbodiimide, N,N'-di-cyclohexylcarbodiimide, or N-ethyl-N'- γ -dimethylaminopropylcarbodiimide; a suitable carbonyl compound, for example, N,N'-carbonyldiimidazole or N,N'-carbonylditriazole; an isoxasolinium salt, for example N-ethyl-5-phenylisoxazolinium-3-sulphonate or N- γ -butyl-5-methylisoxazolinium perchlorate or an N-alkoxycarbonyl-2-alkoxy-1,2-dihydroquinoline, such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. Other condensing agents include Lewis acids (for example BBr₃-C₆H₆); or a phosphoric acid condensing agent such as diethylphosphorylcyanide. The condensation reaction is preferably carried out in an organic reaction medium, for example methylene chloride, dimethylformamide, acetonitrile, alcohol, benzene, dioxan or tetrahydrofuran.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics, and the invention therefore includes within its scope a pharmaceutical composition comprising a compound of formula (I) above together with a pharmaceutical carrier or excipient.

The compositions may be formulated for administration by any route, although an oral administration is preferred. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

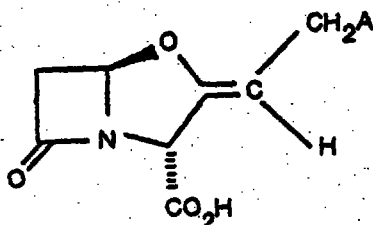
Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired convention flavouring or colouring agents.

Suppositories will contain conventional suppository bases, eg cacao-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection is supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10% to 60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50 to 500 mg, of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg, per day, for instance 1500 mg, per day, depending on the route and frequency of administration.

The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics may be employed. Advantageously the compositions also comprise a compound of formula (IX) or a pharmaceutically acceptable salt or ester thereof:



(IX)

10 wherein A is hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, mono- or di-hydrocarbyl-substituted amino, or mono- or di-acylamino.

Preferably, A is hydroxyl, i.e. the compound of formula (IX) is clavulanic acid or a pharmaceutically acceptable salt thereof, in particular an alkali metal salt.

15 It has been stated that the penicillin α -ester of formula (II), although covered generically by the claims of US Patent No 3,853,849, is considerably and unpredictably superior to the remaining esters claimed in that patent. To support this statement, table 1 shows the serum concentration, the area under curve, and urinary excretion of α -carboxy-3-thienylmethylpenicillin (hereinafter called ticarcillin) produced when the phenyl, and o-tolyl esters of ticarcillin were administered orally to a panel of human

20 volunteers, in four separate experiments, referred to as A—D.

To obtain the results shown in table 1, the two esters of ticarcillin were each given to a panel of fasting human volunteers in a syrup formulation in an amount equivalent to provide either 200 or 400 mg (as stated in table 1) of the free ticarcillin after the expected *in vivo* hydrolysis. Periodic blood samples were taken from the volunteers and each assayed for ticarcillin content by a standard bioassay technique. The urine excreted by each volunteer within the 6 hours following administration was

25 also collected and assayed for the free ticarcillin. All three parameters (viz the urinary excretion level, the peak serum concentration achieved and the total area under the curve when the serum concentration is plotted against time) are indications of the minimum degree to which the penicillin ester has been absorbed after oral administration and then hydrolysed *in vivo*. After oral administration of the two esters of ticarcillin, analysis of blood and urine samples showed that very little of the esters was present

30 in the blood stream ($< 0.2 \mu\text{g}/\text{m}$) or urine (ca 1% of dose for the phenyl ester, and ca 2% of dose for the o-tolyl ester). Therefore, it is valid to talk of the absorption of these esters in terms of ticarcillin in the blood stream and urine.

The results achieved were as follows:

TABLE 1

α -Ester of ticarcillin	Mean serum concentration ($\mu\text{g/ml}$) of ticarcillin							AUC ($\mu\text{g min ml}^{-1}$)	urinary excretion 0—6 h (% of dose)
	15 m	30 m	45 m	1 h	1.5 h	2 h	4 h		
Experiment A — oral dose equivalent to 200 mg ticarcillin									
phenyl	1.62	2.88	2.34	1.92	1.30	1.10	< 0.4	253.65	15.14
o-tolyl	3.77	6.80	6.98	6.20	4.93	3.82	< 0.4	808.75	39.26
Experiment B — oral dose equivalent to 200 mg ticarcillin									
phenyl	1.35	2.73	2.67	2.45	1.45	0.82	< 0.8	343.50	22.46
o-tolyl	4.22	7.85	6.73	5.20	3.58	3.25	< 0.8	1103.30	41.74
Experiment C — oral dose equivalent to 400 mg ticarcillin									
phenyl	2.7	6.7	7.3	5.8	4.3	2.4	< 0.8	686.7	23.7
o-tolyl	4.8	11.7	11.1	9.5	8.2	6.5	1.4	1520.9	36.4
Experiment D — oral dose equivalent to 400 mg ticarcillin									
phenyl	1.4	6.0	5.1	4.6	3.8	2.6	< 0.8	599.5	21.7
o-tolyl	5.7	10.6	12.6	10.8	8.3	5.7	0.8	1428.8	39.0

AUC = Area under curve

The results in table 1 demonstrate that the bioavailability of ticarcillin after oral administration of the α -ortho-tolyl ester is considerably greater than after administration of the phenyl ester. The parameter which can be most directly compared to show this difference is the area under curve (AUC). Table 2 shows the percentage increase in the AUC for the ortho-tolyl ester compared to the phenyl ester, calculated from the data in table 1.

TABLE 2

Experiment	% increase in AUC
A	219%
B	223%
C	121%
D	138%

It can be seen from Table 2 that the bio-availability of ticarcillin, measured by AUC, after oral administration of the α -*ortho*-tolyl ester is some two- to three-fold greater than that after administration of the α -phenyl ester. This conclusion is confirmed by the greater urinary recovery of ticarcillin detected after administration of the α -*ortho*-tolyl ester.

The improved bioavailability can also be seen from the individual mean serum concentration figures in table 1. In contrast the α -*para*-tolyl ester disclosed in British Patent No 1,455,529 is much less well absorbed than the α -*ortho*-phenyl ester. This can be seen by the comparison with the phenyl ester and for convenience the data from Specification No 1,455,529 is repeated in table 3 below:

TABLE 3

(Administration as syrup containing equivalent of 400 mg ticarcillin)

Monoester group	Mean serum concentration (μ g/ml)						Peak serum concentration (μ g/ml)	Urinary excretion 0—6 h (%)
	20 m	40 m	1 h	1.5 h	2 h	3 h		
phenyl	5.4	7.5	5.2	3.6	2.4	< 1.6	7.5	23
p-tolyl	5.9	8.6	6.8	4.9	3.7	< 1.6	8.6	30

Although the p-tolyl ester is absorbed to a greater extent than the phenyl ester, the difference is small compared to the dramatic improvement seen with the *ortho*-tolyl ester. The percentage increase of the peak serum levels of the p-tolyl compared to the phenyl ester is only 14.7%. In fact the differences in mean serum concentrations in table 3 are not statistically significant.

The following Examples illustrate this invention.

Example 1

Sodium 6, β -[2-(2'-methylphenoxyacetyl)-2-thien-3'-ylacetamido]penicillanate

2-Methylphenyl hydrogen thien-3-ylmalonate (110.0 g, 0.40 mole), dimethylformamide (1.0 ml) and thionyl chloride (29.2 ml, 48.8 g, 0.41 mole) in dichloromethane (880 ml) were heated under reflux for 1.5 hours then evaporated to dryness *in vacuo* at <30° to give 2-(2-methylphenoxyacetyl)-2-thien-3'-ylacetyl chloride.

This acid chloride in acetone (200 ml) was cooled to $-17^{\circ}\pm 2^{\circ}$ then added to a suspension, prepared from 6-APA (90.8 g, 0.42 mole) in water (320 ml) cooled to 10° adjusted to pH 8.5—9.0 with 2N sodium hydroxide then treated with acetone (400 ml) and sodium hydrogen carbonate (100 g), cooled to $-17^{\circ}\pm 2^{\circ}$. The reaction mixture was stirred for 45 minutes, treated with charcoal (20 g), filtered through celite, washed through with 50% aqueous acetone (3 x 80 ml) then the filtrate diluted with water (800 ml) and washed with ether (600 ml, 300 ml). The aqueous solution was covered with ether (600 ml), acidified to pH 2.0 with 2N hydrochloric acid with vigorous stirring then the layers separated. The aqueous phase was extracted with ether (200 ml) then the combined ether extracts washed with a mixture of water (320 ml) and saturated brine (80 ml) then with saturated brine (2 x 400 ml) and dried over anhydrous magnesium sulphate.

The ether was removed *in vacuo* to give the free acid as a foam which was dissolved in fresh ether (3 l) and treated with 2M sodium 2-ethylhexanoate in 4-methylpentan-2-one (200 ml, 0.40 mole). The suspension was diluted with more ether (1 l) then the solid collected, washed with ether and dried *in vacuo* over phosphorus pentoxide, 149 g, 75% yield, $\nu_{\max}$ (KBr) 1765, 1680, 1607, 1460, 775 and 750 cm^{-1} , δ (D_2O) 1.47 (6H, s, 2 x 2CH_3), 1.80 (3H, s, ArCH_3), 4.27 (1H, s, 3H), 5.55 (2H, s, 5 and 6H), 6.8—7.5 (7H, m, thienyl and C_6H_4).

Example 2

Sodium 6, β -[2-(2-methylphenoxyacetyl)-2-thien-3'-ylacetamido]penicillanate

Disodium ticarcillin (4.3 g, 100 μ mole) in water (50 ml) was covered with ethyl acetate (30 ml) and acidified to pH 2.0 with 40% phosphoric acid. The ethyl acetate was separated, the aqueous phase extracted with further ethyl acetate (20 ml) then the extracts washed with water (50 ml) and brine (20 ml), dried and evaporated to a foam (4.12 g).

This ticarcillin diacid in ethyl acetate (20 ml) was cooled in an ice bath and treated with 2-methyl-phenol (1.19 g, 11 μ mole) followed by dicyclohexylcarbodiimide (2.74 g, 12 μ mole) then the mixture was stirred at room temperature overnight. The precipitated dicyclohexyl urea was filtered off,

washed with ethyl acetate (10 ml), and the filtrate extracted with dilute sodium bicarbonate solution (2 x 25 ml) and water (20 ml). The aqueous solution was washed with ether (2 x 20 ml), acidified to pH 3.7 with 40% phosphoric acid and extracted with ether (3 x 20 ml). The extracts were washed with water (2 x 50 ml) and brine (20 ml), dried and evaporated to a foam (2.71 g).

The foam in fresh ether (50 ml) was treated with 2N sodium 2-ethylhexanoate in 4-methylpentan-2-one (2.85 ml) and the precipitated sodium salt collected, washed with ether and dried *in vacuo* to give the title compound, 2.59 g, 52.2%, $\nu_{\max}$ (KBr) 1765, 1675, 1605, 1460, 775 and 750 cm^{-1} , δ [(CD₃)₂SO] 1.48, 1.57 (6H, 2 x s, 2 x 2CH₃), 2.08 (3H, s, ArCH₃), 3.96 (1H, s, 3H), 5.3—5.6 (3H, m, CHCONH, 5 and 6 H), 6.9—7.6 (7H, m, thienyl and C₆H₅), 9.0—9.3 (1H, m, CONH).

Example 3

Preparation of oral dosage units in the form of a tablet

(a) Sodium 6,β-[2-(2-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate as sole therapeutic agent.

Ingredients:—	mg
1. Sodium 6,β-[2-(2-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate	494 (free acid)
2. Carboxymethyl sodium starch glycolate	15
3. Magnesium stearate	12
4. Microcrystalline cellulose	to 750

Items 1, 2 and 4 are blended with two thirds of item 3, and compressed on a rotary tablet machine. The slugs produced are milled, and the milled material blended with the remainder of item 3. The mixture is then compressed on a rotary tablet machine to form the final tablets.

(b) Sodium 6,β-[2-(2-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate and potassium clavulanate

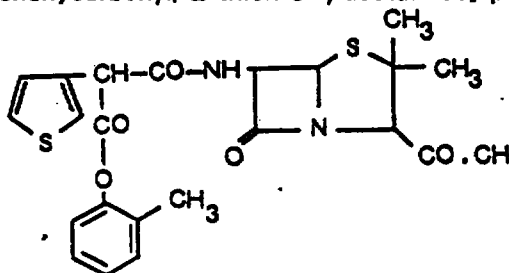
Ingredients:—	mg
1. Sodium 6,β-[2-(2-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate	494 (free acid)
2. Potassium clavulanate	100 (free acid)
3. Carboxymethyl sodium starch glycolate	15
4. Magnesium stearate	12
5. Microcrystalline cellulose	to 850

Tablets are prepared as in Example 3(a), both active ingredients being incorporated in the first stage slugging operation.

The tablets from Example 3(a) or 3(b) may be uncoated or a conventional film coating may be applied.

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

1. 6β-[2-(2'-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanic acid of formula (II):



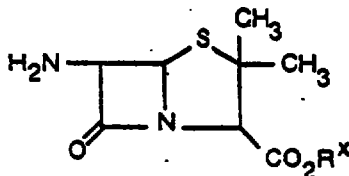
(II)

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

2. Sodium 6,β-[2-(2'-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate.

3. A process for the preparation of a penicillin as claimed in claim 1 which process comprises:

A) reacting a compound of formula (III):



(III)

washed with ethyl acetate (10 ml), and the filtrate extracted with dilute sodium bicarbonate solution (2 x 25 ml) and water (20 ml). The aqueous solution was washed with ether (2 x 20 ml), acidified to pH 3.7 with 40% phosphoric acid and extracted with ether (3 x 20 ml). The extracts were washed with water (2 x 50 ml) and brine (20 ml), dried and evaporated to a foam (2.71 g).

The foam in fresh ether (50 ml) was treated with 2N sodium 2-ethylhexanoate in 4-methylpentan-2-one (2.85 ml) and the precipitated sodium salt collected, washed with ether and dried *in vacuo* to give the title compound, 2.59 g, 52.2%, $\nu_{\max}$ (KBr) 1765, 1675, 1605, 1460, 775 and 750 cm^{-1} , δ [(CD₃)₂SO] 1.48, 1.57 (6H, 2 x s, 2 x 2CH₃), 2.08 (3H, s, ArCH₃), 3.96 (1H, s, 3H), 5.3—5.6 (3H, m, CHCONH, 5 and 6 H), 6.9—7.6 (7H, m, thienyl and C₆H₄), 9.0—9.3 (1H, m, CONH).

Example 3

Preparation of oral dosage units in the form of a tablet

(a) Sodium 6,β-[2-(2-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate as sole therapeutic agent.

Ingredients:—	mg
1. Sodium 6,β-[2-(2-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate	494 (free acid)
2. Carboxymethyl sodium starch glycolate	15
3. Magnesium stearate	12
4. Microcrystalline cellulose	to 750

Items 1, 2 and 4 are blended with two thirds of item 3, and compressed on a rotary tablet machine. The slugs produced are milled, and the milled material blended with the remainder of item 3. The mixture is then compressed on a rotary tablet machine to form the final tablets.

(b) Sodium 6,β-[2-(2-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate and potassium clavulanate

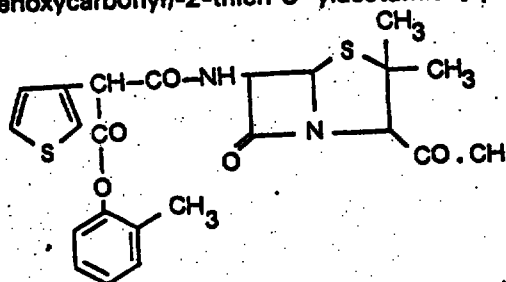
Ingredients:—	mg
1. Sodium 6,β-[2-(2-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate	494 (free acid)
2. Potassium clavulanate	100 (free acid)
3. Carboxymethyl sodium starch glycolate	15
4. Magnesium stearate	12
5. Microcrystalline cellulose	to 850

Tablets are prepared as in Example 3(a), both active ingredients being incorporated in the first stage slugging operation.

The tablets from Example 3(a) or 3(b) may be uncoated or a conventional film coating may be applied.

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

1. 6β-[2-(2'-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanic acid of formula (II):

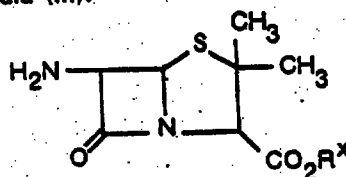


or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

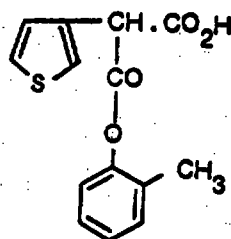
2. Sodium 6,β-[2-(2'-methylphenoxyacarbonyl)-2-thien-3'-ylacetamido] penicillanate.

3. A process for the preparation of a penicillin as claimed in claim 1 which process comprises:

A) reacting a compound of formula (III):

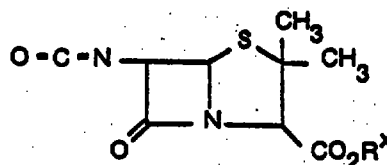


wherein the amino group is optionally substituted with a removable group which permits acylation to take place and wherein R^x is hydrogen or a carboxyl blocking group; with an N-acylating derivative of the acid of formula (IV):



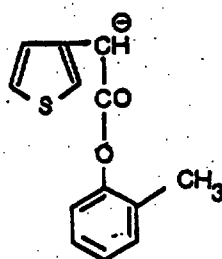
(IV)

- and thereafter if necessary carrying out one or more of the following steps:
- (i) removal of any substituent on the amide group;
 - (ii) removal of any carboxyl blocking group R^x ;
 - (iii) converting the product to a salt or *in vivo* hydrolysable ester thereof;
- or B) reacting a compound of formula (V):



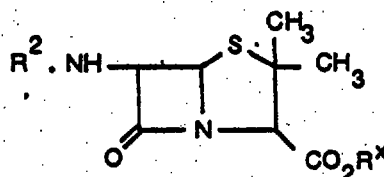
(V)

wherein R^x is as defined above with respect to formula (III) above; with the acid of formula (IV) or the carbanion of formula (IVA):



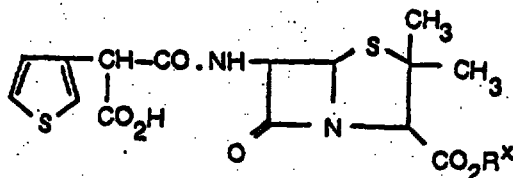
(IVA)

- and thereafter if necessary carrying out one or more of the following steps:
- (i) removal of any carboxyl blocking group R^x ;
 - (ii) converting the product to a salt or *in vivo* hydrolysable ester thereof;
- or C):
- a) treating a compound of formula (VI):



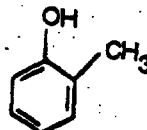
(VI)

- wherein R^x is a carboxyl-blocking group, and R^2 is an acyl group, with an agent forming an imino halide;
- b) treating the imino halide with a compound to introduce a group QR_1 on the imino carbon atom, wherein Q is oxygen, sulphur or nitrogen and R_1 is an alkyl group of from 5 to 14 carbon atoms, to form an iminoether, iminothioether, or amidine (when Q is O, S, or N respectively);
 - c) reacting with an N-acylating derivative of an acid of formula (IV) above;
 - d) treating with water; and
 - e) optionally removing the carboxyl-blocking group R^x ;
- or D) esterification of a compound of formula (VII) or a salt thereof:



(VII)

wherein R^x is hydrogen or a carboxyl blocking group; with compound of formula (VIII):



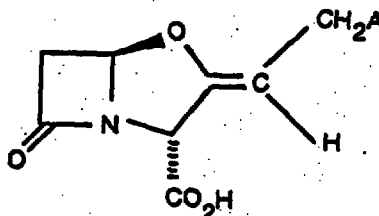
(VIII)

and thereafter if necessary carrying out one or more of the following steps:

- (i) removal of any carboxyl blocking groups R^x;
- (ii) converting the product to a salt or *in vivo* hydrolysable ester thereof.

4. A pharmaceutical composition comprising a penicillin as claimed in claim 1 together with a pharmaceutically acceptable carrier or excipient.

5. A pharmaceutical composition comprising a penicillin as claimed in claim 1 and a compound of formula (IX) or a pharmaceutically acceptable salt or ester thereof:



(IX)

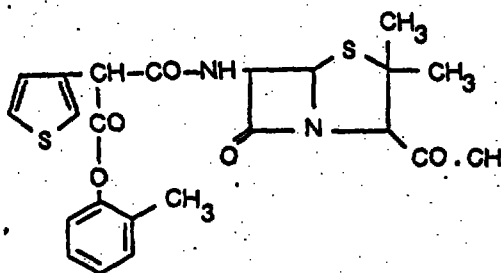
wherein A is hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, mono- or di-hydrocarbyl substituted amino, or mono- or di-acylamino.

6. A composition as claimed in claim 5 which comprises a compound as claimed in claim 1 and clavulanic acid or an alkali metal salt thereof.

7. A composition as claimed in claim 6 which comprises sodium 6β-[2-(2'-methylphenoxy-carbonyl)-2-thien-3'-ylacetamido] penicillinate and potassium clavulanate.

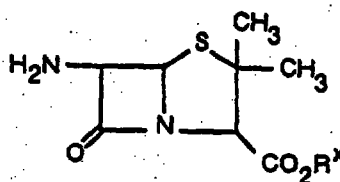
Claims for the Contracting State: AT

1. A process for the preparation of 6β-[2-(2'-methylphenoxy-carbonyl)-2-thien-3'-ylacetamido] penicillanic acid of formula (II):



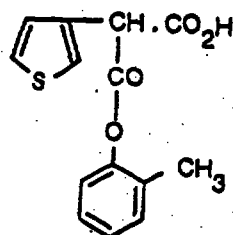
(II)

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, which process comprises:
A) reacting a compound of formula (III):



(III)

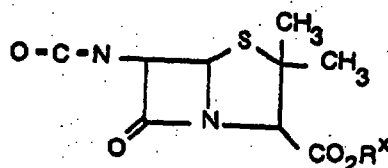
wherein the amino group is optionally substituted with a removable group which permits acylation to take place and wherein R^* is hydrogen or a carboxyl blocking group; with an N-acylating derivative of the acid of formula (IV):



(IV)

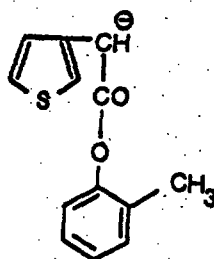
and thereafter if necessary carrying out one or more of the following steps:

- (i) removal of any substituent on the amide group;
 - (ii) removal of any carboxyl blocking group R^* ;
 - (iii) converting the product to a salt or *in vivo* hydrolysable ester thereof.
- or B) reacting a compound of formula (V):



(V)

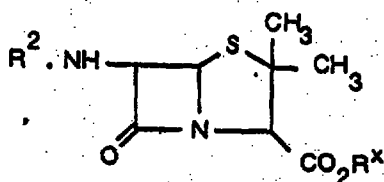
wherein R^* is as defined above with respect to formula (III) above; with the acid of formula (IV) or the carbanion of formula (IVA):



(IVA)

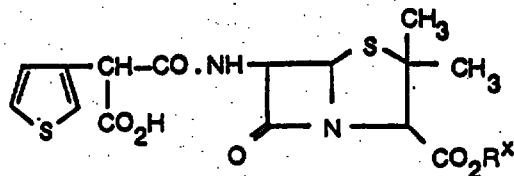
and thereafter if necessary carrying out one or more of the following steps:

- (i) removal of any carboxyl blocking group R^* ;
 - (ii) converting the product to a salt or *in vivo* hydrolysable ester thereof.
- or C):
- a) treating a compound of formula (VI):



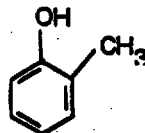
(VI)

- wherein R^* is a carboxyl-blocking group, and R^2 is an acyl group, with an agent forming an imino halide;
- b) treating the imino halide with a compound to introduce a group QR_1 on the imino carbon atom, wherein Q is oxygen, sulphur or nitrogen and R_1 is an alkyl group of from 5 to 14 carbon atoms, to form an iminoether, iminothioether, or amidine (when Q is O, S or N respectively);
 - c) reacting with an N-acylating derivative of an acid of formula (IV) above;
 - d) treating with water; and
 - e) optionally removing the carboxyl-blocking group R^* .
- or D) esterification of a compound of formula (VII) or a salt thereof:



(VII)

wherein R^x is hydrogen or a carboxyl blocking group; with compound of formula (VIII):



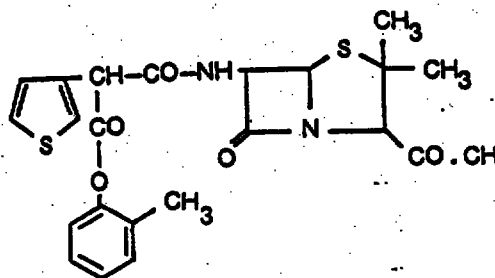
(VIII)

and thereafter if necessary carrying out one or more of the following steps:

- (i) removal of any carboxyl blocking groups R^x ;
 - (ii) converting the product to a salt or *in vivo* hydrolysable ester thereof.
2. A process as claimed in claim 1 for the preparation of sodium 6 β -[2'-methylphenoxycarbonyl]-2-thien-3'-ylacetamido] penicillanate.

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

1. Acide 6 β -[2-(2'-méthylphénoxycarbonyl)-2-thién-3'-ylacétamido] pénicillanique de formule (II):

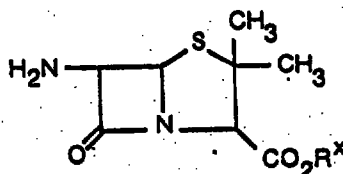


(II)

ou sel pharmaceutiquement acceptable ou ester hydrolysable *in vivo* de ce composé.

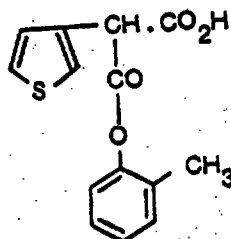
2. 6 β -[2-(2'-Méthylphénoxycarbonyl)-2-thién-3'-ylacétamido] pénicillanate de sodium.
3. Procédé pour la préparation d'une pénicilline suivant la revendication 1, ce procédé consistant:

A) à faire réagir un composé de formule (III):



(III)

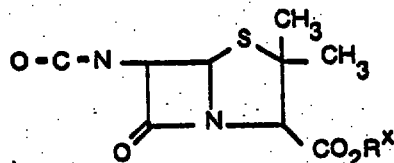
dans laquelle le groupe amino est éventuellement substitué par un groupe éliminable qui permet à l'acylation de se produire et dans laquelle R^x est de l'hydrogène ou un groupe de blocage du carboxyle, avec un dérivé d'acylation à l'azote de l'acide de formule (IV):



(IV)

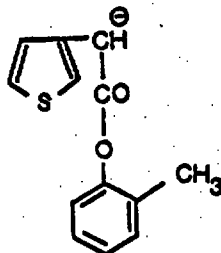
puis si nécessaire à effectuer un ou plusieurs des stades opératoires ci-après:

- i) élimination de tout substituant sur le groupe amide;
 - ii) élimination de tout groupe de blocage du carboxyle R^x ;
 - iii) conversion du produit en un sel ou en un ester hydrolysable in vivo de celui-ci;
- 5 ou B) à faire réagir un composé de formule (V):



(V)

- 15 dans laquelle R^x a la même signification que ci-dessus pour la formule (III), avec l'acide de formule (IV) ou le carbanion de formule (IVa):

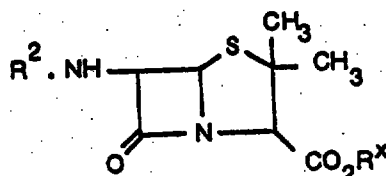


(IVa)

puis si nécessaire, à effectuer un ou plusieurs des stades opératoires ci-après:

- 30 i) élimination de tout groupe de blocage du carboxyle R^x ;
 - ii) conversion du produit en un sel ou en un ester hydrolysable in vivo de celui-ci;
- ou C):

a) à traiter un composé de formule (VI):



(VI)

- 45 dans laquelle R^x est un groupe de blocage du carboxyle et R^2 est un groupe acyle avec un agent de formation d'un imino-halogénure;

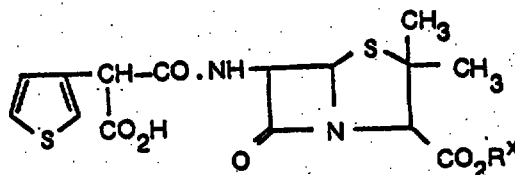
b) à traiter l'imino-halogénure avec un composé pour introduire un groupe QR, sur l'atome de carbone de l'imino, où Q est de l'oxygène, du soufre ou de l'azote et R, est un groupe alcoyle ayant de 5 à 14 atomes de carbone pour former un iminoéther, un iminothioéther ou une amidine (lorsque Q est O, S ou N respectivement);

- 50 c) à faire réagir avec un dérivé d'acylation à l'azote d'un acide de formule (IV) ci-dessus;

d) à traiter avec de l'eau; et

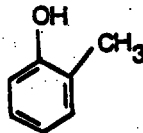
e) éventuellement à éliminer le groupe de blocage du carboxyle R^x ;

ou D) à effectuer l'estérification d'un composé de formule (VIII) ou d'un sel de celui-ci;



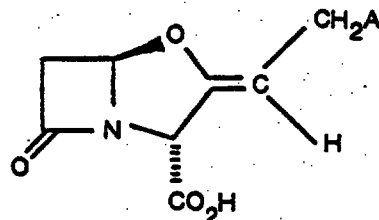
(VII)

65 dans laquelle R^x est de l'hydrogène ou un groupe de blocage du carboxyle avec un composé de formule (VIII):



puis, si nécessaire, à effectuer un ou plusieurs des stades opératoires suivants:

- i) élimination de tout groupe de blocage du carboxyle R^x;
 - ii) conversion du produit en un sel ou en un ester hydrolysable in vivo de celui-ci.
4. Composition pharmaceutique renfermant une pénicilline suivant la revendication 1 conjointement à un véhicule ou excipient pharmaceutiquement acceptable.
5. Composition pharmaceutique renfermant une pénicilline suivant la revendication 1 et un composé de formule (IX) ou un sel ou ester pharmaceutiquement acceptable de celui-ci:



(IX)

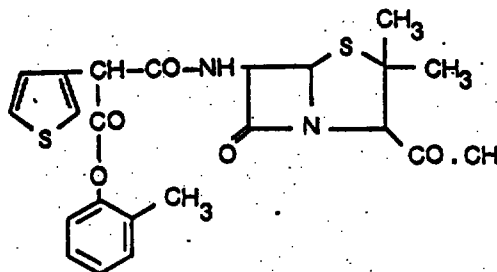
dans laquelle A est un hydroxy, hydroxy substitué, thiol, thiol substitué, amino, amino à substituant mono- ou dihydrocarbyle, ou bien mono- ou di-acylamino.

6. Composition suivant la revendication 5 renfermant un composé suivant la revendication 1 et de l'acide clavulanique ou un sel de métal alcalin de celui-ci.

7. Composition suivant la revendication 6 renfermant du 6,β-[2-(2'-méthylphénoxy-carbonyl)-2-thiën-3'-ylacétamido] pénicillanate de sodium et du clavulanate de potassium.

Revendications pour l'Etat contractant: AT

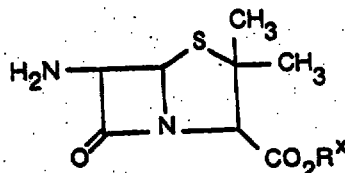
1. Procédé pour la préparation d'acide 6,β-[2-(2'-méthylphénoxy-carbonyl)-2-thiën-3'-ylacétamido] pénicillanique de formule (II):



(II)

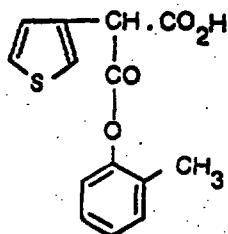
ou d'un sel pharmaceutiquement acceptable ou d'un ester hydrolysable in vivo de celui-ci, ce procédé consistant:

A) à faire réagir un composé de formule (III):



(III)

dans laquelle le groupe amino est éventuellement substitué par un groupe éliminable qui permet à l'acylation de se produire et dans laquelle R^x est de l'hydrogène ou un groupe de blocage du carboxyle avec un dérivé d'acylation à l'azote de l'acide de formule (IV):

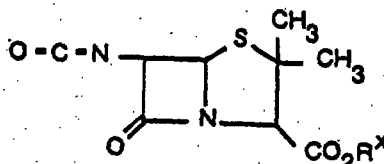


(IV)

puis si nécessaire à effectuer un ou plusieurs des stades opératoires ci-après:

- i) élimination de tout substituant sur le groupe amide;
- ii) élimination de tout groupe de blocage du carboxyle R^x;
- iii) conversion du produit en un sel ou en un ester hydrolysable in vivo de celui-ci;

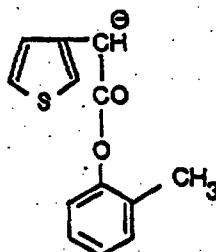
ou B) à faire réagir un composé de formule (V):



(V)

dans laquelle R^x a la même signification que ci-dessus pour la formule (III), avec l'acide de formule (IV)

ou le carbanion de formule (IVa):



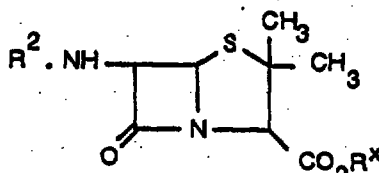
(IVa)

puis si nécessaire, à effectuer un ou plusieurs des stades opératoires ci-après:

- i) élimination de tout groupe de blocage du carboxyle R^x;
- ii) conversion du produit en un sel ou en un ester hydrolysable in vivo de celui-ci;

ou C):

a) à traiter un composé de formule (VI):



(VI)

dans laquelle R^x est un groupe de blocage du carboxyle et R² est un groupe acyle avec un agent de formation d'un imino-halogénure;

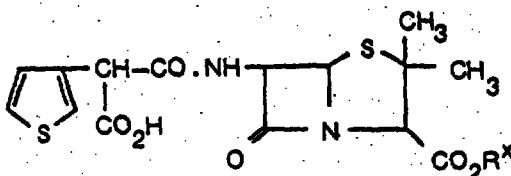
b) à traiter l'imino-halogénure avec un composé pour introduire un groupe QR₁ sur l'atome de carbone de l'imino, où Q est de l'oxygène, du soufre ou de l'azote et R₁ est un groupe alcoyle ayant de 5 à 14 atomes de carbone pour former un iminoéther, un iminothioéther ou une amidine (lorsque Q est O, S ou N respectivement);

c) à faire réagir avec un dérivé d'acylation à l'azote d'un acide de formule (IV) ci-dessus;

d) à traiter avec de l'eau; et

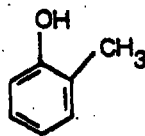
e) éventuellement à éliminer le groupe de blocage du carboxyle R^x;

ou D) à effectuer l'estérification d'un composé de formule (VII) ou d'un sel de celui-ci:



(VII)

dans laquelle R^x est de l'hydrogène ou un groupe de blocage du carboxyle avec un composé de formule (VIII):

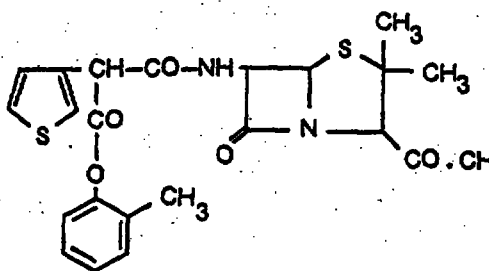


puis, si nécessaire, à effectuer un ou plusieurs des stades opératoires suivants:

- i) élimination de tout groupe de blocage du carboxyle R^x;
 - ii) conversion du produit en un sel ou en un ester hydrolysable in vivo de celui-ci.
2. Procédé suivant la revendication 1, pour la préparation de 6,β-[2-(2'-méthylphénoxycarbonyl)-2-thién-3'-ylacétamido] pénicillanate de sodium.

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

1. 6β-[2-(2'-Methylphenoxyacarbonyl)-2-thien-3'-ylacétamido]-penicillansäure der Formel (II):

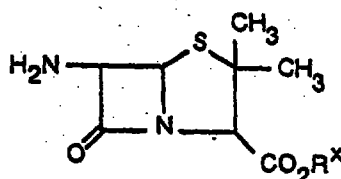


(II)

oder ein pharmakologisch verträgliches Salz oder ein in vivo hydrolysierbarer Ester derselben.

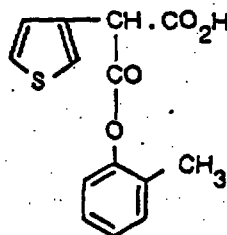
2. 6β-[2-(2'-Methylphenoxyacarbonyl)-2-thien-3'-ylacétamido]-penicillansäure-natriumsalz.
3. Ein Verfahren zur Herstellung eines Penicillins gemäß Anspruch 1, die Maßnahmen umfassend, daß

A) eine Verbindung der Formel (III):



(III)

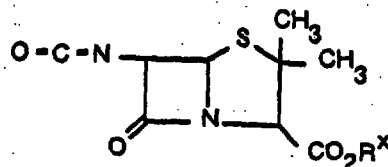
in der die Aminogruppe gegebenenfalls mit einer abspaltbaren, die Acylierung gestattenden Gruppe substituiert ist und in der R^x ein Wasserstoffatom oder eine die Carboxylgruppe blockierende Gruppe ist, mit einem N-acylierenden Derivat der Säure der Formel (IV) umgesetzt wird:



(IV)

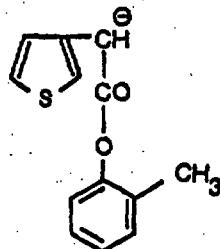
- und anschließend, wenn notwendig, einer oder mehrere der folgenden Schritte durchgeführt werden:
 - (i) Entfernen von Substituenten an der Amidgruppe;
 - (ii) Entfernen von jeglicher die Carboxylgruppe blockierenden Gruppe R^x;
 - (iii) Umwandeln des Produkts in ein Salz oder einen in vivo hydrolysierbaren Ester desselben;

B) eine Verbindung der Formel (V):



(IV)

in der R^x wie in Formel (III) definiert ist, mit der Säure der Formel (IV) oder dem Carbanion der Formel (IVA) umgesetzt wird:



(IVA)

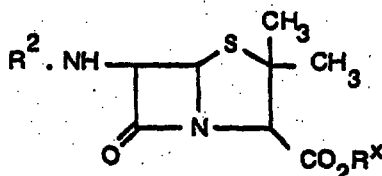
und anschließend, wenn notwendig, einer oder mehrere der folgenden Schritte durchgeführt werden:

- (i) Entfernen von jeglicher die Carboxylgruppe blockierenden Gruppe R^x ;
- (ii) Umwandeln des Produkts in ein Salz oder einen in vivo hydrolysierbaren Ester desselben;

oder

C):

- a) eine Verbindung der Formel (VI):



(VI)

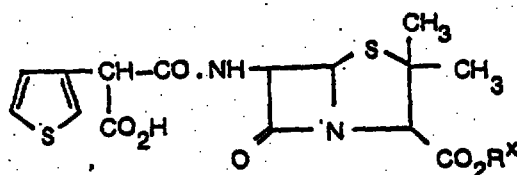
in der R^x eine die Carboxylgruppe blockierende Gruppe ist und R^2 ein Acylgruppe ist, mit einem ein Iminohalogenid bildenden Mittel behandelt wird;

- b) das Iminohalogenid mit einer Verbindung behandelt wird, die eine Gruppe QR , an das Imino-Kohlenstoffatom einführt, wobei Q Sauerstoff, Schwefel oder Stickstoff ist und R, eine Alkylgruppe mit 5 bis 14 Kohlenstoffatomen ist, und so ein Iminoäther, Iminothioäther oder ein Amidin gebildet wird (wenn Q O, S bzw. N ist);

c) mit einem N-acylierenden Derivat einer Säure der Formel (IV) umgesetzt wird;

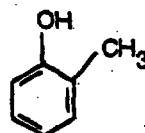
d) mit Wasser behandelt wird; und

- e) gegebenenfalls die die Carboxylgruppe blockierende Gruppe R^x entfernt wird; oder
- D) eine Verbindung der Formel (VII) oder ein Salz derselben:



(VII)

in der R^x ein Wasserstoffatom oder eine die Carboxylgruppe blockierende Gruppe ist, mit einer Verbindung der Formel (VIII) verestert wird:



(VIII)

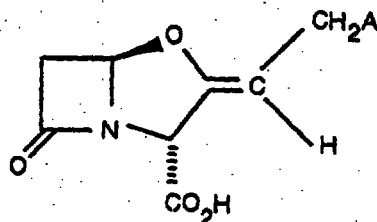
und anschließend, wenn notwendig, einer oder mehrere der folgenden Schritte durchgeführt werden:

- (i) Entfernen von jeglicher die Carboxylgruppe blockierenden Gruppe R^x ;

(ii) Umwandeln des Produkts in ein Salz oder einen in vivo hydrolysierbaren Ester desselben.

4. Eine pharmazeutische Zusammensetzung, enthaltend ein Penicillin gemäß Anspruch 1 zusammen mit einem pharmakologisch verträglichen Träger oder Hilfsmittel.

5. Eine pharmazeutische Zusammensetzung, enthaltend ein Penicillin gemäß Anspruch 1 und eine Verbindung der Formel (IX) oder ein pharmakologisch verträgliches Salz oder Ester desselben:



(IX)

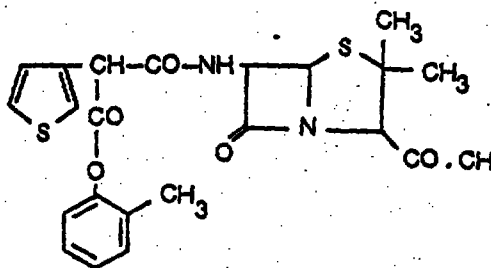
in der A eine Hydroxyl- oder substituierte Hydroxylgruppe, Thiol- oder substituierte Thiolgruppe, Aminogruppe, mono- oder dihydrocarbyl-substituierte Aminogruppe oder eine Mono- oder Diacylamino-
gruppe ist.

6. Eine Zusammensetzung gemäß Anspruch 5, die eine Verbindung gemäß Anspruch 1 und Clavulansäure oder ein Alkalimetallsalz derselben enthält.

7. Eine Zusammensetzung gemäß Anspruch 6, die 6 β -[2-(2'-Methylphenoxy-carbonyl)-2-thien-3'-ylacetamido]-penicillansäure-natriumsalz und Clavulansäure-kaliumsalz enthält.

25 Patentansprüche für den Vertragsstaat: AT

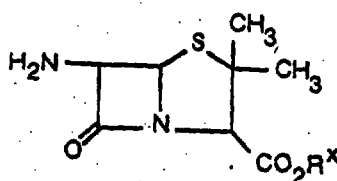
1. Ein Verfahren zur Herstellung von 6 β -[2-(2'-Methylphenoxy-carbonyl)-2-thien-3'-ylacetamido]-penicillansäure der Formel (II):



(II)

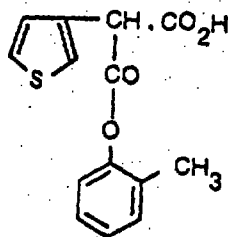
oder eines pharmakologisch verträglichen Salzes oder in vivo hydrolysierbaren Esters derselben, die Maßnahmen umfassend, daß

A) eine Verbindung der Formel (III):



(III)

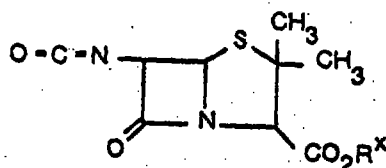
in der die Aminogruppe gegebenenfalls mit einer abspaltbaren, die Acylierung gestattenden Gruppe substituiert ist und R^x ein Wasserstoffatom oder eine die Carboxylgruppe blockierende Gruppe ist, mit einem N-acylierenden Derivat der Säure der Formel (IV) umgesetzt wird:



(IV)

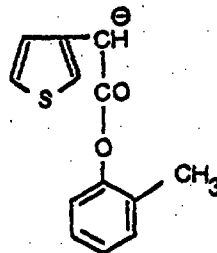
und anschließend, wenn notwendig, einer oder mehrere der folgenden Schritte durchgeführt werden:

- (i) Entfernen von Substituenten der Amidgruppe;
 (ii) Entfernen von jeglicher die Carboxylgruppe blockierenden Gruppe R^x ;
 (iii) Umwandeln des Produkts in ein Salz oder einen in vivo hydrolysierbaren Ester desselben; oder
 B) eine Verbindung der Formel (V):



(V)

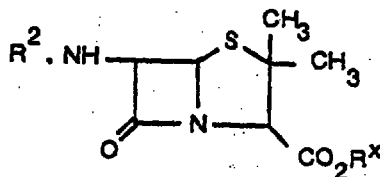
- 15 in der R^x wie in Formel (III) definiert ist, mit der Säure der Formel (IV) oder dem Carbanion der Formel (IVA) umgesetzt wird:



(IVA)

und anschließend, wenn notwendig, einer oder mehrere der folgenden Schritte durchgeführt werden:

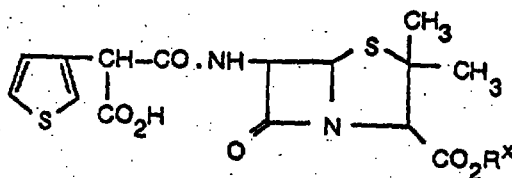
- (i) Entfernen von jeglicher die Carboxylgruppe blockierenden Gruppe R^x ;
 (ii) Umwandeln des Produkts in ein Salz oder einen in vivo hydrolysierbaren Ester desselben; oder
 C)
 a) eine Verbindung der Formel (VI):



(VI)

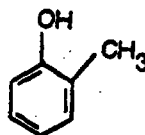
in der R^x eine die Carboxylgruppe blockierende Gruppe ist und R^2 eine Acylgruppe ist, mit einem ein Iminohalogenid bildenden Mittel umgesetzt wird;

- b) das Iminohalogenid mit einer Verbindung behandelt wird, die eine Gruppe QR_i an das Imino-Kohlenstoffatom einführt, wobei Q Sauerstoff, Schwefel oder Stickstoff ist und R_i eine Alkylgruppe mit 5 bis 14 Kohlenstoffatomen ist, und so ein Iminoäther, Iminothioäther oder ein Amidin gebildet wird (wenn Q O, S bzw. N ist);
 c) mit einem N-acylierenden Derivat einer Säure der Formel (IV) umgesetzt wird;
 d) mit Wasser behandelt wird;
 e) gegebenenfalls die Carboxylgruppe blockierende Gruppe R^x entfernt wird; oder
 D) eine Verbindung der Formel (VII) oder ein Salz derselben:



(VII)

in der R^x ein Wasserstoffatom oder eine die Carboxylgruppe blockierende Gruppe ist, mit einer Verbindung der Formel (VIII) verestert wird:



(VIII)

- und anschließend, wenn notwendig, einer oder mehrere der folgenden Schritte durchgeführt werden:
- (i) Entfernen von jeglicher die Carboxylgruppe blockierenden Gruppe R^x;
 - (ii) Umwandeln des Produkts in ein Salz oder einen in vivo hydrolysierbaren Ester desselben.
2. Ein Verfahren gemäß Anspruch 1, zur Herstellung von 6ß-[2-(2'-Methylphenoxy-carbonyl)-2-thien-3'-ylacetamido]-penicillansäure-natriumsalz.