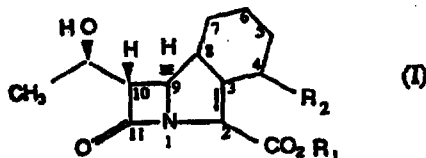


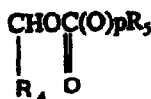
Description

This invention relates to heterocyclic derivatives having antibacterial activity, to processes for their preparation, to compositions containing them and to their use in medicine.

Thus the present invention provides compounds of the general formula (I)



in which R₁ represents the group

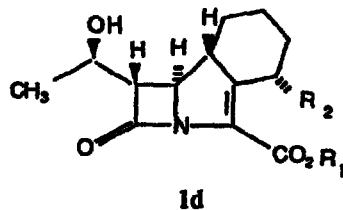
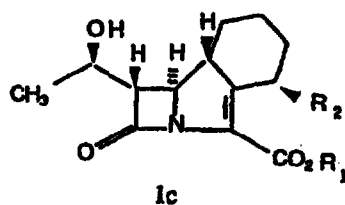
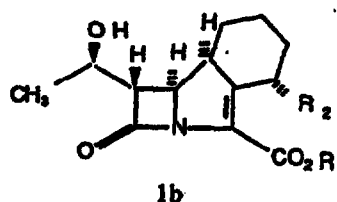
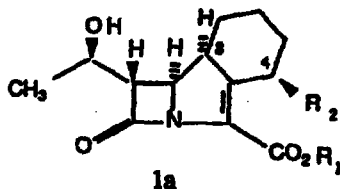


wherein R₄ represents a hydrogen atom or a C₁₋₄ alkyl group; p is zero or one; R₅ represents a group selected from C₁₋₆ alkyl, C₆₋₈ cycloalkyl optionally substituted by a C₁₋₃ alkyl group, phenyl, or C₁₋₄ alkyl substituted by a C₁₋₃ alkoxy group; and

R₂ presents the group OR₃ in which R₃ represents a C₁₋₆ alkyl group.

In addition to the fixed stereochemical arrangement as defined in formula (I) the molecule contains two further asymmetric carbon atoms at the 4 and 8 positions. Also the group R₁ contains at least one asymmetric carbon atom when R₄ is other than hydrogen. It will be appreciated that all stereoisomers including mixtures thereof arising from these additional asymmetric centres are within the scope of formula (I).

The general formula (I) as drawn includes at least 4 stereoisomers and mixtures thereof and these may be represented by the formulae (1a, 1b, 1c and 1d).



The wedge shaped bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

The configuration shown for the carbon atom at the 8-position in formulae 1a and 1b is hereinafter referred to as the β -configuration and in formulae 1c and 1d as the α -configuration.

The configuration shown for the carbon at the 4-position in formulae 1b and 1d is hereinafter referred to as the α -configuration and in formulae 1a and 1c as the β -configuration.

In general, in the specific compounds named below, the β -configuration at the 8-position corresponds to

the S isomer and the β -configuration at the 4-position to the R isomer. The α -configuration at the 8-position corresponds to the R isomer and the α -configuration at the 4-position corresponds to the S isomer. The assignment of the R or S configuration at the 4- and 8-positions has been made according to the rules of Cahn, Ingold and Prelog, *Experientia* 1956, 12, 81.

The term alkyl as used herein refers to a straight or branched chain alkyl group. When R_4 represents a C_{1-4} alkyl group this may be for example methyl, ethyl, propyl, isopropyl or butyl.

When R_5 represents an alkyl group this may conveniently be a C_{1-4} alkyl group such as methyl, ethyl, isopropyl or t-butyl.

When R_5 represents a C_{1-4} alkyl group substituted by C_{1-3} alkoxy, this may be for example a methyl, ethyl, propyl or isopropyl group substituted by methoxy.

When R_5 represents C_{5-8} cycloalkyl optionally substituted by C_{1-3} alkyl this may be for example a cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl group optionally substituted by a methyl or ethyl group.

A preferred class of compounds of formula (I) are those having the β -configuration at the 8-position. Within this class those having the α -configuration at the 4-position are particularly preferred.

A further preferred class of compounds of formula (I) are those wherein R_4 represents hydrogen, methyl, propyl or isopropyl, more particularly hydrogen or methyl.

Yet a further preferred class of compounds of formula (I) are those wherein R_5 represents a C_{1-4} alkyl group such as methyl, ethyl, isopropyl or t-butyl; a C_{1-4} alkyl group substituted by methoxy such as 1-methoxy-1-methylethyl; phenyl; or a C_{5-8} cycloalkyl group such as cyclopentyl or cyclohexyl optionally substituted by a methyl or ethyl group e.g. as in ethylcyclohexyl.

Compounds of formula (I) wherein R_2 is an ethoxy or methoxy group also represent a further preferred class of compounds according to the invention.

A particularly preferred group of esters according to the invention are those wherein R_4 represents a hydrogen atom or a methyl group, p is zero or 1 and R_5 represents a methyl, ethyl, isopropyl, t-butyl, 1-methoxy-1-methylethyl, phenyl, cyclohexyl, or 4-ethylcyclohexyl group.

A particularly preferred group of compounds according to the invention are those in which the carbon atom at the 8-position is in the β -configuration and the carbon atom at the 4-position is in the α -configuration; R_4 represents a hydrogen atom or a methyl group; R_5 represents C_{1-4} alkyl, C_{5-8} cycloalkyl optionally substituted by a C_{1-2} alkyl group, phenyl, or C_{1-4} alkyl substituted by methoxy; p is zero or one and R_2 is methoxy.

Specific preferred compounds include esters of (4S, 8S, 9R, 10S, 12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}] undec-2-ene-2 carboxylic acid such as the pivaloyloxymethyl, 1-pivaloyloxyethyl, acetoxymethyl, 1-acetoxyethyl, 1-methoxy-1-methylethylcarbonyloxymethyl, 1-(1-methoxy-1-methylethylcarbonyloxy)ethyl, 1-benzoyloxyethyl, 1-isopropoxycarbonyloxyethyl, cyclohexyloxycarbonyloxymethyl, 1-(4-ethylcyclohexyloxycarbonyloxy)ethyl or more particularly 1-cyclohexyloxycarbonyloxyethyl ester.

Compounds according to the invention, when administered orally, exhibit a high level of antibacterial activity against a wide range of pathogenic microorganisms and they have a very high resistance to all β -lactamases. Compounds of the invention are also relatively stable to renal dehydropeptidase.

Compounds of the invention have been found to exhibit valuable levels of activity against strains of *Staphylococcus aureus*, *Streptococcus faecalis*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Clostridium perfringens*, *Bacteriodes fragilis* and *Morganella morganii*.

The compounds of the invention may therefore be used for treating a variety of diseases caused by pathogenic bacteria in human beings and animals.

Thus, according to another aspect of the present invention, we provide a compound of formula (I) for use in the therapy or prophylaxis of systemic bacterial infections in a human or animal subject.

According to a further aspect of the invention we provide the use of a compound of formula (I) for the manufacture of a therapeutic agent for the treatment of systemic bacterial infections in human beings and animals.

According to a yet further aspect of the invention we provide a method of treatment of the human or non-human animal body to combat bacterial infections which method comprises administering to the body an effective amount of a compound of formula (I).

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however doses employed for adult human treatment will typically be in the range of 200-2000mg per day e.g. 1000mg per day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

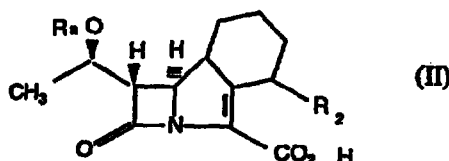
While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation for oral administration comprising a compound of formula (I) together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical compositions according to the invention may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose), fillers (e.g. starch, lactose, micro-crystalline cellulose or calcium phosphate), lubricants (e.g. magnesium stearate, hydrogenated vegetable oils, talc, silica, polyethyleneglycols), disintegrants (e.g. potato starch or sodium starch glycolate), or wetting agents (e.g. sodium lauryl sulphate). Flow aids e.g. silicon dioxide may also be used if desired. The tablets may be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product either for constitution with water or other suitable vehicle before use for administration as a liquid or for direct administration and then washed down with water or other suitable liquid. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats and oils such as hydrogenated castor oil), emulsifying or thickening agents (e.g. lecithin, aluminium stearate or acacia), non-aqueous vehicles (e.g. almond oil, fractionated coconut oil, oily esters or ethyl alcohol), preservatives (e.g. methyl or butyl p-hydroxybenzoates or sorbic acid) and suitable flavouring and sweetening agents.

Compounds of formula (I) may be prepared by esterification of the carboxylic acid (II)



in which R_1 is hydrogen or a hydroxyl protecting group and R_2 is as defined for formula (I), or a salt or reactive derivative thereof and if required or desired subjecting the resulting compound prior to or subsequent to any separation into its stereochemical isomers, to removal of any protecting group R_1 . When R_1 represents a hydroxyl protecting group this may be for example a hydrocarbylsilyl group such as trialkylsilyl e.g. trimethylsilyl or t-butyl dimethylsilyl.

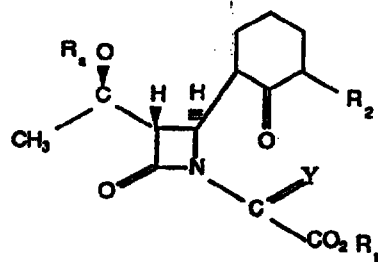
The esterification of a compound of formula (II) or a salt thereof may be carried out by reaction with a compound R_1X in which R_1 has the meanings defined above in formula (I) and X is a leaving group such as a halogen atom, e.g. chlorine, bromine or iodine, or an alkyl or aryl sulphonate such as mesylate or tosylate, in the presence of a base. The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include dimethylformamide, dimethylacetamide, or dimethylsulphoxide.

In one embodiment of this process the reaction is conveniently carried out using a salt such as an alkali metal salt e.g. potassium or sodium salt of the carboxylic acid (II) in the presence of a suitable quaternary ammonium salt such as triethyl benzylammonium chloride, trioctyl-methylammonium chloride or tetrabutylammonium bromide and preferably in the presence of a polar aprotic solvent such as dimethylformamide, dimethylacetamide or N-methylpyrrolidinone.

The esterification reaction may be conveniently carried out using a compound of formula (II) in which R_1 represents a hydrogen atom. If the esterification reaction is carried out on a compound of formula (II) in which R_1 represents a hydroxyl protecting group then this group may be removed by conventional procedures. For example when R_1 is tert butyldimethylsilyl group this may be removed by treatment with tetrabutylammonium fluoride and acetic acid.

The compounds of formula (II) may be prepared by known methods e.g. as described in EP-A-0416953.

The compounds of formula (I) may also be prepared by the cyclisation of a compound of formula (III)



(III)

in which the groups R_1 and R_2 have the meanings defined for formula (I), R_a is a hydroxyl protecting group and Y is an oxygen atom or a phosphine group, and if required or desired subjecting the resulting compound prior to or subsequent to any separation into its stereochemical isomers, to removal of the protecting group R_a .

The cyclisation of a compound of formula (III) in which Y is oxygen is conveniently carried out by heating in the presence of an organic phosphite. The reaction is preferably carried out in a solvent or mixture of solvents at a temperature within the range 60-200°. Suitable solvents include hydrocarbons with an appropriate boiling point, for example aromatic hydrocarbons, such as toluene or xylene.

Suitable organic phosphites include acyclic and cyclic trialkylphosphites, triarylphosphites and mixed alkylarylphosphites. Particularly useful organic phosphites are the trialkylphosphites e.g. triethylphosphite or trimethylphosphite.

The cyclisation of a compound of formula (III) in which Y is a phosphine grouping is preferably carried out in a solvent at a temperature between 40-200°C. Suitable solvents include hydrocarbons such as aromatic hydrocarbons, for example xylene or toluene, aliphatic hydrocarbons and halogenated hydrocarbons such as dichloromethane, chloroform and trichloroethane. Examples of suitable phosphine groups are triarylphosphines e.g. triphenyl phosphine or trialkylphosphines e.g. tri-*t*-butylphosphine.

The hydroxyl protecting group may be removed by well known standard procedures such as those described in *Protective Groups in Organic Chemistry*, pages 46-119, Edited by J F W McOmie (Plenum Press, 1973). For example when R_a is a *tert* butyldimethylsilyl group, this may be removed by treatment with tetrabutyl ammonium fluoride and acetic acid. This process is conveniently carried out in a solvent such as tetrahydrofuran. Similarly when the R_a is trichloroethoxycarbonyl group this may be removed by treatment with zinc and acetic acid.

The compounds of formula (III) may be prepared by methods analogous to those described in EPA 0416953 for preparing structurally related compounds.

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

In the Preparations and Examples, unless otherwise stated:

Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus and are uncorrected. All temperatures refer to °C.

Infrared spectra were measured in chloroform- d_1 solutions on a FT-IR instrument. Proton Magnetic Resonance (1H -NMR) spectra were recorded at 300 MHz as solutions in chloroform- d_1 . Chemical shifts are reported in ppm downfield (δ) from Me_4Si , used as an internal standard, and are assigned as singlets (s), doublets (d), doublet of doublets (dd) or multiplets (m).

Column chromatography was carried out over silica gel (Merck AG Darmstadt, Germany).

Solutions were dried over anhydrous sodium sulphate.

"Petrol" refers to petroleum ether, b.p. 40-60°C.

Methylene chloride was redistilled over calcium hydride; tetrahydrofuran was redistilled over sodium; ethyl ether was redistilled over sodium; xylene was redistilled over phosphorus pentoxide and ethyl acetate was dried over activated molecular sieves.

Intermediate 1

(2-Methoxy-2-methyl) propanoic acid ethenyl ester

To 2-methoxy-2-methylpropanoic acid (1.5g), mercury (II) acetate (0.162g), palladium acetate (0.0285 g), potassium hydroxide (0.067g) and vinyl acetate (1.2g) were added under nitrogen. The resulting solution was heated at 50° C for 4 hrs. To the reaction mixture additional vinyl acetate (2.4g) was then added and the mixture was heated at 50° C for 16 hrs.

After cooling to 20° C, diethyl ether (15ml) was added and the mixture was filtered on a pad of celite. The solution was washed with 10% sodium hydroxide solution (3 x 20ml) and the aqueous phase was filtered on a pad of celite and then extracted with diethyl ether (2 x 70ml). The organic phases were washed with brine (150ml) and dried over anhydrous sodium sulphate to obtain the crude title compound as a pale yellow oil (0.7g); tlc cyclohexane/ethyl acetate 8:2 Rf = 0.7; IR (CDCl₃) V_{max} (cm⁻¹): 1749 (C=O ester) 1640 (C=C); 1H-NMR (300 MHz; CDCl₃) (ppm) 7.30 (m), 4.983(dd), 4.648(dd), 3.297(s), 1.464(s).

Intermediate 2

(2-Methoxy-2-methyl) propanoic acid, 1-chloro ethyl ester

To a solution of the intermediate 1 (2.7g) in ethyl acetate (50ml) anhydrous hydrogen chloride was bubbled for 1 hr at 0° C, then nitrogen was bubbled for 10 minutes. The solvent was evaporated and the residue was purified through kugelrohr distillation (90°C/20m bar (15 mmHg)) to obtain the title compound as a colourless oil (2.1g) Tlc cyclohexane/ethyl acetate 9:1. Rf - 0.9; IR (CDCl₃) V_{max} (cm⁻¹): 1755 (C=O ester); 1H-NMR (CDCl₃; 300 MHz) (ppm) 6.58 (q) 3.296 (s), 1.837(d), 1.442(s).

Intermediate 3

(1-Chloro-2-methyl)propyl methyl carbonate

A solution of 1-chloro-2-methylpropyl chloroformate (1.71g) in dry dichloromethane (5ml) was added dropwise to a solution of methanol (0.83ml) in dry dichloromethane (5ml) at 0° C, under nitrogen, with stirring. A solution of pyridine (0.80ml) in dry dichloromethane (10ml) was then added and the reaction mixture was stirred at 20° for 18 hrs. The mixture was diluted with dichloromethane 950ml, washed with brine (3 x 40ml), dried over anhydrous sodium sulfate and concentrated under a stream of nitrogen at low temperature, to afford the crude title compound as a colourless oil in quantitative yield. H-NMR (300 MHz, CDCl₃): 6.18(d), 3.86(s), 2.28-2.12(m), 1.08(d), 1.06(d) ppm.

Intermediate 4

1-Chloroethyl 4-ethylcyclohexyl carbonate

A solution of 1-chloroethyl chloroformate (5.46 g) in dry dichloromethane (20 ml) was added dropwise, under nitrogen at 0°, to a stirred solution of 4-ethylcyclohexanol (5g) in dry dichloromethane (20ml) in presence of 3A molecular sieves. A solution of pyridine (3 g) in dry dichloromethane (20 ml) was added dropwise to the reaction mixture during 20 min at 0° the mixture was then warmed to 20°, stirred for 20 hours, washed with brine (2x50 ml) and dried. The solvent was removed under vacuum and the residue was distilled to give the title compound as a colourless oil (7.9 g; b.p. 130°/5.2 mbar; t.l.c. cyclohexane/ethyl acetate 9/1 Rf = 0.88; IR (CDCl₃), Vmax (cm⁻¹): 1757 (C=O); 1H-NMR (300 MHz, CDCl₃): 6.43 (q), 6.42 (q), 4.93 (bs), 4.59 (tt), 2.14-2.01 (bs), 2.00-1.88 (bs), 1.88-1.78 (m), 1.83 (d), 1.82 (d), 1.60-1.50 (m), 1.50-1.32 (m), 1.30-1.15 (m), 1.28-1.18 (m) 1.05-0.95 (m), 0.95-0.85 (m).

Intermediate 5

1-Chloro-2-methylpropyl 2,2-dimethylpropionate

2-Methylpropionaldehyde (5.98 g) was added dropwise, during 10 min., to a stirred mixture of zinc chloride (0.11 g) and pivaloyl chloride (10 g), under nitrogen at -20°. The reaction mixture was then warmed to 23° and stirred for further 2 hours. The solid was removed by centrifugation and the oily residue was distilled to obtain the title compound as a colourless oil (11.55 g; b.p. 70°/35 mbar; IR (CDCl₃), Vmax (cm⁻¹): 1749 (C=O); 1H-NMR (300 MHz, CDCl₃): 6.28 (d), 2.16 (m), 1.22 (s), 1.05 (d) ppm

Intermediate 6

Cyclohexyl chloromethyl carbonate

A stream of chlorine was slowly bubbled into cold (-10/+5°) methyl chloroformate (6 ml) under diffuse light. The reaction was monitored by 1H-NMR and stopped before the dichloromethyl chloroformate concentration became more than 5% molar. Nitrogen was bubbled through the solution until it became colourless and the residue was distilled to obtain two main fractions containing the required intermediate chloromethyl chloroformate; fraction a (2.48 g; molar ratio: methyl chloroformate/chloromethyl chloroformate/dichloromethyl chloroformate 19/77/4), fraction b (1.76 g; molar ratio: methyl chloroformate/chloromethyl chloroformate/di-

chloromethyl chloroformate 4/90/6). To an ice cold solution of cyclohexanol (1.37 ml) in dry dichloromethane (5 ml), in presence of 3A molecular sieves and under nitrogen, a solution of the (fraction a) (1.7 g) in dry dichloromethane (5 ml) was added during 5 min. A solution of pyridine (1.06 ml) in dry dichloromethane (5 ml) was then added to the reaction mixture during 30 min. at 0°, and the mixture was slowly warmed to 20-25°. After 5 hours, the solution was filtered, diluted with dichloromethane (30 ml), washed with water (20 ml), brine (3x30 ml) and dried. The solvent was distilled off and the residue was purified by column chromatography on silica gel, using cyclohexane/ethyl acetate 9/1 as eluant, to obtain the title compound as a white wax (1.98 g; t.l.c. cyclohexane/ethyl acetate 9/1 Rf=0.44; IR (CDCl₃), Vmax (cm⁻¹): 1759 (C=O); ¹H-NMR (300 MHz, CDCl₃): 5.73 (s), 4.78-4.66 (m), 2.00-1.90 (m), 1.80-1.70 (m), 1.60-1.20 (m)ppm).

Example 1

1-(Cyclohexyloxycarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

To a solution of potassium (4S,8S,9R,10S,12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (hereinafter referred to as "Intermediate A") (0.5g) in dimethylformamide (8ml) tetrabutylammonium bromide (0.5g) and (1-chloroethyl)-cyclohexyl carbonate (0.65g) were added at 22°. The resulting mixture was stirred at 22° for 15 hr, then poured into diethyl ether (60ml), washed with 1% aq HCl (40ml), 5% aq NaHCO₃ (2x50ml) and brine (2x50 ml), dried and concentrated. The residue (1g) was dissolved in diethyl ether (2ml) and light petroleum (20ml) added with vigorous stirring. The precipitate (0.1g) was filtered off and the mother liquors were concentrated to give a residue, which was dissolved in diethyl ether (1ml) and light petroleum (20ml) added under vigorous stirring to give more precipitate (0.14g). The precipitates were combined (0.24g) and further purified by dissolution in diethyl ether (3ml) and precipitation from light petroleum (30ml) under vigorous stirring to obtain the title compound as a white powder (0.160 g; t.l.c. diethyl ether Rf 0.44, m.p. 90-100°).

IR (CDCl₃) Vmax (cm⁻¹) 1771, 1632; ¹H-NMR (300 MHz, CDCl₃) 6.93-6.85(q+q), 4.92(t), 4.64(m), 4.25-4.05(m), 3.30-3.15(m), 3.25(s), 3.24(s), 2.08(m), 2.0-1.2(m), 1.61(d), 1.59 (d), 1.31(d), 1.30(d).

According the experimental procedures described in the Example 1, the following esters were prepared from Intermediate A.

Example 2

1-(Ethyloxycarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (t.l.c. diethyl ether Rf 0.42). IR (CDCl₃) Vmax (cm⁻¹) 1765, 1738, 1600; ¹H-NMR (300 MHz, CDCl₃) 6.93-6.87(q+q), 4.933(m), 4.3-1.8(m), 3.26-3.24(s+s), 3.32-3.20(m), 2.08(m), 1.94-1.3(m), 1.62 (d), 1.60(d), 1.36-1.28(m) from Intermediate A and (1-chloroethyl)-ethyl carbonate.

Example 3

1-(Isopropyloxycarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

IR (CDCl₃) Vmax (cm⁻¹) 3614, 1767, 1632; ¹H-NMR (300 MHz, CDCl₃) 6.90(q), 6.89(q), 4.95-4.83(m), 4.3-4.2(m), 4.191(dd), 3.35-3.20(m), 3.257(s), 3.243(s), 2.07(m), 1.93-1.75(m), 1.7-1.3 (m), 1.613(d), 1.33-1.29(d+d+d), t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.4 was obtained from Intermediate A and (1-chloroethyl)-isopropyl carbonate.

Example 4

1-(Acetoxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

was obtained as an oil (0.160 g; t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.4)

IR (CDCl₃) Vmax (cm⁻¹) 3605, 1769, 1700; ¹H-NMR (300 MHz, CDCl₃) 6.99(q), 6.98(q), 4.93(t), 4.25(m), 4.19(dd), 3.3-3.2(m), 3.25(s), 3.24(s), 2.10(s), 2.07(s), 2.08(m), 1.95-1.3(m), 1.56(d), 1.55(d), 1.31(d), 1.30(d) from Intermediate A and (1-chloroethyl)acetate.

Example 5

1-(Cyclohexylcarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

IR (CDCl₃) Vmax (cm⁻¹) 1774, 1750, 1630; ¹H-NMR (300 MHz, CDCl₃) 6.997(q), 6.977(q), 4.931(t), 4.913(t), 4.24(m), 4.193(dd), 3.3-3.2(m), 3.25(s), 3.245(s), 2.38-2.24(m), 2.05(m), 1.95-1.2(m), 1.65 (dd), 1.566(d), 1.555(d), 1.326(d), 1.314(d) was obtained from Intermediate A and (1-chloroethyl) cyclohexanecarboxylate.

Example 6

1-(Benzoyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.045 g; t.l.c. cyclohexane, ethyl acetate 1:1 Rf 0.25);

IR (CDCl₃) Vmax (cm⁻¹) 1776, 1738, 1640, 1603; ¹H-NMR (300 MHz, CDCl₃) 8.1-8.02(m), 7.58(tt), 7.48-7.4(m), 7.27(m), 4.948(t), 4.914(t), 4.3-4.2(m), 4.20(dd), 3.3-3.2(m), 3.23(s), 3.21(s), 2.05(m), 1.9-1.3(m), 1.725(d), 1.708(d), 1.326(d), 1.302(d) from Intermediate A and (1-chloroethyl)-benzoate.

Example 7

1-[(1,1-Dimethylethyl)carbonyloxy]ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.160 g; t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.37);

IR (CDCl₃) Vmax (cm⁻¹) 3666, 1776, 1744, 1632; ¹H-NMR (300 MHz, CDCl₃) 6.982(q), 6.941(q), 4.94-4.88(m), 4.3-4.16(m), 3.3-3.18(m), 3.238(s), 3.20(s), 2.05(m), 1.9-1.2(m), 1.565(d), 1.554(d), 1.317(d), 1.306(d), 1.207(s), 1.179(s) from Intermediate A and 1-[(1,1-dimethylethyl)carbonyloxy]ethyl chloride.

Example 8

1-[2-Methoxy-2-methyl-propanoyloxy]ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate, was obtained as an oil (0.130 g; t.l.c. diethyl ether Rf 0.35);

IR (CDCl₃) Vmax (cm⁻¹) 1772, 1603; ¹H-NMR (300 MHz, CDCl₃) 7.028(q), 6.984(q), 4.914(m), 4.3-4.2(m), 4.190(dd), 3.3-3.2(m), 3.260(s), 3.248(s), 3.290(s), 3.226(s), 2.06(m), 1.9-1.35(m), 1.604(m), 1.437(s), 1.429(s), 1.403(s), 1.400(s), 1.315(d) from Intermediate A and 2-methoxy-2-methyl-propanoic acid chloroethyl ester.

Example 9

Acetoxymethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.240 g; t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.24); IR (CDCl₃) Vmax (cm⁻¹) 1769, 1730, 1640; ¹H-NMR (300 MHz, CDCl₃) 4.996(t), 4.802(s), 4.3-4.2(m), 4.23(dd), 3.774(s), 3.36-3.24(m+dd), 3.28(s), 2.1(m), 1.94-1.30(m), 1.769(d), 1.327(d) from Intermediate A and chloromethyl acetate.

Example 10

[(1,1-Dimethyl-ethyl)carbonyloxy]methyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.260 g; t.l.c. cyclohexane, ethyl acetate 1:1 Rf 0.26);

IR (CDCl₃) Vmax (cm⁻¹) 3569, 1772, 1751, 1600; ¹H-NMR (300 MHz, CDCl₃) 5.95(d), 5.85(d), 4.88(t), 4.24(m), 4.20(dd), 3.27(m), 3.25(dd), 3.23(s), 2.1(m), 2.0(bs), 1.95-1.6(m), 1.5-1.20(m), 1.31(d), 1.21(s) from Intermediate A and [(1,1-dimethylethyl)carbonyloxy]methyl iodide.

Example 11

1-(2-Methoxy-2-methyl-propanoyloxy)methyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.110 g; t.l.c. diethyl ether Rf 0.33);

IR (CDCl₃) Vmax (cm⁻¹) 3600, 1772, 1740, 1640; ¹H-NMR (300 MHz, CDCl₃) 5.964(d+d), 4.904(m), 4.242(m), 4.203(dd), 3.984(dd), 3.33-3.22(m+dd), 3.292(s), 3.240(s), 2.1(m), 1.95-1.2(m), 1.441(s), 1.429(s), 1.315(s) from Intermediate A and (2-methoxy-2-methyl)propanoic acid chloromethylester.

Example 12

1-(Methyloxycarbonyloxy)-2-methylpropyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil, (0.040 g; t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.36); IR (CDCl₃) Vmax (cm⁻¹) 1767, 1734, 1680; ¹H-NMR (300 MHz, CDCl₃) 6.661(d), 6.636(d), 4.974(m), 4.936(m), 4.3-4.15(m), 3.824(s), 3.805(s), 3.262(s), 3.242(s), 3.32-3.18(m), 1.327(d), 1.308(d), 1.15-0.95(m), 2.4-1.2(m) from Intermediate A and (1-chloro-2-methyl)propylmethylcarbonate.

Example 13

1-(Acetyloxy)butyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.050 g; t.l.c. cyclohexane, ethyl acetate 1:1 Rf 0.33); IR (CDCl₃) Vmax (cm⁻¹) 1769, 1732, 1632; ¹H-NMR (300 MHz, CDCl₃) 6.925(q), 4.948(m), 4.28-4.16(m), 3.3-3.2(m), 3.251(s), 3.243(s), 2.105(s), 2.069(s), 2.12-2.04(m), 1.94-1.74(m), 1.74-1.58(m), 1.54-1.349(m), 1.318(d), 1.307(d), 0.962(t), 0.957(t) from Intermediate A and 1-bromobutyl acetate.

Example 14

1-[(4-ethylcyclohexyloxy)carbonyloxy]ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

To a solution of the Intermediate A (0.3 g) in N,N-dimethylformamide (5ml), tetra-n-butylammonium bromide (0.3 g) and the intermediate 4 (0.47 g) were added under nitrogen and stirring was continued for 16 h at 22°. The reaction mixture was diluted with diethylether (15 ml), washed with saturated ammonium chloride (2x20 ml), brine (2x20 ml), dried and evaporated in vacuo. The oily residue was chromatographed on silica gel, using cyclohexane/ethyl acetate 7/3 as eluant, to obtain the title compound as a white foam (0.169 g; t.l.c. cyclohexane/ethyl acetate 1/1 Rf = 0.41; IR (CDCl₃) Vmax (cm⁻¹): 3640 (OH), 1761 (C=O), 1634 (C=C); ¹H-NMR (300 MHz, CDCl₃) : 6.88 (m), 4.92 (m), 4.91 (m), 4.95-4.85 (m), 4.54 (m), 4.28-4.18 (m), 4.18 (dd), 3.30-3.20 (m), 3.24 (s), 3.23 (s), 2.05 (m), 2.00-1.75 (m), 1.70-1.50 (m), 1.60 (m), 1.50-1.09 (m), 1.31 (d), 1.29 (d), 1.25-1.15 (m), 0.86 (m) ppm)

Example 15

(Cyclohexyloxycarbonyloxy)methyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

To a solution of the Intermediate A (0.22 g) in N,N-dimethylformamide (6.5 ml), in presence of 3A molecular sieves, tetra-n-butylammonium bromide (0.222 g) and the intermediate 6 (0.191 g) were added. The resulting mixture was stirred at 22° for 5 hours, diluted with diethylether (50 ml), washed with water (30 ml), saturated ammonium chloride (2x30 ml), 5% aq sodium hydrogen carbonate (30 ml), brine (2x30 ml), water (30 ml) and dried. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel, using cyclohexane/ethyl acetate 100/0 to 65/35, to obtain the title compound as a white foam (0.1 g; t.l.c. cyclohexane/ethyl acetate 1/1 Rf=0.18; IR (CDCl₃) Vmax (cm⁻¹) : 3614 (OH), 1772 (C=O β-lactam), 1717 (C=O ester), 1640 (C=C); ¹H-NMR (300 MHz, CDCl₃) : 5.90 (dd), 4.93 (t), 4.67 (m), 4.30-4.20 (m), 4.20 (dd), 3.35-3.25 (m), 3.25 (s), 2.08 (m), 2.00-1.80 (m), 1.80-1.30 (m), 1.32 (d) ppm).

Example 16

1-[(1,1-dimethylethyl)carbonyloxy]-2-methylpropyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

To a solution of the Intermediate A (0.3 g) in N,N-dimethylformamide (5ml), tetra-n-butylammonium bromide (0.3 g) and the intermediate 5 (0.398 g) were added under nitrogen and stirring was continued for 16 h at 22°. The reaction mixture was diluted with diethylether (15 ml), washed with saturated ammonium chloride (2x30 ml), brine (2x30 ml), dried, and evaporated in vacuo. The oily residue was chromatographed on silica gel, using cyclohexane/ethyl acetate 7/3 as eluant, to obtain the title compound as a colourless oil (0.057 g;

t.l.c. cyclohexane/ethyl acetate 1/1 R_f = 0.45; IR (CDCl₃), V_{max} (cm⁻¹): 3611 (NH), 1774 (C=O β-lactam), 1747 (C=O ester), 1632 (C=C); ¹H-NMR (300 MHz, CDCl₃): 6.76 (d), 6.72 (d), 4.95 (t), 4.92 (t), 4.30-4.16 (m), 3.32-3.19 (m), 3.24 (s), 3.23 (s), 2.10 (m), 2.06 (m), 1.94-1.80 (m), 1.75-1.60 (m), 1.50-1.20 (m), 1.32 (d), 1.31 (d), 1.22 (s), 1.19 (s), 1.06-0.98 (d) ppm

Example 17

1-(Cyclohexyloxycarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

To a solution of sodium (4S,8S,9R,12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (194mg) in dimethylformamide (8ml) triethylbenzylammonium chloride (146mg) and (1-chloroethyl)-cyclohexyl carbonate (0.142ml) were added at room temperature. The resulting mixture was stirred at 60° for 97min, diluted with diethyl ether (30ml) and washed with cold water (60ml). The aqueous layer was re-extracted with diethyl ether (30ml) and the combined organic phases were washed with brine (30ml) and dried over sodium sulphate. The organic layer was concentrated under reduced pressure and the resultant white foam (288mg) was crystallised from diethyl ether/petroleum to give the title compound (220mg) as a white solid.

Pharmacy Examples

Tablets

Example A

	mg/tab
Compound of Example 1	320
Lactose	150
Ethyl cellulose	20
Sodium lauryl sulphate	7
Magnesium stearate	3
Tablet core	500mg

The active ingredient and the lactose are blended together and then granulated using water as the granulating fluid. The dried granules are blended with the ethyl cellulose, sodium lauryl sulphate and magnesium stearate and the tablet core formed using an appropriate punch. The tablet may then be coated using conventional techniques and coatings.

Example B

	mg/tab
Compound of Example 1	320
Compressible sugar	170
Sodium lauryl sulphate	7
Magnesium stearate	3
Tablet core	500

The active ingredient and the excipients are blended together and then compressed using an appropriate punch. If required the tablet thus formed may be coated in a conventional manner.

GranulesExample C

5

mg/unit dose

10

Compound of Example 1	320
Starch	100
Cellulose	40
Polymethacrylate	30
Sodium lauryl sulphate	7
Magnesium stearate	3
Flavouring agent	qs

15

20

Example D

25

mg/unit dose

30

Compound of Example 1	320
Ethyl cellulose	140
Polymethacrylate	30
Sodium lauryl sulphate	7
Magnesium stearate	3
Flavouring agent	qs

35

Example E

40

mg/unit dose

45

Compound of Example 1	320
Compressible sugar	140
Polymethacrylate	30
Sodium laurylsulphate	7
Magnesium & stearate	3
Flavouring agent	qs

50

55

A solution of the active ingredient in ethanol is sprayed into a suitable fluid bed granulator charged with the major excipients. The granules so formed are dried and screened. If desired the granules may then be coated with a suitable enteric coating and dried. The dried granules are then blended with the remaining excipients including any flavouring agent and coated, for example with an enteric coating. The granules thus obtained may be filled into capsules or the like for a single dose presentation or filled into bottles for subsequent preparation of a multi dose oral liquid presentation.

Activity Data

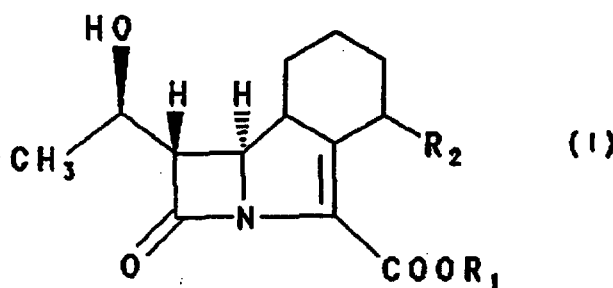
In conventionally conducted protection tests using mice, orally administered compounds of the invention exhibited very high activity against pathogenic bacteria, as illustrated in the following table, where compounds are compared with the known orally administrable broad spectrum antibiotic cefuroxime axetil:-

<u>ED₅₀ (mg/kg)</u>		
<u>Compound</u>	<u>Staph. aureus</u>	<u>E. Coli</u>
Example 1	<1	<1
Example 3	<1	<1
Example 10	<1	<1
Cefuroxime axetil	6	26

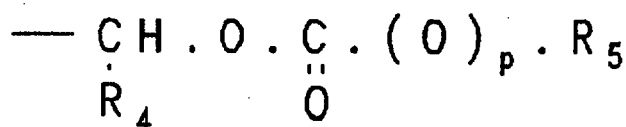
The compounds of the invention are also essentially non-toxic at therapeutically useful dose levels. For example, no adverse effects were observed when the compound of Example 1 was orally administered to mice at doses up to 1000 mg/kg.

Claims

1. Compounds of general formula (I)



in which R₁ represents the group



where R₄ represents a hydrogen atom or a C₁₋₄ alkyl group; p is 0 or 1; R₅ is a group selected from C₁₋₈ alkyl, C₆₋₈ cycloalkyl optionally substituted by a C₁₋₃ alkyl group, phenyl and C₁₋₄ alkyl substituted by a C₁₋₃ alkoxy group; and R₂ is a group OR₃ where R₃ is a C₁₋₅ alkyl group.



Activity Data

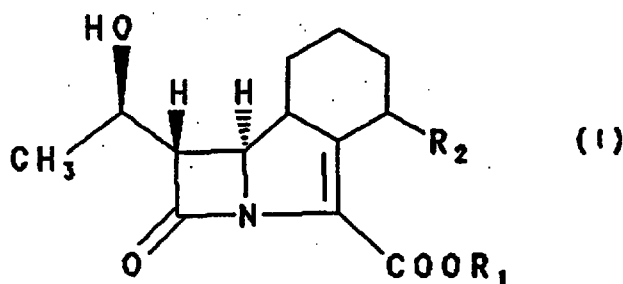
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<u>ED₅₀ (mg/kg)</u>			
<u>Compound</u>	<u>Staph. aureus</u>	<u>E. Coli</u>	
Example 1	<1	<1	
Example 3	<1	<1	
Example 10	<1	<1	
Cefuroxime axetil	6	26	

The compounds of the invention are also essentially non-toxic at therapeutically useful dose levels. For example, no adverse effects were observed when the compound of Example 1 was orally administered to mice at doses up to 1000 mg/kg.

Claims

- Compounds of general formula (I)



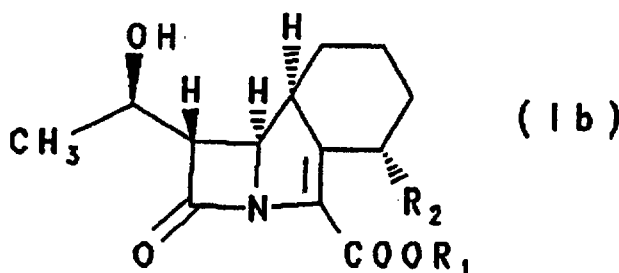
in which R₁ represents the group



where R₄ represents a hydrogen atom or a C₁₋₄ alkyl group; p is 0 or 1; R₅ is a group selected from C₁₋₆ alkyl, C₅₋₈ cycloalkyl optionally substituted by a C₁₋₃ alkyl group, phenyl and C₁₋₄ alkyl substituted by a C₁₋₃ alkoxy group; and R₂ is a group OR₃ where R₃ is a C₁₋₅ alkyl group.

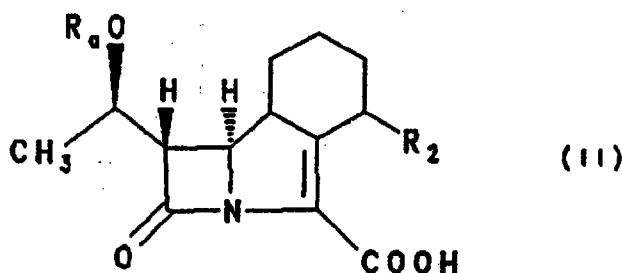


2. Compounds as claimed in claim 1 having the configuration



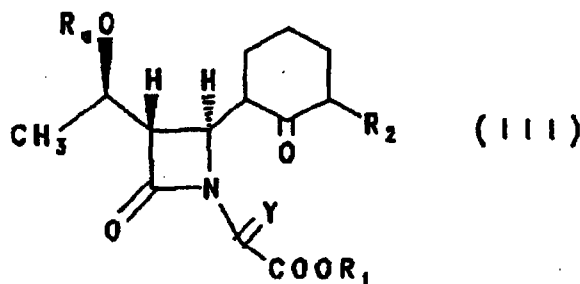
15 (where R_1 and R_2 are as defined in claim 1).

3. Compounds as claimed in claim 1 or claim 2 wherein R_4 represents a hydrogen atom or a methyl group.
4. Compounds as claimed in any of claims 1 to 3 wherein R_2 represents a methoxy or ethoxy group.
- 20 5. Compounds as claimed in any of claims 1 to 4 wherein R_5 represents a methyl, ethyl, isopropyl, t-butyl, 1-methoxy-1-methylethyl, phenyl, cyclohexyl or 4-ethylcyclohexyl group.
- 25 6. Compounds as claimed in claim 2 wherein R_4 represents a hydrogen atom or a methyl group; R_5 is a group selected from C_{1-4} alkyl, C_{5-6} cycloalkyl optionally substituted by a C_{1-2} alkyl group, phenyl and C_{1-4} alkyl substituted by methoxy; and R_2 is a methoxy group.
- 30 7. The pivaloyloxymethyl, 1-pivaloyloxyethyl, acetoxymethyl, 1-acetoxyethyl, 1-methoxy-1-methylethylcarbonyloxymethyl, 1-(1-methoxy-1-methylethylcarbonyloxy)ethyl, 1-benzoyloxyethyl, 1-isopropoxycarbonyloxyethyl, cyclohexyloxycarbonyloxymethyl and 1-(4-ethylcyclohexyloxycarbonyloxy)ethyl esters of (4S, 8S, 9R, 10S, 12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic acid.
- 35 8. 1-Cyclohexyloxycarbonyloxyethyl (4S, 8S, 9R, 10S, 12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate.
9. Compounds as claimed in any of claims 1 to 8 for use in therapy or prophylaxis of systemic bacterial infections in a human or animal subject.
- 40 10. The use of a compound as claimed in any of claims 1 to 8 in the manufacture of a therapeutic agent for the treatment or prophylaxis of systemic bacterial infections in a human or animal body.
11. Pharmaceutical compositions comprising a compound as claimed in any of claims 1 to 8 in admixture with one or more physiologically acceptable carriers or excipients.
- 45 12. A process for the preparation of compounds of general formula (I) as defined in claim 1 which comprises either (a) reacting a compound of general formula (II)



(where R_2 is as defined in claim 1 and R_4 represents a hydrogen atom or a hydroxyl protecting group) or

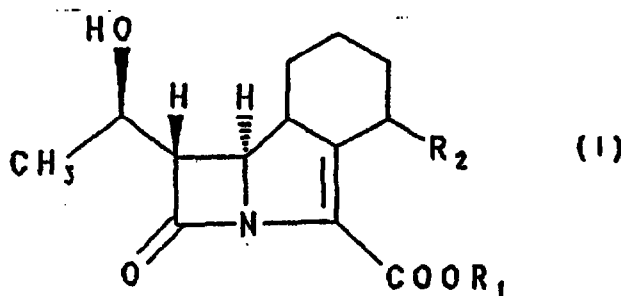
a salt or reactive derivative thereof with an esterifying agent serving to introduce a group R_1 as defined in claim 1, or (b) cyclising a compound of general formula (III)



(where R_1 and R_2 are as defined in claim 1, R_4 is a hydroxyl protecting group and Y is an oxygen atom or a phosphine group), and thereafter, if necessary or desired, reacting the product to replace a hydroxyl protecting group R_4 by a hydrogen atom and/or separating a particular desired isomer of a compound of general formula (I) from one or more other isomers thereof.

Patentansprüche

1. Verbindungen der allgemeinen Formel (I)



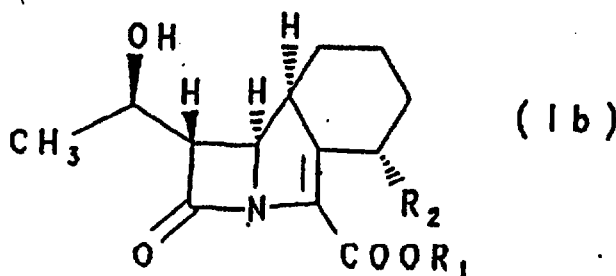
worin R_1 die Gruppe



darstellt, worin R_4 ein Wasserstoffatom oder eine C_1 - C_4 -Alkylgruppe ist; p ist 0 oder 1; R_5 ist eine Gruppe, ausgewählt unter C_1 - C_6 -Alkyl, C_5 - C_6 -Cycloalkyl gegebenenfalls substituiert durch eine C_1 - C_3 -Alkylgruppe, Phenyl und C_1 - C_4 -Alkyl substituiert durch eine C_1 - C_3 -Alkoxygruppe; und R_2 ist eine Gruppe OR_3 , worin R_3 eine C_1 - C_6 -Alkylgruppe ist.

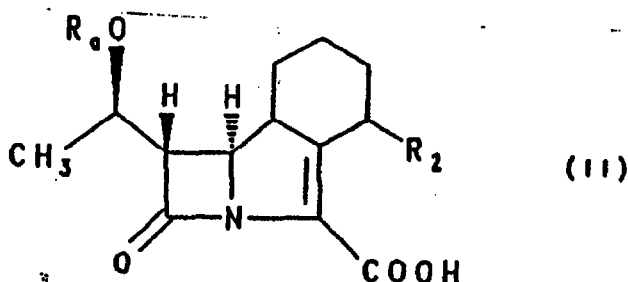
2. Verbindungen nach Anspruch 1, die die Konfiguration





haben (worin R_1 und R_2 wie in Anspruch 1 definiert sind).

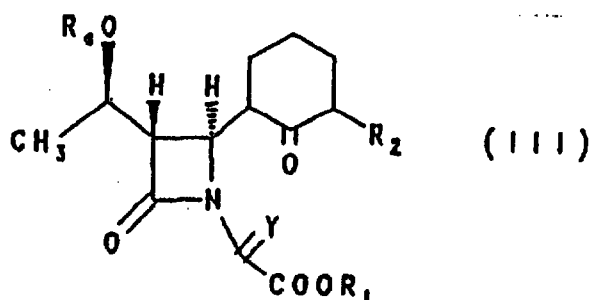
3. Verbindungen nach Anspruch 1 oder Anspruch 2, worin R_4 ein Wasserstoffatom oder eine Methylgruppe darstellt.
4. Verbindungen nach einem der Ansprüche 1 bis 3, worin R_2 eine Methoxy- oder Ethoxygruppe darstellt.
5. Verbindungen nach einem der Ansprüche 1 bis 4, worin R_5 eine Methyl-, Ethyl-, Isopropyl-, t-Butyl-, 1-Methoxy-1-methyl-ethyl-, Phenyl-, Cyclohexyl- oder 4-Ethylcyclohexylgruppe darstellt.
6. Verbindungen nach Anspruch 2, worin R_4 ein Wasserstoffatom oder eine Methylgruppe darstellt; R_5 ist eine Gruppe, ausgewählt unter C_1 - C_4 -Alkyl, C_6 - C_6 -Cycloalkyl gegebenenfalls substituiert durch eine C_1 - C_2 -Alkylgruppe, Phenyl und C_1 - C_4 -Alkyl substituiert durch Methoxy; und R_2 ist eine Methoxygruppe.
7. Pivaloyloxymethyl-, 1-Pivaloyloxyethyl-, Acetoxymethyl-, 1-Acetoxylethyl-, 1-Methoxy-1-methylethylcarboxyloxymethyl-, 1-(1-Methoxy-1-methylethylcarboxyloxy)ethyl-, 1-Benzoyloxyethyl-, 1-Isopropoxycarboxyloxyethyl-, Cyclohexyloxycarboxyloxymethyl- und 1-(4-Ethylcyclohexyloxycarboxyloxy)ethyl-ester der (4S,8S,9R,10S,12R)-4-Methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-en-2-carbonsäure.
8. 1-Cyclohexyloxycarboxyloxyethyl-(4S,8S,9R,10S,12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-en-2-carboxylat.
9. Verbindungen nach einem der Ansprüche 1 bis 8 zur Verwendung in Therapie oder Prophylaxe systemischer bakterieller Infektionen bei Mensch oder Tier.
10. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 8 bei der Herstellung eines therapeutischen Mittels für die Behandlung oder Prophylaxe systemischer bakterieller Infektionen in einem menschlichen oder tierischen Körper.
11. Pharmazeutische Zusammensetzungen, enthaltend eine Verbindung nach einem der Ansprüche 1 bis 8 im Gemisch mit einem oder mehreren physiologisch annehmbaren Trägern oder Exzipienten.
12. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel (I), wie in Anspruch 1 definiert, das umfaßt entweder
 - (a) die Reaktion einer Verbindung der allgemeinen Formel (II)



(worin R_2 die in Anspruch 1 definierte Bedeutung hat und R_4 ein Wasserstoffatom oder eine Hydroxy-



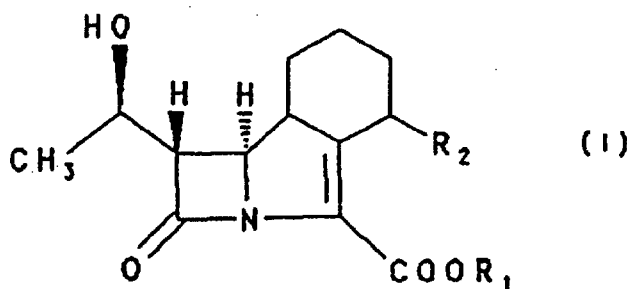
schutzgruppe ist) oder eines Salzes oder eines reaktionsfähigen Derivates davon mit einem Veresterungsmittel, das zur Einführung einer wie in Anspruch 1 definierten Gruppe R₁ dient, oder
(b) Cyclisieren einer Verbindung der allgemeinen Formel (III)



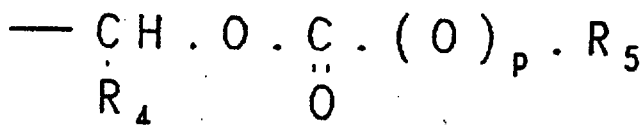
(worin R₁ und R₂ wie in Anspruch 1 definiert sind, R_a ist eine Hydroxyschutzgruppe und Y ist ein Sauerstoffatom oder eine Phosphingruppe), und danach, falls erforderlich oder gewünscht, Reaktion des Produktes, um die Hydroxyschutzgruppe R_a durch ein Wasserstoffatom zu ersetzen und/oder Abtrennung eines besonderen gewünschten Isomeren einer Verbindung der allgemeinen Formel (I) von einem oder mehreren anderen Isomeren davon.

Revendications

1. Composés de formule générale (I)



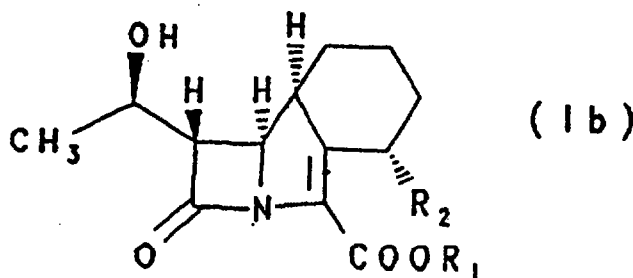
dans laquelle R₁ représente le groupe



dans lequel R₄ représente un atome d'hydrogène ou un groupe alkyle en C₁-C₄; p est zéro ou un; R₅ représente un groupe choisi parmi les groupes alkyle en C₁-C₆, cycloalkyle en C₅-C₆, éventuellement substitué par un groupe alkyle en C₁-C₃, un groupe phényle ou un groupe alkyle en C₁-C₄ substitué par un groupe alcoxy en C₁-C₃; et
R₂ représente le groupe OR₃, dans lequel R₃ représente un groupe alkyle en C₁-C₅.

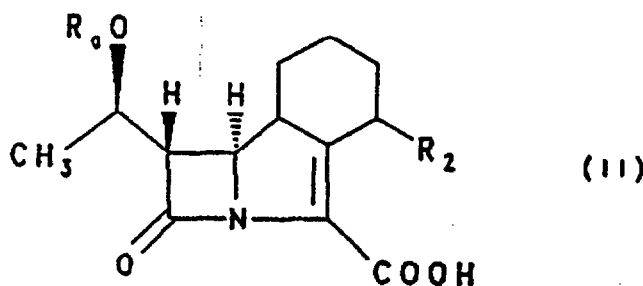
2. Composés selon la revendication 1, ayant pour configuration





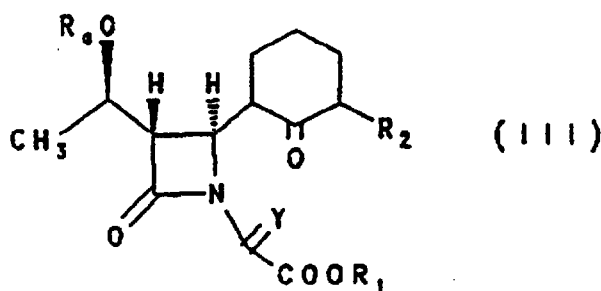
(dans laquelle R_1 et R_2 sont tels que définis dans la revendication 1).

3. Composés selon la revendication 1 ou la revendication 2, dans lesquels R_4 représente un atome d'hydrogène ou un groupe méthyle.
4. Composés selon l'une quelconque des revendications 1 à 3, dans lesquels R_2 représente un groupe méthoxy ou éthoxy.
5. Composés selon l'une quelconque des revendications 1 à 4, dans lesquels R_5 représente un groupe méthyle, éthyle, isopropyle, t-butyle, 1-méthoxy-1-méthyléthyle, phényle, cyclohexyle ou 4-éthylcyclohexyle.
6. Composés selon la revendication 2, dans lesquels R_4 représente un atome d'hydrogène ou un groupe méthyle ; R_5 est un groupe choisi parmi les groupes alkyle en C_1-C_4 , cycloalkyle en C_5-C_6 éventuellement substitué par un groupe alkyle en C_1-C_2 , phényle et alkyle en C_1-C_4 substitué par un groupe méthoxy ; et R_2 est un groupe méthoxy;
7. Esters pivaloyloxyméthyllique, 1-pivaloyloxyéthyllique, acétoxyméthyllique, 1-acétoxyéthyllique, 1-méthoxy-1-méthylthylcarbonyloxyméthyllique, 1-(1-méthoxy-1-méthyléthylcarbonyloxy)éthyllique, 1-benzoyloxyéthyllique, 1-isopropoxycarbonyloxyéthyllique, cyclohexyloxycarbonyloxyméthyllique, 1-(4-éthylcyclohexyloxycarbonyloxy)éthyllique d'acide (4S, 8S, 9R, 10S, 12R)-4-méthoxy-10-(1-hydroxyéthyl)-11-oxo-1-azatricyclo[7,2,0^{3,8}]undéc-2-ène-2-carboxylique.
8. (4S, 8S, 9R, 10S, 12R)-4-Méthoxy-10-(1-hydroxyéthyl)-11-oxo-1-azatricyclo[7,2,0^{3,8}]undéc-2-ène-2-carboxylate de 1-cyclohexyloxycarbonyloxyéthyle.
9. Composés selon l'une quelconque des revendications 1 à 8, utilisables en thérapeutique ou en prophylaxie des infections bactériennes systémiques chez un sujet humain ou animal.
10. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 pour fabriquer un agent thérapeutique servant au traitement ou à la prophylaxie d'infections bactériennes systémiques dans un corps humain ou animal.
11. Compositions pharmaceutiques comprenant un composé selon l'une des revendications 1 à 8, en mélange avec un ou plusieurs véhicules ou excipients physiologiquement acceptables.
12. Procédé de préparation de composés de formule générale (I), tels que définis dans la revendication 1, qui comprend (a) la réaction d'un composé de formule générale (II)



(dans laquelle R₂ est tel que défini dans la revendication 1 et R_a représentent un atome d'hydrogène ou un groupe protecteur d'hydroxyle) ou d'un de ses sels ou dérivés réactifs, avec un agent d'estérification, pour introduire un groupe R₁ tel que défini dans la revendication 1, ou

(b) la cyclisation d'un composé de formule générale (III)



(dans laquelle R₁ et R₂ sont tels que définis dans la revendication 1, R_a est un groupe protecteur d'hydroxyle et Y est un atome d'oxygène ou un groupe phosphine) et, ensuite, le cas échéant, la réaction du produit pour remplacer un groupe protecteur d'hydroxyle R_a par un atome d'hydrogène et/ou la séparation d'un isomère désiré particulier d'un composé de formule générale (I) d'un ou de plusieurs autres isomères de ce composé.

