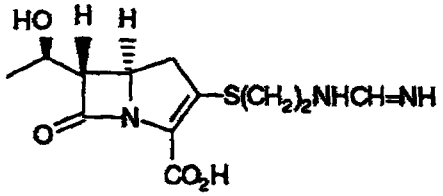
ESTERS OF CARBAPENEMS

This invention relates to novel antibacterial compounds, processes for their preparation, pharmaceutical and veterinary compositions comprising them, and their use in antibacterial therapy.

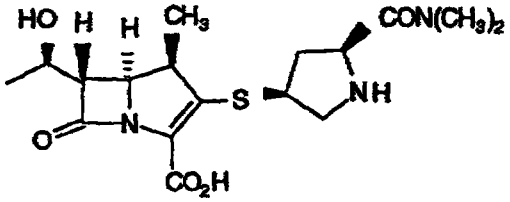
Carbapenems such as imipenem, the compound of formula (A):



(A)

have a potent, broad spectrum of antibacterial activity (see US 3 950 357 and US 4 194 047; Merck and Co). Such carbapenems however tend to be vulnerable to hydrolysis by the enzyme renal dehydropeptidase-1 (DHP-1) and this limits their use in chemotherapy. In the case of imipenem, this problem may be overcome by the co-administration of an inhibitor of DHP-1.

Stability towards DHP-1 may also be imparted by chemical modification of the carbapenem nucleus, for instance by incorporating a 1β-methyl substitutent, as in the compound meropenem, the compound of formula (B):



(B)

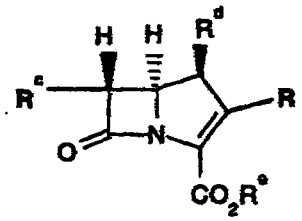
(see Shih D.H. *et al.*, Heterocycles, 1984, 21, 29 and Sunagawa M. *et al.*, J. Antibiotics, 1990, 43, 519). More recently, this has been extended to a 1β-aminoalkyl substituent (see EP 0 433 759, Bristol-Meyers Squibb).

An alternative approach to imparting improved stability to DHP-1 utilises 2-carbon substituted carbapenems, for instance, 2-aryl, 2-heteroaryl and 2-heteroaromatic carbapenems (US 4 543 257, US 4 260 627, US 4 962 101, US 4 978 659, EP 0 14 493, EP 0 414 489, EP 0 010 316 and EP 0 030 032 Merck & Co) and 2-(substituted)methyl carbapenems (Schmidt *et al*, J.Antibiotics, 41, 1988, 780).

UK Patent 1 593 524, Merck & Co. discloses a number of 5-membered heteroaromatic carbapenem derivatives including diazolyl and tetrazolyl compounds. However, in the case of the pyrazolyl derivatives the heterocyclic compound is attached to the carbapenem nucleus through the C-4 position.

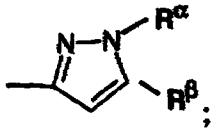
Other structural modifications introduced at position-2 include a substituted vinyl group $-C(R_a)=CHR_b$ in which, for instance, R_a is hydrogen or methyl and R_b is hydrogen or lower alkyl (EP 0 330 108; Fujisawa) or R_a and R_b are selected from hydrogen, lower alkyl, aminocarbonyl, lower alkoxy, cyano, nitro and lower alkoxycarbonyl (EP 0 430 037, Banyu Pharmaceutical Co.). In the absence of a 1β-methyl substituent, such a modification does not however appear to impart DHP-1 stability.

International Patent Application No. PCT/GB94/02347 describes compounds of the general formula (C):



(C)

in which R is:



wherein

R^{α} is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl;

R^{β} is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl; or

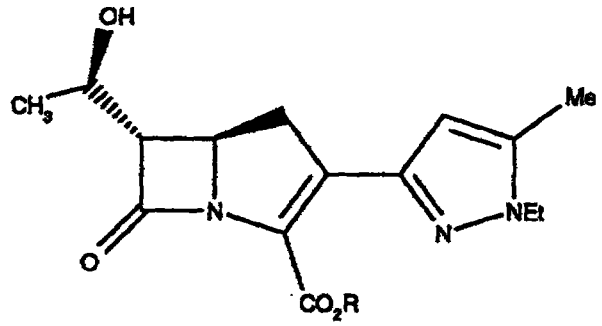
R^{α} and R^{β} together form an optionally substituted 5 or 6 membered heterocyclic ring with or without additional heteroatoms;

R^{c} is (C_{1-6})alkyl which is unsubstituted or substituted by fluoro, a hydroxy group which is optionally protected by a readily removable hydroxy protecting group, or by an amino group which is optionally protected by a readily removable amino protecting group;

R^{d} is hydrogen or methyl; and

$-CO_2R^{e}$ is carboxy or a carboxylate anion or the group R^{e} is a readily removable carboxy protecting group.

According to the present invention, there is provided the compound of formula (I):



(I)

wherein R is selected from the group consisting of isobutyryloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, and benzoyloxymethyl.

Particular compounds in accordance with the present invention are:

isobutyryloxymethyl (5R, 6S)-2-[1-ethyl-5-methylpyrazol-3-yl]-6-[(1R)-1-hydroxyethyl]-carbapen-2-em-3-carboxylate,

(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl (5R, 6S)-2-[1-ethyl-5-methylpyrazol-3-yl]-6-[(1R)-1-hydroxyethyl]-carbapen-2-em-3-carboxylate, and

benzoyloxymethyl (5R, 6S)-2-[1-ethyl-5-methylpyrazol-3-yl]-6-[(1R)-1-hydroxyethyl]-carbapen-2-em-3-carboxylate.

Since each carbapenem compound of the present invention is intended for use in pharmaceutical compositions, it will be understood that it is provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compound may be used for preparing the more pure forms used in the pharmaceutical compositions. Preferably, whenever possible, each compound of the present invention is obtained in crystalline form

When each compound of this invention is allowed to crystallise or is recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be present in the crystalline product. This invention includes within its scope stoichiometric hydrates.

The carbapenem antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, according to techniques and procedures *per se* known in the art with reference to other antibiotics, and the invention therefore includes within its scope a pharmaceutical composition comprising an antibiotic compound according to the present invention together with a pharmaceutically acceptable carrier or excipient.

The compositions may be formulated for administration by any suitable route, such as oral, parenteral or topical application, although the oral route is particularly preferred. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams 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 polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting 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, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, 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, oily esters, glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid; and, if desired conventional flavouring or colouring agents. Suppositories will contain conventional suppository base, eg cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilising 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 sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, agents 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 lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be 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 sterilisation cannot be accomplished by filtration. The compound can be sterilised 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 composition may contain from 0.1% to 99.5% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 mg to 12 g per day for an average adult patient (body weight 70 kg), for instance 1500 mg per day, depending on the route and frequency of administration. Such dosages correspond to approximately 1.5 to 170 mg/kg per day. Suitably the dosage is from 1 to 6g per day.

The daily dosage is suitably given by administering a compound of the invention several times in a 24-hour period. Typically, 250 mg is administered 4 times a day although, in practice, the dosage and frequency of administration which will be most suitable for an individual patient will vary with the age, weight and response of the patients, and there will be occasions when the physician will choose a higher or lower dosage and a different frequency of administration. Such dosage regimens are within the scope of this invention.

No toxicological effects are indicated when any compound of the invention is administered in the above mentioned dosage range.

The present invention also includes a method of treating bacterial infections in humans and animals which method comprises administering a therapeutically effective amount of an antibiotic compound of the present invention of the formula (I).

In a further aspect, the present invention also provides for the use of a compound of formula (I) for the manufacture of a medicament for treating bacterial infection.

The compounds of the present invention of formula (I) are active against a broad range of Gram-positive and Gram-negative bacteria, and may be used to treat a wide range of bacterial infections including those in immunocompromised patients.

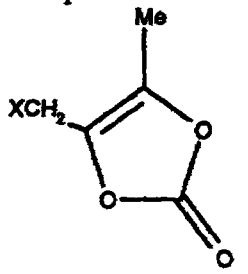
Amongst many other uses, the compounds of the invention are of value in the treatment of skin, soft tissue, respiratory tract and urinary tract infections in humans and may also be used to treat mastitis in cattle.

A particular advantage of the antibacterially active compounds of this invention is their stability to β-lactamase enzymes and they are therefore effective against β-lactamase producing organisms.

The present invention further provides a process for the preparation of a compound of formula (I) wherein R is isobutyryloxymethyl or benzoyloxymethyl, which process comprises treating a corresponding compound of formula (I), wherein R is an alkali metal cation, with a compound of formula $XCH_2OCOCHMe_2$ or $XCH_2OCOC_6H_5$, wherein X is a leaving group such as halogen, more particularly bromine or iodine.

The reaction is typically carried out at between 0 and 60 C, for example at ambient temperature, under an inert, for example argon, atmosphere, in a suitable organic solvent , for example, N-methylpyrrolidin-2-one. Other suitable solvent systems include N, N'-dimethylformamide and N, N'-dimethylacetamide.

The present invention further provides a process for the preparation of a compound of formula (I) wherein R is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, which process comprises treating a corresponding compound of formula (I), wherein R is an alkali metal cation, with a compound of formula:



wherein X is a leaving group such as halogen, more particularly bromine or iodine.

The reaction is typically carried out at between 0 and 60 C, for example at ambient temperature, in a suitable organic solvent , for example, N-methylpyrrolidin-2-one, and in the presence of an acid-binding agent, such as 2,6-lutidine. Other suitable acid-binding agents include pyridine and diisopropylethylamine. Other suitable solvents include N, N'-dimethylformamide and N, N'-dimethylacetamide.

Compounds of formula (I) wherein R is an alkali metal cation,, such as sodium, are described in International Patent Application No. PCT/GB94/02347, and hereinbelow in Preparation 1.

The compound of formula $ICH_2OCOCHMe_2$ (iodomethyl isobutyrate) and iodomethyl benzoate can be prepared from the corresponding chlorides *via* the Finkelstein reaction, which is well known to those skilled in the art.

Chloromethyl isobutyrate and chloromethyl benzoate can be prepared by esterifying isobutyric acid or benzoic acid respectively with chloromethyl chlorosulphate (Binderup et al., *Synthetic Commun.*, 14(9), 857-864 (1984)).

The following Examples illustrate the present invention further:

General Instructions - Solutions were dried using anhydrous magnesium sulphate and solvents were removed by evaporation under reduced pressure using a rotary evaporator. Column chromatography on silica gel used Merck silica gel 60, particle size <0.063mm.

Example 1

Isobutyryloxymethyl-(5*R*, 6*S*)-2-(1-ethyl-5-methylpyrazol-3-yl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate

The product from Preparation 1 (200 mg, 0.61 mmol) was dissolved in N-methylpyrrolidin-2-one (2 ml). A solution of isobutyryloxymethyl iodide (360 mg, 1.6 mmol) in N-methylpyrrolidin-2-one (0.5 ml) was added to this solution at room temperature under argon and after 0.5 h the reaction mixture was diluted with ethyl acetate (15 ml) and the solution was washed with water (3 x 15 ml), 5% sodium thiosulfate solution (15 ml) and then saturated brine (15 ml). The organic extract was dried (Na_2SO_4) and concentrated to an oil which was purified by chromatography on silica gel eluting with an acetone/toluene gradient mixture to yield a pale yellow solid which was recrystallised from diethyl ether to afford the *title compound* as pale yellow microneedles (100 mg, 40%), m.p. 107-8°C; (Found: M^+, 405.1899. $C_{20}H_{27}N_3O_6$ requires M 405.1900); $\nu_{max}(CHCl_3)$ 3458, 3019, 1772 and 1734 cm^{-1}; $\delta_H(CDCl_3)$ 1.19 (6H, d, *J*7.1 Hz), 1.36 (3H, d, *J*6.1 Hz), 1.40 (3H, t, *J*7.2 Hz), 1.76 (1H, d, *J*4.9 Hz), 2.29 (3H, s), 2.62 (1H, septet, *J*7.1 Hz), 3.18 (1H, dd, *J*2.7, 6.5 Hz), 3.30 (1H, dd, *J*9.0, 18.8 Hz), 3.64 (1H, dd, *J*9.8, 18.8 Hz), 4.08 (2H, q, *J*7.2 Hz), 4.16-4.30 (2H, m), 5.92 (1H, d, *J*5.6 Hz), 5.98 (1H, d, *J*5.6 Hz) and 7.02 (1H, s).

Example 2

(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methyl-pyrazol-3-yl)carbapen-2-em-3-carboxylate

Sodium (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate (300 mg) in *N*-methylpyrrolidinone (4 ml) was treated with 2,6-lutidine (*ca.* 30 mg) followed by 4-bromomethyl-5-methyl-1,3-dioxol-2-one (290 mg) [F. Sakamoto, S. Ikeda and G. Tsukamoto, *Chem. Pharm Bull.* **32**, (6), 2241 - 2248 (1984)] in tetrahydrofuran (1 ml). The mixture was stirred for 1.25 h. Ethyl acetate and water were added and the layers separated. The aqueous layer was re-extracted with ethyl acetate and the combined ethyl acetate layers were washed with water, followed by saturated brine solution, and then dried ($MgSO_4$). The filtered solution was stored in a refrigerator overnight and then evaporated and chromatographed on silica gel (230 - 400 mesh ASTM) (2.5 x 12 cm column), loading in CH_2Cl_2 / hexane, and eluting with ethyl acetate. Fractions containing the product were combined and evaporated to give a colourless solid which was recrystallised from acetone to give crystals of (5-methyl-2-oxo-1,3-dioxolen-4-

yl)methyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate, m. p. 148 - 151°C; $\upsilon_{max}(CH_2Cl_2)$ 3605, 2975, 1823, 1776, 1737 (sh), 1721, 1598, 1546, 1314, 1231, and 1182 cm^{-1}; λ_{max}(EtOH/nm 325 (ε /$dm^3mol^{-1}cm^{-1}$ 14,654), 260.5 (ε/$dm^3mol^{-1}cm^{-1}$ 3404); $\delta(CDCl_3)$ 1.36 (3H, d, *J* 6.2 Hz), 1.40 (3H, t, *J ca.* 7.3 Hz), 1.76 (1H,d, *J* 4.9 Hz), 2.21 (3H, s), 2.30 (3H, s), 3.19 (1H, dd, *J* 2.7 & 6.5 Hz), 3.31 (1H, dd, *J* 9.0 & 18.7 Hz), 3.61 (1H, dd, *J* 9.9 & 18.7 Hz), 4.08 (2H, q, *J* 7.3 Hz), 4.16 - 4.30 (2H, m), 5.00 & 5.07 (2H, ABq, J 13.9 Hz), 6.88 (1H, s) ppm; Found (EI ms) *m/z* 417 (M^+).

Example 3

Benzoyloxymethyl (5*R*,6*S*)-2-(1-ethyl-5-methylpyrazol-3-yl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate

The product from Preparation 1 (200 mg, 0.61 mmol) was dissolved in N-methylpyrrolidin-2-one (2 ml). A solution of benzoyloxymethyl iodide (336 mg, 1.28 mmol) in N-methylpyrrolidin-2-one (0.5 ml) was added to this solution at room temperature under argon and after 0.5 h the reaction mixture was diluted with ethyl acetate (15 ml) and the solution was washed with water (3 x 15 ml), 5% sodium thiosulfate solution (15 ml) and then saturated brine (15 ml). The organic extract was dried (Na_2SO_4) and concentrated to an oil which was purified by chromatography on silica gel eluting with an acetone/toluene gradient mixture to yield a pale yellow solid which was recrystallised from acetone/diethyl ether to afford the *title compound* as a white solid (143 mg, 53%), m.p. 131-4°C; (Found: M^+, 439.1743. $C_{22}H_{25}N_3O_6$ requires *M* 439.1743); $\upsilon_{max}(CHCl_3)$ 3021, 1740, 1602, 1452 and 1440 cm^{-1} ; δ $_H(CDCl_3)$ 1.34 (6H, m), 1.70 (1H, d, *J*4.9 Hz), 2.25 (3H,s), 3.19 (1H, dd, *J*2.4, 6.3 Hz), 3.30 (1H, dd, *J*8.8, 18.8 Hz), 3.64 (1H, dd, *J*10.1, 18.8 Hz), 4.07 (2H, q, *J*7.2 Hz), 4.18-4.31 (2H, m), 6.20 (2H, s), 7.42-7.48 (2H, m), 7.56-7.61 (1H, m), and 8.10 (2H, d, *J*7.1 Hz) ppm.

Preparation 1

Sodium (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate

(a) Ethyl 1-ethyl-5-methylpyrazole-3-carboxylate

N-Ethylhydrazine oxalate (12 g) in glacial acetic acid (100 ml) was cooled in an ice-bath and treated with ethyl 2,4-dioxovalerate (11.24 ml). After addition was complete

the mixture was stirred at room temperature; after *ca.* 45 min the mixture was warmed to dissolve insoluble ethylhydrazine oxalate. The mixture was stirred for a further 2 h and then poured into water(*ca.* 300 ml) / ethyl acetate (*ca.* 700 ml) and solid K_2CO_3 was carefully added, with stirring, until the pH was neutral. After separation the aqueous layer was re-extracted with ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$), and the solvents removed to leave an oil. Chromatography on silica gel, loading in CH_2Cl_2/hexane and eluting with a gradient elution of ethyl acetate/hexane mixtures (from 2:8 to 1:1) gave ethyl 1-ethyl-5-methylpyrazole-3-carboxylate as an oil (13.2 g); υ_{max} (CH_2Cl_2) 1717, 1446, 1389, and 1219 cm^{-1}; $\delta(CDCl_3)$ 1.38 (3H, t, *J* 7.2 Hz), 1.42 (3H, t, *J* 7.3 Hz), 2.30 (3H, s), 4.17 (2H, q, *J* 7.3 Hz), 4.38 (2H, q, *J* 7.1 Hz), 6.55 (1H, s); (Found *m/z* 182.1055. $C_9H_{14}N_2O_2$ requires *m/z* 182.1055).

(b) 1-Ethyl-5-methylpyrazole-3-carboxylic acid

Ethyl 1-ethyl-5-methylpyrazole-3-carboxylate (10.93 g) in ethanol (70 ml) was treated with KOH (3.69 g), followed by water (30 ml), and the mixture was stirred and heated under reflux for 6 h. The ethanol was removed using a rotary evaporator and ethyl acetate/water were added. The pH of the mixture was adjusted to 3.0 and the layers were separated. The aqueous layer was re-extracted with ethyl acetate. The combined ethyl acetate layers were extracted with excess aqueous $NaHCO_3$. The $NaHCO_3$ extract was poured into excess acid, and the pH was then adjusted to 3, and NaCl was added to the solution. The mixture was then repeatedly extracted with ethyl acetate, and the combined extracts were dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether to give the acid as a solid (5.65 g); υ_{max} (CH_2Cl_2) 2754, 2598, 1698, 1498, 1464, 1387, and 1233 cm^{-1}; $\delta(CDCl_3)$ 1.40 (3H, t, *J* 7.3 Hz), 2.32 (3H,s), 4.19 (2H, q, *J* 7.3 Hz), 6.61 (1H,s) ppm; (Found *m/z* 154.0740. $C_7H_{10}N_2O_2$ requires *m/z* 154.0742).

(c)*N*-Methoxy-*N*-methyl-1-ethyl-5-methylpyrazole-3-carboxamide

1-Ethyl-5-methylpyrazole-3-carboxylic acid (5.25 g) in dry dichloromethane (100 ml) containing *N,N*-dimethylformamide (0.26 ml) was cooled in an ice-bath and treated with a solution of oxalyl chloride (3.27 ml) in dichloromethane (25 ml), added dropwise. The mixture was stirred in the cold for 25 min, and then allowed to warm to room temperature, when evolution of a gas was observed. After 10 min the solvent was removed by evaporation *in vacuo* and toluene was added and removed (x 2) to

ensure any residual HCl and oxalyl chloride had been removed. The resultant acid chloride was redissolved in dry dichloromethane and then treated with *N,O*-dimethylhydroxylamine hydrochloride (3.61 g). The mixture was cooled in an ice-bath and treated with pyridine (6.0 ml). the mixture was then allowed to stir at room temperature for 1.5 h and then diluted with ether (100 ml) and washed with brine. The organic layer was then dried ($MgSO_4$) and evaporated to leave an oil. This was the chromatographed on silica gel, loading in dichloromethane, and eluting with ethyl acetate / hexane mixtures to give, after evaporation of requisite fractions, the hydroxamate (5.2 g) as a solid;

$\upsilon_{max}(CH_2Cl_2)$ 2982, 2937, 1641, 1489, 1445, 1379,and 975 cm^{-1}; $\delta(CDCl_3)$ 1.43 (3H, t, *J* 7.3 Hz), 2.29 (3H, s), 3.42 (3H, s), 3.76 (3H, s,), 4.13 (2H, q, *J* 7.3 Hz), 6.49 (1H, s); (Found *m/z* 197.1164. $C_9H_{15}N_3O_2$ requires *m/z* 197.1164).

(d) 3-Acetyl-1-ethyl-5-methylpyrazole

N-Methoxy-*N*-methyl-1-ethyl-5-methylpyrazole-3-carboxamide (3.12 g) in dry tetrahydrofuran (60 ml) was cooled in an ice-bath and treated with a 3.0M solution of methylmagnesium bromide in ether (11.08 ml). After stirring for 1.5 h the mixture was poured into a mixture of methanol (100 ml) and 5M aqueous HCl (10 ml) in an ice-bath. The mixture was then evaporated to lower volume and treated with a mixture of dichloromethane, water and saturated brine. After separation the aqueous layer was re-extracted with dichloromethane. The combined dichloromethane extracts were dried ($MgSO_4$) and evaporated to leave an oil (2.26 g), which solidified on standing; υ_{max} (CH_2Cl_2) 1680, 1446, 1425, 1380, 1324, 1208, and 945 cm^{-1}; δ ($CDCl_3$) 1.44 (3H, t, *J* 7.3 Hz), 2.30 (3H, s), 2.53 (3H, s), 4.13 (2H, q, *J* 7.3 Hz,), 6.51 (1H,s); (Found: *m/z* 152.0949. $C_8H_{12}N_2O$ requires *m/z* 152.090).

(e) (3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]azetidin-2-one

3-Acetyl-1-ethyl-5-methylpyrazole (3.51 g) in dry tetrahydrofuran (THF) (150 ml) under an argon atmosphere was cooled in an acetone / solid carbon dioxide bath and then treated with a 1M solution of lithium bis(trimethylsilyl)amide (50 ml). The mixture was stirred for 45 minutes and then (3*R*,4*R*)-4-acetoxy-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]azetidinone (6.6 g) was added as a solid under a blanket

of argon. The mixture was stirred in the cold for 3.5h. Saturated aqueous ammonium chloride was then added, followed by ethyl acetate, and the mixture was allowed to warm to room temperature. A little water was added and the layers were separated and the aqueous layer was re-extracted with ethyl acetate. The combined ethyl acetate extracts were washed with saturated brine, dried and evaporated. Chromatography on silica gel, eluting with ethyl acetate/hexane mixtures gave the title compound (3.65 g), υ_{max} (CH_2Cl_2) 3411, 1761, 1678, 1376, 1151, and 838 cm^{-1}; $\delta(CDCl_3)$ 0.064 (6H, s), 0.86 (9H, s), 1.20 (3H,d, *J* 6.3 Hz), 1.44 (3H, t, *J* 7.3 Hz), 2.31 (3H, s), 2.89 (1H, dd, *J* 1.8 & 4.9 Hz), 3.15 (1H, dd, *J* 10.0 & 17.1 Hz), 3.50 (1H, dd, *J* 3.5 & 17.0 Hz), 4.06 - 4.25 (4H, m), 6.11 (1H, s), 6.53 (1H, s). (Found *m/z* 379.2296. $C_{19}H_{33}N_3O_3Si$ requires *m/z* 379.2291).

(f) Allyl (2*R* and 2*S*)-2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-oxoazetidinyl}-2-hydroxyacetate.

(3*S*,4*R*)-4-[(1-Ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]azetidin-2-one (3.6 g) and allyl glyoxylate hydrate (1.66 g) in toluene (100 ml) were heated under reflux in a Dean and Stark apparatus under an atmosphere of argon for 3.5h. T.l.c. of the reaction mixture showed the reaction had almost prceeded to completion, so more allyl glyoxylate hydrate (190 mg) was added and the mixture was heated under reflux for a further 45 min. The mixture was cooled, the toluene was removed to give crude allyl (2*R* and 2*S*)-2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-oxoazetidinyl}-2-hydroxyacetate, which was used in the next stage; υ_{max} (CH_2Cl_2) 3681, 3518, 1758, 1676, 1448, 1376, 1326, 1209, 1148, 1092, 954, and 836 cm^{-1}; $\delta(CDCl_3)$ *inter alia* 0.035 (s), 0.061 (s) (together 6H,), 0.858 (s), 0.865 (s) (together 9H), 1.21 (d, *J* 6.2 Hz), 1.24 (d, *J* 6.2 Hz), (together 3H), 1.44 (3H, t, *J* 7.2 Hz), 2.31 (3H, s), 2.95 - 3.00 (1H, m), 3.25 - 3.64 (2H, m), 6.53 (s), 6.56 (s) ppm.

(g) Allyl 2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-oxoazetidinyl}-2-(tri-*n*-butylphosphoranylidene)acetate.

Allyl (2*R* and 2*S*)-2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-oxoazetidinyl}-2-

hydroxyacetate (crude from the above preparation) in dry THF (125 ml) under argon was cooled to -20°C and treated with 2,6-lutidine (1.98 ml), followed by thionyl chloride (1.24 ml). The mixture was stirred at -20°C for 30 minutes, and then allowed to warm to room temperature and filtered, washing the residue with THF (20 ml). The filtrate was evaporated *in vacuo*, toluene (70ml) was added and removed *in vacuo* and the residual oil was dried *in vacuo*. The oil was then taken up in 1,4-dioxan (40 ml) under an argon atmosphere, and treated with tri-*n*-butylphosphine (3.11 ml). The mixture was stirred for 1 h. 2,6-Lutidine (1.59 ml) was then added and the mixture was stirred for a further 30 minutes. The mixture was diluted with ethyl acetate , washed with water, then with brine, and dried ($MgSO_4$). After removal of the ethyl acetate the crude product was chromatographed on silica gel, eluting with ethyl acetate/hexane mixtures to give the phosphorane, which was used in the next stage.

(h) Allyl 2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-hydroxyethyl]-2-oxoazetidinyl}-2-(tri-*n*-butylphosphoranylidene)acetate.

The phosphorane prepared above was taken up in 1,4-dioxan (60 ml) and treated with 5M HCl (20 ml). After 1 h the mixture was carefully treated with *ca.* 40 ml saturated aqueous $NaHCO_3$, followed by solid $NaHCO_3$ until the pH was slightly alkaline. Saturated brine was added and the mixture was extracted twice with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel, eluting with ethyl acetate/hexane mixtures to give the hydroxy compound, (2.60 g), υ_{max} (CH_2Cl_2) 3454, 1741, 1667, 1606, 1448, 1403, 1379, 1155, 1087, 953, and 811 cm^{-1}.

(i) Allyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate

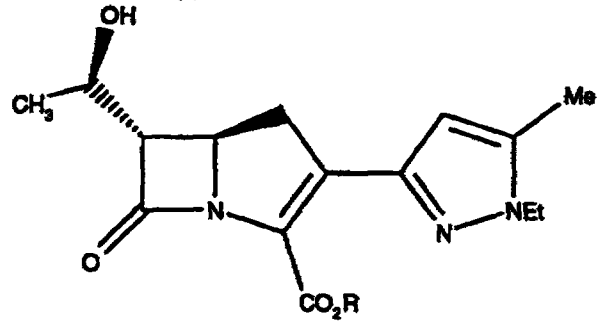
Allyl 2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-hydroxyethyl]-2-oxoazetidinyl}-2-(tri-*n*-butylphosphoranylidene)acetate (2.6 g), in toluene (120 ml) containing hydroquinone (20 mg) was heated under reflux in an argon atmosphere for 4 h, allowed to stand for 64 h, and then heated under reflux for a further 2 h. The mixture was cooled and then loaded onto a column (4.5 x 12 cm) of silica gel (particle size 0.040 -0.063 mm), eluting with ethyl acetate/hexane mixtures; 1:1; 6:4; 7:3; 8:2; 9:1 (250 ml of each), followed by ethyl acetate. This gave the carbapenem (436 mg); $\upsilon_{max}(CH_2Cl_2)$ 3604, 2976, 1774, 1716, 1600, 1546, 1311, 1189 cm^{-1}; λ_{max}(EtOH)/nm 321.5 (ε/$dm^3mol^{-1}cm^{-1}$ 14,856), $\delta(CDCl_3)$ 1.36 (d, *J* 6.3 Hz), 1.39 (t, *J* 7.3 Hz) (together 5H), 1.80 (1H, d, *J* 5.0 Hz), 2.28 (3H,s), 3.19 (1H, dd *J* 2.7 & 6.7 Hz), 3.28 (1H, dd, *J* 9.0 & 18.6 Hz), 3.60 (1H, dd, *J* 9.9 & 18.5 Hz), 4.08 (2H, q, *J* 7.3 Hz), 4.16 - 4.30 (2H, m), 4.68 - 4.90 (2H, m), 5.27 (1H, m, approx d, *J ca.* 12 Hz), 5.46 (m, approx d, *J ca.* 17 Hz), 5.93 - 6.08 (1H, m), 7.00 (1H, s) ppm; [Found *m/z* 345.1693. $C_{18}H_{23}N_3O_4$ requires *m/z* 345.1689].

(j) Sodium (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methyl-pyrazol-3-yl)carbapen-2-em-3-carboxylate

Allyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate (267 mg) in dichloromethane (3ml) and ethyl acetate (3 ml) under argon was treated with sodium 2-ethylhexanoate (183 mg), followed by triphenylphosphine (24 mg), followed by tetrakis(triphenylphosphine)palladium(0) (35 mg) and the mixture was stirred for 45 min. Diethyl ether (100ml) was then added, and after stirring for 90 minutes, the mixture was centrifuged. The residual solid was dried under a stream of argon, and then in a desiccator. The solid was then taken up in water containing sodium chloride and chromatographed on DIAION HP20SS resin, eluting with water, followed by water/THF mixtures; 1%, 2%, and 3%,THF. Fractions were monitored by HPLC, and those containing the product were combined, reduced in volume and freeze-dried to give sodium (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate as a solid (168 mg); υ_{max}(KBr) 1761, 1608, 1577, 1381, 1225 cm^{-1}; $\lambda_{max}(H_2O)$/nm 298 (ε/$dm^3mol^{-1}cm^{-1}$ 8,531); $\delta(D_2O)$ 1.26 (d, *J ca.* 6 Hz), 1.27 (d, *J ca.* 7 Hz) (together 5H), 2.23 (3H, *s*), 3.17 (2H, approx d, *J ca.* 9 Hz), 3.44 (1H, dd, *J* 2.9 & 6.0 Hz), 4.04 (2H, q, *J* 7.3 Hz), 4.15 - 4.25 (2H, m), 6.41 (1H, *s*) ppm.

Claims

1. A compound of formula (I):



(I)

wherein R is selected from the group consisting of isobutyryloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, and benzoyloxymethyl.

2. Isobutyryloxymethyl (5R, 6S)-2-[1-ethyl-5-methylpyrazol-3-yl]-6-[(1R)-1-hydroxyethyl]-carbapen-2-em-3-carboxylate.

3. (5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl (5R, 6S)-2-[1-ethyl-5-methylpyrazol-3-yl]-6-[(1R)-1-hydroxyethyl]-carbapen-2-em-3-carboxylate.

4. Benzoyloxymethyl (5R, 6S)-2-[1-ethyl-5-methylpyrazol-3-yl]-6-[(1R)-1-hydroxyethyl]-carbapen-2-em-3-carboxylate.

5. A pharmaceutical composition comprising a compound according to any one of the preceding claims together with a pharmaceutically acceptable carrier or excipient.

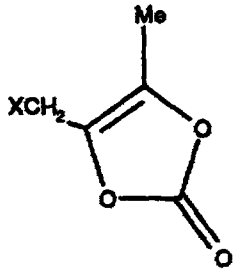
6. A method of treating bacterial infections in humans and animals which method comprises administering a therapeutically effective amount of a compound according to any one claims 1 to 4.

7. Use of a compound according to any one of claims 1 to 4 for the manufacture of a medicament for treating bacterial infection.

8. A process for the preparation of a compound of formula (I) as defined in claim 1 wherein R is isobutyryloxymethyl or benzoyloxymethyl, which process comprises treating a corresponding compound of formula (I), wherein R is an alkali

metal cation, with a compound of formula $XCH_2OCOCHMe_2$ or $XCH_2OCOC_6H_5$, wherein X is a leaving group.

9. A process for the preparation of a compound of formula (I) as defined in claim 1 wherein R is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, which process comprises treating a corresponding compound of formula (I), wherein R is an alkali metal cation, with a compound of formula:



wherein X is a leaving group.

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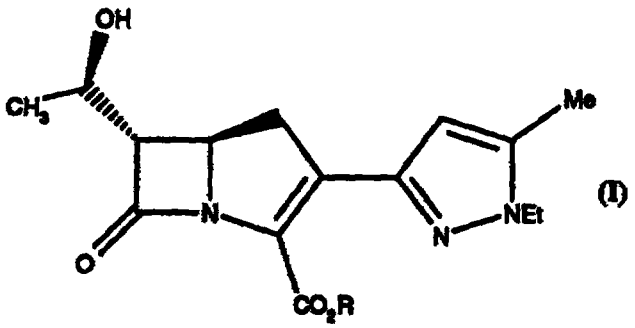
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(57) Abstract

A compound of formula (I), wherein R is selected from the group consisting of isobutyryloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, and benzoyloxymethyl, is useful in the treatment of bacterial infections.



(I)