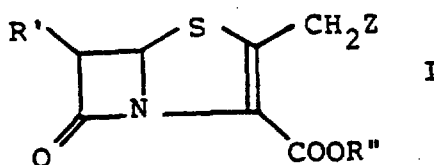


Esters of 2-carbamoyloxymethyl-6-hydroxyethyl-2-penem-3-carboxylic acid

The invention relates to penem esters, to a process for their preparation and to pharmaceutical compositions containing them. The penem esters are active against gram-positive, gram-negative, β -lactamase-producing and anaerobic bacteria, which makes them useful as therapeutic and prophylactic agents against bacterial infections in animals, including man and poultry.

British Patent Specification No. 2043639B describes penem derivatives of the general formula I:



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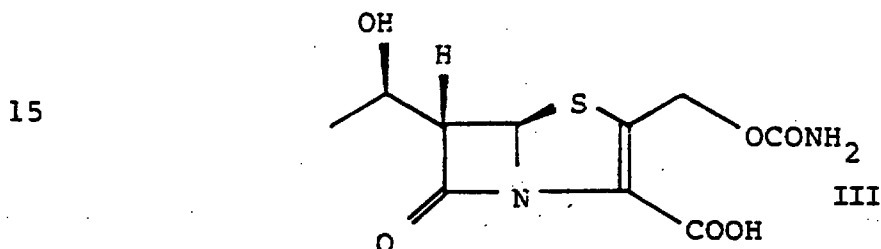
wherein R'' represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a 2,2,2-trichloroethyl, benzyl, acetyl, p-nitrobenzyl, p-methoxybenzyl, phenyl, p-nitrophenyl, benzhydryl, acetoxymethyl, pivaloyloxymethyl or phthalidyl group or a group of the formula $\text{CH}(\text{CH}_3).\text{OCOOC}_2\text{H}_5$ or $\text{CH}_2\text{NHCOR}_2$ wherein R_2 represents an alkyl group having from 1 to 4 carbon atoms or a cycloalkyl or aryl group, Z represents a carbamoyloxy or pyridinium group, or a group of the formula OCOR_1 or SR_3 wherein R_1 represents an alkyl group having from 1 to 4

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carbon atoms and R_3 represents an alkyl group having from 1 to 4 carbon atoms or a 5-methyl-1,3,4-thiadiazol-2-yl, 1-methyl-1H-tetrazol-5-yl, 1,2,3-triazol-5-yl or pyrazinyl group; and R' represents a hydroxyalkyl group having from 1 to 4 carbon atoms, the alcoholic function of the hydroxyalkyl group being free or protected by a p-nitrobenzyloxycarbonyl group. The 6-substituent may have the α - or β -configuration, 6 α -substitution being preferred.

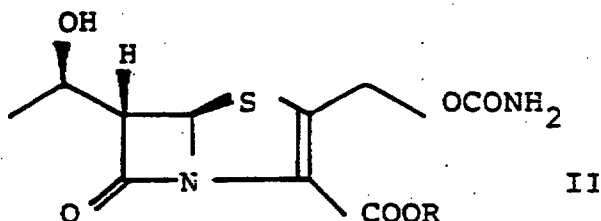
British Patent Specification No. 2097786 specifically describes (5R,6S)-2-carbamoyloxymethyl-6-(1R-hydroxyethyl)-2-penem-3-carboxylic acid and its sodium salt. This compound has the formula III.



In the fight against infectious diseases, the availability of new antibiotic compounds which are orally well adsorbed, and therefore allow a safe and suitable treatment of bacterial infections, is very important. The present invention is based on the discovery that some esters of the penem carboxylic acid III exhibit considerable bio-availability after oral administration in mice and rats, while the corresponding

penem carboxylic acid and its sodium salt are adsorbed only when given parenterally. This dramatic difference could not have been predicted from a knowledge of known penem derivatives. No orally adsorbed penem esters have been known hitherto. Indeed, in the broader field of β -lactam antibiotics (penems and cepems) it is known that the esters of acids which are not orally adsorbed are themselves not orally adsorbed.

Accordingly, the invention provides penem carboxylic esters of the general formula II:



in which R represents an acetoxymethyl, pivaloyloxymethyl, methoxymethyl, methoxyethoxymethyl, phthalidyl, α -ethoxycarbonyloxyethyl, acetamidomethyl or benzamidomethyl group.

The compounds of the formula II above may be prepared by esterification of the penem carboxylic acid III or a salt or reactive esterifying derivative thereof with a compound of the formula R-X wherein R is as defined above and X is halogen atom, a hydroxy group or a group of the formula OSO_2R_2 wherein R_2 is a lower alkyl or a substituted or unsubstituted aryl group. Suitable halogen atoms which X may represent are chlorine, bromine and iodine; preferred groups R_2 are methyl and p-tolyl groups.

The esterification may be performed for example, by reaction of the free acid III with the appropriate compound of the formula R-X in the presence of a base or by reaction of a salt of the free acid III, optionally generated in situ, with the appropriate compound of the formula R-X. Alternatively in place of the free acid III there may be used a suitable salt such as any of the lithium, sodium, potassium or magnesium salts, or salts with an organic base, preferably an aromatic base or an aliphatic tertiary amine, most preferably triethylamine, dimethylaminopyridine or pyridine. Other reactive esterifying derivatives of the acid III include the reactive intermediate formed by reaction in situ with a condensing agent such as a carbodiimide, for example N,N-diethyl- or N,N-dicyclohexylcarbodiimide, or a suitable carbonyl compound, for example N,N'-carbonyldimidazole.

The reaction is preferably carried out in an organic reaction medium, for example methylene dichloride, dimethylformamide, acetonitrile, an alcohol, benzene, dioxan or tetrahydrofuran, at a temperature of from 0° to 70°C.

Another method that may be used for preparing compounds of the formula II is that which is generally described and claimed in British Patent Specification No. 2111496A.

The present invention includes within its scope a pharmaceutical composition comprising a compound of the formula II above in admixture with a pharmaceutically acceptable diluent or carrier.

- 5 It has been stated that the penem esters of the formula II, although covered generically by the claims of British Patent No. 2043639, are considerably and unpredictably superior to the remaining derivatives claimed in that patent, as they are administrable per os.
- 10 To support this statement, Table 1 shows the plasma levels and the area under curve produced when the acetoxymethyl and pivaloyloxymethyl esters of (5R,6S)-2-carbamoyloxymethyl-6-(1R-hydroxyethyl)-2-penem-3-carboxylic acid (hereinafter referred to as FCE 22101)
- 15 were administered orally to mice and rats.

To obtain the results shown in Table 1, the two esters of FCE 22101 were each given orally in solution to mice and rats in an amount equivalent to provide 40 mg of FCE 22101 per kg of body weight after the expected

20 in vivo hydrolysis.

Periodic blood samples were taken from the animals and each assayed for FCE 22101 content by a standard bio-assay technique.

TABLE 1

Species	Ester of FCE 22101	Mean plasma concentration ($\mu\text{g/ml}$) of FCE 22101 minutes after administration										Area under curve $\mu\text{g min.}/\text{ml}$	Peak plasma concentration ($\mu\text{g/ml}$)
		2	4	5	6	10	20	30	45				
Mouse	Acetoxymethyl	13.5	21	-	19.5	11.2	3.5	1.12	0.78			253.8	21
	Pivaloyloxymethyl	-	-	16.0	-	10.1	2.4	1	0.45			182.7	16.0
		5	10	15	20	30	45	60	75				
Rat	Acetoxymethyl	5.8	10	-	4.1	6.5	2.7	1.8	1.2			288.36	10
	Pivaloyloxymethyl	3.5	4.7	4.2	2.7	2.5	1.9	2.1	1.4			155.5	4.7

The data in Table 1 demonstrate that the esters of FCE 22101 are orally adsorbed and then hydrolysed in blood to give the active drug. This is a totally unexpected and beneficial result, as the penem carboxylic acids and their salts described in the above cited British Patent specifications are not adsorbed as such in the stomach and intestinal tract.

Corresponding tests carried out on mice with the acetoxymethyl and pivaloyloxymethyl esters of (5R,6S)-2-acetoxymethyl-6-(1R-hydroxymethyl)-2-penem-3-carboxylic acid gave area under curve values of 119.3 and 45.7 $\mu\text{g min/ml}$ respectively and peak plasma concentrations of 12.2 and 3.53 $\mu\text{g/ml}$ respectively. These values are from a quarter to a half of those of the compounds according to the invention given in Table 1.

The acetoxymethyl ester of FCE 22101 is adsorbed by the oral route at a rate of 56%, as calculated by the area under curve ratio for administration os/iv at a dose of 20 mg/kg in mice. Corresponding values for the remaining esters claimed in British Patent No. 2043639 are from 10-20%, which is too low for oral administration.

The therapeutic efficacy in mice, tested after oral administration, confirmed the bioavailability of the antibiotic by oral route, with ED_{50} comparable to FCE 22101 given subcutaneously as reported in Table 2.

T A B L E 2

Compound	Administration Route	Infection i.p.	ED_{50} mg/kg
FCE 22101	s.c.	Staf.aureus Smith	1
Acetoxymethyl ester of FCE 22101	per os	" "	3.2
Pivaloyloxymethyl ester of FCE 22	per os	" "	1.7

Owing to their high antibacterial activity either in animals or in humans against both Gram-positive and Gram-negative bacteria the compounds of the present invention are useful in the treatment of the infections caused by said microorganisms, such as respiratory tract infections, for example bronchitis, bronchopneumonia, pleurisy; hepatobiliary and abdominal infections for example septicemia; urinary tract infections for

example pyelonephritis, cystitis; obstretrical and gynecological infections, for instance, cervicitis, endometritis; ear, nose and throat infections, for instance, otitis, sinusitis, parotitis. The toxicity of the compounds of the invention is quite negligible and therefore they can be safely used in therapy.

The compounds of the invention are useful in the treatment of bacterial infections in mammals, including man. They are administered orally and may be in capsule form, or as tablets, powders, liquid solutions, suspensions, elixirs, or the like. The compounds may be used alone or in combination with other active ingredients. They may be used in compositions including one or more pharmaceutically acceptable carriers or diluents as well as other ingredients such as stabilizers, binders, antioxidants, preservatives, lubricating agents, suspending agents, viscosity agents and/or flavouring.

Acceptable carriers and diluents are, for example, water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils and cellulose.

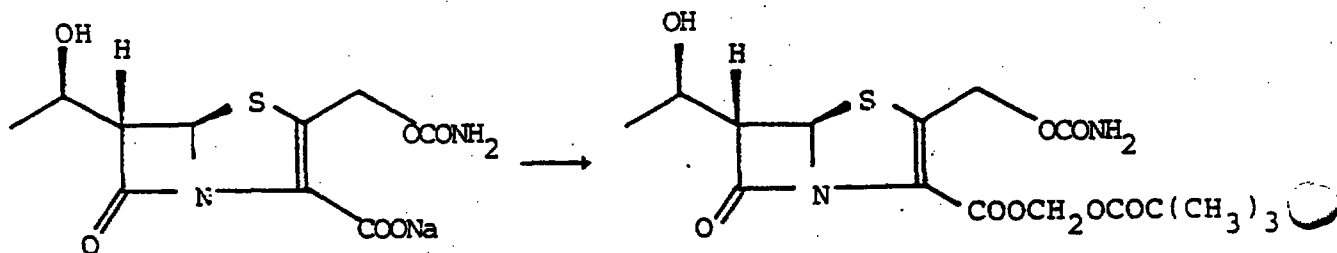
Daily doses in the range of about 1 to about 100 mg per kg of body weight may be used, in various animal species, the exact dose depending on the age, weight and condition of the subject to be treated and on the frequency of administration. The compounds may be administered, for example to adult humans, in an amount ranging from about 100 mg to about 300 mg pro dose, preferably about 200 mg pro dose, 1-4 times a day. They are also useful as nutritional supplements in animal feeds.

The following examples illustrate the invention.

EXAMPLE 1

Pivaloyloxymethyl (5R,6S)-2-carbamoyloxymethyl-6-(1R-hydroxyethyl)-2-penem-3-carboxylate.

5 II:R= CH₂O.COC(CH₃)₃



775 mg of sodium (5R,6S)-2-carbamoyloxymethyl-6-(1R-hydroxyethyl)-2-penem-3-carboxylate were dissolved in 15 ml of dimethylformamide and treated with 50 mg of dimethylaminopyridine and 1.15 ml of pivaloyloxymethyl chloride at 40°C for 4 hours. The reaction mixture was diluted with ethyl acetate, washed with water and dried over anhydrous sodium sulphate. The solvent was evaporated off.

The residue consisted of 480 mg of the title compound in pure form.

U.V. (EtOH 95%) : λ max 325 nm (ϵ 7000)

15 I.R. (CH₂Cl₂)_v max : 3600; 1795; 1725 cm⁻¹

P.M.R. (200 MHz, CDCl₃), δ (ppm):

1.21 (s, 9H, (CH₃)₃)

1.33 (d, J=6.3Hz, 3H, CHCH₃)

3.75 (dd, J=1.5, 6.4 Hz, 1H, H-6)

20 4.23 (m, 1H, CHOH)

4.76 (bs, 2H, CONH₂)

5.08, 5.42 (two d, J=15.8Hz, CH₂OCONH₂)

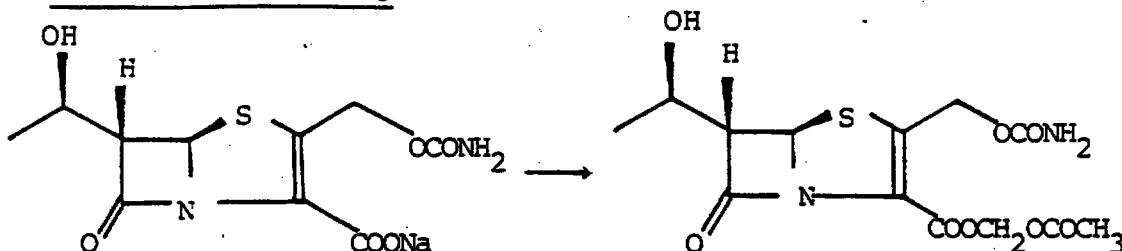
5.62 (d, J=1.5Hz, 1H, H-5)

5.81, 5.91 (two d, J=5.5 Hz, OCH₂OCOO(CH₃)₃)

EXAMPLE 2

Acetoxymethyl (5R,6S)-2-carbamoyloxymethyl-6-(1R-
-hydroxyethyl)-2-penem-3-carboxylate.

II: R= $-\text{CH}_2\text{O.COCH}_3$



- 5 1.3 g of sodium (5R,6S)-2-carbamoyloxymethyl-6-(1R-
 -hydroxyethyl)-2-penem-3-carboxylate were dissolved in
 30 ml of anhydrous dimethylformamide and treated with
 0.65 g of acetoxymethyl bromide at room temperature
 for 3 hours.
- 10 The reaction mixture was then diluted with ethyl acetate,
 washed with water, dried over anhydrous sodium sulphate
 and evaporated to dryness.

The obtained crude compound was crystallized from
 chloroform:cyclohexane and then from hot chloroform.

- 15 m.p. 127°C (from CHCl_3);
 $[\alpha]_{\text{D}}^{20} = +137^{\circ}$ (1% in acetone)
 I.R. (KBr): ν_{max} 3500-3300, 1800, 1760, 1720 and 1590 cm^{-1} .
 U.V.: λ_{max} (EtOH 95%) 327 nm (ϵ 7800)
 P.M.R. (200 MHz, acetone d_6), δ (ppm) :
 20 1.26 (d, $J=6.0\text{ Hz}$, 3H, CH_3CH)
 2.06 (s, 3H, $-\text{C}-\text{CH}_3$)
 3.78 (s, 1H, OH)
 3.80 (dd, $J=1.7$ and 6.4 Hz , 1H, H-6)
 4.14 (m, 1H, CH_3CH)

5.08, 5.34 (two d, $J=16.0$ Hz, 2H, $\text{CH}_2\text{OCONH}_2$)

5.69 (d, $J=1.7$ Hz, 1H, H-5)

5.80, 5.86 (two d, $J=5.8$ Hz, 2H, COOCH_2OCO)

6.10 (bs, 2H, NH_2)

5 EXAMPLE 3

Methoxymethyl (5R,6S)-2-carbamoyloxymethyl-6-(1R-
-hydroxyethyl)-2-penem-3-carboxylate.

II: R= CH_2OCH_3

Operating as described in Example 2, but employing
10 methoxymethyl-bromide in place of acetoxymethyl-bromide,
the title compound was obtained in 65% yield.

I.R. (CH_2Cl_2) $\nu_{\text{max}} = 3610, 1795, 1720 \text{ cm}^{-1}$.

EXAMPLE 4

Methoxyethoxymethyl (5R,6S)-2-carbamoyloxymethyl-6-(1R-
15 -hydroxyethyl)-2-penem-3-carboxylate.

II : R= $\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$

Operating as described in Example 1, but employing
methoxyethoxymethyl-chloride in place of
pivaloyloxymethyl-chloride, the title compound was

obtained in 58% yield.

I.R. (CH_2Cl_2) $\nu_{\text{max}} = 3590, 1795, 1720 \text{ cm}^{-1}$.

EXAMPLE 5

Phthalidyl (5R,6S)-2-carbamoyloxymethyl-6-(1R-
5 -hydroxyethyl)-2-penem-3-carboxylate.

II : R=phthalidyl

Operating as described in Example 2, but employing 3-bromophthalide in place of acetoxymethyl bromide, the title compound was obtained in 62% yield.

10 I.R. (CH_2Cl_2) $\nu_{\text{max}} = 3600, 1795, 1750, 1720 \text{ cm}^{-1}$.

EXAMPLE 6

α -Ethoxycarbonyloxyethyl (5R,6S)-2-carbamoyloxymethyl-
-6-(1R-hydroxyethyl)-2-penem-3-carboxylate.

II : R=CH(CH₃)O.CO.OC₂H₅

15 Operating as described in Example 1, but employing chlorodiethyl carbonate in place of pivaloyloxymethyl chloride, the title compound was obtained in 40% yield.

I.R. (CH_2Cl_2) $\nu_{\text{max}} = 3600, 1795, 1720, 1420 \text{ cm}^{-1}$.

20 EXAMPLE 7

Acetamidomethyl (5R,6S)-2-carbamoyloxymethyl-6-(1R-
-hydroxyethyl)-2-penem-3-carboxylate.

II : R= CH₂NHCOCH₃

Operating as described in Example 1, but employing
25 acetamidomethyl chloride in place of

pivaloyloxymethyl chloride, the title compound was obtained in 45% yield.

I.R. (CH_2Cl_2) $\nu_{\text{max}} = 3600, 1795, 1720, 1690 \text{ cm}^{-1}$.

EXAMPLE 8

Benzamidomethyl (5R,6S)-2-carbamoyloxymethyl-6-(1R-hydroxyethyl)-2-penam-3-carboxylate.

II : R = $-\text{CH}_2-\text{NH}-\text{COC}_6\text{H}_5$

Operating as described in Example 7, but employing benzamidomethyl chloride in place of acetamidomethyl chloride, the title compound was obtained in 43% yield.

I.R. (CH_2Cl_2) $\nu_{\text{max}} = 3600, 1795, 1715, 1690 \text{ cm}^{-1}$.



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CLAIMS:

1. A penem carboxylic ester having the general formula
II as defined herein.
2. Acetoxymethyl (5R,6S)-2-carbamoyloxymethyl-6-(1R-
5 -hydroxyethyl)-2-penem-3-carboxylate.
3. Pivaloyloxymethyl (5R,6S)-2-carbamoyloxymethyl-6-
-(1R-hydroxyethyl)-2-penem-3-carboxylate.
4. A pharmaceutical composition comprising a penem
carboxylic ester according to any preceding claim
10 in admixture with a pharmaceutically acceptable diluent
or carrier.
5. A process for the preparation of a penem carboxylic
ester according to claim 1, the process comprising
esterifying (5R,6S)-2-carbamoyloxymethyl-6-(1R-hydroxy-
15 ethyl)-2-penem-3-carboxylic acid or a salt or reactive
esterifying derivative thereof with a compound having
the general formula RX as defined herein.
6. A process according to claim 5 carried out in the
presence of a base in an organic reaction medium at a
20 temperature of from 0° to 70°C.
7. A process according to claim 6 in which organic
reaction medium is methylene dichloride, dimethyl-

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-15-

formamide, acetonitrile, an alcohol, benzene,
dioxan or tetrahydrofuran.

8. A process for the preparation of a penem
carboxylic ester according to claim 1, the process
5 being substantially as described in any of the
Examples.
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