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Antibacterial agents and β-lactamase inhibitors

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(58) Field of search
C2C

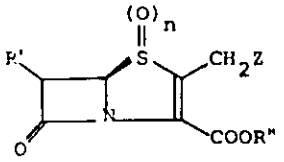
SPECIFICATION

Antibacterial agents and β-lactamase inhibitors

Description

The invention relates to processes for the preparation of β-lactam containing compounds, to certain of the β-lactam containing compounds and to compositions containing them.

More particularly, the invention relates to penem-carboxylic acids and esters of the general formula (1)



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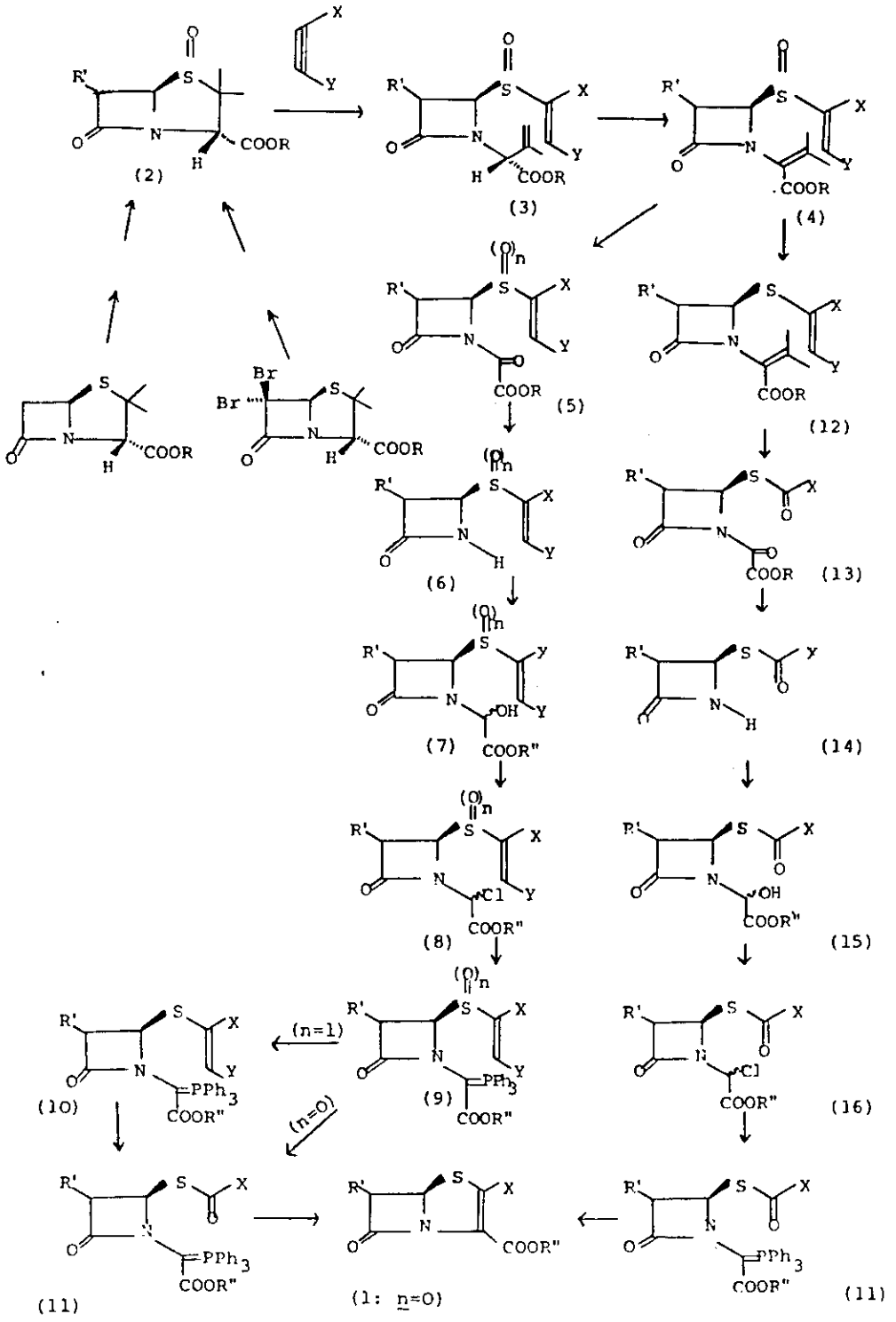
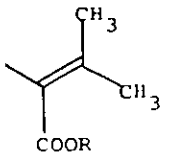
wherein n is 0 or 1, R″ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a 2,2,2-trichloroethyl, benzyl, acetonyl, *p*.nitrobenzyl, *p*.methoxybenzyl, phenyl, *p*.nitrophenyl, benzhydryl, acetoxymethyl, pivaloyloxymethyl or phthalidyl group or a group of the formula $-CH(CH_3).OCOOC_2H_5$ or $-CH_2NHCOR_2$ wherein R_2 represents an alkyl group having from 1 to 4 carbon atoms or a cycloalkyl or aryl group; Z represents a hydroxy, amino, carbamoyloxy, mercapto or pyridinium group, or a group of the formula OR_1, $OCOR_1$ or SR_3 wherein R_1 represents an alkyl group having from 1 to 4 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-1 H-tetrazol-5-yl, 1,2,3-triazol-5-yl or pyrazinyl group; R′ represents a hydrogen atom or an alkyl, alkoxy or hydroxyalkyl group, each of which has 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-configuraion. 6 α-substitution is preferred.

The invention provides a process for the preparation of compounds of the general formula (1) in which *n*, R′ and R″ are as above defined and Z has any of the meanings ascribed to it above except a mercapto or pyridinium group of a group of the formula SR_3. The process is illustrated by the following reaction scheme, in which R′, R″, and *n* have the meanings ascribed to them above, R represents an alkyl group, X represents a group of the formula CH_2Z' in which Z′ has any of the meanings ascribed to Z above except a mercapto or pyridinium group or a group of the formula SR_3, Y represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a cyano or alkoxycarbonyl group or a group of the formula CH_2Z' in which Z′ has the meaning ascribed to its above, and Ph represents a phenyl group.



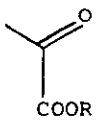
The process comprises condensing, in an inert solvent at elevated temperature, a penicillanic acid S-oxide ester of the general formula (2) with an acetylenic compound of the general formula XC ≡ CY, isomerising the resultant compound of the general formula (3) in basic conditions, converting the resultant azetidinone derivative of the general formula (4) into one of the general formula (11) by the steps of

(a) ozonolysis of the 1-substituent of the formula



in solution at reduced temperature,

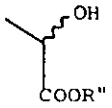
(b) removal of the 1-substituent of the formula



resulting from step (a) by mild alkaline hydrolysis or by the action of silica gel,

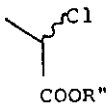
(c) condensation of the 1-unsubstituted azetidinone resulting from step (b) with a glyoxylate of the formula CHO.COOR'' by refluxing in a solvent,

(d) chlorination of the 1-substituent of the formula

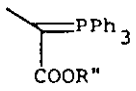


introduced in step (c) by the action of a chlorinating agent,

(e) conversation of the 1-substituent of the formula



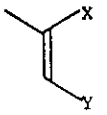
introduced in step (d) into one of the formula



by reaction with triphenylphosphine,

(f) reduction of the 4β-(substituted vinylsulphinyl) group by the action of a reducing agent, and

(g) ozonolysis of the double bond of the group of the formula



in solution at reduced temperature, the steps being carried out in the order (a), (b), (c), (d), (e), (f), (g) or (a), (f), (b), (c), (d), (e), (g) or (f), (a) and (g) simultaneously, (b), (c), (d), (e), step (f) being carried out in acidic conditions if carried out after step (e), and cyclising the compound of the general formula (11) by heating it in an inert solvent at from 50°C to 140°C to obtain a compound of the general formula (1) in which *n* is 0, and optionally converting that compound to one of the general formula (1) in which *n* is 1 by oxidation.

The preparation of the remaining compounds of the general formula (1), that is those in which *n*, R' and R'' are as above defined and Z represents a mercapto or pyridinium group or a group of the formula SR_3 wherein R_3 is as above defined, is carried out according to the above process with the additional step of converting the substituent X into a substituent of the formula CH_2Z wherein Z is as defined in this sentence. The additional step may be carried out at any stage in the above process after the condensation of the penicillanic acid S-oxide ester (2) with the acetylenic compound XC ≡ CY, and is necessary because of the difficulty of condensing the penicillanic acid S-oxide ester (2) directly with an acetylenic compound $HSCH_2-C\equiv CY$, $R_3SCH_2-C=CY$ or $PyCH_2C=CY$ in which Py represents a pyridinium ion. This process is also within the scope of the invention.

The starting materials of the general formula (2) in which R' represents a hydrogen atom may be prepared from (5R)-6-aminopenicillanic acid following known procedures (see CIGNARELLA et al., Journal of Organic Chemistry, *27*, 2668 and EVRARD et al., Nature, *201*, 1124).

When R' represents a C_1-C_4 alkyl or hydroxyalkyl group, it can be introduced according to the procedure of Di Ninno et al., Journal or Organic Chemistry *42*, 2960 (1977). When R' represents a C_1-C_4 alkoxy group, it may be introduced to the procedures of Hauser et al., Helv. Chem. Acta, *50*, 1327 (1967) and Giddings et al., Tetrahedron Letters, *11*, 995 (1978). Alternatively compounds of general formula (2) in which R' represents a hydrogen atom can be converted to compounds of the general formula (2) in which R' represents a C_1-C_4

alkyl or hydroxyalkyl group by introducing the substituent into the 6-position using a strong base, as illustrated in the following Examples. Compounds of the general formula (2) in which R' represents a C_1-C_4 alkyl or hydroxyalkyl group can also be prepared starting from a suitable ester of penicillanic acid S-oxide, as illustrated in th following Examples. The substitution at the 6-position is stereospecifically directed to the 6α-derivatives.

The reaction sequence (a), (b), (c), (d), (e), (f), (g) is possible when Y is not a strong electron withdrawing group. Then the compound (6, n=1) is surprisingly stable.

The reduction step (f) may be carried out using phosphorus tribromide or sodium iodide in acetyl chloride as reducing agent.

When R' represents a hydroxyalkyl group in the desired compound of the general formula (1), the reaction sequence is preferably carried out with the alcoholic function protected.

Compounds of the general formula (1) in which R" represents a hydrogen atom can be obtained by hydrolysis or hydrogenolysis of the corresponding esterified compounds.

Compounds of the general formula (1) in which n is 1 are readily prepared starting from compounds of the general formula (1) in which n is 0 following known oxidation processes. Peracids can be advantageously used; *m*.chloroperbenzoic acid and peracetic acid are preferred.

The compounds of the general formula (1) as above defined possess a wide spectrum of an antibacterial activity as well as a β-lactamase inhibiting activity. It should be pointed out that the stereochemistry at C_5 of the compounds of the general formula (1) as above defined, as well as that of all the intermediates of their preparation, is the same as in naturally occurring penicillins and cephalosporins.

Certain of the compounds of the general formula (1) as above defined themselves form part of the invention. They are those in which n and R" are as above defined, Z represents a carbamoyloxy or pyridinium group or a group of the formula $OCOR_1$ or SR_3 wherein R_1 and R_3 are as above defind 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. Preferably R' represents a 1-hydroxyethyl or 1-(*p*-nitrobenzyloxycarbonyloxy)-ethyl group. Pharmaceutically acceptable salts of these penem-carboxylic acids, such as sodium, potassium, benzathin and procaine salts and salts of other bases conventionally used for salt formation with penicillins and cephalosporins are also included within the scope of the invention.

The compounds of the general formulae (3), (4), (9) and (14) are claimed in our Patent Applications Nos. 8224128, 8224129 and 2104893, divided herefrom.

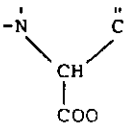
The following Examples illustrate the invention.

EXAMPLE 1

4β-(1-acetoxymethyl-3-acetoxy-1-propenylsulphinyl)-1-(1-methoxycarbonyl-2-methyl-allyl)-azetidin-2-one

(3): R=CH_3; R'=H, X=Y=$CH_2O.CO.CH_3$

A solution of 2.0 g of methyl penicillinate S-oxide and 2.8 g of butyndiol diacetate in 40 ml of toluene was refluxed for 24 hours. 1.4 g of the title compound was obtained after purification by column chromatography on silica gel eluting with 96:4 by volume dichloromethane:ethyl acetate.

PMR ($CDCl_3$): 2.03δ (s, CH_3-C"-), 2.15 and 2.20 δ (two s, 2 CH_3CO),
2.88 δ (dd, Jgem = 14Hz, Jvic cis = 4 Hz, C-3-Hα),
3.38 δ (dd, Jgem = 14Hz, Jvic trans = 2Hz, C-3-Hβ),
3.83 δ (s, CH_3O),
4.88 δ (d, Jvic = 6Hz, CH_2-C=)
(H)
4.92 δ (broad s, CH_2-C=),
4.93-5.33 δ (m, =CH_2 and 
5.32 δ (dd, Jvic = 4 and 2Hz, C-4-H),
6.47 δ (t, Jvic = 6Hz, =C-C(H_2))
H

EXAMPLE 2

4β-(1-acetoxymethyl-3-acetoxy-1-propenylsulphinyl)-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-azetidin-2-one

(4): R=CH_3, R' =H, X=Y=$CH_2O.CO.CH_3$

1.7 g of the compound prepared in Example 1 were dissolved in 80 ml of dichloromethane. 0.5 ml of triethylamine were added and the solution was left for a few hours at room temperature. After evaporating

off the solvent, the title compound was obtained in pure form in quantitative yield.

PMR ($CDCl_3$): 2.13 (9H) and 2.32 (3H) δ (two s, 2 CH_3CO and 2 CH_3-C=), 2.92 δ (dd, Jgem=15Hz, Jvic cis = 5Hz, C-3-Hα), 3.38 δ (dd, Jgem=15Hz, Jvic trans = 2.5 Hz, C-3-Hβ), 3.82 δ (s, CH_3O) 4.88 δ (d, Jvic=6.5 Hz, CH_2-C=),

(H)

4.92 δ (s, CH_2-C=), 5.15 δ (dd, Jvic = 5 and 2.5Hz, C-4-H), 6.50 δ (t, Jvic 6.5Hz, =C-(H_2))

H

EXAMPLE 3

4β-(1-acetoxymethyl-3-acetoxy-1-propenylsulphinyl)-1-methoxyoxalyl-azetidin-2-one

(5): R=CH_3, R'=H, X=Y=$CH_2O.CO.CH_3$, n=1

2.0 g of the compound prepared in Example 2 were dissolved in 150 ml of dichloromethane and, after cooling to -78°C, a flow of ozone in oxygen was bubbled through the solution until a slightly blue colour appeared. The solution was raised to room temperature, shaken with an aqueous solution of sodium pyrosulphite and dried over anhydrous sodium sulphate. The resulting organic phase gave, after evaporation "in vacuo" of the solvent therefrom, 1.4 g of the title compound.

PMR ($CDCl_3$): 2.05 and 2.08 δ (two s, 2CH_3CO), 3.03 δ (dd, Jgem=17Hz, Jvic cis = 5.5Hz, C-3-Hα), 3.50 δ (dd, Jgem = 17Hz, Jvic trans = 3Hz, C-3-Hβ), 3.90 δ (s, CH_3O), 4.82 (d, Jvic = 6.5Hz, CH_2-C=),

(H)

4.90 δ (s, CH_2-C=), 5.32 δ (dd, Jvic = 5.5 and 3Hz, C-4-H), 6.47 δ (t, Jvic = 6.5Hz, =C-C(H_2).

H

IR (CH_2Cl_2): 1830 cm^{-1} β-lactam C=O
1750 cm^{-1} esters C=O
1715 cm^{-1} amide C=O

EXAMPLE 4

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-1-methoxy-oxalyl-azetidin-2-one

(5): R=CH_3, R'=H, X=Y=$CH_2O.CO.CH_3$, n=O

A solution of 1.4 g of the compound prepared in Example 3 in 10 ml of anhydrous dimethylformamide was cooled to -25°C and 0.9 ml of phosphorus tribromide were added. After 10 minutes the mixture was diluted with ethyl acetate and washed twice with a saturated solution of sodium bicarbonate. After drying the solution over anhydrous sodium sulphate and evaporating the solvent therefrom, 0.9 g of the title compound were obtained.

PMR ($CDCl_3$): 2.07 δ (s, 2CH_3CO), 3.17 δ (dd, Jgem = 19Hz, Jvic trans = 3.5Hz, C-3-Hβ), 3.65 δ (dd, Jgem = 19Hz, Jvic cis = 5Hz, C-3-Hα), 3.90 δ (s, CH_3O), 4.73 δ (d, Jvic =6.5 Hz, CH_2-C=),

(H)

4.88 δ (broad s, CH_2-C=), 5.52 δ (dd, Jvic = 5 and 3.5 Hz, C-4-H), 6.25 δ (t, Jvic = 6.5Hz, =C-C(H_2).

H

IR ($CHCl_3$): 1815 cm^{-1} β-lactam C=O
1745 cm^{-1} esters C=O
1710 cm^{-1} amide C=O

EXAMPLE 5

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-azetidin-2-one

(6): R'=H, X=Y=$CH_2O.CO.CH_3$, n=O

1.5 g of the compound prepared in Example 4 were dissolved in 100 ml of methanol and a few grams of silica gel were added under stirring. After one hour the silica gel was filtered off and the methanolic solution evaporated to give 0.8 g of the title compound.

PMR ($CDCl_3$): 2.25 δ (s, $2CH_3CO$), 2.98 δ (dd, Jgem = 15Hz, Jvic trans = 2Hz, C-3-Hβ), 3.48 δ (dd, Jgem = 15Hz, Jvic cis = 4.5Hz, c-3-Hα), 4.78 δ (d, Jvic = 7Hz, CH_2-C(H)=),

4.87 (s, CH_2-C=), 5.03 δ (dd, Jvic = 4.5 and 2Hz, C-4-H), 6.02 δ (t, Jvic = 7Hz, =C-C(H$_2$)),

7.13 δ (broad, N-H).

IR ($CHCl_3$): 1770 cm^{-1} β-lactam C=O
1740cm^{-1} esters C=O.

EXAMPLE 6

4β-(1-acetoxymethyl-3-acetoxy-1-propenylsulphinyl)-azetidin-2-one.

(6): R'=H, X=Y=$CH_2O.CO.CH_3$, n=1

0.800 g of the compound prepared in Example 3 were dissolved in 80 ml of methanol and a few grams of silica gel were added under stirring. After one hour the silica gel was filtered off and the solvent was evaporated off. 0.5 g of the title compound were obtained.

PMR ($CDCl_3$): 2.13 δ (s, $2CH_3CO$), 3.0-3.3 δ (m, 2 protons at C-3), 4.70 δ (m, C-4-H), 4.88 δ (d, Jvic = 6Hz, CH_2-C(H)=),

4.93 δ (s, CH_2-C=), 6.53 δ (t, Jvic = 6Hz, =C-C(H$_2$)),

7.23 δ (s, NH).

IR ($CHCl_3$): 1790 cm^{-1} β-lactam C=O
1745 cm^{-1} esters C=O

EXAMPLE 7

4β-acetylglycolloylthio-1-acetoxymethoxyoxalyl-azetidin-2-one.

(13): R=X=$CH_3O.CO.CH_2$, R'=H

0.8 g of 4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-1-(1-acetoxymethoxycarbonyl-2-methyl-1-propenyl)-azetidin-2-one were dissolved in 80 ml of dichloromethane and cooled to -78°C. A flow of ozone in oxygen was bubbled through the solution until a blue colour appeared. The solution, after shaking with an aqueous solution of sodium pyrosulphite, was dried over anhydrous sodium sulphate. The solvent was removed by evaporation to give 0.45 g of the title compound.

PMR ($CDCl_3$): 2.10 and 2.13 δ (two s, $2CH_3CO$), 3.20 δ (dd, Jgem = 17Hz, Jvic trans = 3.5Hz, C-3-Hβ), 3.77 δ (dd, Jgem = 17Hz, Jvic cis = 5.5Hz, C-3-Hα), 4.73 δ (s, -CO-CH_2-OCO-), 5.73 δ (dd, Jvic=5.5 and 3.5Hz, C-4-H), 5.87 δ (s, COO-CH_2-OCO).

EXAMPLE 8

4β-acetylglycolloylthio-azetidin-2-one

(14): R'=H, X=$CH_2O.CO.CH_3$

0.6 g of 4β-acetylglycolloylthio-1-methoxyoxalyl-azetidin-2-one were dissolved in 100 ml of methanol and a few grams of silica gel were added under stirring. After one hour the silica gel was filtered off and the resulting solution gave, after evaporation of the solvent therefrom, 0.35 g of the title compound.

PMR ($CDCl_3$): 2.20 δ (s, CH_3CO), 3.03 δ (dd, Jgem = 16Hz, Jvic trans = 2.5Hz, C-3-Hβ), 3.50 δ (dd, Jgem = 16Hz, Jvic cis = 4.5Hz, C-3-Hα), 4.77 δ (s, -CO-CH_2-OCO-), 5.32 δ (dd, Jvic = 4.5 and 2.5Hz, C-4-H), 6.40 δ (broad s, NH).

EXAMPLE 9

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-1-(1-acetoxymethoxycarbonyl-1-hydroxymethyl)-azetidin-2-one.

(7): R'=H, R''=X=Y=$CH_2O.CO.CH_3$, n=O

0.7 g of acetoxymethyl glyoxylate (freshly prepared by ozonolysis of diacetoxymethyl fumarate) were dissolved in 30 ml of benzene and the resulting solution was refluxed for 20 minutes through a Dean-Stark apparatus. After cooling to 50°-60°C, 0.7 g of the compound prepared in Example 5 dissolved in 10 ml of benzene were added and the resulting solution was refluxed for 2 hours. The title compound was obtained in almost quantitative yield and can be used as crude mixture for the next step. A pure sample was obtained by

preparative TLC, for analytical purposes.

PMR ($CDCl_3$): 2.07 δ (s, $3CH_3CO$), 2.97 δ (dd, Jgem = 18Hz, Jvic trans = 2Hz, C-3-Hβ), 3.40 δ (dd, Jgem = 18Hz, Jvic cis = 4Hz, C-3-Hα), 4.70 δ (d, Jvic = 6Hz, CH_2-C=),

4.77 δ (s, CH_2-C=), 5.0-5.4 δ (m, C-4-H) and -N-CH-COO-),

5.77 δ (s, -COO-CH_2-OCO-), 6.12 δ (t, Jvic = 6Hz, =C-C(H_2)).

EXAMPLE 10

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-1-(1-acetoxy-methoxycarbonyl-1-chloromethyl)-azetidin-2-one.

(8): R'=H, R''=X=Y=$CH_2O.CO.CH_3$, *n*=O

0.6 g of the compound prepared in Example 9 dissolved in 15 ml of tetrahydrofuran were cooled to 0°C. 0.115 ml of pyridine and 0.104 ml of thionyl chloride were added and the mixture was left under stirring for 10 minutes. The insoluble material was filtered off and the solution was evaporated "in vacuo" at room temperature to give the title compound in high yield. A sample was purified on preparative TLC for analytical purposes, but the crude mixture can be used without purification for the next step.

PMR ($CDCl_3$): 2.14 δ (s, $3CH_3CO$), 3.10 δ (dd, Jgem = 15.5 Hz, Jvic trans = 2Hz, C-3-Hβ), 3.55 δ (dd, Jgem = 15.5 Hz, Jvic cis = 5Hz, C-3-Hα), 4.77 δ (d, Jvic=6.5Hz, CH_2-C=),

4.83 δ (s, CH_2-C=), 5.4-5.9 δ (m, C-4-H) and -N-CHCl-COO-), 5.88 δ (s, -COO-CH_2-OCO-), 6.13 δ (t, Jvic = 6.5Hz, =C-C(H_2).

EXAMPLE 11

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-1-(1-acetoxymethoxycarbonyl-1-triphenylphosphoranylidenemethyl)-azetidin-2-one

(9): R'=H, R''=X=Y=$CH_2O.CO.CH_3$, *n*=O

A solution of 0.430 g of the compound prepared in Example 10 in 5 ml of tetrahydrofuran and 5 ml of dioxan containing 0.520 g of triphenylphosphine and 0.08 ml of pyridine was stirred overnight at 50°C. The resulting phosphorane was purified by column chromatography on silica gel eluting with 70:30 by volume dichloromethane:ethyl acetate. 0.400 g of the title compound was obtained.

PMR ($CDCl_3$): 2.05 δ (s, $3CH_3CO$), 4.70 δ (d, Jvic = 6.5Hz, CH_2-C=),

4.73 δ (s, CH_2-C=), 5.77 δ (s, -COO-CH_2-OCO-), 5.90 δ (t, Jvic = 6.5Hz, =C-C(H_2)),

7.1-8.0 δ (m, $3C_6H_5$).

EXAMPLE 12

4β-acetylglycolloylthio-1-(1-acetoxymethoxycarbonyl-1-triphenylphosphoranylidenemethyl)-azetidin-2-one.

(11): R'=H, R''=X=$CH_2O.CO.CH_3$

0.7 g of the compound prepared in Example 11 were dissolved in 40 ml of dichloromethane and, after cooling to -20°C, 50 ml of a 10% solution of trifluoroacetic acid in dichloromethane were added. After a few minutes, a flow of ozone in oxygen was bubbled through the solution at -20°C until a slightly blue colour appeared. At this point, the reaction was stopped and a few drops of trimethylphosphite were added. The organic solution was washed with a saturated solution of sodium bicarbonate and dried over anhydrous sodium sulphate. The solvent was evaporated off to give 0.550 g of the title compound.

PMR ($CDCl_3$): 2.10 and 2.15 δ (two d, $2CH_3CO$), 4.72 δ (s, -CO-CH_2-OCO-), 5.64 δ (s, -COO-CH_2-OCO), 7.1-8.0 δ (m, $3C_6H_5$).

EXAMPLE 13

acetoxymethyl (5R)-2-acetoxymethyl-2-penem-3-carboxylate.

(1) R'=H, R''=X=$CH_2O.CO.CH_3$, *n*=O

0.7 g of the compound prepared in Example 12 were dissolved in 30 ml of dry toluene and refluxed for 2 hours. The reaction mixture, consisting of the title compound and triphenylphosphine oxide, was purified by a short column chromatography on silica gel, eluting with 97:3 by volume dichloromethane:ethyl acetate, to give 0.250 g of the title compound.

PMR ($CDCl_3$): 2.11 and 2.13 δ (two s, $2CH_3CO$), 3.49 δ (dd, Jgem = 16.5Hz, Jvic trans = 2Hz, (C-6-Hβ), 3.86 δ (dd, Jgem = 16.5Hz, Jvic cis = 3.8Hz, C-6-Hα), 5.12 and 5.45 δ (two d, Jgem = 15.5Hz, =C-CH_2), 5.68 δ (dd, Jvic = 3.8 and 2Hz, C-5-H), 5.87 δ (s, -COO-CH_2-OCO-).

IR ($CHCl_3$): 1800 cm^{-1} β-lactam C=O
1750-1725 cm^{-1} esters C=O
U.V. (EtOH): $^{\lambda}$max 325 nm.
MS: m/e 315.04108 (M^+) calculated for $C_{12}H_{13}NO_7S$ 315.04127.

EXAMPLE 14

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-1-(1-p.-nitrobenzyloxycarbonyl-1-hydroxymethyl)-azetidin-2-one.

(7): R'=H, R''=*p*.$NO_2.C_6H_4.CH_2$, X=Y=$CH_2O.CH_3$, *n*=O

The title compound was obtained following the procedure described in Example 9, using *p*-nitrobenzyl glyoxylate (freshly prepared by ozonolysis of *p*-nitrobenzyl fumarate) instead of acetoxymethyl glyoxylate. Quantitative yield.

PMR ($CDCl_3$): 2.1 (s, 6H); 2.8-3.7 (m, 2H); 4.7-4.9 (m, 5H); 5.1-5.6 (m, 2H); 5.2 (m, 1H); 6.1 (m, 1H); 7.5-8.3 (m, 4H).

EXAMPLE 15

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-1-(1-p.nitrobenzyloxycarbonyl-1-chloromethyl)-azetidin-2-one.

(8): R'=H, R''=*p*.$NO_2.C_6H_4.CH_2$, X=Y=$CH_2O.CO.CH_3$, *n*=O

The title compound was obtained following the procedure described in Example 10, but using the compound prepared in Example 14 instead of that prepared in Example 9.

PMR ($CDCl_3$)δ : 2.1 (s, 6H); 2.8-3.7 (m, 2H); 4.7-4.9 (m, 4H); 5.2-5.4 (m, 1H); 5.4 (m, 2H); 6.1-6.3 (m, 2H); 7.5-8.4 (m, 4H).

EXAMPLE 16

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-1-(1-p.nitrobenzyloxycarbonyl-1-triphenylphosphoranylidenemethyl)-azetidin-2-one.

(9): R'=H, R''=*p*.$NO_2.C_6H_4.CH_2$, X=Y=$CH_2O.CO.CH_3$, *n*=O

The title compound was obtained following the procedure described in Example 11, but using the compound prepared in Example 15 instead of that prepared in Example 10.

EXAMPLE 17

4β-acetylglycolloylthio-1-(1-p.nitrobenzyloxycarbonyl-1-triphenylphosphoranylidenemethyl)-azetidin-2-one.

(11): R'=H, R''=*p*.$NO_2.C_6H_4.CH_2$, X=$CH_2O.CO.CH_3$

The title compound was obtained following the procedure described in Example 12, but using the compound prepared in Example 16 in place of that prepared in Example 11.

EXAMPLE 18

p.nitrobenzyl(5R)-2-acetoxymethyl-2-penem-3-carboxylate.

(1) R'=H, R''=*p*.$NO_2.C_6H_4.CH_2$, X=$CH_2O.CO.CH_3$, *n*=O

The title compound was obtained following the procedure described in Example 13, but using the compound prepared in Example 17 instead of that prepared in Example 12.

PMR ($CDCl_3$) δ : 3.75 (1 H, dd, J = 2.3Hz, 16.8Hz, H-6α); 3.87 (1 H, dd, J = 3.6Hz, 16.8Hz, H-6β);5.14 (1 H, d, J = 15.8, =C-CH_2O-); 5.50 (1 H, d, J = 15.8Hz, =C-CH_2O); 5.71 (1 H, dd, J = 2.3Hz, 3.6Hz, H-5).

$[\alpha]_D$ + 87° (c=1.2 $CHCl_3$).

I.R. ($CHCl_3$): 1800 (β-lactam), 1750 and 1720 cm^{-1}.
U.V. (EtOH): 265 (ε11000) and 322 (ε 7000) nm.
M.S.: m/e 378 (M^+)
M.p. 122°-123°C.

EXAMPLE 19

(5R)-2-acetoxymethyl-2-penem-3-carboxylic acid.

(1) R'=R''=H, X=$CH_2O.CO.CH_3$, *n*=O

200 mg of the compound prepared in Example 18 were dissolved in 12 ml of ethyl acetate. 8 ml of 0.2 M sodium bicarbonate solution and 400 mg of 10 percent palladium-on-charcoal were added and the resulting two phase mixture was shaken under hydrogen for 60 minutes. After filtering off the catalyst, the aqueous phase was acidified with 20 ml of 5 percent aqueous citric acid and extracted three times with dichloromethane. The organic layers were dried over anhydrous sodium sulphate and evaporated to give 60 mg of the title compound.

I.R. ($CHCl_3$): 1790 (β lactam), 1735 and 1700 cm^{-1}.
U.V. (EtOH): 300 nm

EXAMPLE 20

4β-(1-hydroxymethyl-vinylsulphinyl)-1-(1-methoxycarbonyl-2-methyl-allyl)-azetidin-2-one.

(3): R=CH_3, R'=Y=H, X=CH_2OH

4 g of methyl penicillanate S-oxide were dissolved in 15 ml of toluene and refluxed with 15 ml of propargyl alcohol for 8 hours. After evaporating off the solvent *in vacuo*, the residue was purified by short column chromatography on silica gel, eluting with dichloromethane:ethyl acetate (1:1 by volume). 2.8 g of the title compound were obtained.

PMR ($CDCl_3$) δ : 1.96 (bs, 3 H, $\overset{''}{C}$-*CH_3*); 2.91 and 3.35 (dd, 2H, J = 2Hz, 5Hz, 15Hz, CO-*CH_2*-CH-S); 3.78 (s, 3 H, COO*CH_3*); 4.36 (bs, 2 H, *CH_2*OH); 4.90-5.25 (m, 3 H, *CH*-$COOCH_3$, C-C=CH_2); 5.35 (m, 1 H, CH_2-*CH*-S); 5.88 (s, 2 H, *CH_2*=C-S).

EXAMPLE 21

4β(1-hydroxymethyl-vinylsulphinyl)-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-azetidin-2-one.

(4): R=CH_3, R'=Y=H, X=CH_2OH

3.0 g of the compound prepared in Example 20 were dissolved in 100 ml of dichloromethane and left at room temperature for a few hours. After evaporating the solvent from the solution, the residue consisted of the title compound in pure form. Quantitative yield.

PMR ($CDCl_3$) δ : 2.08 (s, 3 H, =$\overset{'}{C}$-*CH_3*); 2.18 (s, 3 H, =C-*CH_3*); 2.7-3.6 (m, J 2Hz, 16Hz, CO-*CH_2*-CH-S); 3.78 (s, 3 H, COO*CH_3*); 4.35 (s, 2 H, CH_2OH); 5.32 (m, 1 H, *CH*-S); 5.90 (bs, 2 H, =*CH_2*).

EXAMPLE 22

4β-(1-bromomethyl-vinylthio)-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-azetidin-2-one.

(12): R=CH_3, R'=Y=H, X=CH_2Br

1.8 g of the compound prepared in Example 21 were dissolved in 40 ml of dimethylformamide and cooled to -20°C. 0.7 ml of pyridine and 3.0 ml of phosphorus tribromide were added and the mixture was left for 15 minutes under stirring. Ethyl acetate was added and the organic layer was shaken with a saturated solution of sodium bicarbonate, washed with water and then dried over anhydrous sodium sulphate to give, after evaporating off the solvent, 1.6 g of the title compound.

PMR ($CDCl_3$) δ : 2.04 (s, 3 H, $=\overset{CH_3}{}$); 2.24 (s, 3 H = $_{CH_3}$); 3.24 (dd, J = 2.8, 5, 16Hz, 2H, O ‖ C-CH_2-CH); 3.75 (s, 3 H, OCH_3); 4.02 (s, 2 H, CH_2Br); 5.24 (bs, 1 H, =CH); 5.37 (dd, J = 2.8Hz, 5 Hz, 1 H, CH_2-*CH*-S); 5.60 (bs, 1 H, =CH).

EXAMPLE 23

4β[1-(methyl-1H-tetrazol-5-yl-thiomethyl)-vinylthio]-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-azetidin-2-one

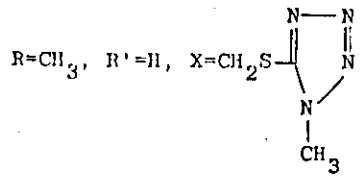
(12): R=CH_3, R'=Y=H, X=CH_2S-(tetrazole ring)-CH_3

1.4 g of the compound prepared in Example 22 were dissolved in 25 ml of tetrahydrofuran and cooled to 0°C. 0.8 g of 1-methyl-5-mercapto-tetrazole sodium salt were added and the mixture was left under stirring for three hours at room temperature. After filtering off the insoluble matter, the mixture was diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue consisted of 2.0 g of the title compound in pure form.

PMR ($CDCl_3$) δ : 2.00 (s, 3 H, =C-*CH_3*); 2.22 (s, 3 H, =C-*CH_3*); 2.70-3.80 (m, 2 H, J = 2Hz, 5Hz, 15hz, CO-*CH_2*-CH-S); 3.72 (s, 3 H, COO*CH_3*); 3.95 (s, 3 H, N-*CH_3*); 4.10 (s, 2 H, *CH_2*-S); 5.18 (bs, 1 H, S-C=*CH*); 5.36 (m, 1 H, CH_2-*CH*-S); 5.57 (bs, 1 H, S-C=C-H).

EXAMPLE 24

4β-[(1-methyl-1-H-tetrazol-5-yl-thio)-acetylthio]-1-methoxyoxalyl-azetidin-2-one.

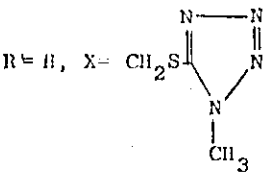
(13): 

1.8 g of the compound prepared in Example 23 were dissolved in 200 ml of dichloromethane and cooled to -78°C. A flow of ozonized oxygen was bubbled through the solution until a blue colour appeared. A few drops of trimethylphosphite were added and the mixture was raised to room temperature. Removal of the solvent by evaporation gave 1.3 g of the title compound.

PMR ($CDCl_3$) δ : 2.9-3.7 (m,2 H, CO*CH_2*CH S); 3.85 (s, 3 H, COO*CH_3*); 3.98 (s, 3 H, N-*CH_3*); 4.35 (s, 2 H, *CH_2*S); 5.75 (m, 1 H, CH_2*CH* S).

EXAMPLE 25

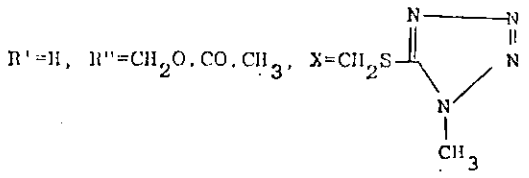
4β-[(1-methyl-1-H-tetrazol-5-yl-thio)-acetylthio]-azetidin-2-one.

(14): 

1.2 g of the compound prepared in Example 24 were dissolved in a 1:1 by volume ethyl acetate:methanol mixture and a few grams of silica gel were added under vigorous stirring. After one hour the insoluble matter was filtered off and the solution was evaporated in vacuo. The title compound was crystallized from methanol:diethyl ether: 0.6 g were obtained.

EXAMPLE 26

4β-[(1-methyl-1-H-tetrazol-5-yl-thio)-acetylthio]-1-(1-acetoxymethoxycarbonyl-1-hydroxymethyl)-azetidin-2-one.



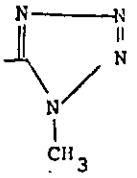
1.5 g of the compound prepared in Example 25 were refluxed in 50 ml of benzene with 1.2 g of acetoxymethyl glyoxylate (freshly prepared by ozonolysis of diacetoxymethyl fumarate). The reaction was complete after 3 hours. The crude oil obtained after evaporating off the solvent can be used for the next step without further purification. A sample was purified on TLC for spectroscopic data.

PMR ($CDCl_3$) δ : 2.06 (s, 3 H); 2.7-3.8 (m, 2 H); 3.95 (s, 3 H); 4.30 (s, 2 H); 5.40 (s, 1 H); 5.50 (m, 1 H); 5.80 (s, 2 H).

EXAMPLE 27

4β-[(1-methyl-1-H-tetrazol-5-yl-thio)-acetylthio]-1-(1-acetoxymethoxycarbonyl-1-chloromethyl)-azetidin-2-one

(16): R'=H, R''=$CH_2O.CO.CH_3$, X=CH_2S-

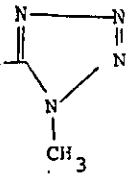


The oil obtained from the last preceding Example was dissolved in anhydrous tetrahydrofuran (20 ml) and treated at 0°C with equimolar amounts of pyridine and thionyl chloride until all starting material had disappeared. After filtering off the insoluble matter, the filtrate was used immediately for the next step.

EXAMPLE 28

4β-[(1-methyl-1-H-tetrazol-5-yl-thio)-acetylthio]-1-(1-acetoxymethoxycarbonyl-1-triphenylphosphoranylidenemethyl)-azetidin-2-one.

(11): R'=H, R''=$CH_2O.CO.CH_3$, X=CH_2S-

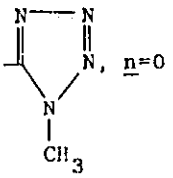


To the filtrate obtained in the last preceding Example were added 800 mg of triphenylphosphine and 0.4 ml of pyridine. The resulting mixture was heated to 60°-70°C and maintained at that temperature for a few hours. The phosphorane was purified on silica gel eluting with dichloromethane:ethyl acetate (1:1 by volume).

EXAMPLE 29

acetoxymethyl (5R)-2-(1-methyl-1-H-tetrazol-5-yl-thio-methyl)-2-penem-3-carboxylate

(1): R'=H, R''=$CH_2O.CO.CH_3$, X=CH_2S-, n=0



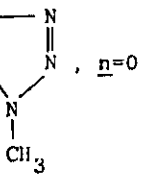
0.500 g of the compound prepared in Example 28 were dissolved in 30 ml of toluene. The solution was heated to 100°C and maintained at that temperature for two hours. The title compound was purified from triphenylphosphine oxide by short column chromatography on silica gel eluting with dichloromethane:ethyl acetate (8:2 by volume).

PMR ($CDCl_3$) δ : 2.15 (s, 3 H, $COCH_3$); 3.30-4.03 (m, J = 4Hz, 2Hz, $-CH_2-$(6); 3.97 (s, 3 H, $-NCH_3$); 4.56 (d, J = 14Hz, 1 H, *H*CH-S); 4.84 (d, J = 14Hz, 1 H, HC*H*-S), 5.65 (dd, J = 4Hz 2Hz, 1 H, H-5α); 5.88 (s, 2 H, $COOCH_2O$).

EXAMPLE 30

(5R)-2-(1-methyl-1-H-tetrazol-5-yl-thiomethyl)-2-penem-3-carboxylic acid.

(1): R'=R''=H, X=CH_2S-, n=0



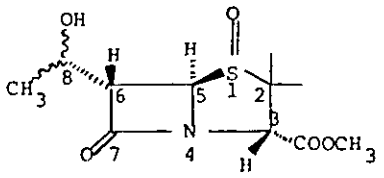
The title compound was prepared by catalytic reduction of *p*.nitrobenzyl (5R)-2-(1-methyl-1-H-tetrazol-5-yl-thiomethyl)-2-penem-3-carboxylate, obtained by a process substantially as described in Examples 20 to 29

but using *p*.nitrobenzyl glyoxylate instead of acetoxymethyl glyoxylate. The catalytic reduction was effected following the method described in Example 19.

I.R. ($CHCl_3$) : 1800 (β lactam), 1750 and 1720.

EXAMPLE 31

methyl 6α-(1'-hydroxyethyl)-penicillinate-S-oxide.



A solution of methyl penicillinate S-oxide (2.3 g) in 50 ml of anhydrous tetrahydrofuran was cooled to -78°C. Lithium diisopropylamide (freshly prepared from 5 ml of diisopropylamine and 20 ml of a 1.6 M solution of butyl lithium in hexane) dissolved in anhydrous tetrahydrofuran was added and the mixture left at -78°C for 10 minutes. 5 ml of acetaldehyde were then added and the mixture was stirred for 15 minutes. The reaction was then quenched with a saturated aqueous solution of ammonium chloride, extracted with ethyl acetate, washed twice with water and dried over anhydrous sodium sulphate. After evaporating off the solvent the residue was shortly purified by column chromatography on silica gel eluting with dichloromethane:ethyl acetate (1:1 by volume). 1.5 g of the title compound were obtained consisting of a 2:3 mixture of epimers at the hydroxyl bearing carbon based on the PMR, being the new C_6-C_8 bond only in the α position because of the stereospecificity of the reaction in the used conditions.

PMR ($CDCl_3$) δ : 1.27 (s, 3 H, α-*CH_3*); 1.40 (d, 3 H, J = 5.7Hz, *CH_3*-CHOH) major isomer; 1.48 (d, 3 H, J = 5.7Hz, CH_3-CHOH) minor isomer; 1.70 (s, 3 H, β-*CH_3*); 3.4-3.8 (m, 1 H, *H*-6); 3.80 (s, 3 H, $COOCH_3$); 4.1-4.7 (m, 1 H, *CH*OH); 4.50 (s, 1 H, *H*-3); 4.98 (d, J = 1.9Hz, 1 H, *H*-5) minor isomer; 5.05 (d, J = 1.9Hz, 1 H, *H*-5) major isomer.

EXAMPLE 32

methyl 6-(1-hydroxyethyl)-3-penicillanate

To a solution of 2.2 g of methyl penicillanate in 30 ml of anhydrous tetrahydrofuran, a slight excess of lithium diisopropylamide was added at -78°C under nitrogen. An excess of acetaldehyde was dropped in and the mixture was stirred for 5 minutes. The reaction was then quenched with a trace of acetic acid; the mixture was poured into water and extracted with dichloromethane. The organic layers were dried over anhydrous sodium sulphate and evaporated "in vacuo" to give 0.8 g of the title compound.

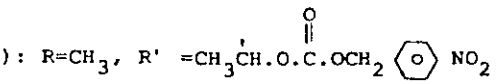
EXAMPLE 33

methyl 6-(1-p-nitrobenzyloxycarbonyloxyethyl)-3-penicillanate.

1.2 g of methyl 6-(1-hydroxyethyl)-3-penicillanate, prepared as described in Example 32, were dissolved in 40 ml of tetrahydrofuran cooled to -78°C and treated with one equivalent of butyl lithium. 1.2 equivalents of *p*-nitrobenzyloxycarbonyl chloride were added to the mixture. After 30 minutes at -78°C, the reaction mixture was left at room temperature for 60 minutes, poured into water and extracted with dichloromethane. 1.4 g of the title compound were obtained after drying over anhydrous sodium sulphate and evaporating off the solvent.

EXAMPLE 34

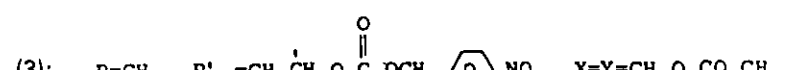
methyl 6-(1-p-nitrobenzyloxycarbonyloxyethyl-3-penicillanate-S-oxide



1.8 g of methyl 6-[1-p-nitrobenzyloxycarbonyloxyethyl]-3-penicillanate, prepared as described in Example 33, were dissolved in 50 ml of dichloromethane and treated at 0°C with 1.5 equivalents of *m*-chloroperbenzoic acid. The organic phase was shaken with a saturated solution of sodium bicarbonate, extracted, dried over anhydrous sodium sulphate and evaporated: 1.4 g of the expected sulphoxide were obtained.

EXAMPLE 35

4β-(1-acetoxymethyl-3-acetoxy-1-propenylsulphinyl)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(1-methoxycarbonyl-2-methyl-allyl)-azetidin-2-one

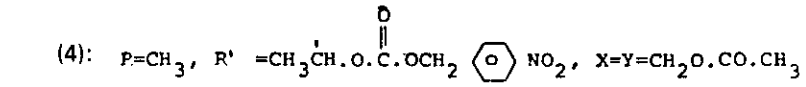


(3): P=CH_3, R' =$CH_3CH.O.C(=O).OCH_2$ <benzene> NO_2, X=Y=$CH_2O.CO.CH_3$

A solution of 2.0 g of the compound prepared in Example 34 and 2.4 g of butyndiol diacetate in 50 ml of toluene was refluxed for 24 hours. The trapped compound was then purified by silica gel column chromatography eluting with 9:1 by volume dichloromethane:ethyl acetate. 1.1 g of the title compound were obtained.

EXAMPLE 36

4β-(1-acetoxymethyl-3-acetoxy-1-propenylsulphinyl)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-azetidin-2-one

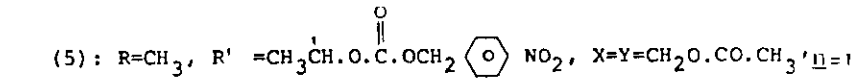


(4): P=CH_3, R' =$CH_3CH.O.C(=O).OCH_2$ <benzene> NO_2, X=Y=$CH_2O.CO.CH_3$

1.3 g of the compound prepared in Example 35 were dissolved in 80 ml of dichloromethane. 0.3 ml of triethylamine were added and the mixture was left at room temperature for 2 hours. The title compound was obtained in pure form in quantitative yield by evaporating off the solvent.

EXAMPLE 37

4β-(1-acetoxymethyl-3-acetoxy-1-propenylsulphinyl)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-methoxyoxalyl-azetidin-2-one

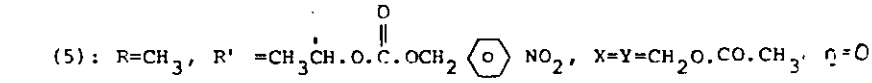


(5): R=CH_3, R' =$CH_3CH.O.C(=O).OCH_2$ <benzene> NO_2, X=Y=$CH_2O.CO.CH_3$, n=1

A solution of 1.1 g of the compound prepared in Example 36 in 100 ml of dichloromethane was cooled to -78°C. Ozone in oxygen was then bubbled through the solution until a blue colour appeared. The solution was shaken with an aqueous solution of sodium pyrosulphite and dried over anhydrous sodium sulphate. 0.5 g of the title compound were obtained after evaporation off of the solvent.

EXAMPLE 38

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-methoxyoxalyl-azetidin-2-one.

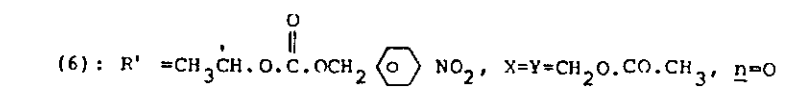


(5): R=CH_3, R' =$CH_3CH.O.C(=O).OCH_2$ <benzene> NO_2, X=Y=$CH_2O.CO.CH_3$, n=0

A solution of 0.8 g of the compound prepared in Example 37 in 15 ml of anhydrous dimethylformamide was cooled to -20°C and 0.6 ml of phosphorus tribromide were added. The reaction mixture was diluted with ethyl acetate after 10 minutes and washed twice with a solution of sodium bicarbonate. The organic phase was dried over anhydrous sodium sulphate and the solvent was then evaporated off giving 0.4 g of the title compound.

EXAMPLE 39

4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-azetidin-2-one

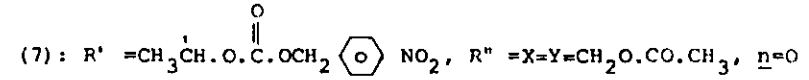


(6): R' =$CH_3CH.O.C(=O).OCH_2$ <benzene> NO_2, X=Y=$CH_2O.CO.CH_3$, n=0

1.2 g of the compound prepared in Example 38 were dissolved in methanol and 2 g of silica gel were added to the solution. After 60 minutes the insoluble matter was filtered off and the organic phase was evaporated: a short column chromatography afforded 0.4 g of the title compound.

EXAMPLE 40

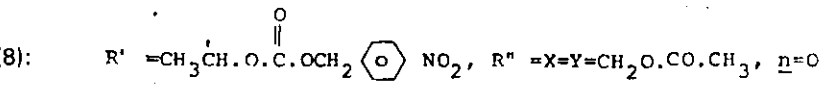
4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(1-acetoxymethoxy-carbonyl-1-hydroxymethyl)-azetidin-2-one.



0.6 g of the compound prepared in Example 39, dissolved in 30 ml of benzene, and 0.6 g of acetoxymethyl glyoxylate (freshly prepared by ozonolysis of diacetoxymethyl fumarate), were refluxed together. The reaction was completed after two hours. The condensation product can be used for the next step without further purification.

EXAMPLE 41

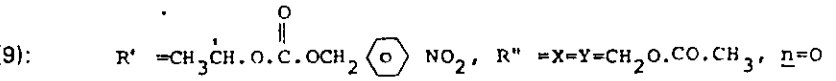
4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(1-acetoxymethoxycarbonyl-1-chloromethyl)-azetidin-2-one.



0.5 g of the compound prepared in Example 40 were dissolved in 12 ml of anhydrous tetrahydrofuran and cooled to 0°C. 1.1 Equivalents of pyridine and 1.1 equivalents of thionyl chloride were added and the mixture was left under stirring for 10 minutes. The insoluble matter was filtered off and the solvent was evaporated off at room temperature to give the title compound in nearly quantitative yield. The product can be used without further purification for the next step.

EXAMPLE 42

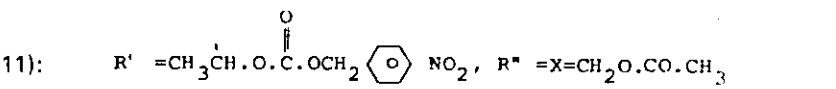
4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(acetoxymethoxycarbonyl-1-triphenylphosphoranylidenemethyl)-azetidin-2-one.



A solution of 0.760 g of the compound prepared in Example 41 in 10 ml of tetrahydrofuran and 10 ml of dioxan was stirred overnight at 50°C with 2 equivalents of triphenylphosphine and 1.1 equivalents of pyridine. The phosphorane was purified by silica gel column chromatography, eluting with 70:30 by volume dichloromethane:ethyl acetate. 0.480 g of the title compound were obtained.

EXAMPLE 43

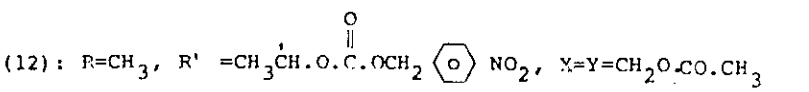
4β-acetylglycoloylthio-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(1-acetoxymethoxycarbonyl-1-triphenylphosphoranylidenemethyl)-azetidin-2-one.



0.45 g of the compound prepared in Example 42 were dissolved in 50 ml of dichloromethane and cooled to -20°C. 30 ml of trifluoroacetic acid dissolved in dichloromethane were added. After a few minutes ozone in oxygen was bubbled through the solution until a slightly blue colour appeared. The reaction was stopped and a few drops of trimethylphosphite were added. The organic phase was washed with a saturated solution of sodium bicarbonate and dried over anhydrous sodium sulphate: 0.260 g of the title compound were obtained.

EXAMPLE 44

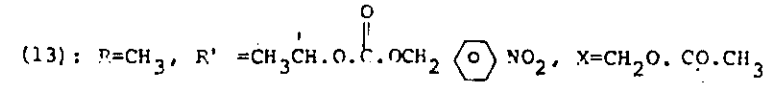
4β-(1-acetoxymethyl-3-acetoxy-1-propenylthio)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(methoxycarbonyl-2-methyl-1-propenyl)-azetidin-2-one.



1.5 g of the compound prepared in Example 36 were dissolved in 10 ml of anhydrous dimethylformamide and cooled to -20°C. 0.8 ml of phosphorus tribromide were added, and the mixture was stirred for 10 minutes. It was then diluted with ethyl acetate and washed twice with a saturated solution of sodium bicarbonate. The organic layer was dried over anhydrous sodium sulphate and evaporation off of the solvent gave 1.1 g of the title compound.

EXAMPLE 45

4β-acetylglycolloylthio-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-methoxyoxalyl-azetidin-2-one.

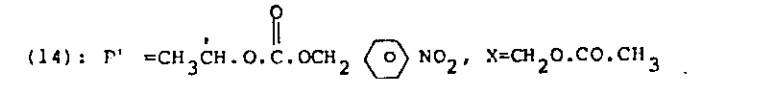


(13): R=CH_3, R' =$CH_3CH.O.C(=O).OCH_2$ <benzene ring> NO_2, X=$CH_2O.CO.CH_3$

1.4 g of the compound prepared in Example 44 in 120 ml of dichloromethane were cooled to -78°C. Ozone in oxygen was bubbled through the solution until a blue colour appeared. The solution was shaken with an aqueous solution of sodium pyrosulphite and dried over anhydrous sodium sulphate. Evaporation off of the solvent gave 0.8 g of the title compound.

EXAMPLE 46

4β-acetylglycolloylthio-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-azetidin-2-one.

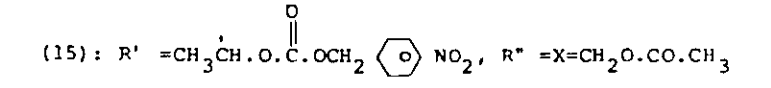


(14): R' =$CH_3CH.O.C(=O).OCH_2$ <benzene ring> NO_2, X=$CH_2O.CO.CH_3$

0.800 g of the compound prepared in Example 45 were dissolved in 50 ml of methanol and a few grams of silica gel were added. The mixture was left at room temperature for 60 minutes, and then the insoluble material was filtered off. The filtrate, after the solvent had been removed by evaporation, gave 0.300 g of the title compound.

EXAMPLE 47

4β-acetylglycolloylthio-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(1-acetoxymethoxycarbonyl-1-hydroxymethyl)-azetidin-2-one.

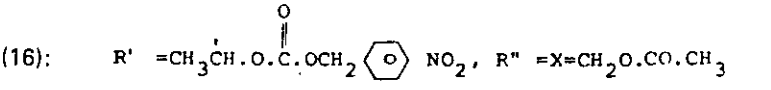


(15): R' =$CH_3CH.O.C(=O).OCH_2$ <benzene ring> NO_2, R" =X=$CH_2O.CO.CH_3$

0.5 g of the compound prepared in Example 46 and 0.5 g of acetoxymethyl glyoxylate in 30 ml of benzene were refluxed until the reaction was complete (two hours). The title compound was obtained and can be used for the next step without further purification.

EXAMPLE 48

4β-acetylglycolloylthio-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(1-acetoxymethoxycarbonyl-1-chloromethyl)-azetidin-2-one.

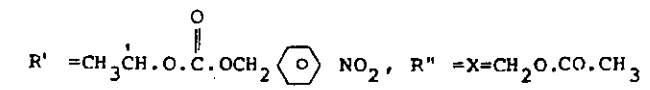


(16): R' =$CH_3CH.O.C(=O).OCH_2$ <benzene ring> NO_2, R" =X=$CH_2O.CO.CH_3$

0.35 g of the compound prepared in Example 47 were dissolved in 10 ml of anhydrous tetrahydrofuran at 0°C. 1.1 Equivalents of pyridine and 1.1 equivalents of thionyl chloride were added and the mixture was stirred for 10 minutes. The precipitate was filtered off and the filtrate, after evaporation off of the solvent, gave the title compound in quantitative yield. The crude product was used as such for the next step.

EXAMPLE 49

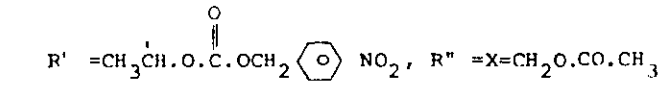
4β-acetylglycolloylthio-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-(1-acetoxymethoxycarbonyl-1-triphenylphosphoranylidenemethyl)-azetidin-2-one.

(11): 

0.400 g of the compound prepared in Example 48 were dissolved in 20 ml of a 1:1 by volume mixture of tetrahydrofuran and dioxan; 2 equivalents of triphenylphosphine and 1.1 equivalents of pyridine were added and the mixture was stirred overnight at 50°C. The title compound was obtained and was purified by silica gel column chromatography, eluting with 70:30 by volume dichloromethane:ethyl acetate. 0.280 g of the phosphorane were obtained.

EXAMPLE 50

acetoxymethyl (5R)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-2-acetoxymethyl-2-penem-3-carboxylate

(1): 

0.210 g of the compound prepared in Example 43 or Example 49 were dissolved in 7 ml of toluene and the solution was refluxed for two hours. Purification by short column chromatography, eluting with 95:5 by volume dichloromethane:ethyl acetate, afforded 0.050 g of the title compound.

EXAMPLE 51

acetoxymethyl (5R)-6-(1-hydroxyethyl)-2-acetoxymethyl-2-penem-3-carboxylate.

(1): $R'=CH_3\dot{C}H.OH$, $R''=X=CH_2O.CO.CH_3$

0.060 g of the compound prepared in Example 50 were poured into a water:ethanol:dipotassium monohydrogen orthophosphate mixture and hydrogenolysed with 10% palladium-on-carbon. A quick purification by silica gel column chromatography gave 0.015 g of the title compound.

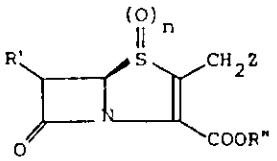
EXAMPLE 52

Operating as described in the previous Examples, but employing 5-methyl-2-mercapto-1,3,4-thiadiazole,5-mercapto-1,2,3-triazole or mercaptopyrazine instead of 1-methyl-1H-5-mercapto-tetrazole, (5R)-2-(5'-methyl-1',3',4'-thiadiazol-2'-yl-thiomethyl)-2-penem-3-carboxylic acid, (5R)-2-(1',2',3'-triazol-5-yl-thiomethyl)-2-penem-3-carboxylic acid, (5R)-2-(pyrazinyl-thiomethyl)-2-penem-3-carboxylic acid, (5R)-6-(1'-hydroxyethyl)-2-(5''-methyl-1'',3'',4''-thiadiazol-2''-yl-thiomethyl)-2-penem-3-carboxylic acid, (5R)-6-(1'-hydroxyethyl)-2-(1'',2'',3''-triazol-5''-yl-thiomethyl)-2-penem-3-carboxylic acid, (5R)-6-(1'-hydroxyethyl)-2-(pyrazinyl-thiomethyl)-2-penem-3-carboxylic acid were prepared.

Operating as previously described, but reducing the methyl 6-(1'-hydroxyethyl)-3-penicillinate following the widely known procedure, the corresponding 6-ethyl-derivatives were obtained.

CLAIMS

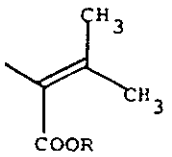
1. A process for the preparation of a penem-carboxylic acid or ester of the general formula (1)



wherein *n* is 0 or 1, R'' represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a 2,2,2-trichloroethyl, benzyl, acetonyl, *p*-nitrobenzyl, *p*-methoxybenzyl, phenyl, *p*-nitrophenyl, benzhydryl, acetoxymethyl, pivaloyloxymethyl or phthalidyl group or a group of the formula $-CH(CH_3).OCOOC_2H_5$ or CH_2NHCOR_2 wherein R_2 represents an alkyl group having from 1 to 4 carbon atoms or a cycloalkyl or aryl group, Z represents a hydroxy, amino or carbamoyloxy group, or a group of the formula OR_1 or $OCOR_1$ wherein R_1 represents an alkyl group having from 1 to 4 carbon atoms, and R' represents a hydrogen atom

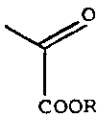
or an alkyl, alkoxy or hydroxyalkyl group, each of which has from 1 to 4 carbon atoms, the alcoholic function of the hydroxyalkyl group being free or protected by a *p*-nitrobenzyloxycarbonyl group, the process comprising condensing, in an inert solvent at elevated temperature, a penicillanic acid S-oxide ester of the general formula (2) as herein defined with an acetylenic compound of the general formula XC ≡ CY as herein defined, isomerising the resultant compound of the general formula (3) in basic conditions, converting the resultant azetidinone derivative of the general formula (4) into one of the general formula (11) by the steps of

(a) ozonolysis of the 1-substituent of the formula



in solution at reduced temperature,

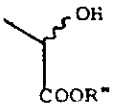
(b) removal of the 1-substituent of the formula



resulting from step (a) by mild alkaline hydrolysis or by the action of silica gel,

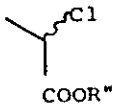
(c) condensation of the 1-unsubstituted azetidinone resulting from step (b) with a glyoxylate of the formula CHO.COOR" as herein defined by refluxing in a solvent,

(d) chlorination of the 1-substitutent of the formula

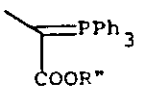


introduced in step (c) by the action of a chlorinating agent,

(e) conversion of the 1-substituent of the formula



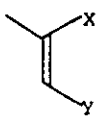
introduced in step (d) into one of the formula



by reaction with triphenylphosphine,

(f) reduction of the 4β-(substituted vinylsulphinyl) group by the action of a reducing agent, and

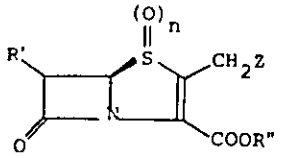
(g) ozonolysis of the double bond of the group of the formula



in solution at reduced temperature, the steps being carried out in the order (a), (b), (c), (d), (e), (f), (g) or (a), (f), (b), (c), (d), (e), (g) or (f), (a) and (g) simultaneously, (b), (c), (d), (e), step (f) being carried out in acidic conditions if carried out after step (e), and cyclising the compound of the general formula (11) by heating it in an inert solvent at from 50°C to 140°C to obtain a compound of the general formula (1) in which *n* is 0, and optionally converting that compound to one of the general formula (1) in which n is 1 by oxidation.

2. A process for the preparation of a penem-carboxylic acid or ester of the general formula (1) in which *n*, R′ and R″ are as defined in claim 1 and Z represents a mercapto or pyridinium group or a group of the formula SR_3 wherein 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, the process being according to claim 1 and further comprising converting the substituent X into a substituent of the formula CH_2Z wherein Z is as defined in this claim by a substitution reaction carried out at any stage in the process according to claim 1 after the condensation of the penicillanic acid S-oxide ester of the general formula (2) with the acetylenic compound of the general formula XC=CY.

3. A penem-carboxylic acid or ester of the general formula (1)



in which *n* and R″ are as defined in claim 1, Z represents a carbamoyloxy or pyridinium group or a group of the formula $OCOR_1$ or SR_3 wherein R_1 is as defined in claim 1 and R_3 is as defined in claim 2, 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-nitrobenzyl-oxycarbonyl group; or a pharmaceutically acceptable salt thereof.

4. A penem-carboxylic acid or ester according to claim 3 wherein R′ represents a 1-hydroxyethyl or 1-(*p*-nitrobenzyloxycarbonyloxy)-ethyl group.

5. (5R)-2-Acetoxymethyl-6-(1′-hydroxyethyl)-2-penem-3-carboxylic acid.

6. (5R)-6-(1′-Hydroxyethyl-2-(1″-methyl-1″H-tetrazol-5″-yl-thiomethyl)-2-penem-3-carboxylic acid.

7. (5R)-6-(1′-Hydroxyethyl)-2-(5″-methyl-1″,3″,4″-thiadiazol-2″-yl-thiomethyl)-2-penem-3-carboxylic acid.

8. (5R)-6-(1′-Hydroxyethyl)-2-(1″,2″,3″-triazol-5″-yl-thiomethyl)-2-penem-3-carboxylic acid.

9. (5R)-6-(1′-Hydroxyethyl)-2-pyrazinylthiomethyl-2-penem-3-carboxylic acid.

10. A pharmaceutical composition comprising a penem-carboxylic acid or ester according to any of claims 3 to 9, or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

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