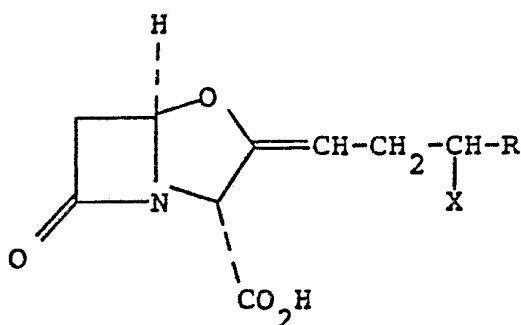




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(54) Title: CLAVAM DERIVATIVES



(II)

(57) Abstract

A compound of formula (II), or a salt or ester thereof; wherein R is hydrogen or a hydrocarbon group and X is hydroxy, substituted hydroxy, mercapto, substituted mercapto, azido, cyano, halo, isothiocyanato, substituted amino or X represents the residue of a carbon nucleophile or is an activated aryl or heteroaryl group. Processes for the preparation of these compounds and pharmaceutical compositions containing them are also described.

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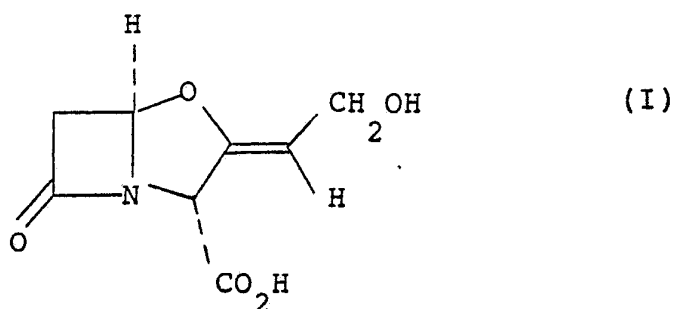
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CLAVAM DERIVATIVES

This invention relates to novel β -lactam containing compounds, their preparation and their use, and in particular to a novel class of clavams. These compounds have antibacterial and β -lactamase inhibitory properties, and therefore are of use in the treatment of bacterial infection either alone or in a synergistic composition with other β -lactam antibacterial agents, such as penicillins and cephalosporins.

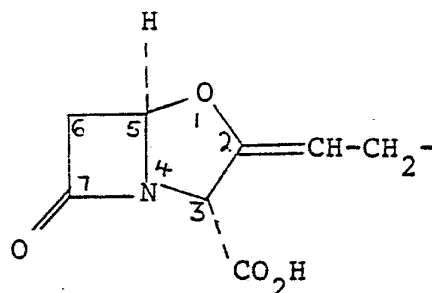
Clavulanic acid has the structure:



and is described in UK Patent Number 1508977. Many derivatives of that compound are known.

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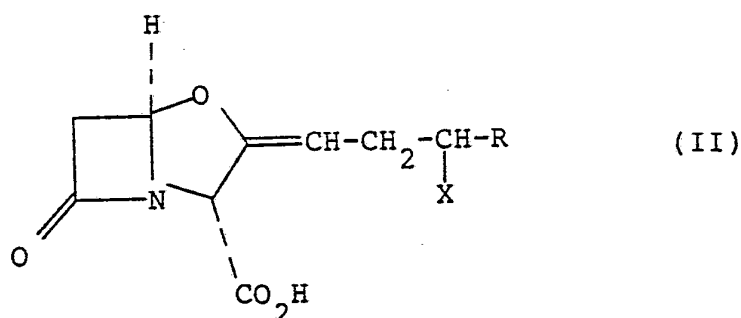
Clavulanic acid and its derivatives have in common the 3-carboxy-2-ethylidene clavam nucleus, i.e. the moiety of the structure:



We have now produced compounds having a chain of at least three carbon atoms attached to the 2-position of the clavam.

In particular the present invention provides certain 3-carboxyclavam derivatives having a propylidene moiety at the 2-position of the clavam nucleus.

The present invention comprises compounds of the formula (II):



and salts and esters thereof, wherein R is hydrogen or

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a hydrocarbon group and where X is hydroxy, substituted hydroxy, mercapto, substituted mercapto; azido, cyano, halo, isothiocyanato, substituted amino or X represents the residue of a carbon nucleophile or is an activated aryl or heteroaryl group.

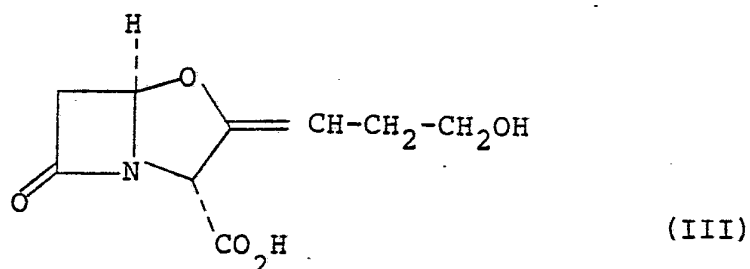
Suitable substituted hydroxy groups for X include etherified and acylated hydroxy and suitable substituted mercapto groups include etherified and acylated mercapto. Suitable substituted amino groups for X include alkylated or acylated amino.

The term 'hydrocarbon' includes groups having up to 18 carbon atoms, suitably up to 10 carbon atoms, conveniently up to 6 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)-alkyl, aryl, and aryl(C₁₋₆)-alkyl.

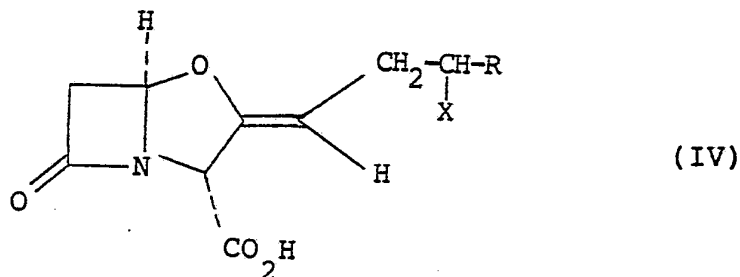
When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, C₁₋₆ alkyl, phenyl, C₁₋₆ alkoxy, halo(C₁₋₆) alkyl, hydroxy, amino, nitro, carboxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkoxycarbonyl-(C₁₋₆)-alkyl C₁₋₆ alkylcarbonyloxy, or C₁₋₆ alkylcarbonyl groups.



Of particular interest are the compounds comprising 2-(3-hydroxypropylidene)clavam-3-carboxylic acid of the formula (III) and derivatives thereof:



Suitably the compounds of the formula (II) are presented with Z stereochemistry about the double bond, that is to say they may be represented as in formula (IV):



Suitably X is hydroxy or substituted hydroxy. Examples of substituted hydroxy groups include $-OR^1$, $-OCOR^1$, $-OCSR^1$, $-OCO_2R^1$, $-OCS_2R^1$, $OCOSR^1$, $-OCSOR^1$, $-OSO_3H$, $-OPO_3H$, $-OSO_2R^1$ and $-OCONR^2R^3$ wherein R^1 is a substituted or unsubstituted hydrocarbon group of 1 to 20 carbon atoms; and R^2 and R^3 are each independently hydrogen or substituted or unsubstituted hydrocarbon groups of 1 to 20 carbon atoms.

More suitably R^1 is C_1 -10 alkyl, C_2 -10 alkenyl, aryl (C_1 -6) alkyl, heterocyclyl (C_1 -6) alkyl, aryl (C_2 -6) alkenyl, heteroaryl (C_1 -6) alkyl, C_3 -8 cycloalkyl, aryl, heteroaryl, heterocyclyl or C_3 -8 cycloalkyl (C_1 -6) alkyl, any of such groups being optionally substituted.

Suitable optional substituents for the group R^1 include C_1 -6 alkyl, amino, C_1 -6 alkanoylamino, mono- and di- (C_1 -6) alkylamino, hydroxy, C_1 -6 alkoxy, mercapto, C_1 -6 alkylthio, heteroarylthio, arylthio,

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oxo, sulphamoyl, carbamoyl, amidino, guanidino, nitro, chloro, bromo, fluoro, carboxy and salts and esters thereof, C₁-6 alkanoyloxy, arylcarbonyl and heteroarylcarbonyl.

Suitably R² and R³ are hydrogen or C₁-6 alkyl.

In one favourable aspect X is C₁-6 alkoxy or benzyloxy optionally substituted by one, two or three halogen atoms, cyano, azido, hydroxy, C₁-6 alkoxy, C₂-6 alkanoyloxy, C₁-4 alkylthio, aryloxy such as phenoxy, amino, C₁-6 alkanoylamino, carboxy or esterified carboxy.

Suitably X is methoxy.

In another aspect X is C₁-6 alkanoyloxy such as acetoxo, C₁-6 alkyl sulphonyloxy such as methane-sulphonyloxy or arylsulphonyloxy such as p-toluene-sulphonyloxy, or C₁-6 alkylcarbamoyloxy such as methylcarbamoyloxy.

Suitably X is mercapto or substituted mercapto. Examples of substituted mercapto groups include -SCOR⁴, -S-R⁴, -SCSR⁴, -SCO₂R⁴, -SCS₂R⁴, -SCOSR⁴, -SCSOR⁴, -SSO₂R⁴, -SCONR⁵R⁶, -S(O)R⁴, -S(O)₂R⁴ and -S-SR⁴, wherein R⁴, R⁵ and R⁶ are independently substituted or unsubstituted hydrocarbon groups of 1 to 20 carbon atoms. Suitably substituents for R⁴, R⁵ and R⁶ include those described hereinabove as being suitable as substituents for R¹.

More suitably R⁴ is a C₁-10alkyl, C₂-10 alkenyl, aryl (C₁-6) alkyl, heterocyclyl (C₁-6) alkyl, aryl, (C₂-6) alkenyl, C₃-8 cycloalkyl (C₁-6) alkyl,



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heterocyclyl, heterocyclyl (C₁₋₆) alkyl, aryl, heteroaryl, heteroaryl (C₁₋₆) alkyl or C₃₋₈ cycloalkyl group, any of such groups being optionally substituted.

More suitably X is a group -S(O)_nR⁷ wherein n is zero, one or two, and R⁷ is benzyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, aryl or heteroaryl, any of such groups R⁷ being optionally substituted by one, two or three halogen atoms, azido, hydroxy, C₁₋₆ alkoxy, C₂₋₆ alkanoyloxy, C₁₋₄ alkylthio, aryloxy such as phenoxy, amino, C₁₋₆ alkanoylamino, carboxy or esterified carboxy.

Preferably X is S(O)_nR⁷ wherein n is zero or two, and R⁷ is C₁₋₆ alkyl such as methyl, benzyl, phenyl or tetrazolyl.

Suitably X is thiophenyl.

Suitably X is substituted amino. Examples of substituted amino groups include -NHR¹⁰, -NR¹⁰R¹¹, -NR¹⁰R¹¹R¹², -NHCX¹R¹⁰, -NHCX¹ZR¹⁰, -NHSO₂R¹⁰, -NHCX¹NR¹⁰R¹¹, -N(CX¹R¹²)R¹³, -N(CX¹R¹²)CZR¹³, -N(CX¹R¹²)ZR¹³, -N(CX¹ZR¹²)R¹³ and -N(CX¹ZR¹²)CX¹ZR¹³ wherein X¹ and Z are each oxygen or sulphur and R¹⁰, R¹¹, R¹² and R¹³ are independently substituted or unsubstituted hydrocarbon groups of 1 to 20 carbon atoms. Suitably substituents for R¹⁰ - R¹³ include those described hereinabove as being suitable as substituents for R¹. Additionally the groups R¹⁰ and R¹¹, or alternatively the groups R¹² and R¹³, may be joined to form a heterocyclic ring containing from three to ten carbon atoms and not more than four heteroatoms selected from oxygen, nitrogen and sulphur.



More suitably R¹⁰, R¹¹, R¹² and R¹³ are independently selected from C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, aryl (C₁₋₆) alkyl, heterocyclyl (C₁₋₆) alkyl, aryl (C₂₋₆) alkenyl, C₃₋₈ cycloalkyl (C₁₋₆) alkyl, heterocyclyl, heterocyclyl (C₁₋₆) alkyl, aryl, heteroaryl and heteroaryl (C₁₋₆) alkyl, any of such groups being optionally substituted.

In a preferred aspect X is an amino group substituted by at least one acyl and/or acyloxy group.

In particular X is an acetylamino or an N-acetyl-N-acetoxy amino group.

Most suitably X is C₁₋₆ alkylamino such as methylamino, ethylamino, propylamino and butylamino, di-(C₁₋₆) alkylamino such as diethylamino, benzylamino, C₁₋₈ alkanoylamino such as acetamido, succinimido or phthalimide, any of such groups being optionally substituted by one, two or three halogen atoms, or by an azido, hydroxy, C₁₋₆ alkoxy, C₂₋₆ alkanoyloxy, C₁₋₄ alkylthio, aryloxy such as phenoxy, amino, C₁₋₆ alkanoylamino, carboxy or esterified carboxy group.

Suitably X is succinimido.

Preferably X is C₁₋₆ alkylamino, benzylamino, C₁₋₆ alkanoylamino or di-(C₁₋₆) alkylamino.

Suitably X is an aryl or heteroaryl group bonded to the adjacent -CHR group via a carbon atom, for example phenyl, furyl, pyrrolyl, thienyl and such ring systems fused to a benzene ring, any of such groups being optionally substituted.

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Other heteroaryl groups for X which can be bonded to the adjacent CHR group by a nitrogen include triazolyl, tetrazolyl and trioxoimidazolidinyl, optionally substituted with C₁-6 alkyl or C₁-6 alkoxy carbonyl.

Suitably X is triazolyl.

Suitably X is the residue of a carbon nucleophile such as of the sub-formula -CR¹⁴R¹⁵R¹⁶ wherein R¹⁴ and R¹⁵ are the same or different and at least one of them represents a group capable of producing a stabilised carbanion, such as an electron withdrawing group, and R¹⁶ is hydrogen or a substituted or unsubstituted hydrocarbon group of 1 to 20 carbon atoms. Thus R¹⁴ and R¹⁵ may be selected from groups -CX¹R¹⁰ and CX¹ZR¹⁰ as previously described. Similarly R¹⁶ may be defined as for R¹⁰ hereinabove.

More suitably X is -CH(COOR¹⁷)COR¹⁸ or -CH(COR¹⁷)COR¹⁸ wherein R¹⁷ and R¹⁸ are independently selected from C₁-10 alkyl, C₃-8 cycloalkyl, aryl such as phenyl, aryl (C₁-6) alkyl such as benzyl, any of groups R¹⁷ and R¹⁸ being optionally substituted by one, two or three halogen atoms, C₁-6 alkoxy, C₂-6 alkanoyloxy, C₁-4 alkylthio, aryloxy such as phenoxy, C₁-6 alkanoylamino or esterified carboxy.

Suitably X is -CH(COCH₃)₂.

Suitably also X is azido or cyano. Aptly X is a halo moiety for example iodo, bromo or chloro. Compounds wherein X is azido or halo are of particular interest as useful chemical intermediates.

Suitably X is iodo.



The major use of the compounds of the formulae (II)-(IV) and salts and esters thereof is as pharmaceuticals and accordingly the salts and esters of the compounds of the formulae (II)-(IV) are preferably pharmaceutically acceptable. The compounds of this invention both pharmaceutically acceptable and non-pharmaceutically acceptable may be used as intermediates and also as antibacterial agents or β -lactamase inhibitors in non-pharmaceutical usage such as a disinfectant or paint additive.

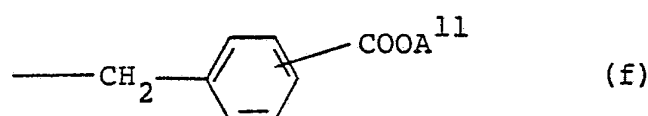
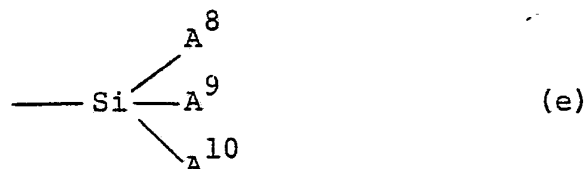
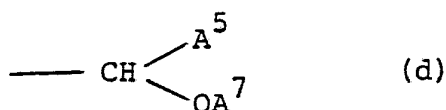
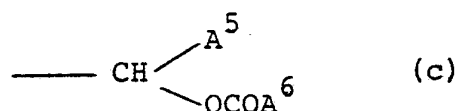
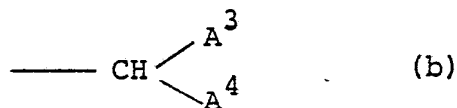
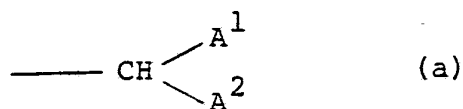
Suitable pharmaceutically acceptable salts of the compounds of formula (II)-(IV) include metal salts such as aluminium, alkali metal salts such as sodium and potassium, and alkaline earth metal salts such as calcium or magnesium; and ammonium and substituted ammonium salts, for example those with lower alkylamines such as triethylamine, cycloalkylamines such as bicyclohexylamine, 1-phenamine, N-ethylpiperidine and N-benzyl- β -phenethylamine.

Non-pharmaceutically acceptable salts for use as intermediates include the lithium and silver salts.

Suitable esters of the compounds of the formulae (II)-(IV) include those cleavable by biological methods such as enzymatic hydrolysis, in vivo hydrolysis, and those cleavable by chemical methods such as hydrogenolysis, hydrolysis, electrolysis or photolysis.

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Suitably the carboxylic acid is esterified by a group of the sub-formula (a), (b), (c), (d), (e) or (f):



wherein A¹ is a hydrogen atom, C₁-6 alkanoyl or an C₁-5 alkyl group optionally substituted by C₁-7 alkoxy or C₁-7 carboxylic acyloxy, or an alkenyl or alkynyl group of up to 5 carbon atoms; A² is a hydrogen atom or a methyl group; A³ is a phenyl group or a phenyl group substituted by a fluorine, chlorine or bromine atom or a nitro, C₁-3 alkyl or C₁-3 alkoxy group; A⁴ is a hydrogen atom or a phenyl group or phenyl group substituted by a fluorine, chlorine or bromine atom or a nitro, C₁-3 alkyl or C₁-3 alkoxy group; A⁵ is a hydrogen atom or a methyl group; A⁶ is a C₁-4 alkyl, phenyl or C₁-4 alkoxy group or A⁵ is joined to A⁶ to form a phthalidyl, dimethylphthalidyl or dimethoxyphthalidyl group; A⁷ is a C₁-4 alkyl, phenyl, chlorophenyl or nitrophenyl group; A⁸ is a C₁-4 alkyl

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or phenyl group; A⁹ is a C₁₋₄ alkyl or phenyl group; A¹⁰ is C₁₋₄ alkyl; and A¹¹ is C₁₋₄ alkyl; or CHA¹A² is a phenacyl or bromophenacyl group.

Favourably A¹ is a hydrogen atom or a methyl, ethyl, vinyl or ethynyl group. Favourably A² is a hydrogen atom. Favourably R³ is a phenyl, p-bromophenyl, p-methoxyphenyl or p-nitrophenyl group. Favourably A⁴ is a hydrogen atom. Favourably A⁶ is a methyl, t-butyl or ethoxy group or is joined to A⁵. Favourably A⁷ is a methyl group.

Preferred groups of the sub-formula (a) include the methyl, ethyl and acetyl groups.

Preferred groups of the sub-formula (b) include the benzyl and p-nitrobenzyl groups.

Preferred groups of sub-formula (c) include the acetoxymethyl, pivaloyloxymethyl, α -ethoxycarbonyloxymethyl and phthalidyl groups.

A preferred group of the sub-formula (d) is the methoxymethyl group.

Preferred groups of the sub-formula (e) include the trimethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl groups and tri-isopropylsilyl.

A preferred group of the sub-formula (f) is p-methoxycarbonylbenzyl.

Particularly preferred esterifying groups are the p-nitrobenzyl and phthalidyl groups.

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Pharmaceutically acceptable in vivo hydrolysable esters are those esters which hydrolyse in the human body to produce the parent acid or its salt. Such esters may be identified by administration to a test animal such as a rat or mouse by intravenous administration and thereafter examining the test animal's body fluids for the presence of the compound of the formulae (II)-(IV) or salt.

Suitable esters of this type include those of sub-formula (c) as hereinbefore defined.

Further suitable esters include di(C₁₋₆) alkylamino C₁₋₆ alkyl esters such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl and diethylaminoethyl.

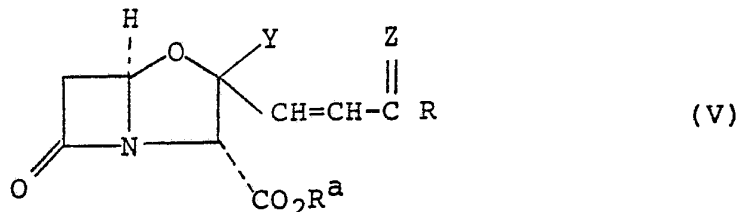
Esters of the compounds of the formula (II)-(IV) such as those of the sub-formula (a)-(f) if desired, may be presented in the form of their acid addition salts if an amino group is present in group X. The acid used to form the salt will most suitably be pharmaceutically acceptable, but non-pharmaceutically acceptable acid addition salts are also envisaged, for example as intermediates in the preparation of the pharmaceutically acceptable salts by ion exchange. Suitable pharmaceutically acceptable acid addition salts include those of inorganic and organic acids, such as hydrochloric, phosphoric, sulphuric, methanesulphonic, toluenesulphonic, citric, malic, acetic, lactic, tartaric, propionic and succinic acid.

Most suitably the acid addition salt is provided as a solid and preferably as a crystalline solid.



Compounds of this invention when in crystalline form may be solvated, for example hydrated.

The present invention provides a process for producing a compound of formula II by reduction of a compound of formula V



wherein R is as defined above in relation to formula (II), R^a is hydrogen or a carboxy blocking group, Y is tetrazolyl or triazolyl each of which may be optionally substituted and each of which is bonded to the oxazolidene ring via a nitrogen atom, or $-O.CO.R^b$ where R^b is hydrogen, alkyl, alkenyl, arylalkyl, aryl, cycloalkyl or heterocyclyl, and Z is an oxygen or sulphur atom and thereafter if necessary

- i) converting a compound of formula II where X is hydroxy or mercapto to a compound of formula (II) wherein X is not hydroxy or mercapto;
- ii) removing any carboxy blocking group R^a ;
- iii) converting the product into a salt or ester.

The reduction is effected by conventional methods preferably using one or more mild reducing agents. Care must be taken not to reduce the CO_2R^a group at the same time.

Preferably Z is oxygen.

In formula V, when Y is tetrazolyl or triazolyl, suitable substituents are esterified or salified carboxy, optionally substituted C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, or aryl, azido, isocyano, cyano, nitro, bromo, chloro, or a group of the sub-formula

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$-(CO)_n-NR^XRY$ wherein n is zero or one, R^X is hydrogen or optionally substituted C_{1-6} alkyl, C_{1-6} alkanoyl, or arylcarbonyl, and R^Y is hydrogen, C_{1-6} alkyl or C_{1-6} alkanoyl, or R^X and RY may be joined to form (with the nitrogen atom to which they are attached) an optionally substituted 4,5 or 6-membered ring.

Preferred substituents are optionally substituted C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, or aryl; azido, isocyano, cyano, nitro, bromo, chloro, or a group of the sub-formula $-NR^XRY$ wherein R^X is hydrogen or optionally substituted C_{1-6} alkyl, C_{1-6} alkanoyl, or arylcarbonyl, and R^Y is hydrogen, C_{1-6} alkyl or C_{1-6} alkanoyl, or R^X and R^Y may be joined to form (with the nitrogen atom to which they are attached) an optionally substituted 4,5 or 6-membered ring.

Within group R^b in formula (V), alkyl and alkenyl groups or moieties have from 1 to 6 carbon atoms; aryl groups include those selected from phenyl; phenyl substituted in one or more positions in the ring by one or more of alkyl, alkenyl, alkoxy, halo such as chloro, alkyl substituted by halo such as trifluoromethyl, nitro, amino, mono- or di-alkylamino, carboxy, alkoxy carbonyl, acylamino and like substituents; naphthyl, quinolyl each of which may be optionally substituted as defined above in relation to 'phenyl'; and cycloalkyl and heterocyclyl groups have from 3 to 10 atoms selected from C, N, O and S such as pyrrolyl, furyl, thienyl and pyridyl.

Suitably, Y is tetrazolyl or triazolyl, each of which may be optionally substituted by C_{1-6} alkyl, C_{2-6} alkenyl, bromo or chloro, or $-O.CO.R^b$ where R^b is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or optionally substituted phenyl.



Preferably, Y is 2-tetrazolyl, optionally 5-substituted by alkyl; triazolyl; or $-O.CO.R^b$ where R^b is alkyl or aryl.

More preferably, Y is 2-tetrazolyl, optionally 5-substituted by C_{1-4} alkyl; triazolyl; or $-O.CO.R^b$ where R^b is C_{1-4} alkyl or phenyl. Preferred C_{1-4} alkyl groups are methyl and ethyl. An especially preferred C_{1-4} alkyl group is methyl.

Suitable carboxy-protecting groups for the group $-CO_2R^a$ in formula (V) include ester derivatives of the carboxylic acid. The derivative is preferably one which may readily be cleaved at a later stage of the reaction.

Suitable ester-forming carboxy-protecting groups are those which may be removed under conventional conditions. Such groups for R^a include benzyl, p-methoxybenzyl, 2,4,6-trimethylbenzyl, 3,5-di-t-butylbenzyl, 4-pyridylmethyl, allyl, diphenylmethyl, triphenylmethyl, 2-benzyloxyphenyl, 4-methylthiophenyl, methoxymethyl, a silyl or a phosphorus-V-containing group, or methyl or ethyl, but especially benzyl.

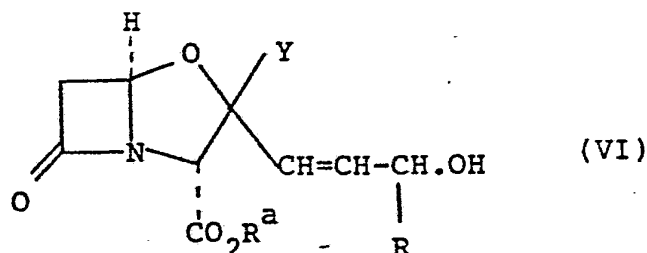
The free carboxylic acid or a salt thereof may be regenerated from any of the above esters by usual methods appropriate to the particular R^a group; for example, by base-catalysed hydrolysis, by enzymically-catalysed hydrolysis or by hydrogenation.

The reduction of the compound (V) to give compound (II) involves two steps, namely reduction of the moiety

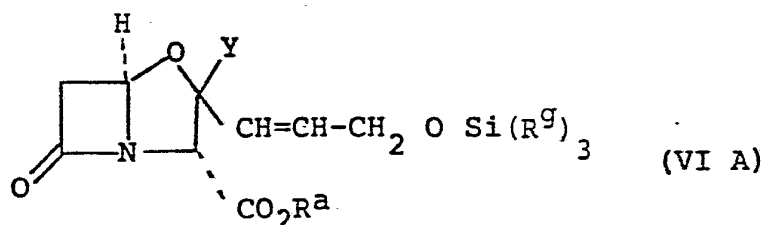
$$-CH=CH-\overset{\overset{Z}{||}}{C}.R$$
 and removal of the group Y. These two



steps may be performed in one reaction or separately, depending on the nature of the groups involved. For example, when Y represents a group $-O.CO.R^b$, the process is conveniently carried out in two stages, by initially reducing the compound (V), for example with zinc borohydride to give an allylic alcohol of formula (VI):



The group Y may then be removed by further reduction, for example catalytic hydrogenation, preferably after protection of the alcohol group. For example, the alcohol may be protected by silylation to form a protected derivative of formula (VI A):



where R^g is a hydrocarbon group as defined hereinbefore.

Suitable silylating agents include halosilanes or silazanes, particularly trimethylchlorosilane, dimethyl-dichlorosilane or bis(trimethyl silyl) acetamide.

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This protected intermediate can then be reduced using standard reactions with conventional reducing agents for example hydrogen in the presence of palladium catalyst.

The hydrogenation reaction is effected in a solvent inert under reaction conditions such as toluene, tetrahydrofuran, dioxan, ethanol or aqueous ethanol or mixtures thereof.

The protecting group is subsequently cleaved after the hydrogenation to yield the free acid, ester or salt of formula (II).

When Y is tetrazolyl, the reduction and removal of the Y group to produce a compound of formula II may be effected in one stage using an appropriate reducing agent such as zinc borohydride.

This reaction normally takes place in a solvent inert under the reaction conditions such as toluene, dichloromethane, tetrahydrofuran or dioxan, or mixtures thereof, but especially tetrahydrofuran and toluene.

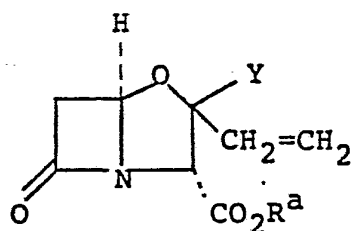
The reaction is generally carried out at a depressed or non-elevated temperature, for example -80° to +30°C, and preferably at a depressed temperature, for example -20° to + 20°C, and conveniently at about 0°C.

This process may produce isomers of formula II with both Z and E stereochemistry about the double bond. The two isomers can be separated using conventional methods and where required the E isomer can be converted to the Z isomer using ultra violet light.

Compounds of formula V are novel and form part of the invention.



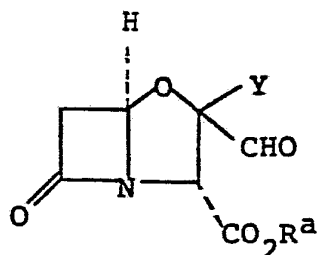
They are derived from compounds of formula (VII):



(VII)

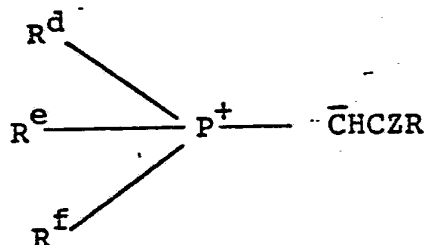
wherein R^a and Y are as defined above in relation to formula (V).

A compound of formula (VII) is subjected to ozonolysis to produce an intermediate compound of formula (VIII)



(VIII)

followed by reaction of this compound with a Wittig reagent of formula (IX)



(IX)

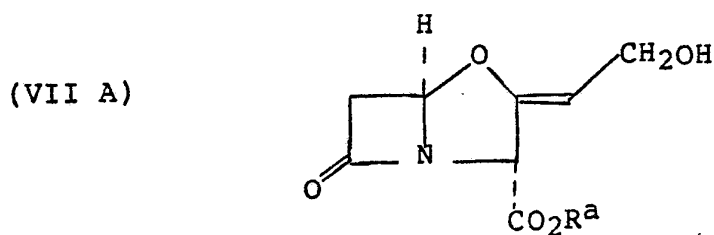
where Z is as defined in relation to formula (V), R is as defined in relation to formula II, and R^d, R^e and R^f are each independently C₁-6 alkyl, aryl or aryl (C₁-6)

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alkyl. Preferably R^d , R^e and R^f are phenyl.

Compounds of formula (VII) are also novel and hence form part of the invention.

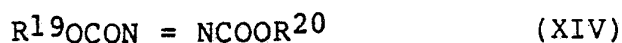
Compounds of formula (VII), are obtained by reacting a compound of formula (VIIA)



wherein R^a is as defined in relation to formula (V) with

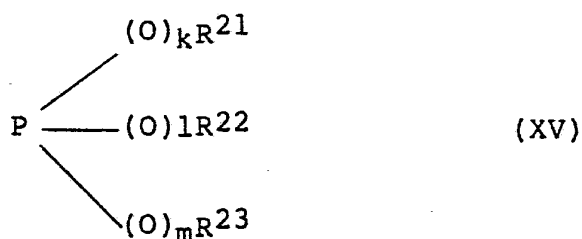
(i) YH wherein Y is as defined in formula (V) and, where appropriate, is bonded to the hydrogen atom via a nitrogen atom (ie YH is tetrazole, triazole, or $RCOOH$);

(ii) a compound of formula (XIV):



wherein R^{19} and R^{20} are each independently C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl; and

(iii) a compound of formula (XV):



wherein k , l and m are each independently 0 or 1, and R^{21} , R^{22} and R^{23} are each independently C_1 -6 alkyl, aryl or aryl(C_1 -6)alkyl.

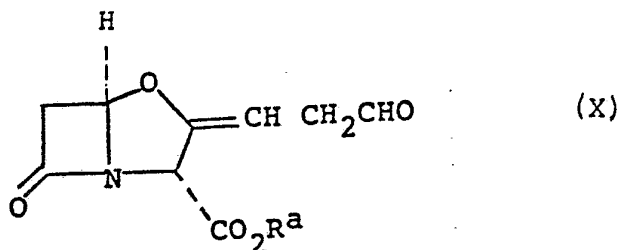
Suitable compounds of formula (XIV) include those wherein R^{19} and R^{20} are each independently methyl, ethyl, propyl, butyl, phenyl or benzyl. It is generally convenient that R^{19} and R^{20} represent the same moiety. Particularly suitable compounds of the formula (XIV) include those wherein R^{19} and R^{20} each represent ethyl, *t*-butyl or isopropyl, but especially ethyl.

Suitable compounds of formula (XV) include those wherein R^{21} , R^{22} and R^{23} are each independently methyl, ethyl, *n*-propyl, *n*-butyl, benzyl, phenyl or methoxyphenyl. It is generally convenient that R^{21} , R^{22} and R^{23} each represent the same moiety. Favoured compounds of formula (XV) include tri-arylphosphines and tri-alkylphosphites. Particularly suitable compounds of formula (XV) include triphenylphosphine, trimethylphosphite, triethylphosphite and tri-*p*-methoxyphenylphosphine, but especially triphenylphosphine.

Compounds of formula VIIA can be derived by conventional methods from clavulanic acid of formula (I).



The present invention also provides a process for the production of a compound of formula II wherein R is hydrogen by reduction of a compound of formula X



where R^a is as defined hereinbefore in relation to formula (V);

and thereafter if necessary

- i) converting a compound of formula (II) where X is hydroxy to a compound of formula (II) where X is not hydroxy,
- ii) removing any carboxy blocking groups R^a ,
- iii) converting the product to a salt or ester.

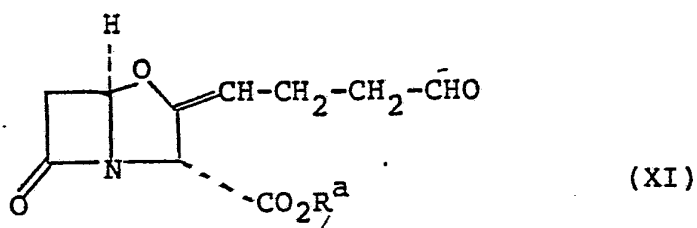
The reduction is carried out using standard methods. A suitable method of reduction utilises a complex hydride such as a borohydride, for example lithium borohydride, sodium cyanoborohydride, di-isobutyl aluminium hydride; or a reagent such as aluminium tri-isopropoxide. Such reaction may be performed in an inert organic solvent such as a hydrocarbon, a chlorinated hydrocarbon or an ether, for example toluene, cyclohexane, diethyl ether, heptane, hexane, dichloromethane or tetrahydrofuran. The reaction may be performed at any non-extreme

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temperature for example -30°C to $+60^{\circ}\text{C}$, more suitably 0°C to $+30^{\circ}\text{C}$ and most conveniently at ambient temperature.

Compounds of the formula (II) wherein X is hydroxy may be converted to the compounds of the formula (II) where X is not OH in conventional manner, using methods appropriate to the formation of each functional group.

Compounds of formula (X) are novel and as such form part of the invention. They can be produced from compounds of formula (XI).



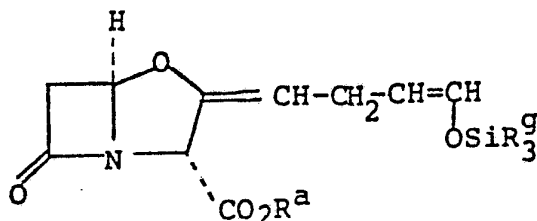
where R^a is as defined hereinabove in relation to formula (V).

Compounds of formula (XI) together with processes for their preparation are described in European Patent Application Publication No. 0080286.

A compound of formula (XI) is treated with a silylating agent. Suitable silylating agents include halosilanes or silazanes. A particularly preferred

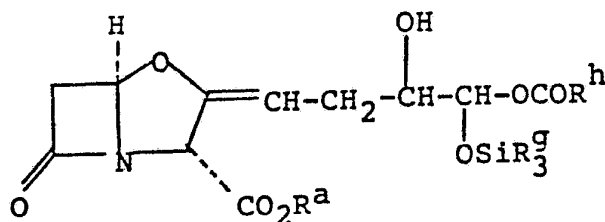
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silylating agent is trimethylsilyl trifluoro methane sulphonate. The silylated intermediate has the formula



where R^a and R^g are as defined hereinbefore in relation to formula (V) and (VI A) respectively.

This intermediate is not stereospecific with respect to the double bond at the 3 carbon position in the side chain. It is then subjected to a peracid oxidation step to give a second intermediate of formula

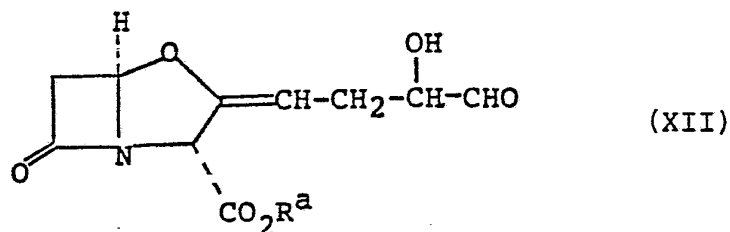


where R^h is a residue of carboxylic acid. Suitable peracids include peracetic acid and perbenzoic acid.

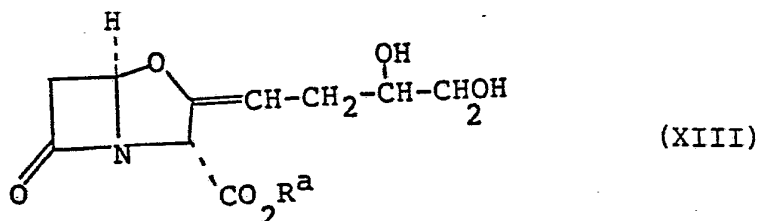
The second intermediate is reacted with a tetra alkyl ammonium fluoride, for example tetraethyl

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ammonium fluoride dihydrate which produces a compound of formula XII



This compound is conveniently reduced in situ to form a compound (XIII)



wherein R^a is as defined hereinbefore in relation to formula V.

This compound (XIII) is novel and forms part of the invention. The reduction reaction can be carried out by conventional methods. A suitable method of reduction utilizes a complex hydride such as borohydride. For example lithium borohydride, sodium or potassium borohydride, sodium cyanoborohydride, di-isobutyl aluminium hydride; or a reagent such as aluminium tri-isopropoxide.

Reaction of a compound of formula (XIII) with an oxidising agent such as periodic acid or lead tetracetate yields a compound of formula (X).

This process is advantageous in that when the starting material of formula X is stereospecific with respect to the double bond attached to the oxazolidine ring, the product will have the same stereochemistry.

In order to convert a compound of formula II where X is hydroxy or an ester or salt thereof to a compound of formula II where X is other than hydroxy, conventional methods appropriate to the functional group required are employed.

For example, compounds wherein X is halo may be prepared by reaction with a halogenating agent such as a non-metallic halide for example phosphorus trichloride, phosphorus tribromide, thionyl chloride, thionyl bromide or the halogenating agent may be a hydrocarbonsulphonyl halide generally used in the presence of halide ions, for example an alkanesulphonyl halide such as methanesulphonylchloride or an arylsulphonyl halide such as p-toluenesulphonyl chloride; the source of halide ions may be lithium halide or an amine salt. Preferably in the halogenation reaction a base is present such as pyridine, and the reaction is preferably performed at a depressed or ambient temperature for example -60°C to +20°C. The compounds of the formula (II) wherein X is iodo are most conveniently prepared by a halogen exchange reaction, reacting the corresponding chloro or bromo compound with a source of iodide ions such as lithium iodide or trimethylphosphite methiodide.

Compounds of the formula (II) wherein X is substituted hydroxy or mercapto may be prepared by conventional methods, for example by etherification or acylation. Etherification of -OH or -SH may be effected by the



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reaction of a diazoalkane in the presence of a Lewis acid catalyst for example boron trifluoride preferably at a depressed or ambient temperature in an inert solvent. Acylation of -OH or -SH may be effected by reaction with an acylating agent e.g. RCY-T or RSO₂T wherein T is a leaving group displaceable by a nucleophile. Suitably T is halo such as chloro or bromo, or a sulphonyloxy moiety, for example C₁-6 alkyl- or aryl- sulphonyloxy such as a mesylate or tosylate, or T is a carboxylate moiety, for example a C₁-6 alkanoyloxy group optionally substituted by 1 to 3 halogen atoms, in particular acetoxy or is an arylcarbonyloxy for example benzoyloxy.

Preferably such reaction is performed in the presence of a base such as an alkali or alkaline earth metal salt, in particular lithium, sodium or potassium carbonates; or an organic base such as amine for example pyridine or a tertiary amine and in particular triethylamine. Suitable solvents include chloroform, dichloromethane, tetrahydrofuran, dimethylformamide, dimethylsulphoxide and acetone. Generally the acylation reaction is performed at a non-extreme temperature for example at an ambient or slightly depressed temperature, such as -20°C to +20°C. Alternatively T is a hydroxy group or hydrocarbyloxy for example C₁-6 alkoxy or aryloxy such as phenoxy. When T is hydroxy preferably a dehydrating agent such as dicyclohexylcarbodi-imide is present.

Compounds of the formula (II) wherein X is azido may be prepared by the reaction of an azide with a compound of the formula (II) wherein X is a readily displaceable group such as a halogen atom (chlorine or bromine) or a sulphonyloxy group. The azide is suitably an alkali metal azide such as sodium azide or an organic azide such as tetramethylguanidinium azide or tetrabutylammonium azide. The reaction is preferably



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performed in an inert polar organic solvent such as acetonitrile, dimethylsulphoxide, ethyl acetate, dichloromethane, acetone or tetrahydrofuran at a non-extreme temperature.

Azide derivatives can also be prepared by the reaction of a compound of formula (II) wherein X is OH with hydrazoic acid in the presence of a compound of formula (XIV) as hereinbefore defined:

and a compound of formula (XV) as herenbefore defined.

The reaction is suitably performed in an inert organic solvent such as tetrahydrofuran or benzene, at a non-extreme temperature such as -20°C to $+100^{\circ}\text{C}$ usually at -50°C to 50°C and conveniently at ambient temperature.

Compounds of the formula (II) wherein X is substituted amino may be prepared by the reaction of the corresponding primary amine, for example by alkylation and/or acylation. Primary amines can be produced by reduction of the corresponding nitro compound which is described in European patent publication No. 2319 or by reduction of the corresponding azido compound.

Certain acyl and acyloxy amines can be obtained directly from the nitro compound by reaction with an acyl anhydride and zinc in the presence of acetic acid.

Alkylation of the primary amine ($-\text{NH}_2$) may be effected by reaction with a compound RX' wherein X' is a leaving group to form a secondary amine ($-\text{NHR}$). This secondary amine then may be reacted with another compound RX' (which may be the same or different as

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the first) to form a tertiary amine ($-NR_2$). and subsequently, if desired, a quaternary amine ($-NR_3^+$) may be prepared, wherein the substituent groups are the same or different. Suitable groups X'' include halo such as iodo and bromo, or a sulphonate such as a C_{1-6} alkyl- or aryl- sulphonate for example methanesulphonate or p-toluenesulphonate. Such alkylation reactions are conveniently performed in an inert organic solvent such as dimethylformamide, acetonitrile or dichloromethane, preferably in the presence of strong non-nucleophilic organic base at a non-extreme temperature such as $-20^\circ C$ to $+50^\circ C$, preferably $-10^\circ C$ to $+20^\circ C$ and most conveniently between $0^\circ C$ and ambient. Suitable organic bases include 1,5-diazabicyclo [4.3.0]non-5-ene and 1,8-diazabicyclo [5.4.0]undecene.

Secondary and tertiary amines also may be prepared by the reaction of a compound of the formula (II) wherein X is a good leaving group, such as tosyloxy with a secondary amine ($RNHR^O$) to form a tertiary amine. One or both of the groups R and R^O may then be removed, for example by hydrogenation to provide a secondary or primary amine.

Acylation of the primary amine ($-NH_2$) may be effected by reaction with an acylating agent. Apt acylating agents include any N-acylating compound suitable for the performance of analogous reactions with 6-aminopenicillanic acid or 7-aminocephalosporanic acid or salts or esters thereof, for example an acid halide, an anhydride or mixed anhydride or other reactive derivative, such as that produced by the reaction of an acid with an enzyme or a condensation-promoting agent such as dicyclohexylcarbodi-imide. Thus in general the acylating agent is of the formula RX'' where X'' is a



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displaceable group, for example halo, sulphonate, carboxylate. The acylating agent also may be a ketene or isocyanate or isothiocyanate or an activated imide. Preferably the acylation reaction is performed in the presence of a base, for example an inorganic base such as an alkali or alkaline earth metal salt, in particular lithium, sodium or potassium carbonates; or an organic base such as an amine for example triethylamine. Suitably the reaction is performed in an aprotic organic solvent such as dimethylformamide, acetonitrile, ethyl acetate, dimethyl sulphoxide; water may be added to aid solubility if necessary. The reaction is suitably performed at a non-extreme temperature, for example between -20°C and 40°C and preferably at ambient temperature.

Acylation may be effected on the primary amine ($-\text{NH}_2$) once or twice to form the mono-acyl or di-acyl derivatives, in the di-acyl case the acyl groups may be the same or different. Alternatively acylation may be effected on a secondary amine ($-\text{NHR}$) to form the N-alkyl-N-acyl derivative.

Di-acyl derivatives wherein the two acyl groups are joined so as to form a heterocyclic ring are most conveniently prepared by the reaction of a compound of the formula (II) wherein X is OH with a compound of the formula: $\text{HNR}_\text{A}\text{R}_\text{B}$ wherein R_A and R_B form the heterocyclic ring system in the presence of an azodicarboxylate compound of the formula (XIV) and (XV) as hereinbefore defined. The reaction is suitably performed in an inert organic solvent such as tetrahydrofuran and benzene, at a non-extreme temperature such as -20°C to $+100^{\circ}\text{C}$, usually at -50°C to 50°C and conveniently at ambient temperature.



Bis-acyl derivatives can be prepared under similar reaction conditions by the reaction of a compound of formula (II) wherein X is OH with an O-acyl hydroxamic acid derivative of formula $R_c\text{CO.NH.O.CO } R_d$ wherein R_c and R_d are each independently C_1-6 alkyl, C_2-6 alkenyl, C_1-6 alkyl acyl or aryl, in the presence of a compound of formula (XIV) and (XV) as hereinbefore defined.

The foregoing reaction may also be used to prepare di-acyl derivatives wherein the two acyl groups are not joined. If one of the two acyl groups are removable for example hydrogenolysable then a mono-acyl derivative may be formed.

Compounds of the formula (II) wherein X is cyano may be prepared by the reaction of a compound of the formula (II), wherein X is OH with hydrogen cyanide in the presence of a compound of the formula (XIV) and a compound of the formula (XV) under similar reaction conditions to those described above.

Compounds of the formula (II) wherein X is an activated aryl or heteroaryl group may be prepared by the reaction of a compound of the formula (II), wherein X is OH with an appropriate aromatic or heteroaromatic compound. By 'activated aryl or heteroaryl' we mean a group derived from an aromatic or heteroaromatic compound that is sufficiently activated to undergo a Friedel-Crafts alkylation. Suitably such compounds include phenol, phenol substituted by one, two or three atoms or groups selected from hydroxy, halo, C_1-6 alkoxy, C_1-6 alkyl or C_3-8 cycloalkyl; furan optionally substituted by C_1-6 alkyl, thiophene optionally substituted by C_1-6 alkyl, pyrrole optionally substituted by C_1-6 alkyl, or any of the aforementioned ring systems fused to an optionally substituted benzene



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ring. A catalyst is employed which is one known to catalyst reactions known as Friedel-Crafts reactions. Suitable catalysts include aluminium trichloride, zinc chloride, zinc bromide, antimony pentachloride, ferric chloride, stannic chloride, boron trifluoride etherate and chemical equivalents thereof. Of these boron trifluoride etherate is preferred. The reaction is generally performed in the presence of an inert organic solvent, preferably a non-polar solvent such as a halogenated hydrocarbon for example chloroform, carbon tetrachloride or dichloromethane. Suitable the reaction is performed at a depressed or moderate temperature, i.e. between +50°C and -70°C, preferably between 0°C and -30°C. Preferably the reaction is performed under an inert atmosphere.

Compounds of the formula (II) wherein X is the residue of a carbon nucleophile may be prepared from compounds of the formula (II) wherein X is a displaceable group by reaction with a carbon nucleophile. The displaceable group may be halo such as chloro, bromo or iodo or aryl- or C₁₋₆ alkyl- sulphonyloxy for example p-toluenesulphonyloxy or methanesulphonyloxy. Reaction is suitably performed in an aprotic organic solvent at a depressed or ambient temperature for example -70°C to +25°C, preferably at -20°C to 0°C. Suitable solvents include tetrahydrofuran, dimethylformamide or dimethylsulphoxide. The carbon nucleophile may be a compound R-H in which case a base is present, or the carbon nucleophile may be presented as a salt. The cation in such a salt is suitably a metal ion or an ammonium ion, for example sodium, potassium, thallium or a tetra-C₁₋₆-alkyl ammonium cation.

Compounds of this type where X is a carbon nucleophile may be produced by reaction of a compound of formula (II) wherein X is OH with R-H in the presence of a



compound of formula (XIV) and (XV) as described hereinbefore. Similar reaction conditions to those described above in relation to the reaction of compounds of formula (II) with other above-mentioned compounds in the presence of compounds of formula (XIV) and (XV) are applicable.

Suitable salts include both pharmaceutically acceptable and non-pharmaceutically acceptable salts, for example inorganic salts such as metal salts (silver and mercuric), or alkali metal salts (sodium and lithium) and tertiary amine salts.

The present invention also provides a pharmaceutical composition which comprises a compound of this invention and a pharmaceutically acceptable carrier.

The compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of the infection in animals especially mammals including humans.

Suitable forms of the compositions of this invention include tablets, capsules, creams, syrups, suspensions, solutions, reconstitutable powders and sterile forms suitable for injection or infusion. Such compositions may contain conventional pharmaceutically acceptable materials such as diluents, binders, colours, flavours, preservatives, disintegrant and the like in accordance with conventional pharmaceutical practice in the manner well understood by those skilled in the art of formulating antibiotics.



The injectable solution of the compound of this invention may be made up in a sterile pyrogen-free liquid such as water, aqueous ethanol or the like.

An alternative approach to administering the compounds of this invention is to utilise an injectable suspension. Such suspensions may be made up in sterile water; sterile saline or the like and may also contain suspending agents such as polyvinylpyrrolidone, lecithin or the like. For use in such suspensions the zwitterionic compounds of this invention should be in the form of fine particles.

Injectable or infusable compositions of a compound of the invention are particularly suitable as high blood levels of the compound can occur after administration by injection or infusion. Thus, one preferred composition aspect of this invention comprises a compound of the invention in sterile form and most suitably in sterile crystalline form.

Alternatively, such compositions may be prepared in an acceptable oil suspending agent such as arachis oil or its equivalent. For use in such suspensions the compounds of this invention should be in the form of fine particles.

Unit dose compositions comprising a compound of this invention adapted for oral administration form a further suitable composition aspect of this invention.

Unit dose compositions comprising a compound of this invention adapted for topical administration are also presented by this invention.

The compound of the formula may be present in the composition as sole therapeutic agent or it may be present together with other therapeutic agents such as, for example, a penicillin or cephalosporin.

Considerable advantages accrue from the inclusion of a penicillin or cephalosporin which shows instability to β -lactamases since the resulting composition shows enhanced effectiveness (synergy). Suitable penicillins, cephalosporins or other β -lactam antibiotics for inclusion in such synergistic compositions include not only those known to be highly susceptible to β -lactamases but also those which have a degree of intrinsic resistance to β -lactamases.

Suitable penicillins for inclusion in the compositions of this invention include benzylpenicillin, phenoxymethylpenicillin, carbenicillin, azidocillin, propicillin, ampicillin, amoxycillin, epicillin, ticarcillin, cyclacillin, pirlbenicillin, azlocillin, mezlocillin, sulbenicillin, piperacillin, and other well known penicillins including pro-drugs thereof such as their in vivo hydrolysable esters such as the acetoxymethyl, pivaloyloxymethyl, α -ethoxycarbonyloxyethyl or phthalidyl esters of ampicillin benzylpenicillin or amoxycillin, and aldehyde or ketone adducts of penicillins containing a 6- α -aminoacetamide side chain (such as hetacillin, metampicillin and analogous derivatives of amoxycillin) or α -esters of carbenicillin or ticarcillin such as their phenyl or indanyl α -esters.

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Suitable cephalosporins for inclusion in the compositions of this invention include, for example, cefatrizine, cephaloridine, cephalothin, cefazolin, cephalixin, cephacetrile, cephapirin, cephamandole nafate, cephradine, 4-hydroxycephalexin, cefaparole, cephaloglycin, cefoperazone, and other well known cephalosporins or pro-drugs thereof.

Such compounds are frequently used in the form of a salt of hydrate or the like.

Naturally if the penicillin or cephalosporin present in the composition is not suitable for oral administration then the composition will be adapted for parenteral administration.

Highly favoured penicillins for use in the compositions of this invention include ampicillin, amoxycillin, carbenicillin and ticarcillin. Such penicillins may be used as a pharmaceutically acceptable salt such as the sodium salt. Alternatively the ampicillin or amoxycillin may be used in the form of fine particles of the zwitterionic form (generally as ampicillin trihydrate or amoxycillin trihydrate) for use in an injectable suspension, for example, in the manner hereinbefore described for a compound of this invention.

The preferred penicillin for use in the synergistic composition is amoxycillin, for example as its sodium salt or trihydrate.

Particularly suitable cephalosporins for use in the compositions of this invention include cephaloridine and cefazolin which may be in the form of a pharmaceutically acceptable salt, for example the sodium salt.



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When present together with a cephalosporin or penicillin, the ratio of a compound of the invention to the penicillin or cephalosporin agent may vary over a wide range of ratios, such as from 10:1 to 1:10, for example about 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, 1:5 or 1:6 (wt/wt, based on pure free antibiotic equivalent).

The total quantity of a compound of the invention in any unit dosage form will normally be between 25 and 1000 mg and will usually be between 50 and 500 mg, for example about 62.5, 100, 125, 150, 200 or 250 mg.

Compositions of this invention may be used for the treatment of infections of inter alia, the respiratory tract, the urinary tract and soft tissues in humans.

Normally for adult (70kg) human treatment between 50 and 3000 mg of the compounds of the invention will be administered each day of treatment. This corresponds to a dosage of 0.7 to 50 mg/kg per day. More usually between 100 and 1000 mg of the compounds of the invention will be administered per day, corresponding to from 1.5 to 15mg/kg per day, for example at 1-6 doses, more usually as 2, 3 or 4 doses. However for the treatment of more severe systemic infections or infections of particularly intransigent organisms higher doses may be used in accordance with clinical practice.

The penicillins or cephalosporin in the synergistic composition of this invention will normally be present at approximately the amount at which it is conventionally used which will usually be expected to be from about 62.5 to 3000 mg per dose, more usually about 125, 250, 500 or 1000 mg per dose.



One particularly favoured composition of this invention will contain from 150 to 1000 mg of amoxycillin as the trihydrate or sodium salt and from 25 to 500 mg of a compound of this invention.

A further particularly favoured composition of this invention will contain from 150 to 1000 mg of ampicillin or a pro-drug thereof and from 25 to 500 mg of a compound of this invention.

Most suitably this form of composition will contain ampicillin trihydrate, ampicillin anhydrate, sodium ampicillin, hetacillin, pivampicillin, hydrochloride, bacampicillin hydrochloride or talampicillin hydrochloride. Most suitably this form of the composition will contain a zwitterionic compound of the formula (II) when in crystalline form.

Most suitably the preceding composition will contain from 200 to 700 mg of the penicillin component. Most suitably the preceding composition will comprise from 50 to 250 mg of a zwitterionic compound of the formula (II) preferably in crystalline form.

Such compositions may be adapted for oral or parenteral use except when containing an in vivo hydrolysable ester of ampicillin or amoxycillin in which case the compositions will not be adapted for parenteral administration.

Another particularly favoured compositions of this invention will contain from 200 to 2000 mg of carbenicillin, ticarcillin or a pro-drug thereof and from 50 to 500 mg of a compound of this invention.

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Suitably this form of composition will contain di-sodium carbenicillin. Suitably this form of the composition will contain di-sodium ticarcillin.

More suitably this form of the composition will contain from 75 to 250 mg of a zwitterionic compound of the formula (II) preferably in crystalline form. Such compositions containing di-salts of carbenicillin and ticarcillin will be adapted for parenteral administration.

The present invention also provides a method of treating bacterial infections in animals, in particular humans or domestic mammals, which comprises the administration of a composition of this invention

Commonly the infection treated will be due to a strain of Staphylococcus aureus, Klebsiella aerogenes, Escherichia coli, Proteus sp., Bacteroides fragilis or the like. The organisms believed to be most readily treated by an antibacterially effective amount of a compound of this invention is Staphylococcus aureus. The other organisms named are more readily treated by using a synergistically effective amount of the compound of this invention and a penicillin or cephalosporin. The administration of the two components may take place separately but in general we prefer to use a composition containing both the synergist and the penicillin or cephalosporin.

The indications for treatment include respiratory tract and urinary tract infections in humans.



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Preparation 1aBenzyl 2-(tetrazol-2-yl)-2-vinylclavam-3-carboxylate
(both isomers about C-2)

To a solution of benzyl clavulanate (11.56 g) in dry redistilled tetrahydrofuran (250 ml) was added tetrazole (5 g) and triphenylphosphine (12.56 g). The mixture was stirred under nitrogen at about 25°C until all was in solution, then cooled to -10°C and diethyl azodicarboxylate (8.5 ml) added rapidly. The temperature rose to +18°C. After 30 minutes at ambient temperature, the solvents were partially evaporated, toluene (100 ml) added and re-evaporated. Toluene (250 ml) was added and evaporated until a total volume of about 150 ml remained. After cooling for a short time the insolubles were removed by filtration and the filtrate evaporated to circa 70 ml. It was applied to a silica gel column made up to 33% ethyl acetate in hexane and eluted with 30% ethyl acetate in hexane. The first eluted major product (by t.l.c.) was collected and fractions containing it were evaporated to an oil (5.0 g). The isomers of this compound were not readily separable. I.r. (film) 3145, 1806, 1755 and 700 cm^{-1} ..

Preparation 1bBenzyl 2-(2-formylvinyl)-2-(tetrazol-2-yl)-clavam-
3-carboxylate

Benzyl 2-(tetrazol-2-yl)-2-vinyl clavam-3-carboxylate (4.7 g) in ethyl acetate (about 100 ml) was cooled to -65°C and the solution saturated with ozone (pale blue colour). Triphenylphosphine (3.5 g) was added and the



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mixture allowed to warm to -10°C . Formylmethylenetriphenylphosphorane (8 g) was slurried with N,N-dimethylformamide (3 x 50 ml portions), allowing to settle partially each time and then adding the supernatant (and some solid) to the ozonolysis product, the remaining insoluble solid was also added. The mixture was allowed to stir at -10°C to 0°C for 2.5 hours. The insoluble material was filtered off and washed with toluene (1.5 g recovered). The filtrate was diluted with toluene (30 ml) and poured into water (200 ml), slightly acidified (pH 5) and separated. The aqueous phase was washed with three further portions of toluene-ethyl acetate (70 ml, 2:5); the combined solvent layers were then washed with water (50 ml) and dried over Na_2SO_4 . The tlc then showed three KMnO_4 positive zones and triphenyl phosphine oxide. The fastest running zone was triphenyl phosphine.

The solvents were evaporated to low volume and the residue subjected to chromatography on silica gel using hexane-ethyl acetate (2:1) as eluent. The fractions containing the desired product were combined and evaporated to an oil (1.25 g). It had IR (film) 3145 (tetrazole CH), 1805 (β -lactam), 1760 (broad, ester C=O), 1700 (aldehyde C=O) and 700 cm^{-1} (aromatic CH) inter alia. The compound is a mixture of isomers about C-2 of the clavam nucleus, these isomers may be partially separated by chromatography, but this is not necessary for the present purpose.

Example 1a

Benzyl 2-2-(3-hydroxypropylidene)clavam-3-carboxylate

To a solution of the aldehyde (1.25 g) from Preparation 1b in redistilled tetrahydrofuran (20 ml) cooled at -10°C



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and stirred was added a solution of zinc borohydride (50 ml, 0.145M) in ether. The mixture was allowed to stir for a short time whilst warming to ambient temperature. Sufficient 1 M hydrochloric acid was added to give a clear solution (about 8 ml). Saturated brine was added (25 ml), stirred and separated. The non-aqueous phase was washed with a little water and filtered through a phase-separating paper. The solvent phase was collected and evaporated under reduced pressure to an oil, which was subjected to chromatography on silica gel using ethyl acetate-hexane (1:1). A partial separation was obtained. The fractions containing the desired product were combined, evaporated and rechromatographed on silica gel using a reverse gradient: 3:2 ethyl acetate-hexane, graded to 1:1 ratio. The first eluted component was the double-bond E isomer, followed by the title compound (100 mg) with the Z-configuration which had spectral characteristics identical to the material prepared by reduction of the aldehyde of example 3 hereinafter.

Example 1b

Lithium Z-2(3-hydroxypropylidene)clavam-3-carboxylate

A solution of benzyl Z-2(3-hydroxypropylidene)-clavam-3-carboxylate (0.11 g, 0.36 mmol) in ethanol (15 ml) was hydrogenated in the presence of 10% palladium on carbon (0.1 g) at ambient temperature and pressure. The reaction was monitored by thin layer chromatography for the disappearance of substrate after which time (ca. 10 min) the catalyst was filtered off. The ethanolic solution was added to distilled water (15 ml) and the pH was adjusted to pH 7 with 0.01M lithium hydroxide. The solvent was then removed under high vacuum to leave a crystalline solid (0.032 g, 40% yield).



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ν_{max} . (Nujol) 3400, 1786, 1705 and 1603 cm^{-1} .
 n.m.r. (D_2O) 2.21 - 2.45 (2H, m, $\text{C}:\text{CCH}_2$), 3.08 (1H, d, J 16.6 Hz, 6 β -CH), 3.46 - 3.67 (3H, m, 6 α -CH and CH_2OH), 4.69 (1H, t, J 7.7 Hz, $\text{C}:\text{CH}$), 4.90 (1H, s, 3-CH) and 5.67 (1H, d, J 2.5 Hz, 5-CH).

Synergistic Activity of Compound of Example 1b with
Amoxycillin (MIC Amox. in $\mu\text{g/ml}$)

	Inhib conc $\mu\text{g/ml}$	S.aureus Russell	K.aerog. E70	P.mirab C889	E.coli JT39
Amox. alone	0	1000	2000	>2000	2000
Amoxycillin + Compound of Ex 1b	5 1	0.8 3.1	3.1 12.5	2 4	4 16
<u>Antibacterial Activity</u> (MIC $\mu\text{g/ml}$)					
Compound of Example 1b		31.2	62.5	125	31.2

Using the procedures described in Preparation 1a the following compounds were obtained:

Benzyl 2-(5'-aminotetrazolyl)-2-vinyl clavam-3-carboxylate;

Benzyl 2-(1',2',4'-triazolyl)-2-vinyl clavam-3-carboxylate;

Benzyl 2-benzoyloxy-2-vinyl clavam-3-carboxylate;

By following the procedures of Preparation 1b and Examples 1a and 1b, each of the above can be converted to salts or esters of 2-(3-hydroxypropylidene)clavam-3-carboxylic acid.

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Preparation 2aBenzyl 2-acetoxy-2-vinylclavam-3-carboxylate (isomeric mixture)

A solution of benzyl clavulanate (5.78 g) in toluene (100 ml) was cooled to -20°C and treated successively with acetic acid (1.5 ml) triphenylphosphine (6.3 g) and diethyl azodicarboxylate. After stirring for a short time, the precipitated diethyl hydrazodicarboxylate was removed by filtration and the filtrate partially evaporated and subjected to chromatography on silica gel, using ethyl acetate-hexane (1:2) as eluent. Fractions containing the desired products (by tlc) were combined and evaporated to low volume, then the residual solvents removed under high vacuum. The residue weighed 6.3 g and was used without further purification.

Preparation 2bBenzyl 2-acetoxy-2-(2-formylvinyl)clavam-3-carboxylate
(as a mixture of isomers)

The mixture of isomeric acetates (6.3 g) was dissolved in ethyl acetate (100 ml) and cooled to -65°C . A current of ozonised oxygen was passed through until the solution became pale blue, ie saturated with ozone. The mixture was allowed to warm to -30°C and triphenylphosphine (4.74 g) added. When all was in solution and the temperature had reached -10°C , formylmethylenetriphenylphosphorane (11 g) was added in N,N-dimethylformamide by suspending the solid in three successive portions, each of 50 ml, of solvent, adding the remaining solid with the last portion of solvent. The mixture was then stirred at -10° to 0°C for 2.5 hour. The mixture was filtered, diluted with toluene (30 ml) and then with water 200 ml and separated, aqueous phase washed with three further portions of ethyl acetate-toluene (70 ml, 5:2).



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The combined solvent layers were washed with water (50 ml) and dried (Na_2SO_4). The solution was evaporated to low volume and subjected to chromatography on silica gel using ethyl acetate-hexane (1:2) as eluent. Fractions containing the desired compounds (by tlc and ir spectra) were collected and combined, total 1.6 g. The isomers had very similar infra-red spectra in the carbonyl region: ir (film): 1800 (β -lactam), 1750 (esters) and 1695 cm^{-1} ($\text{C}=\text{C}$).

Preparation 2c

Benzyl 2-acetoxy-2-(3-hydroxyprop-1-en-1-yl)-clavam-3-carboxylate

The aldehyde (1 g) in dry tetrahydrofuran was treated with zinc borohydride (19.24 ml of 0.145 M solution). After five minutes the reaction mixture was diluted with water (3 ml) and dilute HCl (2.8 ml 1.0 M) and ether (5 ml). The mixture was filtered through a phase-separating paper, the filtrate dried over Na_2SO_4 and the solvents evaporated to an oil (0.92 g) IR (film) 3300 (broad, OH) 1795 (β -lactam) and 1740 (ester $\text{C}=\text{O}$). The product was used without further purification.

Preparation 2d

Benzyl 2-acetoxy-2-(3-trimethylsilyloxy-prop-1-en-1-yl)-clavam-3-carboxylate

The carbinol (0.92 g) in dry tetrahydrofuran was treated with 1.56 g of bis-trimethylsilylacetamide. After 30 minutes tlc revealed that no starting material remained. The mixture was subjected to rapid chromatography on silica gel, and fractions containing the desired product (by tlc) were combined and evaporated, to give the product as an oil (0.42 g). It had ir (film): 1803 (β -lactam) and 1760 cm^{-1} (esters $\text{C}=\text{O}$).



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Example 2Lithium 2-(3-hydroxypropylidene)clavam-3-carboxylate

The silyl ether (0.1 g) from Preparation 2d in redistilled tetrahydrofuran (15 ml) containing saturated sodium bicarbonate solution (0.25 ml) and 10% palladised charcoal (25 mg) was hydrogenated at ambient temperature and pressure until tlc showed the virtual absence of starting material. The reaction was filtered through a bed of silica to remove catalyst, and the filtrate diluted with water, adjusted to pH 3 by the addition of "Amberlite" IR 120 (H^+ form) resin. After a few minutes the resin was removed by filtration and the filtrate adjusted to pH 7 with lithium hydroxide. The solvent was evaporated and the residual solid triturated with acetone, filtered off and dried in a desiccator, to yield the product as a solid (33 mg). ν_{max} (Nujol mull) 3400 (broad, H_2O and OH) 1785 (β -lactam) 1600 cm^{-1} (very broad, CO_2^-). NMR spectrum (D_2O), 2.32 (2H, m, CH_2CH_2), 3.08 (1H, d, J 17Hz, 6- β -CH), 3.44-3.65 (3H, m, 6 α -CH and CH_2OH), 4.68 (1H, dt, J 7 and 1.5 Hz, 8-CH), 4.89 (1H, d, J 1.5Hz, 3-CH) and 5.67 (1H, d, J 2.5Hz, 5-CH), plus δ 1.9 (acetate ion impurity).

Preparation 3aBenzyl 2-(3,4-dihydroxybutylidene)clavam-3-carboxylate

Benzyl 2-(4-oxobutylidene)clavam-3-carboxylate (3.44 g, 10.92 mmol) as a 9:1 mixture of Z:E double bond isomers was dissolved in dry redistilled tetrahydrofuran (30 ml); this solution was placed under a slow stream of nitrogen and cooled to $-20^\circ C$. To this solution was then added dropwise, and simultaneously, a solution of triethylamine (1.674 ml, 12 mmol) in dry redistilled tetrahydrofuran (3 ml) and trimethylsilyl-trifluoromethanesulphonate (2.179 ml, 12 mmol) in dry



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redistilled tetrahydrofuran (3 ml). After 10 minutes an aliquot of n-pentane (60 ml) was added to the reaction. After a further 30 minutes stirring was halted and when a bilayer had formed (≈ 15 mins.) the n-pentane layer was decanted and evaporated to an oil. This oil was extracted with n-pentane (50 ml) which was filtered through magnesium sulphate and evaporated to give an oil.

This colourless oil (1.262 g) was taken up into dry dichloromethane (10 ml) and treated dropwise with dry m-chloroperbenzoic acid (0.563 g, 3.26 mmol) in dry dichloromethane (15 ml). The reaction was mildly exothermic and the temperature rise was controlled with ice-bath cooling. Thin layer chromatography revealed that the reaction was complete after 10 minutes at which time the solvent was removed *in vacuo*.

The residue was dissolved in dimethoxyethane (15 ml) and placed under a slow stream of dry nitrogen before being cooled to -20°C . Tetraethylammonium fluoride dihydrate (0.61 g, 3.3 mmol) was then added followed after 10 minutes by the addition of sodium borohydride (0.041 g, 1.1 mmol). After a further 18 minutes the reaction was diluted with ethyl acetate and washed with brine (2 x), dilute hydrochloric acid (1 x) and sodium hydrogencarbonate solution (2 x) before being dried (MgSO_4), evaporated and chromatographed (toluene/ethyl acetate, 1:2 as eluent). The title ester was thus obtained as a chromatographically homogenous mixture of C_{10} -hydroxy isomers, 0.36 g 10% yield.

ν_{max} . (film) 3425, 1803, 1750, 1700 cm^{-1} . N.M.R. (CDCl_3) 2.25 (2H, m, 9- CH_2), 2.43 (2H, br, 2 x OH), 3.04 and 3.05 (1H, each d, J 17 Hz, 6 β -CH), 3.31 - 3.74 (4H, m, 6 α -CH and O.CH.CH₂.O) 4.62 and 4.64 (1H, each dt, J 1.2 and 7.5 Hz, 8-CH), 5.07 (1H, br. s, 3-CH), 5.15 and



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5.23 (2H, ABq, J 12.6 Hz, CH_2Ph), 5.66 (1H, d, J 2.5 Hz, 5-CH) and 7.28 - 7.44 (5H, m, aromatics).

Preparation 3b

Benzyl Z-2-(3-oxopropylidene)clavam-3-carboxylate

Benzyl Z-2-(3,4-dihydroxybutylidene)clavam-3-carboxylate (0.3282 g, 0.98 mmol) was dissolved in warm diethylether (30 ml) containing dimethoxyethane (5 ml). To this solution was added a dimethoxyethane solution (4 ml) of anhydrous periodic acid (0.225 g, 0.987 mmol). A precipitate appeared and a further 20 ml of anhydrous diethylether was added. After $\approx$ 3 minutes the reaction was diluted with ethyl acetate and washed with saturated sodium hydrogencarbonate solution (3 x) and brine (2 x) before being dried (MgSO_4) and evaporated. The title ester was thus obtained in 79% yield.

ν_{max} (film) 1801, 1744, 1725 and 1698 cm^{-1} . N.M.R. (CDCl_3) 2.8 - 3.26 (3H, m, $\text{C}:\text{CCH}_2$ and 6 β -CH), 3.43 (1H, dd, J 3 and 17 Hz, 6 α -CH), 4.76 (1H, br. t, J 6 Hz, 8-CH), 5.05 (1H, br. s, 3-CH), 5.16 (2H, s, CO_2CH_2), 5.63 (1H, br. d, J 3 Hz, 5-CH), 7.28 (5H, s, aromatics) and 9.40 - 9.54 (1H, m, $\text{HC}:\text{O}$).

Example 3

Benzyl Z-2-(3-hydroxypropylidene)clavam-3-carboxylate

Benzyl Z-2-(3-oxopropylidene)clavam-3-carboxylate (0.2, 0.665 mmol) was dissolved in dry dimethoxyethane (10 ml) and placed under a slow stream of dry nitrogen before being cooled to -20°C . Sodium borohydride (0.011 g, 0.29 mmol) was added portionwise

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and after 5 mins. the reaction was diluted with ethyl acetate and washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and brine (2 x) before being dried (MgSO_4) and evaporated to an oil, 0.1833 g. The oil was chromatographed on silica-gel using toluene/ethyl acetate 2:1 as eluent affording the title ester in 55% yield 0.113 g.

ν_{max} . (film) 3440, 1803, 1749, 1700 cm^{-1} . N.M.R. (CDCl_3) 1.58 (1H, br. s, OH), 2.34 (2H, dt, J 6.6 and 8.2 Hz, C:C.CH₂), 3.04 (1H, dd, J 0.8 and 16.5 Hz, 6 β -CH), 3.45 (1H, dd, J 3 and 16.5 Hz, 6 α -CH), 3.57 (2H, t, J 6.6 Hz, CH₂.CH₂O), 4.60 (1H, dt, J 1.9 and 8.2 Hz, 8-CH), 5.06 (1H, d, J 1.9 Hz, 3-CH), 5.14 and 5.24 (2H, ABq, J 13.2 Hz, CO₂CH₂), 5.65 (1H, dd, J 0.8 and 3 Hz, 5-CH), 7.28 - 7.44 (5H, m, aromatics).

Preparation 4a

Benzyl E-2-[3-(trimethylsilyloxymethylene)propylidene]-clavam-3-carboxylate

Benzyl E-2-(4-oxobutylidene)clavam-3-carboxylate (3.13 g, 9.94 mmol) was dissolved in dry redistilled tetrahydrofuran (30 ml); placed under a slow stream of dry nitrogen and cooled to -20°C. Triethylamine (1.52 ml, 10.9 mmol) and trimethylsilyl trifluoromethanesulphonate (1.98 ml, 10.9 mmol) were then added dropwise simultaneously, with vigorous stirring. After 20 minutes n-pentane (50 ml) was added and after a further 30 minutes stirring was halted. After 1 hour the n-pentane was decanted, the residue was extracted again with n-pentane (30 ml) at room temperature. The n-pentane extractions were combined and evaporated to a colourless oil which was further extracted with n-pentane (25 ml). Evaporation of the n-pentane afforded the title ester as a chromatographically labile colourless oil of high purity (>90%) in 32.5% yield as a mixture



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of enoether olefinic isomers. $\nu_{\max}$ (film), 1807, 1751, 1698 and 1652 cm^{-1} . N.M.R. (δ CDCl_3) 0.17 (9H, s, $(\text{CH}_3)_3$), 2.2 - 3.12 (3H, m, $6\beta\text{-CH}$ and $:\text{CCH}_2\text{C}:$), 3.37 (1H, dd, J 3 and 16 Hz, $6\alpha\text{-CH}$), 4.32 (1H, m, $:\text{C.C.CH}:$), 5.00 (1H, m, C.C:CH.C), 5.16 (2H, s, CH_2Ph), 5.23 (1H, br. s, 3-CH), 5.60 (1H, d, J 3 Hz, 5-CH), 6.10 (1H, m, C:CHOSi), 7.33 (5H, s, aromatics)

Preparation 4b

Benzyl E-2-(3-hydroxy-4-m-chlorobenzoyloxy-4-trimethylsilyloxybutylidene)clavam-3-carboxylate

Benzyl E-2-[3-(trimethylsilyloxymethylene)-propylidene]clavam-3-carboxylate (1.249 g, 3.23 mmol) was dissolved in dichloromethane (15 ml) and cooled to 0°C . A solution of m-chloroperbenzoic acid (0.587 g, 3.23 mmol, 95%) in dichloromethane (5 ml) was added. After 5 minutes the reaction was complete as judged by thin layer chromatography and the solvent was evaporated affording all four isomers of the title compound in 91% yield. The title ester may be resolved into pairs of isomers by silica gel chromatography (toluene/ethyl acetate 7:1 as eluent) but with concomitant reduction in yield due to its relative instability towards silica-gel.

$\nu_{\max}$ (film), 3500, 1804, 1748, 1730 and sh 1700 cm^{-1} . N.M.R. (CDCl_3) 0.16 (9H, s, SiMe_3), 1.65 (1H, br, s, OH) 2.08 - 2.56 (2H, m, C:CCH_2), 2.78 - 3.84 (3H, m, 6α and β , and CHOH), 5.00 - 5.39 (4H, m, 8-CH, 3-CH and CH_2Ph), 5.53 - 5.73 (1H, m, 5-CH), 6.03 - 6.19 (1H, m, O.CH.O) and 7.20 - 8.05 (9H, m, aromatics).



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Preparation 4cBenzyl E-2-(3,4-dihydroxybutylidene)-clavam-3-carboxylate

Benzyl E-2-(3-hydroxy-4-*m*-chlorobenzoyloxy-4-trimethylsilyloxybutylidene)clavam-3-carboxylate (1.65 g, 2.95 mmol) was dissolved in dry dimethoxyethane (15 ml) and placed under a stream of dry nitrogen. The reaction was cooled to -20°C and tetraethylammonium fluoride dihydrate (0.593 g, 3.2 mmol) was added portionwise. After 10 mins sodium borohydride (0.041 g, 1 mmol) was added. Thin layer chromatography indicated the completion of the reaction after 10 minutes; the reaction mixture was then diluted with ethyl acetate and washed with brine (2 x), dilute HCl (1 x), sodium hydrogencarbonate solution (1 x) and brine (2 x). The organic layer was separated, dried (MgSO₄), evaporated to an oil and chromatographed on silica-gel using toluene/ethyl acetate 1:1 as eluent. The diol was thus obtained in 62% yield. ν_{max} (film) 3430, 1802, 1749 and 1699 cm⁻¹. N.M.R. (CDCl₃) 1.96 - 2.29 (2H, m, C:CCH₂), 2.37 (2H, br. m, 2 x OH), 2.96 - 3.09 (1H, m, 6 β -CH), 3.26 - 3.65 (4H, m, O.CH₂.CHO and 6 α -CH), 5.02 - 5.14 (1H, m, 8-CH), 5.14 - 5.22 (2H, m, CH₂Ph), 5.22 - 5.28 (1H, m, 3-CH), 5.60 - 5.70 (1H, m, 5-CH), and 7.30 - 7.44 (5H, m, aromatics).

Preparation 4dBenzyl E-2-(3-oxopropylidene)clavam-3-carboxylate

Benzyl E-2-(3,4-dihydroxybutylidene)clavam-3-carboxylate (0.162 g, 0.486 mmol) was dissolved in warm diethylether (25 ml). To this solution at room temperature was added anhydrous periodic acid (0.11 g, 0.483 mmol) in diethylether (50 ml) containing



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dimethoxyethane (10 ml). After 15 mins. the reaction was filtered through magnesium sulphate and concentrated to half volume. The solution was then diluted with ethyl acetate and washed with brine (2 x) and with saturated sodium hydrogencarbonate solution (2 x) before being dried (MgSO_4) and evaporated to a syrup of essentially pure title ester, 0.125 g, 86%, which may be chromatographed on silica gel (toluene/ethyl acetate, 1:1 as eluent).

ν_{max} . (film) 1802, 1744, 1725 sh, and 1697 cm^{-1} .
N.M.R. (δCDCl_3) 3.0 - 3.15 (3H, m, $\text{C}:\text{CCH}_2$ and $6\beta\text{-CH}$), 3.47 (1H, dd, J 3 and 16 Hz, $6\alpha\text{-CH}$), 5.11 - 5.27 (4H, m, 3-CH, 8-CH and CO_2CH_2), 5.70 (1H, d, J 3 Hz, 5-CH), 7.29 - 7.45 (5H, m, aromatics), and 9.45 (1H, m, $\text{HC}:\text{O}$).

Example 4

Benzyl E-2-(3-hydroxypropylidene)clavam-3-carboxylate

Benzyl E-2-(3-oxopropylidene)clavam-3-carboxylate (0.126 g, 0.42 mmol) was dissolved in dry dimethoxyethane (5 ml) and placed under a slow stream of dry nitrogen before being cooled to -20°C . Sodium borohydride (0.007 g, 0.18 mmol) was then added portionwise. After 8 minutes the reaction was diluted with ethyl acetate and washed with brine (3 x) dilute hydrochloric acid (1 x) and saturated sodium hydrogen-carbonate solution (1 x) before being dried (MgSO_4) and then evaporated to an oil, 0.092 g. This residue was chromatographed on silica-gel (toluene/ethylacetate 1:1 as eluent) affording the title ester in 67% yield, 0.086 g.

ν_{max} . (film) 3420, 1802, 1749 and 1698 cm^{-1} .
N.M.R. (CDCl_3) 1.85 (1H, br. s, OH), 2.09 - 2.29 (2H, m, $\text{C}:\text{C}.\text{CH}_2$), 3.01 (1H, dd, J 0.67 and 16.7 Hz, $6\beta\text{-CH}$),

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3.42 (1H, dd, J 2.7 and 16.7 Hz, 6 α -CH), 3.46 - 3.52 (2H, br. t, CH₂OH), 5.05 (1H, dt, J 1.5 and 8 Hz, 8-CH), 5.15 and 5.21 (2H, ABq, J 12 Hz, CH₂Ph), 5.21 (1H, m, 3-CH), 5.64 (1H, br.d, J 2.7 Hz, 5-CH), 7.32 - 7.4 (5H, m, aromatics).

Example 5a

Benzyl 2-(N-acetoxy-N-acetyl-3-aminopropylidene)clavam-3-carboxylate and benzyl 2-(N-acetyl-3-aminopropylidene)-clavam-3-carboxylate

A stirred solution of benzyl 2-(3-nitropropylidene)clavam-3-carboxylate in a mixture of acetic acid (30 ml) and acetic anhydride (3 ml) was cooled in a water bath and treated with zinc powder (2 g) added in portions over 10 minutes. The mixture was then stirred at room temperature for 2½ hours. The solution was filtered through Celite and the filter cake washed with acetic acid. The combined filtrates were evaporated under high vacuum and the residue partitioned between ethyl acetate and water. The ethyl acetate solution was washed with sodium bicarbonate solution, water and brine, dried over magnesium sulphate and evaporated. The products were isolated by column chromatography of the residue using gradient elution (Kieselgel 1:1 petroleum ether:ethyl acetate going to ethyl acetate). Eluted were:
Benzyl 2(N-acetoxy-N-acetyl-3-aminopropylidene)clavam 3-carboxylate.

$\nu_{\max}$ (CHCl₃) 1800, 1750 and 1675 cm⁻¹.
 δ (CDCl₃) 1.96 (3H, s), 2.16 (3H, s), 2.36 (2H, apparent q, J 7Hz), 3.01 (1H, d, J 17Hz), 3.46 (1H, dd, J 3 and 17Hz), 3.65 (2H, t, J 7Hz), 4.56 (1H, broad t, J 7Hz), 5.02 (1H, s), 5.17 (2H, s), 5.66 (1H, d, J 3Hz), 7.34 (5H, s).

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Benzyl 2-(N-acetyl-3-aminopropylidene)clavam-3-carboxylate. Mpt 78-80°C from ethyl acetate - 60/80 petroleum ether.

$\nu_{\max}$ (CHCl₃) 3440, 1800, 1750 and 1670 cm⁻¹.
 δ (CDCl₃) 1.87 (3H, s), 2.24 (2H, apparent q, J 7Hz), 2.97 (1H, d, J 17Hz), 3.17 (2H, apparent q, J 7Hz), 3.44 (1H, dd, J 3 and 17Hz), 4.52 (1H, broad t, J 7Hz), 5.02 (1H, s), 5.18 (2H, s), 5.62 (1H, d, J 3Hz), 5.70 (1H, broad s), 7.33 (5H, s).

Analysis. Found: C, 62.90; H, 5.96; N, 8.15;
C₁₈H₂₀N₂O₅ requires: C, 62.78; H, 5.96; N, 8.14.

Example 5b

Lithium 2-(N-acetoxy-N-acetyl-3-aminopropylidene)clavam-3-carboxylate

A solution of benzyl 2-(N-acetoxy-N-acetyl-3-aminopropylidene)clavam-3-carboxylate (621 mg) in tetrahydrofuran (20 ml) was hydrogenated over 10% palladium charcoal (200 mg) for 30 minutes. The solution was filtered through Celite and the filter cake washed with tetrahydrofuran. The solution was evaporated to ≈5 ml and diluted with an equal volume of deionised water. Lithium carbonate (57 mg) was added and the remaining organic solvent evaporated. The residual aqueous solution was washed twice with ethyl acetate, filtered through Celite, and evaporated almost to dryness. The residue was triturated with acetone, and the product was filtered off, washed with acetone and dried under vacuum to give 382 mg of the title product.



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$\nu_{\max}$ (KBr) 1790, 1655, and 1620 cm^{-1} .

δ (D_2O) 2.09 (3H, s), 2.23 (3H, s), 2.40 (2H, apparent q, J 7Hz), 3.01 (1H, d, J 17Hz), 3.53 (1H, dd, J 3 and 17Hz), 2.75 (2H, t, J 7Hz), 4.68 (1H, broad t, J 7Hz), 4.84 (1H, s), 5.66 (1H, d, J 3Hz).

Example 5c

Lithium 2-(N-acetyl-3-aminopropylidene)clavam-3-carboxylate

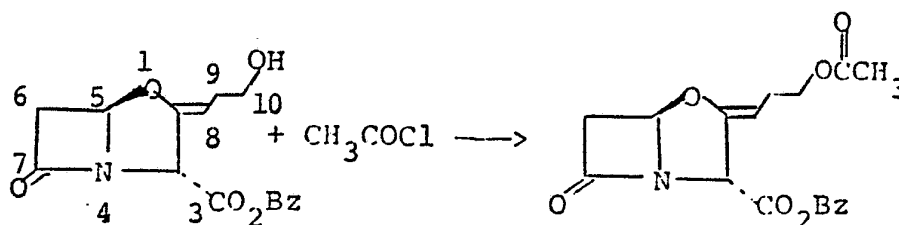
A solution of benzyl 2-(N-acetyl-3-amino-propylidene)clavam-3-carboxylate (275 mg) in tetrahydrofuran (15 ml) was hydrogenated over 10% palladium charcoal (100 mg) for $\frac{1}{2}$ hr. The solution was filtered through Celite and the filter cake was washed with tetrahydrofuran. The combined filtrates were evaporated to about 4 ml and diluted with water (5 ml). Lithium carbonate (29 mg) was added and the mixture stirred for 10 minutes. The solution was filtered through Celite and evaporated to about 0.5 ml. The residue was triturated with acetone/ether and the white solid was filtered off, washed with acetone and dried under vacuum over phosphorous pentoxide to give the title compound as a white solid (111 mg).

I.R. $\nu_{\max}$. (KBr) 3425, 1780, 1692, 1658, 1608.

N.M.R. δ (D_2O) 1.92 (3H, s), 2.1 - 2.3 (2H, m), 3.00 (1H, d, J = 17 Hz) 3.16 (2H, t, J = 7 Hz), 3.52 (1H, dd, J = 3 and 17 Hz), 4.64 (1H, broad t, J = 7 Hz), 4.86 (1H, s), 5.64 (1H, d, J = 3 Hz).



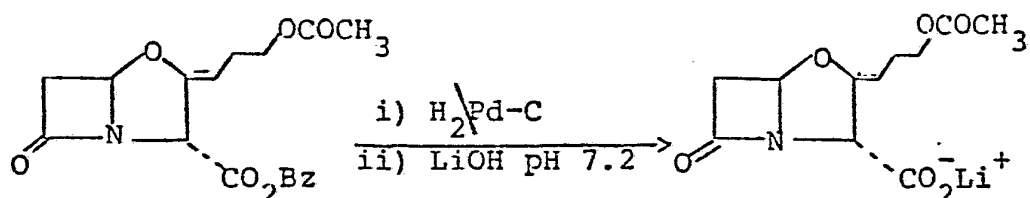
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Example 6aBenzyl 7-2-(3-acetoxypopylidene)clavam-3-carboxylate

A solution of benzyl 7-2-(3-hydroxypropylidene)-clavam-3-carboxylate (244 mg; 0.8 mmol) in dichloromethane (5 ml) was treated with acetyl chloride (68.3 μ l; 0.96 mmol) and pyridine (77.7 μ l, 0.96 mmol) at 0°. The reaction was monitored by t.l.c. (*n*-hexane: ethyl acetate, 2:1; R_f = 0.43) and was complete after 30 minutes. The solution was diluted with dichloromethane (total volume 30 ml) and washed successively with 2N hydrochloric acid (15 ml), water (15 ml), saturated sodium hydrogen carbonate solution (15 ml), water (15 ml), brine (15 ml), dried ($MgSO_4$) and evaporated to an oil. The residue was chromatographed on a short column of silica gel eluting with *n*-hexane/ethyl acetate, 1:1. The product was obtained as a colourless oil in 68.7% yield.

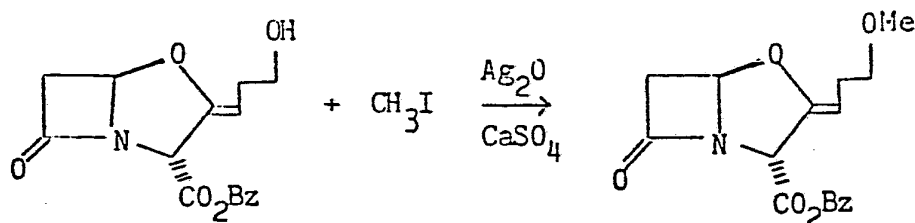
ν_{max} . ($CHCl_3$) 1804, 1740, 1700 (sh) cm^{-1} .
 δ ($CDCl_3$) 2.02 (3H, s, $OCOCH_3$), 2.43 (2H, dt, J 7 and 7 Hz, 9- H_2), 3.05 (1H, d, J 17 Hz, 6 β -H), 3.47 (1H, dd, J 17 and 3 Hz, 6 α -H), 4.01 (2H, m, 10- H_2), 4.58 (1H, dt, J 7 and 1 Hz, 8-H), 5.05 (1H, d, J 1 Hz, 3-H), 5.16, 5.24 (2H, ABq, J 12 Hz, CH_2Ar), 5.67 (1H, d, J 3 Hz, 5-H), 7.28 - 7.43 (5H, m, Ar).

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Example 6bLithium 2-2-(3-acetoxypropylidene)clavam-3-carboxylate

Benzyl 2-2-(3-acetoxypropylidene)clavam-3-carboxylate (172 mg) in dry redistilled tetrahydrofuran (15 ml) was hydrogenolysed over 10% palladium on carbon (86 mg) for 20 minutes, at which time t.l.c. showed the disappearance of starting material. The catalyst was filtered off using glass fibre filter paper and the filtrate was diluted to 50 ml with water and the pH adjusted to pH 7.2 with 1M lithium hydroxide. The solution was evaporated and the product crystallised from aqueous acetone in 73.5% yield.

ν_{max} (KBr) 3423, 1781, 1710 and 1611 cm^{-1} .
 δ (D_2O) 2.06 (3H, s, OCOCH_3), 2.44 (2H, m, 9- H_2), 3.08 (1H, d, J 17 Hz, 6 β -H), 3.53 (1H, dd, J 17 and 3 Hz, 6 α -H), 4.12 (2H, t, J 7 Hz, 10- H_2), 4.69 (1H, dt, J 7.5 and 1 Hz, 8-H), 4.8 (2H, s, CH_2Ar), 4.89 (1H, d, J 1 Hz, 3-H), 5.68 (1H, d, J 3 Hz, 5-H).

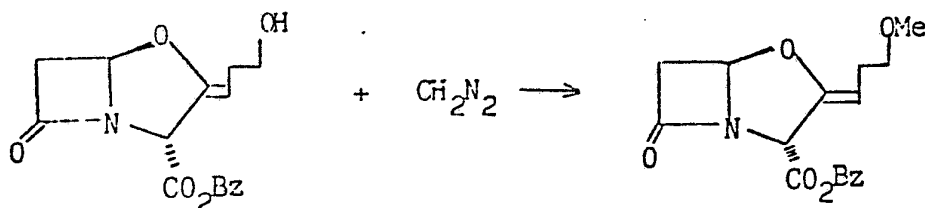
Example 7a(i)Benzyl 2-(3-methoxypropylidene)clavam-3-carboxylate

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To a solution of benzyl 2-(3-hydroxypropylidene) clavam-3-carboxylate (100 mg; 0.33 mmol) in dichloromethane (5 ml) was added silver oxide (50 mg), methyl iodide (2 ml) and 'Drierite' (75 mg) and the reaction mixture was stirred in the dark overnight at room temperature. After this time t.l.c. indicated that some starting material still remained; the mixture was filtered and the filtrate evaporated. Fractionation of the residual oil on silica gel eluting with n-hexane/ethyl acetate, 1:1 gave the desired ether in 30% yield + 50% recovered starting material. The infra-red spectrum was identical to an authentic sample.

Example 7a(ii)

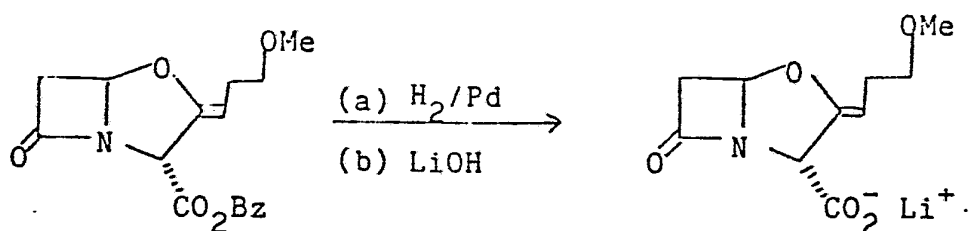
Benzyl 2-(3-methoxypropylidene)clavam-3-carboxylate



Benzyl 2-(3-hydroxypropylidene)clavam-3-carboxylate (244 mg; 0.8 mmol) in dichloromethane (5 ml) was treated with a solution of diazomethane in diethyl ether (20 ml; 0.16 mmol/ml) plus a catalytic amount of boron trifluoride etherate at 0°C. After 1 hour the reaction mixture was worked up followed by chromatography on silica gel eluting with n-hexane/ethyl acetate, 1:1, to give the title ether (128 mg; 50%) as a colourless oil.

$\nu_{\max}$ (CHCl₃) 1800, 1745 and 1700 cm⁻¹, δ (CDCl₃) 2.32 (2H, dt, J7 and 7HZ, 9-H₂), 2.98 (1H, d, J17HZ, 6 β -H) 3.41 (1H, dd, J17 and 3HZ, 6 α -H) 3.26 (5H, m, 10-H₂ and CH₃), 4.58 (1H, dt, J8 and 1.5HZ, 8-H), 5.0 (1H, brs, 3-H), 5.14 (2H, s, CH₂Ph) 5.61 (1H, d, J3HZ, 5-H), 7.3 (5H, s, Ar-H).

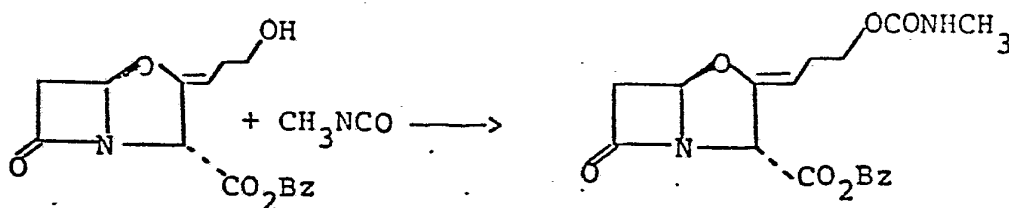
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Example 7bLithium Z-2-(3-methoxypropylidene)clavam-3-carboxylate

. Benzyl 2-(3-methoxypropylidene)clavam-3-carboxylate (115mg; 0.36 mmol) in dry redistilled tetrahydrofuran (15ml) was hydrogenolysed over 10% palladium on charcoal (38mg) for one hour. The catalyst was filtered off and the filtrate was diluted with the same volume of water and the pH of the aqueous solution adjusted to pH 7.2 with 1M lithium hydroxide. Evaporation of the solution and crystallisation of the resultant solid from acetone gave the desired product in 61% yield.

$\nu_{\max}$ (KBr) 3420, 1784, 1760, 1704, 1610 cm^{-1} .

$\delta(\text{D}_2\text{O})$ 2.37 (2H, m, 9- H_2) 3.08 (d, 1H, 6 β -H) 3.34 (3H, s, CH_3) 3.51 (3H, m, 10- H_2 and 6 α -H) 4.68 (1H, dt, J 7.5 and 1Hz, 8-H), 4.89 (1H, d, J 1Hz, 3-H), 5.68 (1H, m, 5-H).

Example 8aBenzyl Z-2-(3-N-methylcarbamoyloxypropylidene)clavam-3-carboxylate

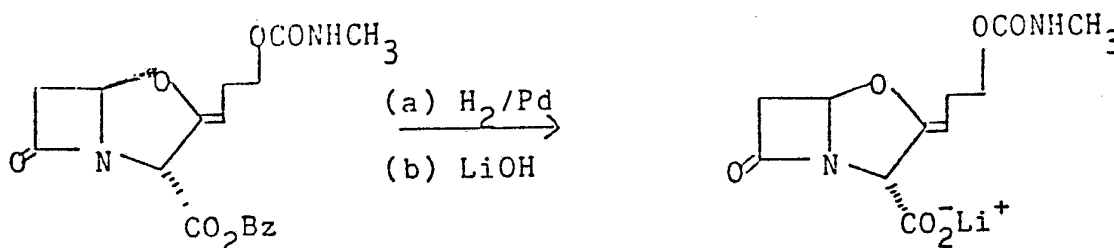
- 59 -

Benzyl Z-2-(3-hydroxypropylidene)clavam-3-carboxylate (200 mg; 0.66 mmol) was treated with methyl isocyanate (3 ml) and the solution allowed to stand at room temperature for 5 days. Evaporation of the excess isocyanate followed by short column chromatography on silica gel using ethyl acetate/n-hexane, 1:1 as eluent gave the required product as a colourless oil in 81% yield.

ν_{max} (CHCl₃) 3470, 1800, 1745 (sh) and 1715 cm⁻¹.
 δ (CDCl₃) 2.38 (2H, m, 9-H₂), 2.73 (3H, d, $\underline{J}$ 5 Hz, NHCH₃) 3.04 (1H, d, $\underline{J}$ 17 Hz, 6 β -H), 3.47 (1H, dd, $\underline{J}$ 17 and 3 Hz, 6 α -H), 4.2 (2H, br.t., $\underline{J}$ 6.5 Hz, 10-H₂), 4.58 (2H, m, NH and 8-H), 5.03 (1H, d, $\underline{J}$ 1 Hz, 3-H), 5.16, 5.23 (2H, ABq, $\underline{J}$ 12.5 Hz, CH₂Ar), 5.66 (1H, d, $\underline{J}$ 3 Hz, 5-H), 7.36 (5H, m, Ar).

Example 8b

Lithium Z-2-(3-N-methylcarbamoyloxypropylidene)clavam-3-carboxylate.



A solution of benzyl Z-2-(3-N-methylcarbamoyloxypropylidene)clavam-3-carboxylate (161mg; 0.45 mmol) in dry redistilled tetrahydrofuran (30ml) was hydrogenolysed for 30 minutes over 10% palladium on carbon (75mg); after which time t.l.c. showed complete deprotection. The catalyst was filtered off and an equal volume of water was added to the filtrate; the aqueous solution was

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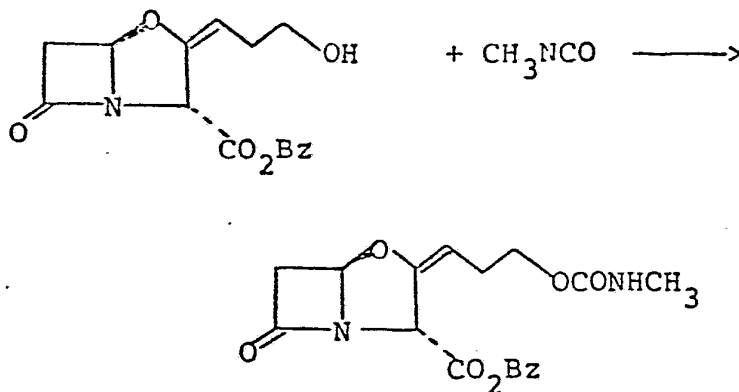
neutralised by the addition of lithium hydroxide solution and evaporated to dryness. The residual solid was crystallised from aqueous acetone to give a 3:1 mixture of lithium Z-2-(3-N-methylcarbamoyloxypropylidene)clavam-3-carboxylate and E-2-(3-N-methylcarbamoyloxypropylidene)-clavam-3-carboxylate as a solid in 68% yield.

$\nu_{\max}$ (KBr) 3395, 1767, 1715 and 1617 cm^{-1} .

$\delta(\text{D}_2\text{O}$ -Z isomer) 2.42 (2.67, m, 9-H₂) 2.68 (3H, s, CH₃)
3.06 (1H, d, J 17Hz, 6 β -H) 3.54 (1H, dd, J 17 and 3Hz, 6 α -H)
4.08 (2H, m, 10-H₂) 4.71 (1H, brt, J 7.5Hz, 8-H) 4.89
(1H, s, 3-H), 5.67 (1H, d, J 3Hz, 5-H).

Example 9a

Benzyl E-2-(3-N-methylcarbamoyloxypropylidene)clavam-3-carboxylate



A solution of benzyl E-2-(3-hydroxypropylidene)-clavam-3-carboxylate (220 mg; 0.73 mmol) in methyl isocyanate (3 ml) was allowed to stand at room temperature for 5 days. The excess isocyanate was removed by evaporation and the crude product was subjected to short column chromatography. Elution

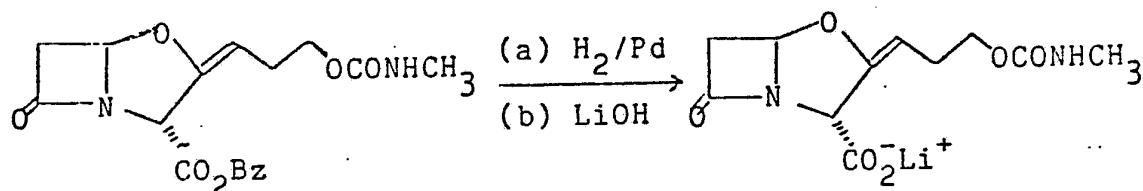
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with ethyl acetate/cyclohexane, 1:1 gave the title compound as a colourless solid which crystallised from carbon tetrachloride as colourless needles in 83.6% yield, m.p. 95°.

ν_{max} (KBr) 3371, 1793, 1733 and 1691 cm^{-1} .
 δ (CDCl_3) 2.16 (1H, m, 9H_A), 2.4 (1H, m, 9H_B), 2.77 (3H, d, J 5 Hz, NHCH_3), 3.03 (1H, d, J 17 Hz, $6\beta\text{-H}$), 3.45 (1H, dd, J 17 and 3 Hz, $6\alpha\text{-H}$), 3.89 (1H, m, 10H_A), 4.06 (1H, m, 10H_B), 4.8 (1H, bs, NH), 5.03 (1H, bt, J 8 Hz, 8-H), 5.2 (2H, s, CH_2Ar), 5.28 (1H, d, 3-H), 5.68 (1H, d, J 3 Hz, 5-CH), 7.36 (5H, m, Ar).

Example 9b

Lithium E-2-(3-N-methylcarbamoyloxypropylidene)clavam-3-carboxylate.



Benzyl E-2-(3-N-methylcarbamoyloxypropylidene)clavam-3-carboxylate (219 mg; 0.61mmol) was dissolved in dry redistilled tetrahydrofuran (30ml) and hydrogenolysed over 10% palladium on carbon (110mg) for 25 minutes. The catalyst was filtered off and the filtrate was diluted with water (25ml) and the solution neutralised with 1M lithium hydroxide. Evaporation to dryness followed by crystallisation from aqueous acetone gave a 55:45 mixture (n.m.r) of lithium E-2-(3-N-methylcarbamoyloxypropylidene)clavam-3-carboxylate and lithium Z-2-(3-N-methylcarbamoyloxypropylidene)clavam-3-carboxylate as a solid in 84.5% yield.

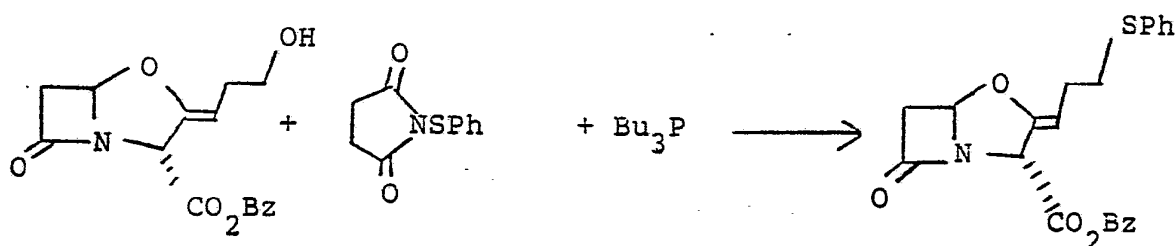
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$\nu_{\max}$ (KBr) 3388, 1772, 1699 and 1616 cm^{-1} .

$\delta(\text{D}_2\text{O}; \text{E+Z isomer})$ 2.39 (4H, m, 9- H_2), 2.68 (6H, s, CH_3)
3.03 and 3.06 (2H, two x d, J17 Hz, 6 β -H E- isomer and
Z- isomer respectively) 3.52 and 5.54 (2H, two x dd, J17
and 3Hz, 6 α -H, E and Z isomers) 4.07 (4H, m, 10- H_2 ,
E + Z isomers) 4.69 (1H, bt, J7.5 Hz, 8-H Z-isomer), 4.88
(1H, bs, 3-H, Z-isomer) 5.02 (2H, m, 8-H and 3-H, E-isomer)
5.68 (2H, m, 5-H, E + Z isomers).

Example 10

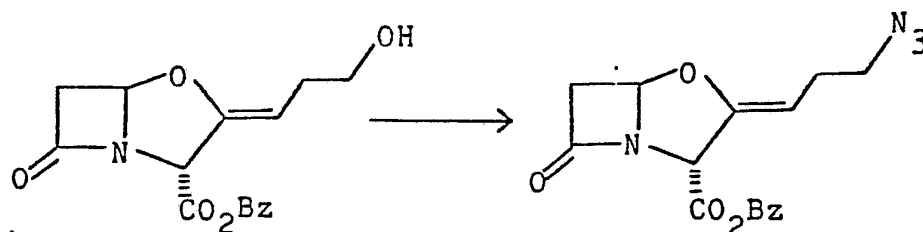
Benzyl Z-2-(3-phenylthiopropylidene)clavum-3-carboxylate



To a stirred solution of tri-n-butylphosphine (115 μl ; 0.47 mmol) in dry benzene (5 ml) at room temperature was added N-(phenylthio)succinimide (96.7 mg; 0.47 mmol). After stirring for five minutes at room temperature a solution of the alcohol (128.7 mg; 0.42 mmol) in benzene (2 ml) was added. Stirring was continued for five hours then the solution was washed with water (3 x 5 ml) and brine (2 x 5 ml), dried (MgSO_4) and evaporated. The residual yellow oil was chromatographed on silica gel and the product $R_f = 0.51$ (n-hexane/ethyl acetate 2:1) was eluted with n-hexane/ethyl acetate 2:1. Yield 84.5%.

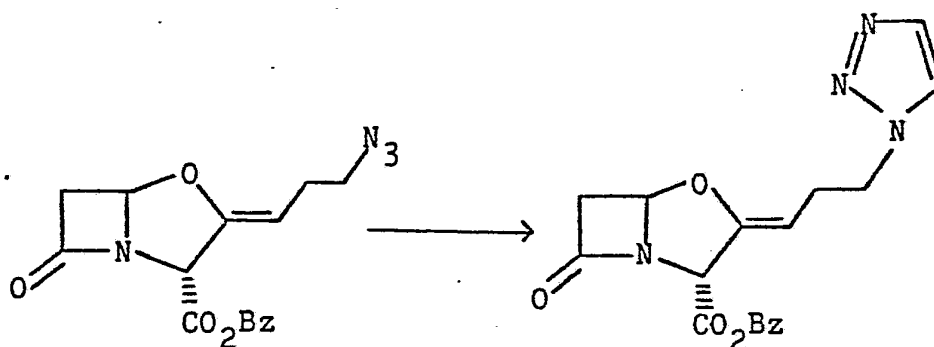
$\nu_{\max}$ (CHCl_3) 1800, 1748, 1698 cm^{-1} .

$\delta(\text{CDCl}_3)$ 2.39 (2H, dt, J7 and 7Hz, 9- H_2), 2.88 (2H, m, 10- H_2), 3.03 (1H, d, J17Hz, 6 β -H), 3.42 (1H, dd, J17 and 3Hz, 6 α -H), 4.65 (1H, dt, J7 and 1Hz, 8-H), 5.03 (1H, d, J1Hz, 3-H), 5.15, 5.23 (2H, ABq, J12Hz, CH_2Ph), 5.64 (1H, d, J 3Hz, 5-H), 7.3 (1H, m, Ar-H).

Example 11aBenzyl Z-2-(3-azidopropylidene)clavam-3-carboxylate

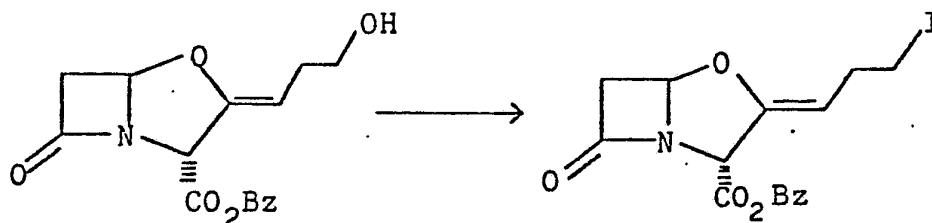
Benzyl Z-2-(3-hydroxypropylidene)clavam-3-carboxylate
 (0.15g, 0.495 mmol) in dry tetrahydrofuran (5ml) was
 treated with triphenylphosphine (0.156g , 0.595 mmol)
 in dry tetrahydrofuran (2ml) and with hydrazoic acid in
 5 dry toluene (2ml of a 1.6M solution). This mixture was
 cooled to 0°C and then diethylazodicarboxylate (0.1 ml,
 0.635 mmol) was added. Thin layer chromatography
 indicated that no further reaction took place after
 10 - 15 minutes. The reaction mixture was diluted
 10 with ethyl acetate and washed with saturated sodium
 hydrogen carbonate solution and with brine. The solution
 was dried (MgSO₄) and evaporated to a syrup which was
 chromatographed on silica gel using *n*-hexane/ethyl-
 acetate (2:1) as eluent. The first eluted material was
 15 the title ester 73.3mg, 69% yield based on consumed
 substrate. The second eluted material was the alcohol
 substrate, 51.8mg.

I.R. (film) 2100, 1800, 1747 and 1696 cm⁻¹. δ(CDCl₃)
 2.37 (2H, dt, J 7 and 7 Hz, C:CCH₂), 3.06 (1H, d, J
 20 17 Hz, 6β -CH), 3.21 (2H, m, CH₂N₃), 3.47 (1H, dd, J
 17 and 3 Hz, 6α -CH), 4.59 (1H, dt, J 7 and 1.7 Hz,
 8-CH), 5.05 (1H, d, J 1.7 Hz, 3-CH), 5.16 and 5.23
 (2H, A Bq, J 12 Hz, CH₂Ph), 5.68 (1H, d, J 3 Hz, 5-CH),
 7.26 - 7.41 (5H, m, aromatics).

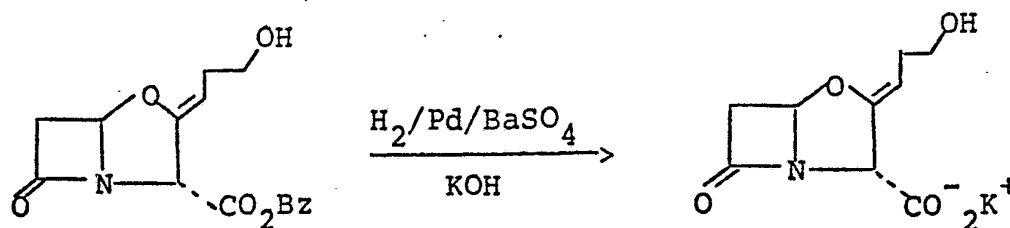
Example 12Benzyl Z-2-[3-(triazol-1-yl)propylidene]clavam-3-
carboxylate

Benzyl Z-2-(3-azidopropylidene)clavam-3-carboxylate
 (73.3mg, 0.224 mmol) in dry toluene (5ml) containing
 phenyl vinyl sulfoxide (0.033ml, 0.247 mmol) was
 refluxed for 6 hours at which time a further aliquot
 5 of phenyl vinyl sulfoxide (0.033ml, 0.247 mmol) was
 added. When the reaction had been refluxed for a total
 of 14 hours it was allowed to cool and was diluted with
 ethyl acetate and washed with saturated sodium hydrogen
 carbonate solution before being dried (MgSO_4) and
 10 evaporated. The residual oil was chromatographed on
 silica gel using *n*-hexane/ethyl acetate (1:1) as eluent.
 The title ester was thus obtained and found to crystal-
 lize from toluene/diethyl ether, 25.2mg, 32% yield.
 I.R. (film) 1783, 1734 and 1698 cm^{-1} . $\delta(\text{CDCl}_3)$ 2.40 -
 3.12 (3H, m, C:CCH₂ and 6 β -CH), 3.48 (1H, dd, J17 and
 3Hz, 6 α -CH), 4.10 - 4.78 (3H, m, CH₂N and 8-CH), 4.99
 15 (1H, brs, 3-CH), 5.19 (2H, s, CH₂Ph), 5.58 (1H, brd,
 J 3Hz, 5-CH) and 7.1 - 7.7 (7H, m, aromatics).

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Example 13Benzyl 2-2-(3-Iodopropylidene)clavam-3-carboxylate

Benzyl 2-2-(3-hydroxypropylidene)clavam-3-carboxylate (0.28g, 0.924 mmol) in dry dimethylformamide (8ml) was treated with triphenylphosphitemethiodide (0.5g, 1.1 mmol) and stirred at room temperature for 2 hours. The reaction was diluted with ethylacetate and washed with brine (2x) and with saturated sodium hydrogen carbonate solution, dried (MgSO_4) and evaporated to an oil. Chromatography on silica gel using toluene/ethylacetate (7:1) as eluent afforded the title ester 121.8mg 32% yield. I.R. (film) 1797, 1723 and 1689 cm^{-1} . $\delta(\text{CDCl}_3)$ 2.63 (2H, ddt, J1, 7.3 and 7.6 Hz, C:CCH₂), 3.01 - 3.10 (3H, m, CH₂I and 6 β -CH), 3.48 (1H, dd, J 17 and 3 Hz, 6 α -CH), 4.59 (1H, dt, J 1.4 and 7.3 Hz, 8-CH), 5.04 (1H, dt, J 1.1 and 1.1 Hz, 3-CH), 5.16 and 5.23 (2H, ABq, J12 Hz, CH₂Ph), 5.66 (1H, dd, J3 and 0.7Hz, 5-CH), 7.32 - 7.41 (5H, m, aromatics).

Example 14Potassium 2-(3-hydroxypropylidene)clavam-3-carboxylate

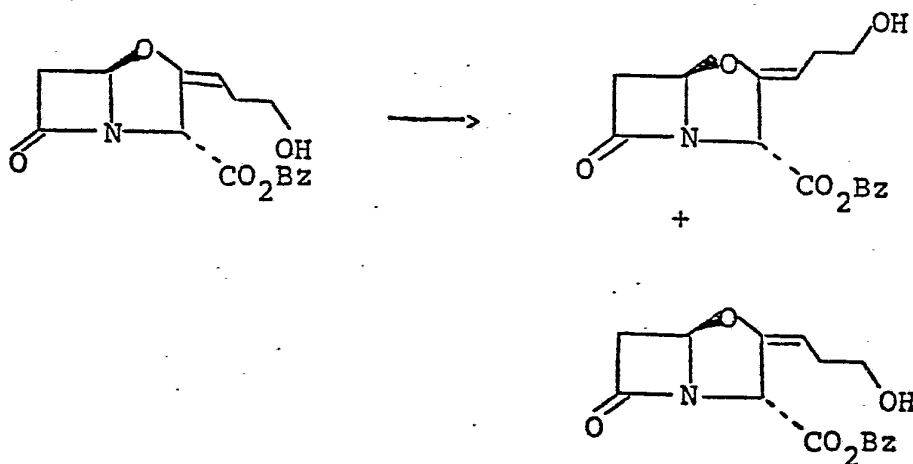
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Benzyl 2-(3-hydroxypropylidene)clavam-3-carboxylate (0.13 g; 0.429 mmol) was hydrogenated at room temperature in tetrahydrofuran (7 ml) over 10% palladium on barium sulphate (0.04 g) for 12 min. after which thin layer chromatography showed that all of the starting material had been consumed. The catalyst was filtered off and washed with tetrahydrofuran. An equal volume of water was added to the combined filtrates and the pH adjusted to 7.2 with potassium hydroxide. After removing the tetrahydrofuran *in vacuo* the aqueous phase was washed with ethyl acetate (2 x) then evaporated and the resulting gum triturated with acetone to produce the title compound as a white solid in 66% yield.

ν_{max} (KBr) 1779, 1696 and 1611 cm^{-1} . δ_{H} (D_2O) 2.26 - 2.41 (2H, m, $\text{CHCH}_2\text{CH}_2\text{OH}$), 3.08 (1H, d, J 16 Hz, 6 β -CH), 3.54 (1H, dd, J 16 and 2 Hz, 6 α -CH), 3.60 (2H, t, J 7 Hz, $\text{CHCH}_2\text{CH}_2\text{OH}$) 4.71 (1H, t, J 7 Hz, $\text{CHCH}_2\text{CH}_2\text{OH}$) 4.91 (1H, s, 3-CH), 5.67 (1H, d, J 2 Hz, 5-CH).

Example 15

Photoisomerisation of benzyl E-2-(3-hydroxypropylidene)clavam-3-carboxylate to benzyl Z-2-(3-hydroxypropylidene)clavam-3-carboxylate

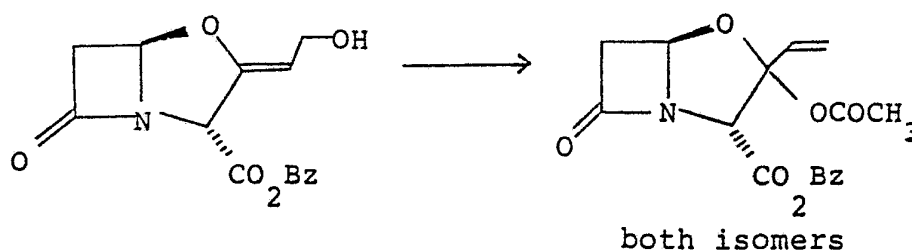


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A solution of benzyl E-2-(3-hydroxypropylidene)-clavam-3-carboxylate (30 mg) in dry degassed benzene (80 ml) was photolysed, using a Hanovia low pressure mercury lamp, for two hours. Filtration followed by evaporation of the solvent under reduced pressure produced a pale yellow oil (19 mg) which was shown by 250 MHz ¹H n.m.r. to contain 31% of the Z-isomer. The mixture of geometrical isomers can be separated by column chromatography as previously described.

Preparation 16a

Benzyl 2-acetoxy-2-vinylclavam-3-carboxylate
(separated isomers)



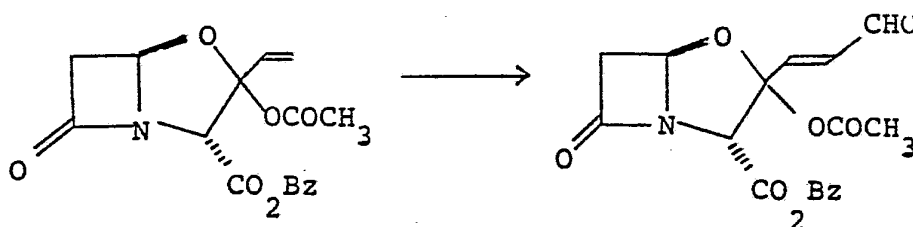
To a solution of benzyl clavulanate (11.5 g) and triphenylphosphine (12.5 g) in toluene (250 ml) was added acetic acid (2.5 ml). The mixture was stirred at ambient temperature until all was in solution, then cooled to -20°C. Diethyl azodicarboxylate (8.5 ml) was added rapidly, whereupon the temperature rose to about 10°C. The mixture was allowed to stir for 30 mins. at -10°C, filtered to remove diethyl hydrazodicarboxylate, and the filtrate evaporated to a syrup. Some carbon tetrachloride was added and re-evaporated. The mixture largely solidified. Dry ether (circa. 50 ml) was added, the insolubles filtered off and washed with cold ether, the filtrates evaporated to a syrup and subjected to chromatography on silica gel using ethyl acetate-hexane (1:3) as eluent. After

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elution of the less polar isomer benzyl 9-0-acetyl clavulanate was eluted followed by the other isomer. Fractions containing the desired products (by t.l.c.) were combined and evaporated to oils, yielding 4.5 g each of the less polar product and the more polar product.

Preparation 16b

Benzyl 2-acetoxy-2-(2-formylvinyl)clavam-3-carboxylate
(less polar isomer)



The less polar isomer from Preparation 16a (4.5 g) was dissolved in ethyl acetate (100 ml), cooled to -65°C and saturated with ozone. Argon was passed through the solution whilst it warmed to -30°C . A solution of triphenylphosphine (2.5 g) in ethyl acetate (15 ml) was added and the mixture allowed to warm to between -20° and 0°C . (T.l.c. was used to monitor the decomposition of oxidants, using a starch-iodide spray to visualize the zones). After about 40 mins. a suspension of formyl-methylenetriphenylphosphorane (8 g) in 2 portions, each in 25 ml of dimethylformamide, was added. The temperature was maintained at -10° to $+5^{\circ}$ for 1.5 hr, then the insolubles were removed by filtration, the filtrate diluted with an equal volume of toluene, and washed with water (300 ml) and then with a dilute (circa. 10%) solution of potassium dihydrogen phosphate (300 ml). The non-

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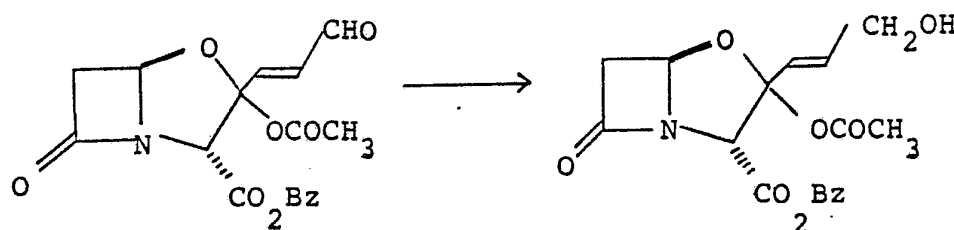


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aqueous phase was separated, dried over Na_2SO_4 , filtered and evaporated to about 40 ml. This material was subjected to chromatography on silica gel using 30% ethyl acetate in hexane as eluent. Fractions containing the desired compound (by t.l.c.) were combined and evaporated to a pale yellow oil (2.5 g). It had i.r. (film) 1810 (β -lactam C=O), 1750 (br, esters C=O) and 1700 cm^{-1} (CHO).

Preparation 16c

Benzyl 2-acetoxy-2-(3-hydroxyprop-1-en-1-yl)-clavam-3-carboxylate (less polar isomer)



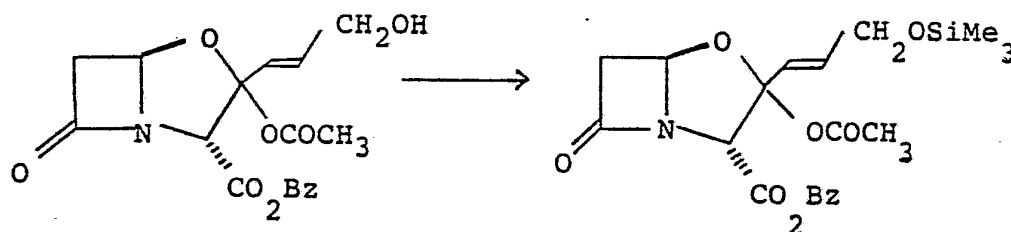
The product of Preparation 16b (2.5g, probably containing a little solvent) in redistilled tetrahydrofuran (25 ml) was cooled to about -20°C with stirring under nitrogen. Portions of approx. 0.15M zinc borohydride (each 10 ml) in ether were added until all the starting aldehyde had reacted (by t.l.c.), and a new more polar zone had appeared. A total of 40 ml of borohydride solution was added. Toluene and water were added (70 ml of each) and the aqueous phase acidified (pH 2.0) by the addition of dilute sulphuric acid. When effervescence had ceased, the mixture was separated, the solvent layer washed with water and dried over Na_2SO_4 . The drying agent was removed by filtration, the filtrate evaporated to an oil (2.2 g) and used without purification for the next stage. It had i.r. (film) 3530 (br, OH), 1803 (β -lactam C=O) and 1750 cm^{-1} (esters C=O).

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Preparation 16d

Benzyl 2-acetoxy-2-(3-trimethylsilyloxyprop-1-en-1-yl)-
clavam-3-carboxylate (less polar isomer) and p-bromo-
benzyl 2-(3-hydroxypropylidene)-clavam-3-carboxylate
(E and Z isomers)



The product of Preparation 16c (2.2g) in dry redistilled tetrahydrofuran (25 ml) was treated with N,O-bis-trimethylsilylacetamide (2.3 g). The mixture was allowed to stand at ambient temperature for 1.5 hr, then evaporated to an oil under reduced pressure and subjected to very rapid chromatography on silica gel to afford the silyl ether (1.7 g). The product was dissolved in tetrahydrofuran containing water ($\approx 10\%$) and sodium hydrogen carbonate (excess) and hydrogenated at ambient temperature and pressure over 10% palladised charcoal until uptake of hydrogen became slow. The mixture was filtered and the filtrate evaporated to dryness; the residue was esterified by treatment with excess p-bromobenzyl bromide in N,N-dimethylformamide for several hours at ambient temperature. T.l.c. showed two products; a smaller less polar zone and a stronger more polar zone. The solvent was removed *in vacuo* and the residue chromatographed on silica gel, using ethyl acetate-hexane as elution solvents. There was obtained 25 mg of the less polar (E) isomer and 150 mg of the more polar product (Z). On storage for some time at -20°C the Z isomer crystallized. It was recrystallized twice from ether at -20°C , when it had m.p. 50°C (corr.). It had p.m.r. (CDCl_3); δ 1.43 (1H, bs, OH), 2.3-2.4 (2H, m, =CH-CH₂), 3.05 (1H, d, J 17 Hz, 6- β -CH), 3.47 (1H, dd, J 17 and 3 Hz, 6- α -CH), 3.60 (2H, t, J 8 Hz, CH₂OH),

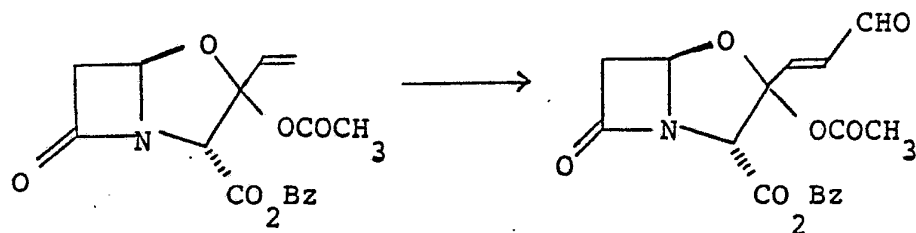
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4.61 (1H, dt, $\underline{J}$ 1 and 7.5 Hz, 8-CH), 5.05 (1H, d, $\underline{J}$ 1 Hz, 3-CH), 5.10 and 5.19 (2H, ABq, $\underline{J}$ 12.5 Hz, PhCH₂), 5.65 (1H, d, $\underline{J}$ 2.5 Hz, 5-CH), 7.22 and 7.51 (4H, A₂B₂q, $\underline{J}$ 8.5 Hz, C₆H₄).

The intermediate silyl ether had i.r. (film) 1805 (β -lactam C=O) and 1755 cm⁻¹ (esters C=O)..

Preparation 16e

Benzyl 2-acetoxy-2-(2-formylvinyl)clavam-3-carboxylate
(more polar isomer)



Benzyl 2-acetoxy-2-vinylclavam-3-carboxylate (14 g) (more polar isomer) was dissolved in ethyl acetate (250 ml) and saturated with ozone at -65°C. A solution of triphenylphosphine (8 g) in ethyl acetate (20 ml) was added and the mixture allowed to warm to -30°C (monitored by t.l.c.). After a short time (<1/2 hr), a solution + suspension of formylmethylene-triphenylphosphorane (25 g) in warm N,N-dimethyl-formamide (150 ml) was added in two portions. The mixture was maintained at between -30° and -5°C for about 1.5 hr, when the reaction appeared to be substantially complete (by t.l.c.). The unreacted phosphorane was removed by filtration, the filtrate diluted with toluene (200 ml) and ice-water to a total of about 1 litre. The mixture was agitated gently and then separated. The aqueous phase was washed with toluene, the solvent layers combined, washed with water, dried over Na₂SO₄, evaporated and subjected to

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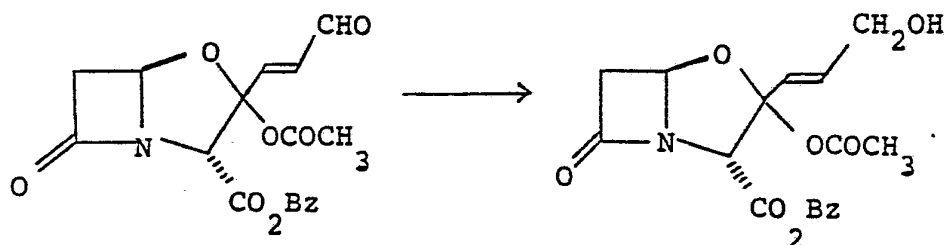


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chromatography on silica gel using ethyl acetate-hexane (2:3) as eluent. Fractions containing the desired compound were combined, evaporated and rechromatographed in the same solvent, to afford the title compound (6 g). It had i.r. (film) 1810 (β -lactam C=O), 1750 (esters C=O) and 1700 cm^{-1} (CHO).

Preparation 16f

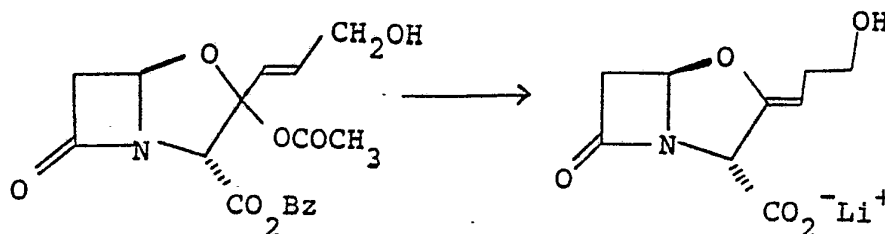
Benzyl 2-acetoxy-2-(3-hydroxyprop-1-en-1-yl)clavam-3-carboxylate (more polar isomer)



The aldehyde of Preparation 16e (6 g) was dissolved in 1,2-dimethoxyethane (100 ml) and dry tetrahydrofuran (50 ml). Sodium borohydride (free from lumps, 0.16 g) was added; after 1/2 hr t.l.c. showed some unreacted aldehyde so a further 0.12 g of NaBH_4 was added. T.l.c. then showed the absence of starting material, so the solution was diluted with an equal volume of water and of toluene, titrated to pH 5 with 1M HCl solution (frothing) and then separated. The solvent layer was washed with a little water, dried over Na_2SO_4 , filtered and evaporated to an oil (5 g). It had p.m.r. (CDCl_3); δ 1.69 (4H, s, OH and CH_3CO), 3.07 (1H, d, $\underline{J}$ 16.5 Hz, 6- β -CH), 3.45 (1H, dd, $\underline{J}$ 3 Hz and 16.5 Hz, 6- α -CH), 4.21 (2H, d, $\underline{J}$ 2 Hz, CH_2OH), 4.63 (1H, s, 3-CH), 5.16 and 5.31 (2H, ABq, $\underline{J}$ 12 Hz, PhCH_2), 5.65 (1H, d, $\underline{J}$ 2.5 Hz, 5-CH), 6.08 (1H, d, $\underline{J}$ 16 Hz, C-CH=) 6.12 (1H, dd, $\underline{J}$ 2 and 16 Hz, =CH- CH_2OH ; coupled to only one H of CH_2OH) and 7.3-7.5 (5H, m, C_6H_5); i.r. (film) 1802 (β -lactam C=O) and 1762 cm^{-1} (esters C=O).

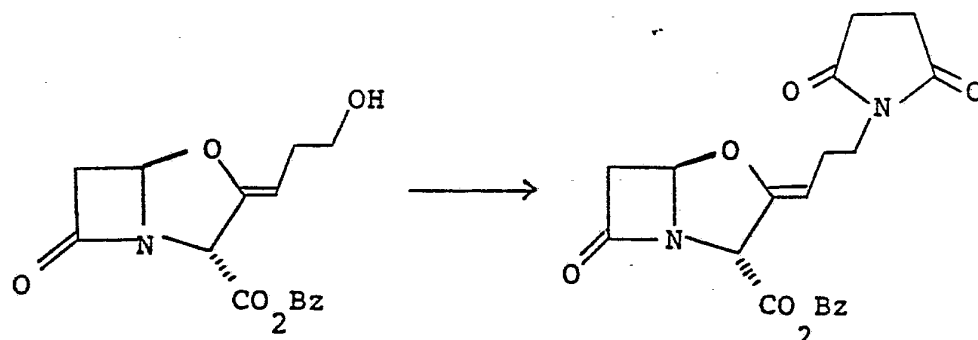
Example 16

Lithium 2-(3-hydroxypropylidene)clavam-3-carboxylate,
benzyl 2-(3-hydroxypropylidene)clavam-3-carboxylate
(from more polar isomer)



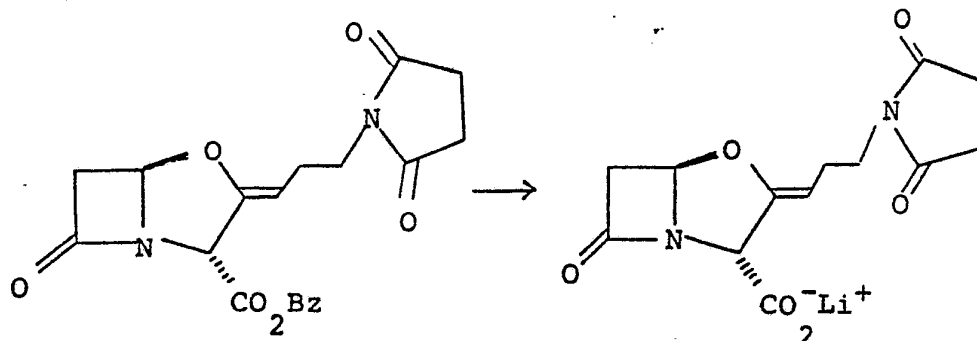
The carbinol of Preparation 16f (5 g) was dissolved in redistilled tetrahydrofuran (50 ml) and hydrogenated over 10% palladised charcoal (1.25 g). About 550 cm³ of hydrogen was absorbed at ambient temperature and pressure before the rate of uptake became very slow. The catalyst was removed by filtration, washed with tetrahydrofuran and the filtrate diluted with an equal volume of water. It was titrated to pH 6 with 1M lithium hydroxide solution. The mixture was extracted with toluene, the aqueous phase evaporated to dryness under reduced pressure and desiccated *in vacuo* overnight to yield the crude lithium salt (3.2 g).

The crude salt was dissolved in N,N-dimethylformamide (25 ml) and treated with benzyl bromide. After 8.5 hr the mixture was poured into water (60 ml) and extracted with 4 x 50 ml portions of 1:1 toluene-tetrahydrofuran. The solvent layers were combined, washed with water, dried over Na₂SO₄ and evaporated to an oil. The oil was extracted with 2 x 50 ml portions of *n*-hexane, decanting from the residue (this treatment removed most of the unreacted benzyl bromide). The residual oil was held *in vacuo*; 2.0 g remained. It was chromatographed on silica gel using a reverse gradient: ethyl acetate-hexane 1:1, graded to 2:3 ratio. The E isomer eluted first (the pure fractions contained 230 mg) followed by some mixed fractions, mostly Z-isomer (200 mg) and then almost pure Z isomer (500 mg).

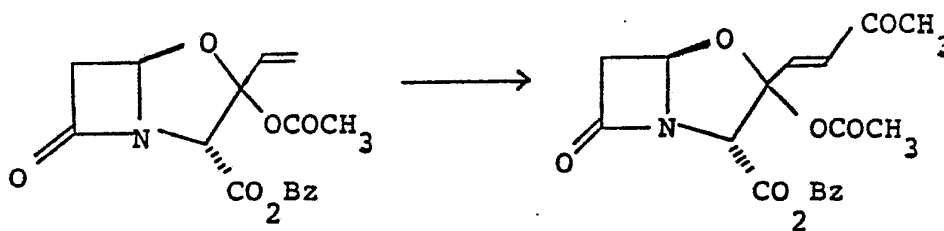
Example 17aBenzyl 2-(3-N-succinimidopropylidene)clavam-3-carboxylate (Z isomer)

Benzyl 2-(3-hydroxypropylidene)clavam-3-carboxylate (mixture of E and Z isomers, mainly Z) (200 mg) in dry tetrahydrofuran (12 ml) containing triphenylphosphine (200 mg) and succinimide (200 mg) was stirred and cooled to 0°C. Diethyl azodicarboxylate (0.2 ml) was added and the mixture was allowed to warm to ambient temperature during 1/2 hr. It was found by t.l.c. that the reaction was incomplete, so 200 mg portions of phosphine, azodicarboxylate and succinimide were added and the reaction mixture stirred overnight at ambient temperature. A zone somewhat more polar than the starting alcohol (on t.l.c.) had appeared. The mixture was evaporated and subjected to chromatography on silica gel using ethyl acetate-hexane 7:3 as eluent. There was obtained 30 mg of the title compound. No significant quantity of the E isomer was isolated. It had p.m.r. (CDCl₃): δ 2.2-2.6 (2H, m, =CH.CH₂), 2.65 (4H, s, COCH₂CH₂CO), 3.03 (1H, dd, J 17 Hz, 6-β-CH), 3.46 (1H, dd, J 17 and 3 Hz, 6-α-CH), 3.54 (2H, dd, J 3.6 and 4.5 Hz, CH₂N); 4.54 (1H, t, J 7 Hz, 8-CH), 5.0 (1H, d, J 1 Hz, 3-CH) 5.19, 5.23 (2H, ABq, J 10 Hz, PhCH₂), 5.63 (1H, d, J 2.5 Hz, 5-CH) and 7.38 (5H, m, C₆H₅). I.r. (film) 1800 (β-lactam C=O) 1750 (ester C=O) and 1710 cm⁻¹ (imide C=O).

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Example 17bLithium 2-(3-N-succinimidopropylidene)clavam-3-carboxylate (Z isomer)

The product of Example 17a (25 mg) in redistilled tetrahydrofuran (5 ml) was hydrogenated over 10% palladised charcoal (12 mg) at ambient temperature and pressure; about 2 cm³ of hydrogen was absorbed. The catalyst was removed by filtration, the filtrate diluted with water, titrated to pH 6.8 with dilute lithium hydroxide solution and evaporated to dryness under reduced pressure. After desiccation *in vacuo*, the residue was triturated with acetone, filtered off, washed with a little acetone and dried *in vacuo*, to yield a white solid (10 mg). P.m.r. (D_2O); δ 2.2-2.55 (2H, m, $=\text{CH}-\text{CH}_2$), 2.77 (4H, s, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.05 (1H, d, J 17 Hz, 6- β -CH), 3.48-3.61 (3H, m, N- CH_2 and 6- α -CH), 4.62 (1H, t, J 7 Hz, 8-CH), 4.84 (1H, s, 3-CH) and 5.64 (1H, d, J 3 Hz, 5-CH). I.r. (Nujol mull) 1785 (β -lactam C=O), 1700 (C=C and imide C=O) and 1615 (CO_2^-).

Preparation 18aBenzyl 2-acetoxy-2-(3-oxobut-1-en-1-yl)clavam-3-carboxylate

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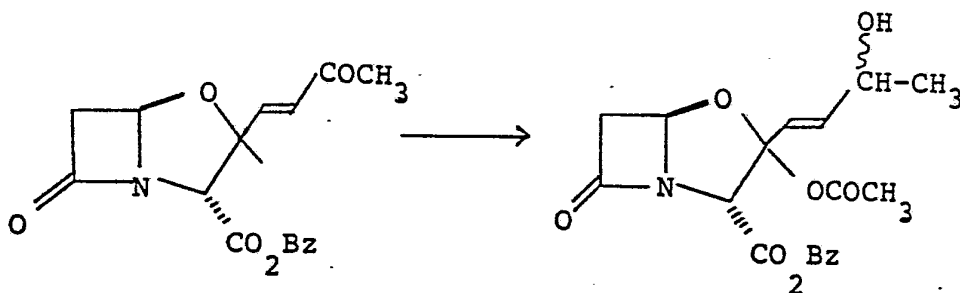


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Benzyl 2-vinyl-2-acetoxyclavam-3-carboxylate (less polar isomer) (4.65 g) in ethyl acetate (100 ml) was cooled to -65°C with stirring and saturated with ozone. The mixture was flushed with argon while the temperature was allowed to rise to -30°C , then triphenylphosphine (3.66 g) was added. The mixture was stirred at 0 to -20°C during 1 hr, then a suspension of acetylmethylene triphenylphosphorane (8.1 g) in *N,N*-dimethylformamide (30 ml) was added. After 1 hr at $0-5^{\circ}\text{C}$, the reaction was filtered, the filtrate diluted with an equal volume of toluene, washed with water and with 10% aqueous potassium dihydrogen phosphate, dried over MgSO_4 , and evaporated to a syrup. This was chromatographed on silica gel using 1:1:2 ethyl acetate-hexane-cyclohexane, to yield 2.1 g of the title product as an oil. This compound eventually crystallized, it was triturated with ether, filtered off and dried *in vacuo*. A small portion was recrystallized from ether: m.p. 98°C . It had p.m.r. (CDCl_3) δ : 2.03 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO), 3.14 (1H, dd, J 17 and 1 Hz, 6- β -CH), 3.52 (1H, dd, J 17 and 3 Hz, 6- α -CH), 5.03 and 5.09 (2H, ABq, J 12 Hz, PhCH_2), 5.21 (1H, s, 3-CH), 5.84 (1H, dd, J 1 and 3 Hz, 5-CH), 6.38 (1H, d, J 16 Hz, $\text{CH}=\text{CH}$), 6.86 (1H, d, J 16 Hz, $\text{CH}=\text{CH}$) and 7.33 (5H, m, C_6H_5). I.r. (Nujol mull) 1800, 1750 and 1675 cm^{-1} .

Preparation 18b

Benzyl 2-acetoxy-2-(3-hydroxybut-1-en-1-yl)clavam-3-carboxylate

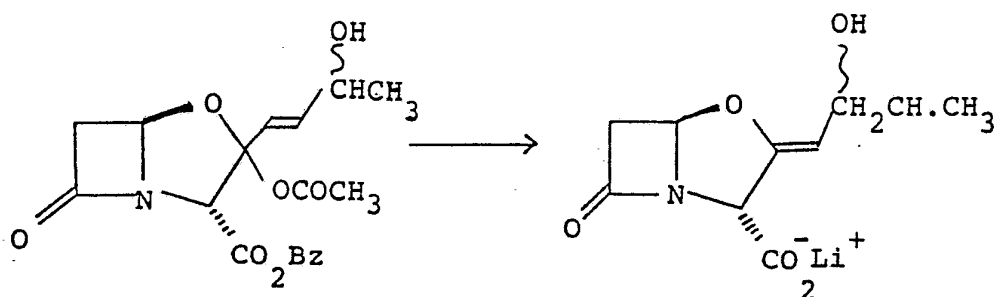


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The product of Preparation 18a (0.71g) in redistilled tetrahydrofuran (20 ml) was stirred under nitrogen at -20°C . A solution of zinc borohydride (0.145M in ether) was added in 10 ml portions, monitored by t.l.c. after each addition. When the reaction was substantially complete, it was filtered, the filtrate diluted with an equal volume of toluene and poured into water (70 ml). The pH was adjusted to about 2 by the addition of dilute sulphuric acid, the organic phase separated, washed with water and dried over MgSO_4 . After filtering, the solution was evaporated to dryness to yield the product as an oil (0.71 g). It had p.m.r. (CDCl_3) δ 1.16 (3H, d, $\underline{\text{J}}$ 6.5 Hz, $\underline{\text{CH}}_3\text{-CH}$) 1.58 (1H, bs, $\underline{\text{OH}}$), 2.01 (3H, s, $\underline{\text{CH}}_3\text{CO}$), 3.14 (1H, dd, $\underline{\text{J}}$ 1 and 17 Hz, 6- $\beta\text{-CH}$), 3.48 (1H, dd, $\underline{\text{J}}$ 3 and 17 Hz, 6- $\alpha\text{-CH}$), 4.09 and 4.17 (1H, 2 br. dq, enantiomers of $\underline{\text{CH}}_3\text{-CH}_2$), 5.07-5.2 (2H, m, ABq distorted by enantiomers - PhCH_2), 5.22 (1H, d, $\underline{\text{J}}$ 1 Hz, 3- $\underline{\text{CH}}$), 5.81 (1H, d, $\underline{\text{J}}$ 2.5 Hz, 5- $\underline{\text{CH}}$), 5.98-6.18 (2H, m, $\underline{\text{CH}}=\underline{\text{CH}}$) and 7.39 (5H, s, C_6H_5). I.r. (film): 3450 (br, OH), 1800 (β -lactam $\text{C}=\text{O}$) and 1745 cm^{-1} (esters $\text{C}=\text{O}$).

Example 18

Benzyl 2-(3-hydroxybutylidene)clavam-3-carboxylate
and the lithium salt therefrom



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Benzyl 2-acetoxy-2-(3-hydroxybut-1-en-1-yl)clavam-3-carboxylate (2.5 g) in redistilled tetrahydrofuran (80 ml) was hydrogenated over 10% palladised charcoal (1 g). When the reaction was complete (by t.l.c.) the catalyst was removed by filtration, the filtrate diluted with an equal volume of water and titrated to pH 7.2 with lithium hydroxide solution. The mixture was evaporated to dryness, dissolved in N,N-dimethylformamide (10 ml) and to it was added benzyl bromide (2 ml); stirring was continued for 4 hr at ambient temperature. The reaction mixture was diluted with toluene, washed with water, dried over MgSO_4 and evaporated to an oil. Excess benzyl bromide was extracted from the residue with hexane and the insoluble gum chromatographed on silica gel using 2:2:1 cyclohexane-hexane-ethyl acetate, fractions containing the desired product were combined and evaporated to yield 450 mg.

Of this product, 100 mg was dissolved in redistilled tetrahydrofuran and hydrogenated at ambient temperature and pressure over 10% palladised charcoal (40 mg). When the reaction was complete the catalyst was filtered off, the filtrate diluted with water, titrated to pH 7.0 with lithium hydroxide solution and evaporated to dryness, to yield 65 mg of the required lithium salt.

Benzyl ester p.m.r. (CDCl_3) δ 1.13 (3H, d, J 6.5 Hz, CH_3CH) 1.44 (1H, bs, exchange with D_2O , OH) 2.23 (2H, t, J 6.4 Hz, $=\text{CH}-\text{CH}_2$), 3.03 (1H, dd, J 1 and 16 Hz, 6- β -CH), 3.47 (1H, dd, J 3 and 16 Hz, 6- α -CH), 3.75 (1H, m, CH_3CH), 4.63 (1H, t, J 6.5 Hz, $\text{CH}=\text{CH}_2$), 5.07 (1H, m, 3-CH), 5.15 and 5.25 (2H, ABq, J 12 Hz, PhCH_2), 5.66 (1H, d, J 2.5 Hz, 5CH), and 7.36 (5H, s, C_6H_5). It

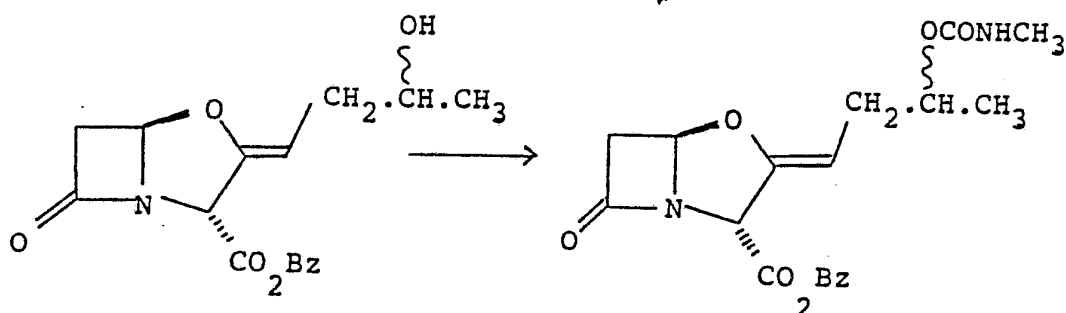


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was a 1:1 mixture of diastereoisomers at the CHOH group, as shown by its p.m.r. spectrum in presence of the chiral shift reagent (+) 2,2,2-trifluoro-1-(9-anthryl) ethanol. I.r. (film) 3400 (br, OH), 1800 (β -lactam C=O), 1745 (ester C=O), 1695 cm^{-1} (C=C).

Example 19

Benzyl 2-(3-N-methylcarbamoyloxybutylidene)clavam-3-carboxylate and the lithium salt therefrom



The benzyl ester of Example 18 (340 mg) was dissolved in methyl isocyanate (5 ml) and stirred at ambient temperature for 7 days. The excess reagent was evaporated by passing dry air through, and then the residue was dried *in vacuo*. The product was chromatographed on silica gel using 2:2:1 hexane-cyclohexane-ethyl acetate to give the product as an oil (395 mg).

Of this product, 190 mg was dissolved in redistilled tetrahydrofuran and hydrogenated over 10% palladised charcoal. The catalyst was removed by filtration, the filtrate neutralised with lithium hydroxide solution and evaporated to dryness, to yield the lithium salt as a solid (143 mg).

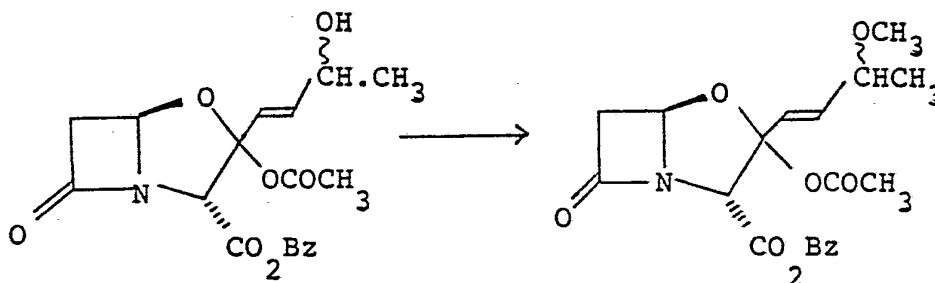
Benzyl ester had p.m.r. (CDCl_3): δ 1.13 (3H, d, J 6 Hz, CH_3CH), 2.32 (2H, bs, $=\text{CH}-\text{CH}_2$), 2.75 and 2.78

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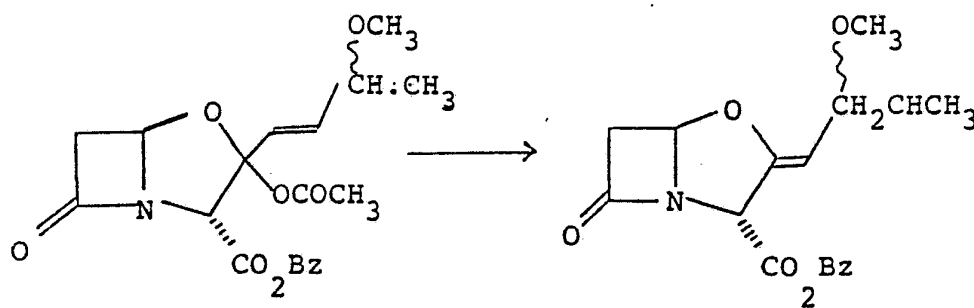
(3H, 2s, CH_3NH , two enantiomers), 3.05 (1H, dd, J 1 and 17 Hz, 6- β -CH), 3.46 (1H, dd, J 2.5 and 17 Hz, 6- α -CH), 4.47 (1H, bs, NH) 4.54-4.64 (1H, m, CHCH_3) 4.72-4.86 (1H, m, CH=), 5.05 (1H, s, 3-CH) 5.17 and 5.22 (2H, ABq, J 12 Hz, PhCH_2), 5.72-5.77 (1H, m, 5-CH) and 7.36 (5H, s, C_6H_5). I.R. (film) 3350 (br, NH), 1802 (β -lactam C=O), 1750 (ester C=O) and 1710 cm^{-1} (br, carbamate C=O, and C=C). The lithium salt had p.m.r. (D_2O) δ 1.21 (3H, d, J 6 Hz, CH_3CH), 2.3-2.5 (2H, br. m, $=\text{CHCH}_2$), 2.66 and 2.68 (3H, 2s, CH_3CH , enantiomers), 3.06 and 3.07 (1H, 2d, J 17 Hz, 6- β -CH, enantiomers), 3.54 (1H, bd, J 17 Hz, 6- α -CH), 8-CH and CH_3CH partially obscured at δ 4.7 by HOD, 4.87 and 4.89 (1H, 2s, 3-CH, enantiomers) and 5.66 (1H, bs, 5-CH).

Preparation 20aBenzyl 2-acetoxy-2-(3-methoxybut-1-en-1-yl)clavam-3-carboxylate

The product of Preparation 18b (375 mg) in ether (25 ml) was treated with diazomethane (2 mmoles) with stirring. The mixture was cooled to -20°C and BF_3 -etherate (2 drops) added as catalyst. After 45 min. the reaction mixture was washed with saturated sodium hydrogen carbonate, then with water and dried over MgSO_4 . The solution was filtered, evaporated to an oil and chromatographed using 1:1:2 ethyl acetate-hexane-cyclohexane, to yield 110 mg of the title compound and 75 mg of recovered starting material. P.m.r. (CDCl_3) δ

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1.15 (3H, d, J 6.5 Hz, CHCH_3), 2.01 (3H, s, CH_3CO), 3.13 (1H, dm, 6- β -CH), 3.20 and 3.21 (3H, 2x s, from enantiomers, CH_3OCH), 3.47 (1H, dd, J 3 Hz and 17 Hz, 6- α -CH) 3.66 (1H, m, MeOCH), 5.03 and 5.16 (2H, ABq, J 12 Hz, PhCH_2), 5.19 (1H, d, J 2 Hz, 3-CH), 5.80 (1H, d, J 3 Hz, 5-CH) 5.9-6.1 (2H, m, $\text{CH}=\text{CH}$) and 7.36 (5H, s, C_6H_5).

Example 20Benzyl 2-(3-methoxybutylidene)clavam-3-carboxylate

The product of Preparation 20 (105 mg) was hydrogenated in redistilled tetrahydrofuran (5 ml) over 10% palladised charcoal (25 mg). When the reaction was complete the catalyst was removed by filtration, the filtrate diluted with water and neutralised with lithium hydroxide. The solution was evaporated to dryness, and the residue chromatographed on silica gel using ethyl acetate-isopropanol-water. A product was collected with an R_f (same solvent system) slightly higher than 9-O-methylclavulanic acid by t.l.c., fractions containing this component were evaporated to dryness to yield about 25 mg of a brownish solid. A 250 MHz p.m.r.spectrum of this indicated that the major constituent was lithium 2-(3-methoxybutylidene)-clavam-3-carboxylate; it was, however, characterised as the benzyl ester by treatment with benzyl bromide in N,N -dimethylformamide. After partial purification

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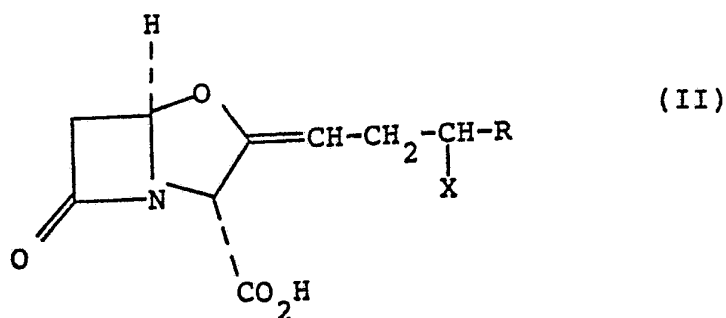
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on a short silica column there was obtained 8 mg of the title compound as an oil. It had δ (CDCl_3) 1.07 (3H, d, J 6 Hz, CH_3CH), 2.1-2.4 (2H, m, $\text{CH}_2\text{CH=}$), 3.03 (1H, d, J 17 Hz, 6- β -CH), 3.28 and 3.29 (3H total, 2s, CH_3O , both enantiomers), 3.46 (1H, dd, J 2.6 and 17 Hz, 6- α -CH), 4.63 (1H, dq, J 1.2 and 7.5 Hz, CH=), 5.05 (1H, d, J 1.1 Hz, 3-CH), 5.18 (2H, s, PhCH_2), 5.66 (1H, 2d, J 2.5 Hz, 2 enantiomers, 5-CH) and 7.36 (C_6H_5).



Claims

- 1) A compound of formula II



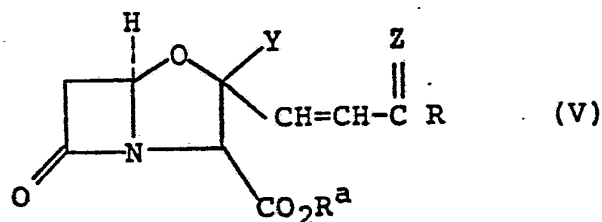
or a salt or ester thereof;

wherein R is hydrogen or a hydrocarbon group and X is hydroxy, substituted hydroxy, mercapto, substituted mercapto, azido, cyano, halo, isothiocyanato, substituted amino or X represents the residue of a carbon nucleophile or is an activated aryl or heteroaryl group.

- 2) A compound according to claim 1 wherein X is hydroxy, $-OR^1$, $-OCOR^1$, $-OCSR^1$, $-OCO_2R^1$, OCS_2R^1 , $OCOSR^1$, $-OCSOR^1$, OSO_3H , $-OPO_3H$, OSO_2R^1 and $CONR^2R^3$ wherein R^1 , R^2 and R^3 are independently hydrogen or substituted or unsubstituted hydrocarbon groups of 1 to 20 carbon atoms.
3. A compound according to claim 1 wherein X is $-NHR^{10}$, $-NR^{10}R^{11}$, $-NR^{10}R^{11}R^{12}$, $-NHCX^1R^{10}$, $-NHCX^1ZR^{10}$, $-NHCO_2R^{10}$, $-NHCX^1NR^{10}R^{11}$,

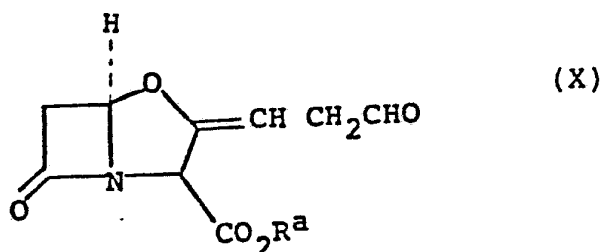
$-N(CX^1R^{12})R^{13}$, $-N(CX^1R^{12})CZR^{13}$, $-N(CX^1R^{12})ZR^{13}$, $-N(CX^1ZR^{12})R^{13}$ and $-N(CX^1ZR^{12})CX^1ZR^{13}$ wherein X^1 and Z are each oxygen or sulphur and R^{10} , R^{11} , R^{12} and R^{13} are independently substituted or unsubstituted hydrocarbon groups of 1 to 20 carbon atoms.

4. 2-(3-hydroxypropylidene)clavam-3-carboxylic acid and derivatives thereof.
5. A process for preparing a compound of formula (II) as defined in claim 1 or a salt or ester thereof; which process comprises either
 - a) reduction of a compound of formula V



wherein R is as defined above in relation to formula II, R^a is hydrogen or a carboxy blocking group, Y is tetrazolyl or triazolyl each of which may be optionally substituted and each of which is bonded to the oxazolidine ring via a nitrogen atom, or $-O.CO.R^b$ where R^b is hydrogen, alkyl, alkenyl, arylalkyl, aryl, cycloalkyl or heterocyclyl, and Z is an oxygen or sulphur atom; or

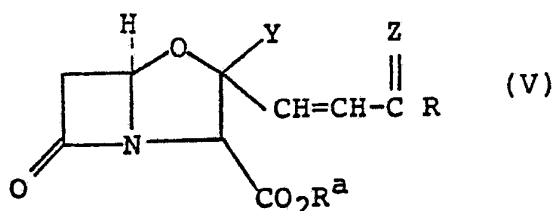
- b) (wherein R is hydrogen and X is hydroxy) reduction of a compound of formula X



where R^a is as defined hereinbefore in relation to formula V;

and thereafter if necessary

- i) converting a compound of formula II where X is hydroxy or mercapto to a compound of formula (II) wherein X is not hydroxy or mercapto;
 - ii) removing any carboxy blocking group R^a ;
 - iii) converting the product into a salt or ester.
- 6) A compound of formula (V)

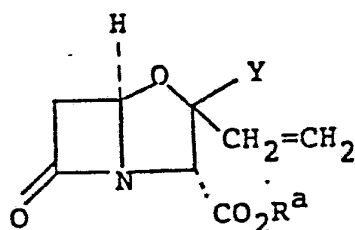


wherein R is as defined in claim 1 in relation to formula II, R^a is hydrogen or a carboxy blocking



group, Y is tetrazolyl or triazolyl each of which may be optionally substituted and each of which is bonded to the oxazolidine ring via a nitrogen atom, or $-O.CO.R^b$ where R^b is hydrogen, alkyl, alkenyl, arylalkyl, aryl, cycloalkyl or heterocyclyl, and Z is an oxygen or sulphur atom.

- 7) A compound of formula VII



VII

wherein R^a is hydrogen or a carboxy blocking group, and Y is as defined in claim 6 in relation to formula (V).

- 8) A pharmaceutical composition which comprises a compound of formula (II) as defined in claim 1 or a salt or ester thereof in combination with a pharmaceutically acceptable carrier.
- 9) A pharmaceutical composition according to claim 8 which further comprises a penicillin or cephalosporin.
- 10) A compound of formula (II) as defined in claim 1 or a salt or ester thereof for use in the treatment of bacterial infection.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 84/00034

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC C 07 D 498/04; C 07 F 7/18; A 61 K 31/42 // (C 07 D 498/04 IPC ³ : 263/00; 205/00) (A 61 K 31/42; 31/43)				
II. FIELDS SEARCHED Minimum Documentation Searched ⁴ <table style="width: 100%; border: none;"> <tr> <td style="width: 20%; border: none; vertical-align: top;"> Classification System Classification Symbols IPC³ C 07 D 498/00; C 07 F 7/00; A 61 K 31/00 Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵ </td> <td style="border: none;"></td> </tr></table>			Classification System Classification Symbols IPC³ C 07 D 498/00; C 07 F 7/00; A 61 K 31/00 Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵	
Classification System Classification Symbols IPC³ C 07 D 498/00; C 07 F 7/00; A 61 K 31/00 Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵				
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴				
Category ⁶	Citation of Document, ¹⁶ with Indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸		
Y	GB, A, 1593275 (GLAXO) 15 July 1981 see claims ---	1,5,8-10		
Y	EP, A, 0002319 (BEECHAM) 13 June 1979 see claims ---	1,5,8-10		
A	EP, A, 0018305 (HOECHST) 29 October 1980 see claims ---	1		
A	GB, A, 1546569 (BEECHAM) 23 May 1979 see claims ---	1		
P,A	EP, A, 0080285 (BEECHAM) 1 June 1983 see claims ---	1,5,8-10		
P,A	EP, A, 0080286 (BEECHAM) 1 June 1983 see claims -----	1,5,8-10		
* Special categories of cited documents: ¹⁵ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the International filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family				
IV. CERTIFICATION				
Date of the Actual Completion of the International Search ¹⁹ 25th April 1984	Date of Mailing of this International Search Report ²⁰ 13 JUN 1984			
International Searching Authority ¹ EUROPEAN PATENT OFFICE	Signature of Authorized Officer ²⁰ G.L.M. Kruidenberg			

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 84/00034 (SA 6530)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/06/84

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		BE-A- 859979	21/04/78
		FR-A- 2368489	19/05/78
		DE-A- 2747350	27/04/78
		JP-A- 53068797	19/06/78
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		US-A- 4242262	30/12/80
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		JP-A- 55130981	11/10/80
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		AU-A- 9081382	02/06/83

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