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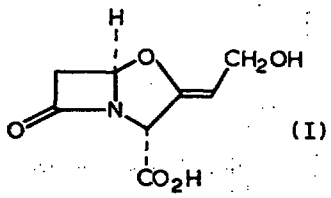
(72) Inventor ROGER JOHN PONSFORD

(54) THERAPEUTIC COMPOUNDS CONTAINING β-LACTAMS

(71) We, BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new β-lactam containing compounds, to the process for their preparation and to pharmaceutical compositions containing them.

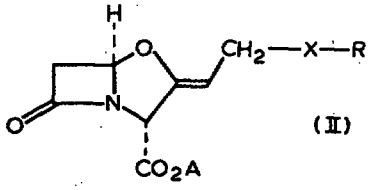
British Patent Specifications Nos. 1508977 and 1508978 (see Also Belgian Patent Specification No 827926) disclose inter alia clavulanic acid which has the formula (I):



(I)

and its salts and esters. It has now been discovered that such compounds can be converted into thioethers which possess β-lactamase inhibitory properties and a degree of antibacterial activity.

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



(II)

wherein X is S, SO or SO_2 and R is an organic group of up to 20 carbon atoms and A is a group such that CO_2A represents a carboxylic acid group or a salt or ester thereof.

The group R will be inert, that is the inclusion of the group R will not lead to the rapid degradation of the compound of the formula (II).

Suitable organic groups R for inclusion in the compounds of the formula (II) include hydrocarbon groups and hydrocarbon groups substituted by halogen and/or groups of the sub-formulae OR^1, $O.COR^1$, $CO.R^1$, CO_2R^1, NHR^1, NR^1R^2, $HN.CO.R^1$, NR^2COR^1, $NHCO_2R^1$, $NR^2CO_2R^1$ wherein R^1 is a hydrogen atom or a hydrocarbon group of up to 8 carbon atoms and R^2 is an alkyl group of 1—3 carbon atoms.

Suitable hydrocarbon groups include alkyl groups especially those of up to 6 carbon atoms.

One particularly suitable sub-group of compounds of the formula (II) are those wherein R is a group CH_2R^3 wherein R^3 is a hydrogen atom or an alkyl group of up to 5 carbon atoms (which is to say methyl, ethyl, propyl, butyl and pentyl) or a naphthyl group or a phenyl group optionally substituted by halogen or hydroxyl or amino, or a group of the formula R^4, OR^4 or NR^4R^5 where R^4 is an alkyl or acyl group of up to 3 carbon atoms and R^5 is a hydrogen atom or an alkyl group of up to 4 carbon atoms.

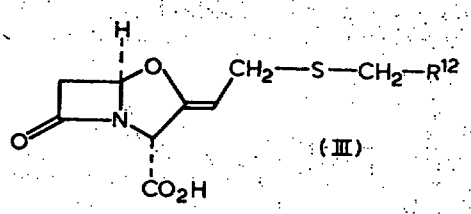
A further suitable sub-group of compounds of the formula (II) are those wherein R is a group $CR^6R^7R^8$ wherein R^6 and R^7 are independently alkyl groups of up to 3 carbon atoms or a phenyl group optionally substituted by halogen or a group of the formula R^9 or OR^9 where R^9 is an alkyl group of up to 3 carbon atoms; and R^8 is a hydrogen atom or an alkyl group of up to 3 carbon atoms or a phenyl group optionally substituted by halogen or a group of the formula R^{10} or OR^{10} where R^{10} is an alkyl group of up to 3 carbon atoms.

Another suitable sub-group of compounds of the formula (II) are those wherein R is a group R^{11} which is an optionally methyl substituted heteroaromatic group of 5- or 6- ring atoms. Suitable groups R^{11} include triazole, tetrazole, thienyl, thiazole, thiadiazole, thiatriazole, oxazole, isoxazolyl, oxadiazole, pyridyl, pyridazinyl, or pyrimidinyl any of which may be optionally substituted by methyl group.

Other suitable groups R include those described in West German Offenlegungsschrift 2503335 as suitable for inclusion at the 3- position of 3-thiomethyl cephalosporins.

Yet another suitable sub-group of compounds of the formula (II) are those wherein R is a phenyl group optionally substituted by a group of the sub-formula OR^1, $O.COR^1$, COR^1, CO_2R^1 as hereinbefore defined.

One group of particularly suitable compounds of the formula (II) are those of the formula (III),

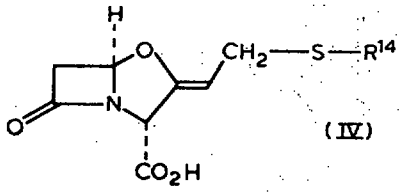


(III)

and pharmaceutically acceptable salts thereof wherein R^{12} is a phenyl group optionally substituted by fluorine, chlorine, bromine or OR^{13}, $O.CO.R^{13}$, COR^{13}, CO_2R^{13} where R^{13} is a hydrocarbon group of up to 8 carbon atoms.

Other particularly suitable compounds of the formula (II) are the sulphoxides and sulphones corresponding to the sulphides of formula (III).

Another group of particularly suitable compounds of the formula (II) are those of the formula (IV):

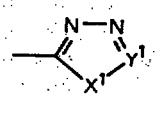


(IV)

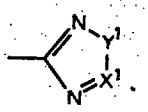
and pharmaceutically acceptable salts thereof wherein R^{14} is a 5- membered heterocyclic group optionally substituted by an alkyl group of up to 3 carbon atoms.

Suitable groups R^{14} include those which contain 3 or 4 heteroatoms at least two of which are nitrogen atoms.

Particularly suitable groups R^{14} include those of the sub-formulae (a) and (b):



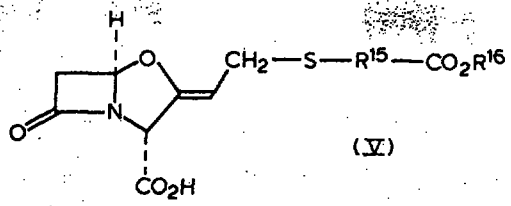
(a)



(b)

wherein X^1—Y^1 represents a S—$N(CH_3)$, O—$N(CH_3)$, N—$N(CH_3)$, N—CH_2, O—CH_2 or S—CH_2 group.

A further group of particularly suitable compounds of the formula (II) are those of the formula (V):



(V)

and pharmaceutically acceptable salts thereof wherein R^{15} is a divalent hydrocarbon group of 1—8 carbon atoms and R^{16} is a hydrogen atom or a hydrocarbon group of 1—8 carbon atoms.

Suitable groups R^{15} include alkylene groups of 1—4 carbon atoms or an alkylene group of 1 or 2 carbon atoms substituted by a phenyl group.

Suitable groups R^{16} include the hydrogen atom and alkyl groups of 1—4 carbon atoms or an alkyl group of 1 or 2 carbon atoms substituted by a phenyl group.

Other particularly suitable compounds of the formula (II) are those sulphoxides and sulphones corresponding to the sulphides of the formula (V).

From the foregoing it will be realised that suitable groups R include the methyl, ethyl, n-propyl, n-butyl, 2-methoxyethyl, 2-benzyloxymethyl, 2-ethoxyethyl, 3-methoxypropyl, benzyl, p-chlorobenzyl, p-methoxybenzyl, m-methoxybenzyl, p-methylbenzyl, phenyl, 4-fluorophenyl, and 2-phenylethyl groups.

Suitable groups A in the compounds of the formula (II) and equivalent groups in subsequently described compounds include hydrogen and salting ions such as the lithium, sodium, potassium, calcium, magnesium, ammonium and amine salts such as alkylamine, dialkylamine, trialkylamine, or pyrrolidine salts. Salts of the compounds of the formula (II) are aptly pharmaceutically acceptable.

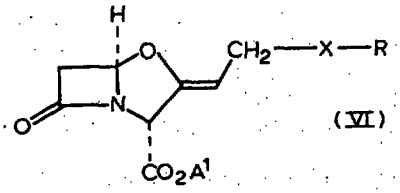
Most suitably the group A represents a pharmaceutically acceptable alkali metal or alkaline earth metal ion.

The lithium salts of the compounds of this invention are frequently advantageous owing to their easy isolation and good storage properties.

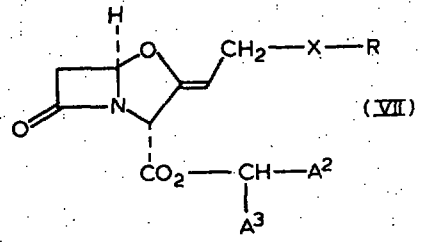
The sodium and potassium salts (especially the sodium salts) of the compounds of this invention are advantageous because of the clear pharmaceutically acceptability of the sodium and potassium ions.

The salts of this invention are preferably crystalline. Further, since they are to be used as pharmaceutical agents or intermediates in the preparation of pharmaceutical agents it is preferable that they have the high degree of purity associated with pharmaceuticals.

Particularly suitable esters of the compounds of the formula (II) and subsequent formulae include those of the formulae (VI) and (VII):



(VI)



(VII)

wherein X and R are as defined in relation to formula (II) and A^1 is an alkyl group of 1—8 carbon atoms optionally substituted by halogen or a group of the formula OA^4, $OCOA^4$, SA^4, SO_2A^4 wherein A^4 is a hydrocarbon group of up to 6 carbon

atoms; A^2 is a hydrogen atom, an alkyl group of up to 4 carbon atoms or a phenyl group optionally substituted by halogen or by a group A^5 or OA^5 where A^5 is an alkyl group of up to 6 carbon atoms; and A^3 is a phenyl group, optionally substituted by halogen or by a group A^5 or OA^5 where A^5 is an alkyl group.

Benzyl and p-methoxybenzyl esters of the compounds of the formula (II) are particularly useful hydrogenolysable esters.

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

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 infection in 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, or disintegrants in accordance with conventional pharmaceutical practice in the manner well understood by those skilled in the art of formulating antibiotics.

Injectable or infusable compositions of salts of a compound of the formula (II) are particularly suitable as high tissue levels of a compound of the formula (II) can occur after administration by injection or infusion. Thus, one preferred composition aspect of this invention comprises a salt of a compound of the formula (II) in sterile form.

Unit dose compositions comprising a compound of the formula (II) or a salt or ester thereof adapted for oral administration form a further preferred composition aspect of this invention.

Under certain conditions, the effectiveness of oral compositions of compounds of the formula (II) and their salts and esters can be improved if such compositions contain a buffering agent or an enteric coating agent such that the compounds of the invention do not have prolonged contact with highly acidic gastric juice. Such buffered or enterically coated compositions may be prepared in accordance with conventional pharmaceutical practice.

The compound of the formula (II) or its salt or ester may be present in the composition as sole therapeutic agent or it may be present together with other therapeutic agents such as penicillin or cephalosporin. Suitable penicillins or cephalosporins 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. Thus, suitable β-lactam antibiotics for inclusion in the compositions of this invention include benzylpenicillin, phenoxymethylpenicillin, carbenicillin, methicillin, propicillin, amphicillin, amoxycillin, epicillin, ticarcillin, cyclacillin, cephaloridine, cephalothin, cefazolin, cephalexin, cephacetrile, cephamandole, cephapirin, cephradine, cephaloglycine and other well known penicillins and cephalosporins, or pro-drugs therefore such as hetacillin, metampicillin, the acetoxymethyl, pivaloyloxymethyl or phthalidyl esters of benzylpenicillin, ampicillin, amoxycillin, or cephaloglycine or the phenyl, tolyl, or indanyl α-esters of carbenicillin or ticarcillin.

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.

When present in a pharmaceutical composition together with a penicillin or cephalosporin, the ratio of the compound of the formula (II) or its salt or ester present to penicillin or cephalosporin present may be from, over a wide range of ratios, for example, 1:3 to 3:1 and advantageously may be for example, 1:1 or 1:2.

The total quantity of antibacterial agent present in any unit dosage form will normally be between 50 and 1500 mg and will usually be between 100 and 1000 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.

Compositions of this invention may also be used to treat infections of domestic animals such as mastitis in cattle.

Normally between 50 and 3000 mg of the compositions of the invention will be administered each day of treatment but more usually between 100 and 1000 mg of the compositions of the invention will be administered per day. However, for the treatment of severe systemic infections or infections of particularly intransigent organisms, higher doses may be used in accordance with clinical practice.

The penicillin or cephalosporin in synergistic compositions of this invention will normally be present up to or at approximately the amount conventionally used when that penicillin or cephalosporin is the sole therapeutic agent used in the treatment of infection.

Particularly favoured compositions of this invention will contain from 150—1000 mg of amoxycillin, ampicillin or a salt, hydrate or in-vivo hydrolysable esters therefore and from 50—500 mg of the compound of the formula (II) hydrolyzable ester thereof and more suitably from 200—500mg of amoxycillin, ampicillin or a salt, hydrate or in-vivo hydrolysable ester thereof and from 50—250 mg of the compound of the formula (II).

Amoxycillin trihydrate and sodium amoxycillin are particularly suitable for inclusion in the compositions of this invention.

The present invention also provides a process for the preparation of the compounds of the formula (II) which process comprises the reaction of an ester of clavulanic acid with a compound of the formula (VIII):

$$H—S—R \qquad \text{(VIII)}$$

wherein R is as defined in relation to formula (II) and thereafter performing one or more of the following optional steps:

(a) de-esterifying the thus produced ester to form the free or salted acid within formula (II);

(b) re-esterifying the thus produced free or salted acid to yield a further ester within formula (II);

(c) oxidizing the sulphide to a sulphoxide or sulphone.

Esters within formula (II) wherein X is S are first prepared by the reaction of a thiol of the formula (VIII) as defined with the corresponding ester of the compound of the formula (I) in the presence of an acid catalyst.

If the group R contains a reactive group such as an amino or a carboxylate function, these reactive groups may be protected in conventional manner prior to the operation of the above process and thereafter regenerated in conventional manner.

Suitably the catalyst is a Lewis acid catalyst such as boron trifluoride or its equivalent such as a boron trifluoride etherate, for example $BF_3.O(C_2H_5)_2$.

The preceding reaction normally takes place in a solvent inert under the reaction conditions (e.g. dry and non-hydroxylic) such as chloroform, dichloromethane, tetrahydrofuran or dioxane.

Most suitably the reaction takes place at a depressed or non-elevated temperature, for example −80° to +30°C, and preferably at a depressed temperature, for example, −50° to 0°C.

Those esters within formula (II) wherein X is SO or SO_2 can be prepared from the corresponding compound wherein X is S by mild oxidation.

Such reactants may take place at an ambient or depressed temperature, for example at −20° to +20°C, more suitably at −12° to +5°C, for example at about 0°C.

The oxidation is best brought about using an organic per-acid as the oxidizing agent. Suitable acids include m-chloroperbenzoic acid and equivalent reagents. Use of one equivalent of the oxidizing agent leads to a compound of the formula (II) wherein X is SO whereas the use of two equivalents of the oxidizing agent leads to a compound of the formula (II) wherein X is SO_2.

It is normal to carry out the oxidation in an inert solvent such as methylene chloride.

Acids and salts within formula (II) may with difficulty be prepared from hydrogenolysable esters such as the benzyl and methoxybenzyl esters within formula (II) by hydrogenation using a medium or low pressure of hydrogen in the presence of a transition metal catalyst such as 10% palladium on charcoal wherein the weight of catalyst to thioether is about 1:3. Suitable solvents include tetrahydrofuran and ethanol. If a base is included the initially produced acid is converted to a salt which is then isolated.

Salts within formula (II) wherein X is S may be prepared from esters within formula (II) by very mild basic hydrolysis, for example by hydrolysis in an aqueous solution maintained at pH 7 to 9 by the slow addition of base. Suitable bases include lithium hydroxide, sodium hydroxide and their chemical equivalents.

Suitable esters for hydrolysis include the methyl, methoxymethyl and the benzyl esters, the methoxymethyl ester being preferred.

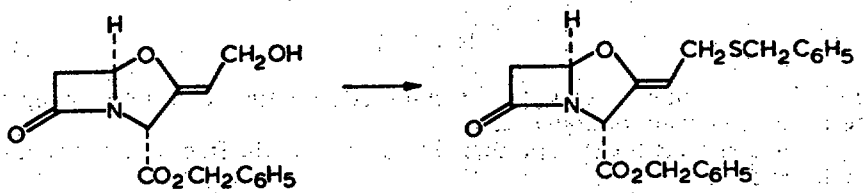
Acids within formula (II) may be prepared by the careful acidification of a corresponding salt such as the sodium salt.

Salts within formula (II) may also be prepared by salt exchange in conventional manner; for example a solution of the lithium salt in water may be passed through a bed of ion exchange resin in the sodium form (e.g. Amberlite 120 (Registered Trade Mark); a sodium salt of a sulphonated polystyrene divinyl benzene co-polymer) in about ten-fold excess until elution is complete; the resulting sodium salt may be obtained by freeze drying. Similarly, a sodium salt may be converted to a lithium salt or to a potassium salt in similar manner.

The following Examples illustrate the invention.

EXAMPLE 1

Benzyl-3-(2-benzylthioethylidene)-7-oxo-4-oxa-1-azabicyclo[3,2,0]heptane-2-carboxylate



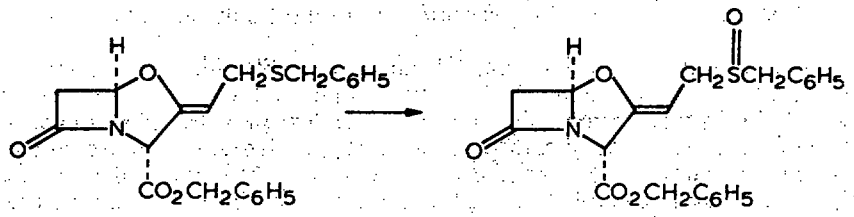
Benzyl clavulanate (500 mg) was dissolved in methylene chloride (50 ml) and cooled to −30°C. Boron trifluoride etherate (7 drops) was added at −30°C followed by a solution of benzyl mercaptan (220 mg) in methylene chloride (5 ml) dropwise at −30°C. The solution was stirred at −30°C to 0°C for 1¼ hours, washed with 3% sodium bicarbonate solution (3×25 ml) and the extract dried over $MgSO_4$. Evaporation of the solvent and chromatography yielded the title compound (150 mg; 25%) as a colourless oil.

I.r. ($CHCl_3$): 1800, 1745, 1690 cm^{-1};
N.m.r. ($CDCl_3$): 3.00 (1H,d,J=17Hz, 6β-*CH*); 3.52 (1H,dd,J=17Hz, J'=2.5 Hz, 6α-*CH*); 3.20 (2H, d, J=8Hz, CH_2SB_2); 3.77 (2H, s, SCH_2Ph); 4.77 (1H, t, J=8 Hz, $=CH—CH_2$); 5.18 (1H, brs, 3—*CH*); 5.30 (2H, s, CO_2CH_2Ph); 5.72 (1H, d, J=2.5 Hz), 6—*CH*); 7.40 and 7.50 (10H, two singlets, SCH_2Ph and CO_2CH_2Ph). M.w. (mass spectrometry) 395.

β-Lactamase Inhibition I_{50} (μg/ml)	
Escherichia coli	0.3
Klebsiella aerogenes E70	0.2
Staphylococcus aureus Russell	<0.07
Pseudomonas aeruginosa A.	1.8
Pseudomonas dalgleish	0.76
Citrobacter mantio	24

EXAMPLE 2

Benzyl-3-(2-benzylsulphinylethylidene)-7-oxo-4-oxa-1-azabicyclo[3,2,0]heptane-2-carboxylate



Benzyl - 3 - (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate (39.5 mg) was dissolved in methylene chloride (5 ml) and treated with *m*-chloroperbenzoic acid (19 mg) at 0°C. The solution was stirred at 0°C for ½ hour and washed with 3%bicarbonate solution (3×5 ml). The solvent was evaporated and the gum chromatographed to yield the title product as a mixture of R and S sulphoxides (30 mg; 73%).

I.r. ($CHCl_3$): 1800, 1750, 1700 cm^{-1};
N.m.r. ($CDCl_3$): 3.10 (1H, d, J=17 Hz, 6β-*CH*); 3.50 (2H, br.d., J=8 Hz, =CH—*CH*$_2$—); 3.62 (1H, dd, J=17 Hz, J'=2.5 Hz, 6α-*CH*); 3.87 and 3.97 (2H, two singlets,

$$\overset{\overset{O}{\uparrow}}{SCH_2Ph},$$

R, and S sulphoxides); 4.86 (1H, br. t., J=8 Hz, =*CH*—CH_2—); 5.26 (1H, brs., 3—*OH*); 5.33 (2H, s, CO_2CH_2Ph); 5.83 (1H, d, J=2.5 Hz, 5—*CH*); 7.48δ (10H, s, CO_2CH_2*Ph* and

$$\overset{\overset{O}{\uparrow}}{SCH_2Ph}).$$

$[\alpha]_D^{20}$=+7.2° (c=0.94; MeOH).

Antibacterial Activity in Vitro (μg/ml)

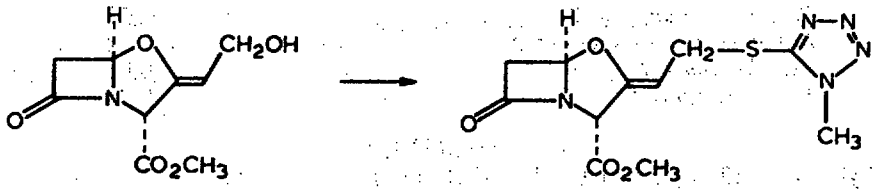
Staphylococcus aureus Oxford	62
Staphylococcus aureus Russell	62

β-Lactamase Inhibition I_{50} (μg/ml)

Escherichia coli JT4	0.07
Klebsiella aerogenes E70	0.8
Staphylococcus aureus Russell	0.16
Pseudomonas aeruginosa A.	0.6
Citrobacter mantio	0.26

EXAMPLE 3

Methyl - 3 - [2 - (1 - methyl - 1,2,3,4 - tetrazol - 5 - yl)thioethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



To methyl clavulanate (213 mg) in dichloromethane (10 ml) at −20°C was added boron trifluoride etherate (5 drops) followed by 1 - methyl - 1,2,3,4 - tetrazol - 5 - thiol (120 mg). The reaction mixture was stirred for 2 hours during which period the temperature was gradually allowed to reach −10°C. The solution was washed with aqueous sodium bicarbonate solution (3%, 3×10 ml). The organic phase was dried and the solvent removed by evaporation. Chromatography of the crude material yielded the title compound (approximately 40% yield).

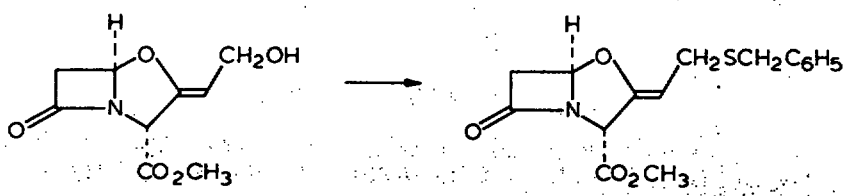
I.r. ($CHCl_3$): 1800, 1750, 1690 cm^{-1}.
N.m.r ($CDCl_3$): 3.04 (1H, d, J=17 Hz, 6β-*CH*); 3.50 (1H, dd, J=17 Hz, J'=2.5 Hz, 6α-*CH*); 3.73 (3H, s, CO_2CH_3); 3.88 (3H, s, N—CH_3); 3.97 (2H, d, J=8 Hz, =CH—*CH*$_2$); 4.92 (1H, br. t, =*CH*—CH_2); 5.00 (1H, br. s, 3-*CH*); 5.72δ (1H, d, J=2.5 Hz, 5-*CH*).
$[\alpha]_D^{21}$=+13° (c=1.34, MeOH).

The approximate β-lactamase inhibition I_{50} values in μg/ml for the title compound were as follows:

Escherichia coli JT4	0.02
Klebsiella aerogenes E70	≫1.0
Staphylococcus aureus Russell	0.21
Proteus mirabilis C889	0.56
Pseudomonas aeruginosa A	0.035
Pseudomonas dalgleish	0.08
Enterobacter P99	0.01

EXAMPLE 4

Methyl 3 - (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



Methyl clavulanate (1 g) was dissolved in dry methylene dichloride (50 ml) and cooled to −30°C. Borontrifluoride etherate (15 drops) was added followed by benzyl mercaptan (620 mg) in methylene chloride (10 ml). The mixture was stirred at −30°C to −10° for 2 hours and washed with 3% sodium bicarbonate solution (3×50 ml), dried over magnesium sulphate and the solvent evaporated to yield a yellow oil. Chromatography provided the title compound as a light yellow oil (219 mg; 20%).

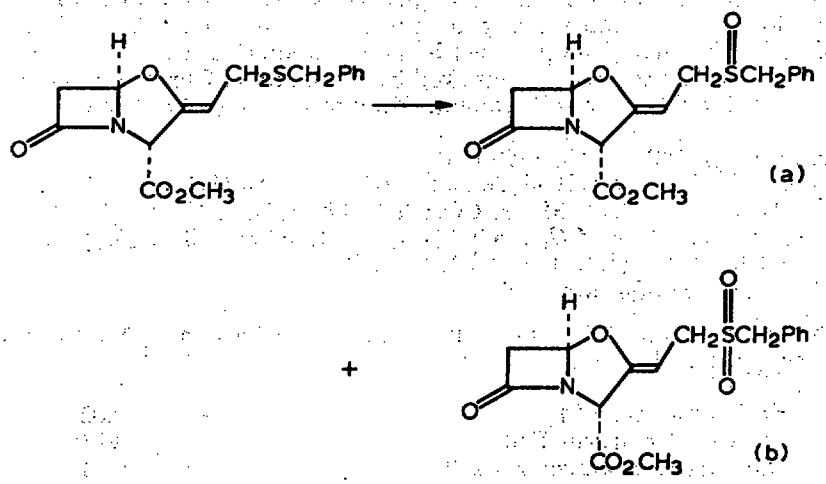
I.r. ($CHCl_3$): 1800, 1750, 1690 cm^{-1};
N.m.r. ($CDCl_3$): 2.93 (1H, d, J=17 Hz, 6β-*CH*); 3.15 (2H, d, J=8 Hz, =CH—*CH*$_2$); 3.45 (1H, dd, J=17 Hz, J'=2.5 Hz, 6α-*CH*); 3.67 (2H, s, S*CH*$_2$Ph); 3.74 (3H, s, CO_2CH_3); 4.67 (1H, br. t, J=8 Hz, =*CH*—CH_2; 5.05 (1H, br. s, 3-*CH*); 5.67 (1H, d, J=2.5 Hz, 5-*CH*); 7.29δ (5H, s, SCH_2*Ph*).
$[\alpha]_D^{21}$=+26° (c=1.69, MeOH).

The approximate β-lactamase inhibition I_{50} values in μg/ml for the title compound were as follows:

Escherichia coli JT4	0.15
Klebsiella aerogenes E70	0.28
Staphylococcus aureus Russell	0.01
Proteus mirabilis C889	0.52
Pseudomonas aeruginosa A	0.54
Pseudomonas dalgleish	0.03
Enterobacter P99	0.34

EXAMPLE 5

Methyl 3 - (2 - benzylsulphinethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate and methyl 3 - (2 - benzylsulphonylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



Methyl 3 - (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate (95 mg) was dissolved in dry methylene chloride (5 ml) and treated with m-chloroperbenzoic acid (78 mg) at 0°C. The

solution stirred at 0°C for half an hour and washed with 3% sodium bicarbonate solution (3×5 ml). The organic phase was dried over magnesium sulphate and the solvent evaporated to yield after chromatography as the first eluted product methyl 3 - (2 - benzylsulphonylethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate (b) as a colourless oil (28 mg; 27%).

I.r. ($CHCl_3$): 1805, 1755, 1695 cm^{-1}.
N.m.r. ($CDCl_3$): 3.02 (1H, d, J=17 Hz, 6β-*CH*); 3.50 (1H, dd, J=17 Hz, J'=2.5 Hz, 6α-*CH*); 3.65 (2H, d, J=8 Hz, =CH—CH_2); 3.75 (3H, s, CO_2CH_3); 4.13 (2H, s, CH_2Ph); 4.74 (1H, br. t, J=Hz, =*CH*—CH_2); 5.14 (1H, br. s, 3-*CH*); 5.75 (1H, d, J=2.5 Hz, 5-*CH*); 7.37δ (5H, s, CH_2Ph).
$[\alpha]_D^{21}$=+8.2° (c=1.15, MeOH).

The approximate β-lactamase inhibition I_{50} values in μg/ml for (b) were as follows:

Escherichia coli JT4	<0.0076
Klebsiella aerogenes E70	0.12
Staphylococcus aureus Russell	0.01
Proteus mirabilis C889	0.16
Pseudomonas aueruginosa A	0.025
Pseudomonas dalgleish	<0.0076
Enterobacter P99	0.015

The second product (a) to be eluted from the column was collected as a colourless oil.

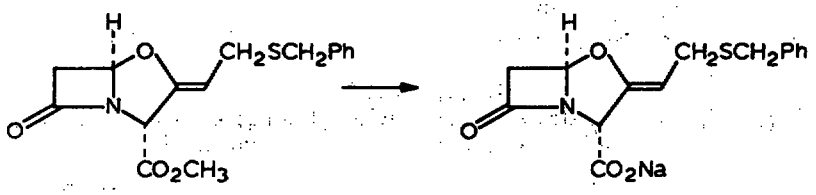
I.r. ($CHCl_3$): 1800, 1755, 1690 cm^{-1}
N.m.r. ($CDCl_3$): 3.00 (1H, d, J=17 Hz, 6β-*CH*); 3.41 (2H, d, J=8 Hz, =CH—CH_2); 3.49 (1H, dd, J=17 Hz, J'=2.5 Hz, 6α-*CH*); 3.75 (3H, s, CO_2CH_3); 3.90 (2H, s, CH_2Ph); 4.78 (1H, br.t, J=8 Hz, =*CH*—CH_2); 5.18 (1H, br.s, 3-*CH*); 5.73 (1H, d, J=2.5 Hz, 5-*CH*); 7.32δ (5H, s, CH_2Ph).
$[\alpha]_D^{21}$=0° (c=0.78; MeOH).

The approximate β-lactamase inhibition I_{50} values in μg/ml for (a) were as follows:

Escherichia coli JT4	0.05
Klebsiella aerogenes E70	0.86
Staphylococcus aureus Russell	0.12
Proteus mirabilis C889	0.56
Psuedomonas aeruginosa A	0.10
Pseudomonas dalgleish	0.03
Enterobacter P99	≪0.076

EXAMPLE 6

Sodium 3 - (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



Methyl 3 - (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate (95.7 mg) was hydrolysed using N NaOH at pH 9.5 (pH stat) until hydrolysis was complete. Chromatography (n-BuOH/EtOH/H_2O, 4/1/1) yielded the sodium salt as an amorphous solid after trituration with ether (32 mg; 31%).

I.r. (KBr): 1785, 1685 cm^{-1}
N.m.r. (D_2O): 3.05 (1H, d, J=17 Hz, 6β-*CH*); 3.15 (2H, d, J=8 Hz, =CH—CH_2);

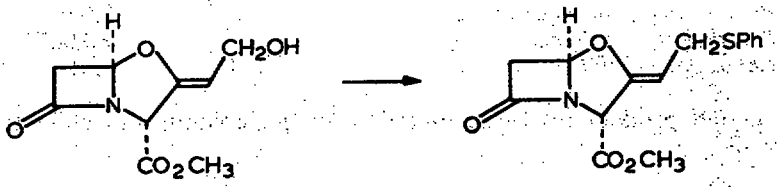
3.60 (1H, dd, J=17 Hz, J'=2.5 Hz, 6α-*CH*); 3.80 (2H, s, *CH*$_2$Ph); 4.78 (=*CH*—CH$_2$ proton partially obscured by D$_2$O peak); 4.93 (1H, br. s, 3-*CH*); 5.70 (1H, d, J=2.5 Hz, 5-*CH*); 7.38δ (5H, s, CH$_2$*Ph*).
$[\alpha]_D^{25}$=+19.8° (c=0.47; MeOH).

The approximate β-lactamase inhibition I_{50} values in μg/ml for the title compound were as follows:

Escherichia coli JT4	0.10
Klebsiella aerogenes E70	0.13
Staphylococcus aureus Russell	<0.0076
Proteus mirabilis C889	0.016
Pseudomonas aeruginosa A	≫4.0
Pseudomonas dalgleish	0.03
Enterobacter P99	≫4.0

EXAMPLE 7

Methyl 3 - (2 - thiophenylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



Methyl clavulanate (1 g) was dissolved in dry methylene dichloride (50 ml) and cooled to −30°C. Borontrifluoride etherate (15 drops; 0.18 ml) was added at −30°C followed by a solution of thiophenol (550 mg) in methylene dichloride (10 ml). The mixture was stirred at −30°C to −10°C for two hours and washed with 3% sodium bicarbonate solution (3×50 ml). The organic phase was dried over magnesium sulphate and the solvent evaporated to yield an oil which after chromatography gave the title compound as a colourless oil (298 mg; 20%).

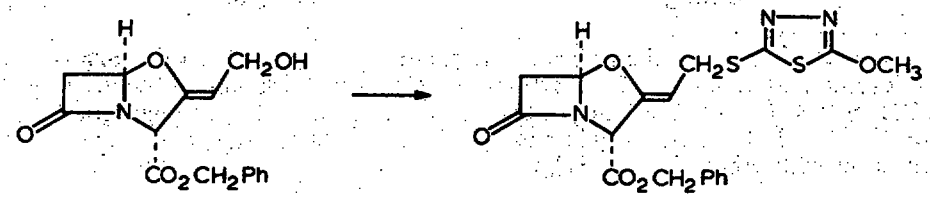
I.r. ($CHCl_3$): 1800, 1755, 1695 cm^{-1}.
N.m.r. ($CDCl_3$): 2.76 (1H, J=17 Hz, 6β-*CH*); 3.38 (1H, dd, J=17 Hz, J'=2.5 Hz, 6α-*CH*); 3.56 (2H, d, J=8 Hz, =CH—*CH*$_2$); 3.64 (3H, s, CO$_2$*CH*$_3$); 4.70 (1H, br. t, J=8 Hz, =*CH*—CH$_2$); 4.97 (1H, br. s, 3-*CH*); 5.60 (1H, d, J=2.5 Hz, 5-*CH*); 7.32δ(5H, br.s, S*Ph*).
$[\alpha]_D^{20}$=+2° (c=1.16; MeOH).

The approximate β-lactamase inhibition I_{50} values in μg/ml for the title compound were as follows:

Escherichia coli JT4	0.01
Klebsiella aerogenes E70	1.1
Staphylococcus aureus Russell	0.04
Proteus mirabilis C889	1.72
Pseudomonas aeruginosa A	0.08

EXAMPLE 8

Benzyl 3 - (2 - thio - 5 - methoxythiadiazolylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo [3,2,0]heptane - 2 - carboxylate



Benzyl clavulanate (2.89 g) was dissolved in dry methylene dichloride (100 ml) and treated with boron trifluoride etherate (50 drops; 0.6 ml) at −30°C. A solution

of 5 - methoxythiadiazolyl - 2 - thiol (1.48 g) in methylene dichloride (10 ml) was added dropwise over half an hour at −30°C. The reaction was stirred at −30° to −10°C for two hours and worked up as described for the previous example. The title product was collected as a colourless oil (625 mg; 15%).

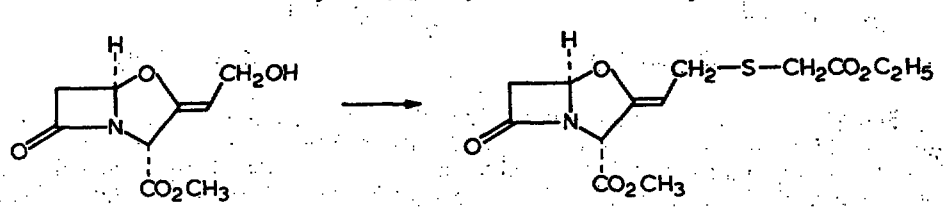
I.r. ($CHCl_3$): 1800, 1750, 1695 cm^{-1}

N.m.r. ($CDCl_3$): 2.92 (1H, d, J=17 Hz, 6β-*CH*); 3.40 (1H, dd, J=17 Hz, J'=2.5 Hz), 6α-*CH*); 3.76 (2H, d, J=8 Hz, =CH—CH_2); 4.03 (3H, s, OCH_3); 5.02 (2H, br. s, =*CH*—CH_2 and 3-*CH*); 5.17 (2H, s, CO_2CH_2pH); 5.69 (1H, d, J=2.5 Hz, 5-*CH*); 7.35δ (5H, s, CO_2CH_2Ph).

$[\alpha]_D^{23}$=+5° (c=0.92; MeOH).

EXAMPLE 9

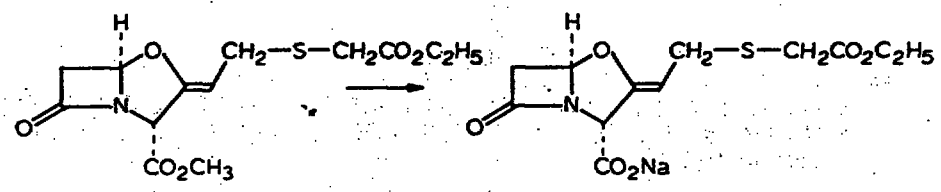
Methyl 3 - [2 - thio(ethoxycarbonylmethyl)ethylidene] - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



The title compound was prepared from methyl clavulanate by a process analogous to that described in Example 7 but in which the thiophenol was replaced by an equivalent amount of ethyl 1-mercaptoacetate.

EXAMPLE 10

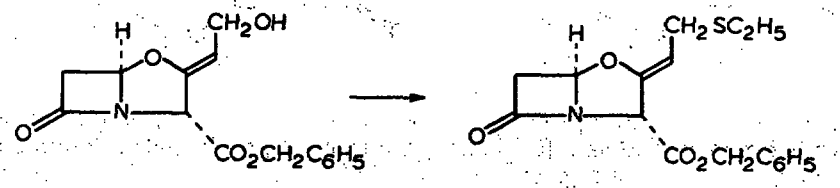
Sodium 3 - [2 - thio(ethoxycarbonylmethyl)ethylidene] - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



The title compound was prepared from the corresponding methyl ester by hydrolysis using N NaOH at pH 9—9.5 (pH stat) until one equivalent of base was consumed. Chromatography yielded the sodium salt as an amorphous solid after trituration with ether.

EXAMPLE 11

Benzyl 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



Benzyl clavulanate (3.18 g) was dissolved in methylene chloride (100 ml) and cooled to −30°C. A solution of ethyl mercaptan (1.0 ml) in methylene chloride (5 ml) was added, followed by boron trifluoride etherate (20 drops). The solution was stirred at −20°C to −10°C for 2.5 hours, washed with dilute sodium bicarbonate solution (x3) and the extract dried over $MgSO_4$. Evaporation of the solvent and chromatography yielded the title compound (804 mg) as a colourless oil;

I.r. ($CHCl_3$) 1800, 1750, 1695 cm^{-1};

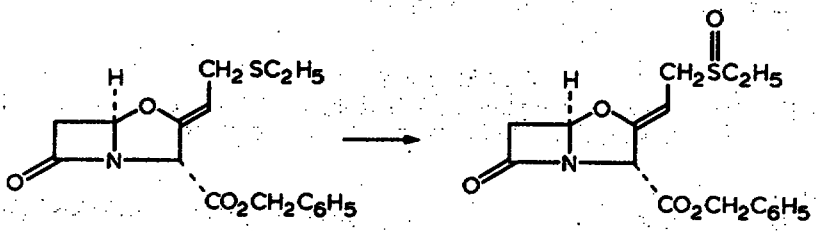
N.m.r. ($CDCl_3$ 1.22 (3H, t, J 6Hz, —CH_2—*CH*$_3$), 2.40 (2H, q, *J* 6Hz, —*CH*$_2$—CH_3), 2.95 (1H, d, *J* 17Hz, 6β-*CH*), 3.42 (1H, d, *J* 17Hz, *J'* 2.5

Hz, 6α-*CH*, 3.17 (2H, d, *J* 8Hz, $CH_2SC_2H_5$), 4.60 (1H, t, *J* 8Hz, =*CH*—CH_2—), 5.00 (1H, br s, 3-*CH*), 5.18 (2H, s, CO_2CH_2Ph), 5.73 (1H, d, *J* 2.5 Hz, 5-*CH*), 7.36 (5H, s, CO_2CH_2Ph);

$[\alpha]_D^{20}$=+13.1° (c=0.88; MeOH); M.w. (Mass spectrometry) $C_{17}H_{19}NO_4S$; 333.103710 (expt.), 333.103469 (calc.).

EXAMPLE 12

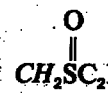
Benzyl 3 - (2 - ethylsulphinylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



Benzyl 3 - (2 - ethylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate (704 mg) was dissolved in methylene chloride (40 ml) and treated with *m* - chloroperbenzoic acid (370 mg). The solution was stirred at 0°C for 1.0 hour and washed with a dilute bicarbonate solution (×2). The extract was dried over $MgSO_4$ and evaporated. Chromatography over silica gel yielded the title product as a mixture of R and S sulphoxides (295 mg);

I.r. ($CHCl_3$) 1805, 1750, 1695 cm^{-1};

N.m.r. ($CDCl_3$) 1.18 (3H, t, *J* 6Hz, —CH_2—*CH*$_3$), 2.46 (2H, q, *J* 6Hz, —*CH*$_2$—CH_3), 2.90 (1H, d, *J* 17Hz, 6β-*CH*), 3.40 (1H, d, *J* 17Hz, J' 2.5 Hz, 6α-*CH*), 3.34 (2H, d, *J* 7Hz,

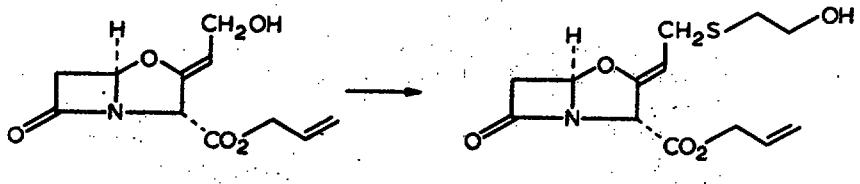


CH$_2$$SC_2H_5$),

4.53 (1H, t, *J* 7Hz, =*CH*—CH_2), 5.03 (3H, br, s, 3-*CH* and CO_2CH_2Ph), 5.72 (1H, d, *J* 2.5Hz, 5-*CH*), 7.30 (5H, s, CO_2CH_2Ph). M.w. (mass spectrometry) 349.

EXAMPLE 13

Allyl 3 - [2 - (β - hydroxyethyl) - thioethylidene] - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



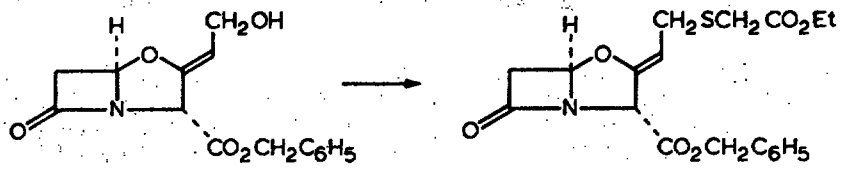
Allyl clavulanate (500 mg) was dissolved in methylene chloride (20 ml) and treated with 2-mercaptoethanol (0.25 ml) and boron trifluoride diethyletherate (25 drops). The solution was stirred at −20° to −10°C for a period of 1.5 hours. The reaction was quenched with dilute sodium hydroxide solution and the organic extract washed with water and dried over $MgSO_4$. Evaporation of the solvent and column chromatography isolated the title compound (22 mg) as a colourless oil;

I.r. ($CHCl_3$) 3450—3550, 1805, 1750, 1695 cm^{-1};

N.m.r. ($CDCl_3$) 2.62 (2H, t, *J* 6Hz, S—*CH*$_2$—CH_2), 3.00 (1H, d, *J* 17Hz, 6β-*CH*), 3.17 (2H, d, *J* 8Hz, =CH—*CH*$_2$S), 3.44 (1H, dd, *J* 17Hz, *J'* 2.5Hz, 6α-*CH*), 3.64 (2H, t, *J* 6Hz, CH_2—*CH*$_2$OH), 4.62 (2H, d, *J* 6Hz, CO_2CH_2), 4.68 (1H, t *J* 8Hz, =C*H*—CH_2S), 5.02 (1H, br.s, 3-*CH*), 5.30 (2H, m, =*CH*$_2$), 5.63 (1H, d, *J* 2.5Hz, 5-*CH*), 5.7—6.1 (1H, m, CH_2—*CH*=CH_2).

EXAMPLE 14

Benzyl 3 - [2 - (β - ethoxycarbonyl)methylthio]ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate

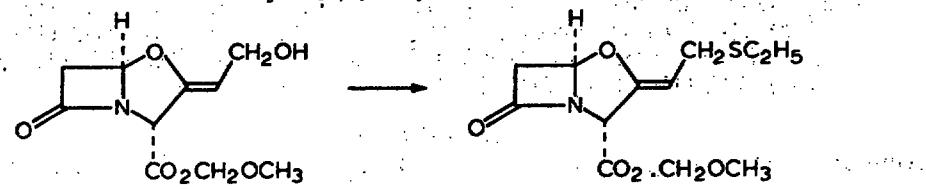


Benzyl clavulanate (1.9 g) and ethyl 2-mercaptoacetate (1.5 g) were dissolved in methylene chloride and stirred at −20°C. Boron trifluoride diethyletherate (0.2 ml) was added and the solution stirred at −20°C to −10°C for 2.0 hours. The reaction was quenched with a 3% solution of sodium bicarbonate. The organic extract was washed with bicarbonate solution, sodium chloride solution, and then dried over $MgSO_4$. The product (95 mg) was isolated as a colourless oil, after chromatography over silica gel (eluting ethyl acetate/cyclohexane);

I.r. ($CHCl_3$), 1800, 1735—1750, 1695 cm^{-1};
N.m.r. ($CDCl_3$) 1.28 (3H, t, *J* 7Hz, CH_2CH_3), 3.12 (2H, s, SCH_2CO_2Et), 3.10 (1H, d, *J* 17Hz, 6β-*CH*), 3.36 (2H, d, *J* 8Hz, =CH—CH_2), 3.55 (1H, d, *J* 17Hz, *J'* 2Hz, 6α-*CH*), 4.23 (2H, q, *J* 7Hz, CH_2CH_3), 4.83 (1H, t, *J* 8Hz, =*CH*—CH_2), 5.18 (1H, s, 3-*CH*), 5.28 (2H, s, CO_2CH_2Ph), 5.76 (1H, d, *J* 2Hz, 5-*CH*), 7.42 (5H, s, CO_2CH_2Ph).

EXAMPLE 15

Methoxymethyl 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



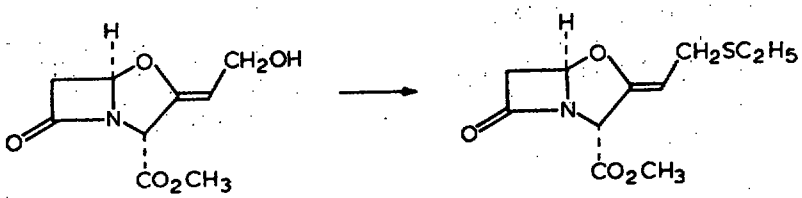
Methoxymethyl clavulanate (1.0 g) was dissolved in methylene chloride (25 ml) and cooled to −30°C. Ethyl mercaptan (0.5 ml) was added, followed by boron trifluoride etherate (0.2 ml). The solution was stirred at −20°C to −10°C for 2.0 hours, washed with dilute sodium bicarbonate solution (×2), and brine (×2), and the extract dried over $MgSO_4$. Evaporation of the solvent and chromatography yielded the title compound (101 mgs) as a colourless oil;

N.m.r. ($CDCl_3$) 1.37, (3H, t, *J* 7Hz, S—CH_2—CH_3), 2.60 (2H, q, *J* 7Hz, S—CH_2—CH_3), 3.13 (1H, d, *J* 17Hz, 6β-*CH*), 3.41 (2H, d, *J* 8Hz, =CH—CH_2S), 3.65 (1H, dd, *J* 17Hz, *J'* 2.5Hz, 6α-*CH*), 3.64, (3H, s, —OCH_3), 4.94 (1H, t, *J* 8Hz, =*CH*—CH_2), 5.27 (1H, br. s, 3-*CH*), 5.85 (1H, d, *J* 2.5Hz, 5-*CH*), 5.48 (2H, q, *J* 4Hz, $CO_2CH_2OCH_3$).

[Methoxymethyl clavulanate may be prepared by the reaction of sodium clavulanate with chloromethyl methyl ether in dimethylformamide].

EXAMPLE 16

Methyl 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



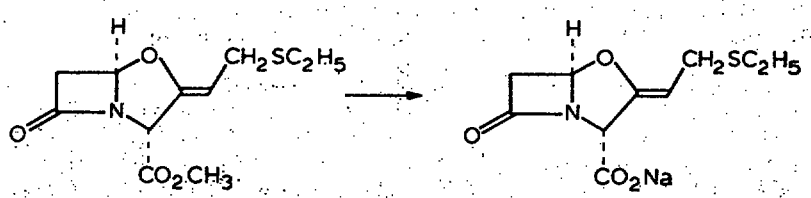
Methyl clavulanate (3.0 g) was dissolved in methylene chloride, and ethyl

mercaptan (0.9 ml) added, followed by boron trifluoride etherate (1.0 ml). The solution was stirred at room temperature for 3.0 hours, quenched with sodium bicarbonate solution, and the organic extract washed with brine. Evaporation of the solvent and chromatography yielded the title compound (78 mgs) as a clear oil; νmax ($CHCl_3$), 1800, 1750, 1690 cm^{-1};

N.m.r. ($CDCl_3$) 1.27 (3H, t, *J* 7Hz, S—CH_2—CH_3), 2.74 (2H, q, J 7Hz, S—CH_2—CH_3), 3.07 (1H, d, *J* 17Hz, 6β-*CH*), 3.30 (2H, d, *J* 7Hz, =CH—CH_2), 3.70 (1H, dd, *J* 17Hz, *J'* 2.5 Hz. 6α-*CH*), 3.86 (3H, s, —CO_2CH_3), 4.84 (1H, t, *J* 7Hz, =*CH*—CH_2), 5.17 (1H, s, 3-*CH*), 5.77 (1H, d, *J* 2.5Hz, 5-*CH*).

EXAMPLE 17

Sodium 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate

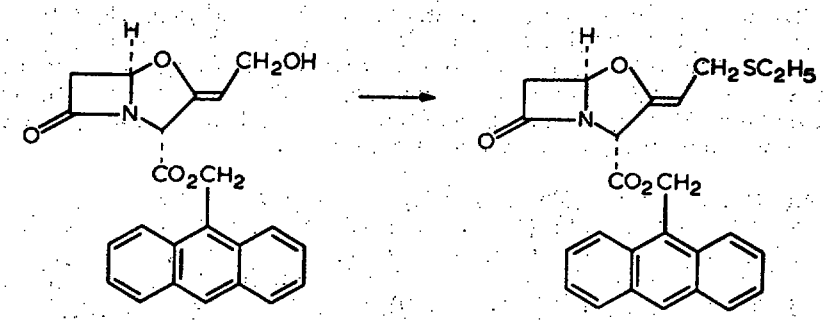


The methyl ester (70 mgs) was dissolved in tetrahydrofuran (10 ml) and water (30 ml). Hydrolysis of the thioether using N NaOH at constant pH (9.0) provided the sodium salt in good yield (50 mgs), ν max (KBr), 1785, 1690 cm^{-1};

N.m.r. (D_2O) 1.05 (3H, t, J 7Hz), SCH_2—CH_3), 2.37 (2H, q, J 7Hz, SCH_2CH_3), 2.90 (1H, d, *J* 17Hz, 6β-*CH*), 3.14 (2H, d, *J* 7Hz, =CH—CH_2), 3.40 (1H, dd, *J* 17Hz), *J'* 2.5 Hz, 6α-*CH*), 4.65 (1H, t, *J* 7Hz, =*CH*—CH_2), 4.79 (1H, s, 3-*CH*), 5.58 (1H, d, *J* 2.5Hz, 5-*CH*).

EXAMPLE 18

Anthrylmethyl 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



Anthrylmethyl clavulanate (1.3 g) was dissolved in methylene chloride, and the solution at −70°C treated with ethyl mercaptan (0.2 ml) and boron trifluoride etherate (20 drops). The reaction mixture was allowed to warm up to −30°C with stirring and then quenched with sodium bicarbonate solution. The organic extract was washed with brine (x2) and dried over $MgSO_4$. Chromatography isolated the product as a yellow oil (207 mgs);

νmax ($CHCl_3$) 1800, 1750, 1695 cm^{-1};
n.m.r. ($CDCl_3$), 1.13 (3H, t, *J* 7Hz), S—CH_2CH_3), 2.28 (2H, q, *J* 7Hz), S—CH_2—CH_3), 2.95 (1H, d, *J* 17Hz, 6β-*CH*), 3.10 (2H, d, *J* 7Hz, =CH—CH_2), 3.40 (1H, dd, J 17Hz, J' 2.5Hz, 6α-*CH*) 4.54 (1H, t, *J* 7Hz, =*CH*—CH_2), 5.05 (1H, s, 3-*CH*), 5.55 (1H, d, *J* 2.5Hz, 5-*CH*), 6.16 (2H, s, —CO_2CH_2), 7.2—8.5 (9H, m, aryl).

The starting material for the preceding example may be produced thus:
Sodium clavulanate (0.5 g) and 9-chloromethylanthracene (1.0 g) was stirred in

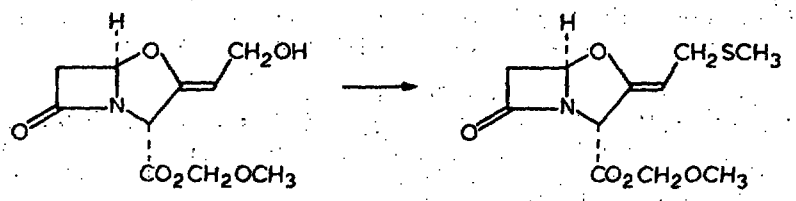
dimethylformamide overnight at room temperature. After evaporation of the solvent, the residue was taken up in ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. Chromatography isolated the product (0.5 g) as a yellow crystalline solid,

m pt. 120°C, ν max 1800, 1740, 1698 cm^{-1}

N.m.r. ($CDCl_3$) 1.36 (1H, br. s, —*OH*), 2.90 (1H, d, *J* 17Hz, 6β-*CH*), 3.35 (1H, dd, *J* 17Hz, *J'* 2.5Hz, 6α-CH), 3.98 (2H, d, *J* 7Hz, =CH—CH_2), 4.62 (1H, t, *J* Hz, =*CH*—CH_2), 4.80 (1H, s, 3-*CH*), 5.52 (1H, d, *J* 2.5Hz, 5-*CH*), 6.14 (2H, s, CO_2CH_2), 7.16—8.42 (9H, m, aryl).

EXAMPLE 19

Methoxymethyl 3 - (2 - thiomethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo [3,2,0]heptane - 2 - carboxylate

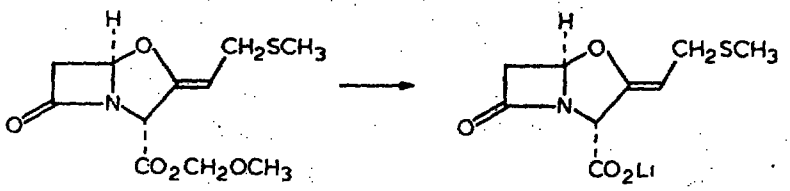


Methoxymethyl clavulanate (2.3 g) was dissolved in methylene chloride (50 ml). The stirring solution was cooled to −30°C and boron trifluoride etherate (0.5 ml) added. Methyl mercaptan was bubbled, at a slow rate, through the solution for 1.0 hour, the temperature being held at −20°C to −10°C. The solution was then stirred at −10°C for a further 0.5 hours. Nitrogen gas was then bubbled through the solution and the reaction subsequently quenched with a 3% solution of sodium bicarbonate. The organic extract was washed with bicarbonate, brine (×2), and dried over sodium sulphate. The solution was filtered and evaporated. Column chromatography over silica gel [eluting ethyl acetate/petrol (60—80)] yielded the title compound as a clear oil. Yield 185 mgs; ν max ($CHCl_3$) 1795—1810, 1755, and 1695 cm^{-1};

N.m.r. ($CDCl_3$) 1.96 (3H, s, S—CH_3) 2.98 (1H, d, *J* 17Hz, 6β-*CH*), 3.17 (2H, d, J 7Hz, =CH—CH_2S), 3.50 (1H, dd, *J* 17Hz, *J'* 2.5 Hz, 6α-*CH*), 3.45 (3H, s, —OCH_3), 4.77 (1H, t, J 7Hz, =*CH*—CH_2), 5.10 (1H, br.s 3-*CH*), 5.32 (2H, m CO_2CH_2), 5.72 (1H, d, *J* 2.5Hz, 5-*CH*).

EXAMPLE 20

Lithium 3 - (2 - thiomethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



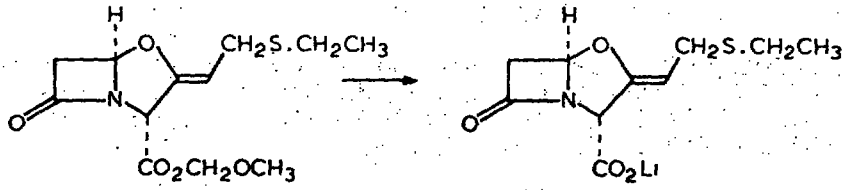
The methoxymethyl ester (130 mgs) was dissolved in tetrahydrofuran (10 ml) and water (40 mls) and the solution subjected to hydrolysis with N lithium hydroxide at a constant pH of 9 for 30 minutes. The volume of the solution was reduced to 5 ml by evaporation under reduced pressure and the residue thoroughly triturated with acetone (15 ml). The solid white product was filtered off and washed with ether.

Yield 98 mgs, ν max (KBr) 1760, 1690, 1610 cm^{-1};

N.m.r. (D_2O) 1.87 (3H, s, S—CH_3) 2.86 (1H, d, *J* 17Hz, 6β-*CH*), 3.03 (2H, d, J 7Hz, =CH—CH_2), 3.38 (1H, dd, *J* 17Hz, *J'* 2.5Hz, 6α-*CH*) 4.61 (1H, t, *J* 7Hz, =C*H*—CH_2, 4.77 (1H, s, 3-*CH*), 5.61 (1H, d, *J* 2.5Hz, 5-*CH*).

EXAMPLE 21

Lithium 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate

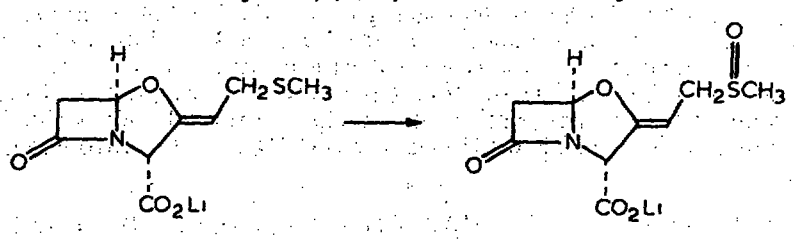


The methoxymethyl ester (70 mgs) was dissolved in tetrahydrofuran (10 ml) and water (30 ml) and the solution subjected to hydrolysis with N lithium hydroxide at a constant pH of 9 for 35 minutes. The solution was evaporated under reduced pressure and the residue thoroughly triturated with acetone (20 ml). The solid product was filtered off and washed with ether (2×10 ml).

Yield (30 mgs), νmax (KBr) 1760, 1690, 1610 cm^{-1};
N.m.r. (D_2O) 1.20 (3H, t, J 7Hz, $SCH_2—CH_3$), 2.50 (2H, q, J 7Hz, SCH_2CH_3), 3.05 (1H, d, J 17Hz, 6β-CH), 3.27 (2H, d, J 7Hz, =CH—CH_2), 3.55 (1H, dd, J 17Hz, J' 2.5Hz, 6α-CH), 4.68 (1H, t, J 7Hz, =CH—CH_2), 4.92 (1H, s, 3-CH), 5.70 (1H, d, J 2.5Hz, 5-CH).

EXAMPLE 22

Lithium 3 - (2 - methylsulphinyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate

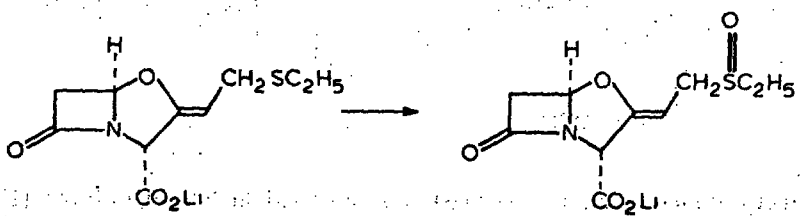


The thioether (60 mg) was dissolved in distilled water (10 ml) and treated with m-chloroperbenzoic acid (44 mg). The mixture was stirred at ice-temperature for 3 hours. The m-chlorobenzoic acid was filtered off. The solution was evaporated under reduced pressure, and the residue triturated with acetone (10 ml). The solid white product was collected and washed with dry ether. Yield 28 mg.

ν_{max} (KBr) 1785, 1690 and 1620 (broad) cm^{-1}.

EXAMPLE 23

Lithium 3 - (2 - ethylsulphinylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate



The thioether (25 mg) was dissolved in distilled water (4 ml) and treated with m-chloroperbenzoic acid (20 mg). The mixture was stirred at ice-temperature for 4 hours. The m-chlorobenzoic acid was filtered off. The solution was freeze-dried to give the sulphoxide salt as a white solid (20 mg).

ν_{max} (KBr) 1780, 1685, and 1630 (broad) cm^{-1}.

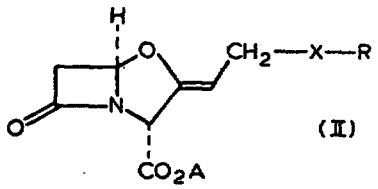
EXAMPLE 24

A. Sodium 3 - (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate (50 mg) may be dissolved in sterile physiological saline (10 ml) to give a solution suitable for injection.

B. Sodium 3 - (2 - ethylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate (50 mg) may be dissolved in sterile physiological saline (10 ml) and mixed with a solution of sodium amoxycillin (250 mg) in water for injection (5 ml) to give a solution suitable for immediate injection.

WHAT WE CLAIM IS:—

1. A compound of the formula (II):



(II)

wherein X is S, SO or SO_2; R is an inert organic group of up to 20 carbon atoms; and A is a moiety such that CO_2A is a carboxylic acid group or a salt or ester thereof.

2. A compound as claimed in Claim 1 wherein X is S.

3. A compound as claimed in Claim 1 wherein X is SO.

4. A compound as claimed in Claim 1 wherein X is SO_2.

5. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a carboxylic acid group.

6. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a pharmaceutically acceptable salt of a carboxylic acid group.

7. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a sodium salt of a carboxylic acid group.

8. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a potassium salt of a carboxylic acid group.

9. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a calcium salt of a carboxylic acid group.

10. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a magnesium salt of a carboxylic acid group.

11. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a lithium salt of a carboxylic acid group.

12. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is an ammonium salt of a carboxylic acid group.

13. A compound as claimed in any of Claims 7 to 10 when in crystalline form.

14. A compound as claimed in any of Claims 1 to 10 wherein R is a hydrocarbon group.

15. A compound as claimed in any of Claims 1 to 10 wherein R is an alkyl group.

16. A compound as claimed in any of Claims 1 to 10 wherein R is an alkyl group of 1 to 6 carbon atoms.

17. A compound as claimed in any of Claims 1 to 10 wherein R is a group of the formula CH_2R^3 wherein R^3 is a hydrogen atom or an alkyl group of 1 to 5 carbon atoms.

18. A compound as claimed in Claim 17 wherein R^3 is a methyl group.

19. A compound as claimed in Claim 17 wherein R^3 is an ethyl group.

20. A compound as claimed in Claim 17 wherein R^3 is a propyl group.

21. A compound as claimed in Claim 17 wherein R^3 is a hydrogen atom.

22. A compound as claimed in any of Claims 1 to 10 wherein R is a phenyl group.

23. A compound as claimed in any of Claims 1 to 10 wherein R is a benzyl group.

24. A compound as claimed in any of Claims 1 to 10 wherein R is a group according to any of Claims 14 to 20 substituted by a halogen atom.

25. A compound as claimed in any of Claims 1 to 10 wherein R is a group according to any of Claims 14 to 20 substituted by a group OR^1 where R^1 is a hydrogen atom.

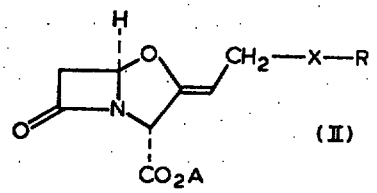
26. A compound as claimed in any of Claims 1 to 10 wherein R is a group according to any of Claims 14 to 20 substituted by a group OR^1 where R^1 is a methyl group.

27. A compound as claimed in any of Claims 1 to 10 wherein R is a group

B. Sodium 3 - (2 - ethylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate (50 mg) may be dissolved in sterile physiological saline (10 ml) and mixed with a solution of sodium amoxycillin (250 mg) in water for injection (5 ml) to give a solution suitable for immediate injection.

WHAT WE CLAIM IS:—

1. A compound of the formula (II):



(II)

wherein X is S, SO or SO_2; R is an inert organic group of up to 20 carbon atoms; and A is a moiety such that CO_2A is a carboxylic acid group or a salt or ester thereof.

2. A compound as claimed in Claim 1 wherein X is S.

3. A compound as claimed in Claim 1 wherein X is SO.

4. A compound as claimed in Claim 1 wherein X is SO_2.

5. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a carboxylic acid group.

6. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a pharmaceutically acceptable salt of a carboxylic acid group.

7. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a sodium salt of a carboxylic acid group.

8. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a potassium salt of a carboxylic acid group.

9. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a calcium salt of a carboxylic acid group.

10. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a magnesium salt of a carboxylic acid group.

11. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is a lithium salt of a carboxylic acid group.

12. A compound as claimed in any of Claims 1 to 4 wherein A is a moiety such that CO_2A is an ammonium salt of a carboxylic acid group.

13. A compound as claimed in any of Claims 7 to 10 when in crystalline form.

14. A compound as claimed in any of Claims 1 to 10 wherein R is a hydrocarbon group.

15. A compound as claimed in any of Claims 1 to 10 wherein R is an alkyl group.

16. A compound as claimed in any of Claims 1 to 10 wherein R is an alkyl group of 1 to 6 carbon atoms.

17. A compound as claimed in any of Claims 1 to 10 wherein R is a group of the formula CH_2R^3 wherein R^3 is a hydrogen atom or an alkyl group of 1 to 5 carbon atoms.

18. A compound as claimed in Claim 17 wherein R^3 is a methyl group.

19. A compound as claimed in Claim 17 wherein R^3 is an ethyl group.

20. A compound as claimed in Claim 17 wherein R^3 is a propyl group.

21. A compound as claimed in Claim 17 wherein R^3 is a hydrogen atom.

22. A compound as claimed in any of Claims 1 to 10 wherein R is a phenyl group.

23. A compound as claimed in any of Claims 1 to 10 wherein R is a benzyl group.

24. A compound as claimed in any of Claims 1 to 10 wherein R is a group according to any of Claims 14 to 20 substituted by a halogen atom.

25. A compound as claimed in any of Claims 1 to 10 wherein R is a group according to any of Claims 14 to 20 substituted by a group OR^1 where R^1 is a hydrogen atom.

26. A compound as claimed in any of Claims 1 to 10 wherein R is a group according to any of Claims 14 to 20 substituted by a group OR^1 where R^1 is a methyl group.

27. A compound as claimed in any of Claims 1 to 10 wherein R is a group

according to any of Claims 14 to 20 substituted by a CO_2R^1 group where R^1 is a hydrogen atom.

28. A compound as claimed in any of Claims 1 to 10 wherein R is a group according to any of Claims 14 to 20 substituted by a CO_2R^1 group where R^1 is a methyl group.

29. A compound as claimed in any of Claims 1 to 5 wherein R is a group according to any of Claims 14 to 20 substituted by a NHR^1 group wherein R^1 is a hydrogen atom.

30. A compound as claimed in any of Claims 1 to 10 wherein R is a CH_2R^3 group where R^3 is naphthyl.

31. A compound as claimed in any of Claims 1 to 10 wherein R is a group CH_2R^3 where R^3 is a phenyl group substituted by a halogen atom, a hydroxyl group, an amino group or a group R^4, OR^4 or NR^4R^5 where R^4 is an alkyl group or acyl group of up to 3 carbon atoms and R^5 is a hydrogen atom or an alkyl group of up to 4 carbon atoms.

32. A compound as claimed in any of Claims 1 to 10 wherein R is a group $CR^6R^7R^8$ where R^6 and R^7 are independently alkyl groups of up to 3 carbon atoms or a phenyl group optionally substituted by halogen or a group of the formula R^9 or OR^9 where R^9 is an alkyl group of up to 3 carbon atoms; and R^8 is a hydrogen atom or an alkyl group of up to 3 carbon atoms or a phenyl group optionally substituted by halogen or a group of the formula R^{10} or OR^{10} where R^{10} is an alkyl group of up to 3 carbon atoms.

33. A compound as claimed in any of Claims 1 to 10 wherein R is a group R^{11} which is a heteroaromatic group of 5- or 6-ring atoms optionally substituted by a methyl group.

34. A compound as claimed in Claim 33 wherein R^{11} is a triazole group.

35. A compound as claimed in Claim 33 wherein R^{11} is a tetrazole group.

36. A compound as claimed in Claim 33 wherein R^{11} is a thienyl group.

37. A compound as claimed in Claim 33 wherein R^{11} is a thiazole group.

38. A compound as claimed in Claim 33 wherein R^{11} is a thiadiazole group.

39. A compound as claimed in Claim 33 wherein R^{11} is a thiatriazole group.

40. A compound as claimed in Claim 33 wherein R^{11} is a oxazole group.

41. A compound as claimed in Claim 33 wherein R^{11} is a isoxazole group.

42. A compound as claimed in Claim 33 wherein R^{11} is a oxadiazole group.

43. A compound as claimed in claim 33 wherein R^{11} is a pyridyl group.

44. A compound as claimed in claim 33 wherein R^{11} is a pyridazinyl group.

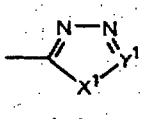
45. A compound as claimed in Claim 33 wherein R^{11} is a pyrimidyl group.

46. A compound as claimed in any of Claims 1 to 10 wherein R is a group CH_2R^{12} wherein R^{12} is a phenyl group optionally substituted by fluorine, chlorine, bromine or OR^{13}, $O.CO.R^{13}$, COR^{13} or CO_2R^{13} wherein R^{13} is a hydrocarbon group of up to 8 carbon atoms.

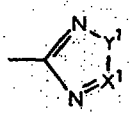
47. A compound as claimed in any of Claims 1 to 10 wherein R is a group R^{14} where R^{14} is a 5-membered heterocyclic group optionally substituted by an alkyl group of up to 3 carbon atoms.

48. A compound as claimed in Claim 47 wherein R^{14} is a heterocyclic group containing 3 or 4 heteroatoms at least two of which are nitrogen atoms.

49. A compound as claimed in Claim 47 wherein R^{14} is a group of the sub-formula (a) or (b):



(a)



(b)

wherein X^1—Y^1 represents a S—$N(CH_3)$, O—$N(CH_3)$, N—$N(CH_3)$, N—CH_2, O—CH_2 or S—CH_2 group.

50. A compound as claimed in any of Claims 1 to 10 wherein R is a group of $R^{15}CO_2R^{16}$ wherein R^{15} is an alkylene group of 1 to 4 carbon atoms or an alkylene group of 1 or 2 carbon atoms substituted by a phenyl group and R^{16} is a hydrogen atom or an alkyl group of 1 to 4 carbon atoms or an alkyl group of 1 or 2 carbon atoms substituted by a phenyl group.

51. A compound as claimed in any of Claims 1 to 10 wherein R is a n-propyl group.

52. A compound as claimed in any of Claims 1 to 10 wherein R is a n-butyl group.

53. A compound as claimed in any of Claims 1 to 10 wherein R is a 2-methoxyethyl group.

54. A compound as claimed in any of Claims 1 to 10 wherein R is a 2-benzyloxymethyl group.

55. A compound as claimed in any of Claims 1 to 10 wherein R is a 2-ethoxyethyl group.

56. A compound as claimed in any of Claims 1 to 10 wherein R is a 3-methoxypropyl group.

57. A compound as claimed in any of Claims 1 to 10 wherein R is a p-chlorobenzyl group.

58. A compound as claimed in any of Claims 1 to 10 wherein R is a p-methoxybenzyl group.

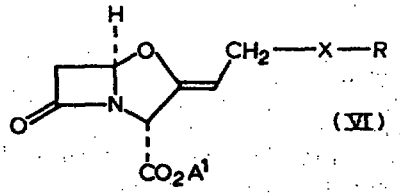
59. A compound as claimed in any of Claims 1 to 10 wherein R is a m-methoxybenzyl group.

60. A compound as claimed in any of Claims 1 to 10 wherein R is a p-methylbenzyl group.

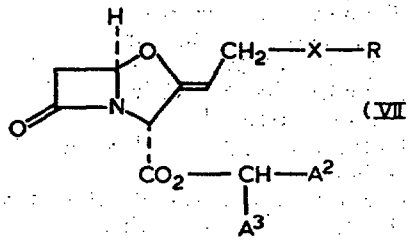
61. A compound as claimed in any of Claims 1 to 10 wherein R is a 4-fluorophenyl group.

62. A compound as claimed in any of Claims 1 to 10 wherein R is a 2-phenylethyl group.

63. A compound as claimed in any of Claims 1 to 4 of the formula (VI) or (VII):



(VI)



(VII)

wherein R and X are as defined in any of Claims 1 to 4 and A^1 is an alkyl group of 1—8 carbon atoms optionally substituted by halogen or a group of the formula OA^4, $OCOA^4$, SA^4, SO_2A^4 wherein A^4 is a hydrocarbon group of up to 6 carbon atoms; A^2 is a hydrogen atom, an alkyl group of up to 4 carbon atoms or a phenyl group optionally substituted by halogen or by a group A^5 or OA^5 where A^5 is an alkyl group of up to 6 carbon atoms; and A^3 is a phenyl group optionally substituted by halogen or by a group A^5 or OA^5 where A^5 is an alkyl group.

64. A compound of the formula (VII) as claimed in Claim 63 wherein CHA^2A^3 is a benzyl group.

65. A compound of the formula (VII) as claimed in Claim 63 wherein CHA^2A^3 is a p-methoxybenzyl group.

66. A compound of the formula (VI) as claimed in Claim 63 wherein A^1 is a methoxymethyl group.

67. A compound of the formula (VI) as claimed in Claim 63 wherein A^1 is a methyl group.

68. A compound of the formula (VI) as claimed in Claim 63 wherein A^1 is an allyl group.

69. A compound as claimed in Claim 1 wherein XR is a benzylthio group.

70. A compound as claimed in Claim 1 wherein XR is a benzylsulphinyl group.

71. A compound as claimed in Claim 1 wherein XR is a (1 - methyl - 1,2,3,4 - tetrazol - 5 - yl)thio group.

72. A compound as claimed in Claim 1 wherein XR is a benzylsulphonyl group.

73. A compound as claimed in Claim 1 wherein XR is a phenylthio group.

74. A compound as claimed in Claim 1 wherein XR is a 2 - thio - 5 - methoxythiadiazol group.

75. A compound as claimed in Claim 1 wherein XR is an ethoxycarbonylmethylthio group.
76. A compound as claimed in Claim 1 wherein XR is an 2 - ethylthio group.
77. A compound as claimed in Claim 1 wherein XR is an 2 - ethylsulphinyl group.
78. A compound as claimed in Claim 1 wherein XR is a β-hydroxyethylthio group.
79. A compound as claimed in Claim 1 wherein XR is a methylthio group.
80. A compound as claimed in Claim 1 wherein XR is a methylsulphinyl group.
81. Benzyl 3 - (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
82. Benzyl 3 - (2 - benzylsulphinylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
83. Methyl 3 - [2 - (1 - methyl - 1,2,3,4 - tetrazol - 5 - yl)thioethylidene] - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
84. Methyl 3 - (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
85. Methyl 3 - (2 - benzylsulphinylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
86. Methyl 3 - (2 - benzylsulphonylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
87. Sodium 3 - (2 - thiobenzylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo-[3,2,0]heptane - 2 - carboxylate.
88. Methyl 3 - (2 - thiophenylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo-[3,2,0]heptane - 2 - carboxylate.
89. Benzyl 3 - (2 - thio - 5 - methoxythiadiazolylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
90. Methyl 3 - [2 - thio(ethoxycarbonylmethyl)ethylidene] - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
91. Sodium 3 - [2 - thio(ethoxycarbonylmethyl)ethylidene] - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
92. Benzyl 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
93. Benzyl 3 - (2 - ethylsulphinylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
94. Allyl 3 - [2 - (β - hydroxyethyl) thioethylidene] - 7 - oxo - 4 - azabicyclo-[3,2,0]heptane - 2 - carboxylate.
95. Benzyl 3 - [2 - (β - ethoxycarbonyl)methylthio]ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
96. Methoxymethyl 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
97. Methyl 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
98. Sodium 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
99. Anthrylmethyl 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
100. Methoxymethyl 3 - (2 - thiomethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
101. Lithium 3 - (2 - thiomethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
102. Lithium 3 - (2 - thioethyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
103. Lithium 3 - (2 - methylsulphinyl)ethylidene - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
104. Lithium 3 - (2 - ethylsulphinylethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate.
105. A pharmaceutical composition which comprises a compound as claimed in any of Claims 1 to 4 and a pharmaceutically acceptable carrier therefor.
106. A pharmaceutical composition which comprises a compound as claimed in any of Claims 5 to 10 and a pharmaceutically acceptable carrier therefor.
107. A pharmaceutical composition which comprises a compound as claimed in any of Claims 11 to 68 and a pharmaceutically acceptable carrier therefor.
108. A pharmaceutical composition which comprises a compound as claimed in Claim 69 and a pharmaceutically acceptable carrier therefor.

109. A pharmaceutical composition which comprises a compound as claimed in Claim 70 and a pharmaceutically acceptable carrier therefor.

110. A pharmaceutical composition which comprises a compound as claimed in any of Claims 71 to 80 and a pharmaceutically acceptable carrier therefor.

111. A pharmaceutical composition which comprises a compound as claimed in Claim 81 and a pharmaceutically acceptable carrier therefor.

112. A pharmaceutical composition which comprises a compound as claimed in Claim 82 and a pharmaceutically acceptable carrier therefor.

113. A pharmaceutical composition which comprises a compound as claimed in any of Claims 83 to 91 and a pharmaceutically acceptable carrier therefor.

114. A pharmaceutical composition which comprises a compound as claimed in any of Claims 92 to 104 and a pharmaceutically acceptable carrier therefor.

115. A pharmaceutical composition as claimed in Claim 105 adapted for oral administration.

116. A pharmaceutical composition as claimed in Claim 105 in the form of a tablet.

117. A pharmaceutical composition as claimed in Claim 106 adapted for oral administration.

118. A pharmaceutical composition as claimed in Claim 107 adapted for oral administration.

119. A pharmaceutical composition as claimed in Claim 108 adapted for oral administration.

120. A pharmaceutical composition as claimed in Claim 109 adapted for oral administration.

121. A pharmaceutical composition as claimed in Claim 110 adapted for oral administration.

122. A pharmaceutical composition as claimed in Claim 111 adapted for oral administration.

123. A pharmaceutical composition as claimed in Claim 112 adapted for oral administration.

124. A pharmaceutical composition as claimed in Claim 113 adapted for oral administration.

125. A pharmaceutical composition as claimed in Claim 114 adapted for oral administration.

126. A pharmaceutical composition as claimed in 105 adapted for administration by injection.

127. A pharmaceutical composition as claimed in any of Claims 105, 115 or 126 which also comprises a penicillin or cephalosporin.

128. A pharmaceutical composition as claimed in any of Claims 106 to 114 or 116 to 125 which also comprises a penicillin or cephalosporin.

129. A pharmaceutical composition as claimed in Claim 127 wherein the weight ratio of compound of Claim 1 to penicillin or cephalosporin is 3:1 to 1:3.

130. A pharmaceutical composition as claimed in Claim 128 wherein the weight ratio of compound of Claim 1 to penicillin or cephalosporin is 3:1 to 1:3.

131. A pharmaceutical composition as claimed in Claim 127 or 129 wherein the penicillin or cephalosporin component is benzylpenicillin, phenoxymethylpenicillin, carbenicillin, propicillin, ampicillin, amoxycillin, epicillin, ticarcillin, cyclacillin, cephaloridin, cephalothin, cephazolin, cephalexin, cephacetrile, cephamanole, cephapirin, cephradine or cephalogycine.

132. A pharmaceutical composition as claimed in Claim 128 or 130 wherein the penicillin or cephalosporin is benzylpenicillin, phenoxymethylpenicillin, carbenicillin, propicillin, ampicillin, amoxycillin, epicillin, ticarcillin, cyclacillin, cephaloridin, cephalothin, cephazolin, cephalexin, cephacetrile, cephamanole, cephapirin, cephradine or cephalogycine.

133. A pharmaceutical composition as claimed in Claim 128 which comprises 150 to 1000 mg of amoxycillin, ampicillin or a salt, hydrate or in-vivo hydrolysable ester thereof and 50 to 500 mg of a compound as claimed in Claim 1.

134. A pharmaceutical composition as claimed in Claim 133 which comprises 200 to 500 mg of amoxycillin, ampicillin or a salt, hydrate or in-vivo hydrolysable ester thereof.

135. A pharmaceutical composition as claimed in Claims 133 or 134 which comprises amoxycillin trihydrate.

136. A pharmaceutical composition as claimed in any of Claims 133 to 135 which comprises 50 to 250 mg of a compound as claimed in Claim 1.

137. A pharmaceutical composition as claimed in any of Claims 133 to 135 wherein the compound as claimed in Claim 1 is as claimed in any of Claims 5 to 10.

138. A pharmaceutical composition as claimed in Claim 137 wherein the compound as claimed in Claim 1 is a compound as claimed in any of Claims 11 to 68.

139. A pharmaceutical composition as claimed in Claim 137 wherein the compound as claimed in Claim 1 is a compound as claimed in Claim 69.

140. A pharmaceutical composition as claimed in Claim 137 wherein the compound as claimed in Claim 1 is a compound as claimed in Claim 70.

141. A pharmaceutical composition as claimed in Claim 138 wherein the compound as claimed in Claim 1 is a compound as claimed in any of Claims 71 to 80.

142. A pharmaceutical composition as claimed in Claim 137 wherein the compound as claimed in Claim 1 is a compound as claimed in Claim 81.

143. A pharmaceutical composition as claimed in Claim 137 wherein the compound as claimed in Claim 1 is a compound as claimed in Claim 82.

144. A pharmaceutical composition as claimed in Claim 137 wherein the compound as claimed in Claim 1 is a compound as claimed in any of Claims 83 to 91.

145. A pharmaceutical composition as claimed in Claim 137 wherein the compound as claimed in Claim 1 is a compound as claimed in any of Claims 92 to 104.

146. A pharmaceutical composition which comprises 50 mg of sodium (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptan - 2 - carboxylate and a pharmaceutically acceptable carrier therefor.

147. A pharmaceutical composition which comprises 50 mg of sodium 3 - (2 - benzylthioethylidene) - 7 - oxo - 4 - oxa - 1 - azabicyclo[3,2,0]heptane - 2 - carboxylate, 250 mg of sodium amoxycillin and a pharmaceutically acceptable carrier therefor.

148. A process for the preparation of the compounds of the formula (II) as in Claim 1 which process comprises the reaction of an ester of clavulanic acid with a compound of the formula (VIII):



(VIII)

wherein R is as defined in relation to formula (II) and thereafter performing one or more of the following optional steps:

(a) de-esterifying the thus produced ester to form the free or salted acid within formula (II).

(b) re-esterifying the thus produced free or salted acid to yield a further ester within formula (II).

(c) oxidising the sulphide to a sulphoxide or sulphone.

149. A process for the preparation of the compounds of the formula (II) as defined in Claim 1 wherein CO_2A is an ester group and X is S which comprises the reaction of a thiol of the formula (VIII) as defined with the corresponding ester of the compound of the formula (I) in the presence of an acid catalyst.

150. A process according to Claim 149 wherein the catalyst is a boron trifluoride etherate.

151. A process for the preparation of a compound claimed in Claim 3 which comprises the oxidation of a compound as claimed in Claim 2.

152. A process for the preparation of a compound as claimed in Claim 4 which comprises the oxidation of a compound as claimed in Claim 2.

153. A process as claimed in Claims 151 or 152 wherein the oxidation is effected by m-chloroperbenzoic acid.

154. A process for the preparation of a compound as claimed in any of Claims 5 to 10 which comprises the very mild basic hydrolysis of a compound as claimed in Claim 63.

155. A process as claimed in Claim 154 wherein the compound of Claim 63 is as claimed in Claims 66 or 67.

156. A process as claimed in Claim 155 wherein the hydrolysis occurs in aqueous solution maintained at pH 7 to 9 by the slow addition of base.

157. A process for the preparation of a comound as claimed in any of Claims 5 to 10 which comprises the hydrogenation of a compound as claimed in Claim 65 or 66 optionally in the presence of a base.

158. A process for the preparation of a pharmaceutical composition as

claimed in any of Claims 105 to 147 which comprises bringing the components thereof into association.

159. A compound as claimed in Claim 1 whenever prepared by a process as claimed in Claim 148.

160. A compound as claimed in Claim 1 whenever prepared by a process substantially as described in Examples 1 or 2 herein.

161. A compound as claimed in Claim 1 whenever prepared by a process substantially as described in any of Examples 3 to 10 herein.

162. A compound as claimed in Claim 1 whenever prepared by a process substantially as described in any of Examples 11 to 23 herein.

163. A pharmaceutical composition substantially as described in Example 24 herein.

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