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**GB 2000138A**
**GB 1332306**
**GB 640713**
**GB 637184**
**Nature *278* 360-361**
**DE-OS 2,824535A**
(58) Field of search
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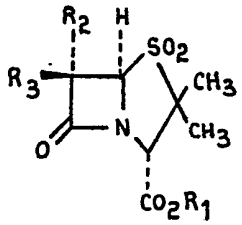
(54) **Penicillin 1,1-dioxides**

(57) Anti-bacterially active penicillin 1,1-dioxides have the formula



or are pharmaceutically acceptable salts thereof,
in which

$R_1$ denotes a hydrogen atom or an ester-forming radical,

$R_2$ denotes a hydrogen or bromine atom, an optionally substituted alkoxy radical, an optionally substituted alkylthio radical, an azido radical, an optionally substituted alkyl radical, an optionally substituted cycloalkyl radical, an aryl, aralkyl, heterocyclyl or acyl radical or a caboxyl or cyano group and

$R_3$ denotes a hydrogen or halogen atom, an azido radical or one of various defined organic radicals.

The compounds are also *inhibitors of* β-*lactamases* so they can be used in conjunction with β-lactamase-susceptible antibiotics. They are useful in fighting bacterial infection, in promoting animal growth and preserving various materials.

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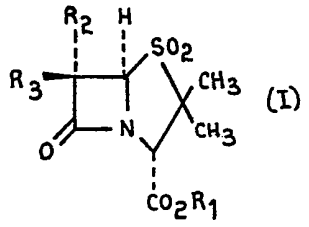
SPECIFICATION

**New penicillanic acid 1,1-dioxide compounds their production and their medicinal use**

The present invention relates to certain new penicillanic acid 1,1-dioxide compounds, to a process for their production and to their use as medicaments in human medicine and in veterinary medicine and as feed additives, and, in particular, their use as β-lactamase inhibitors.

1,1-Dioxides of certain penicillanic acids, for example penicillanic acid 1,1-dioxide can be synthesised and have been recommended as inhibitors of β-lactamases (Nature *278*. 360 - 361; and DE-OS (German Published Specification) 2,824,535).

According to the present invention we provide compounds which are penicillanic acid 1,1-dioxides of the general formula



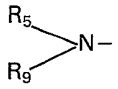
(I)

or a salt thereof, in which

$R_1$ denotes a hydrogen atom or an ester-forming radical,

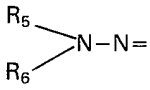
$R_2$ denotes a hydrogen or bromine atom, an optionally substituted alkoxy radical, an optionally substituted alkylthio radical, an azido radical, an optionally substituted alkyl radical, an optionally substituted cycloalkyl radical, an aryl, aralkyl, heterocyclyl or acyl radical or a carboxyl or cyano group and

$R_3$ denotes a hydrogen or halogen atom, an azido radical, an optionally substituted alkyl radical, an optionally substituted alkoxy radical, an optionally substituted cycloalkyl radical, an aralkyl or aryl radical, an optionally substituted alkylthio radical, a heterocyclyl or acyl radical or a radical of the general formula

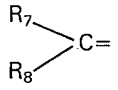


or

$R_2$ and $R_3$ together represent a radical of the formula O=, $R_4$–O–N=,



or



but in which

$R_2$ and $R_3$ cannot simultaneously be hydrogen, azido or acyl,

$R_4$ denotes an optionally substituted alkyl radical, an optionally substituted cycloalkyl radical, an optionally substituted aralkyl radical or an aryl or heterocyclyl radical,

$R_5$ denotes a hydrogen atom, an optionally substituted alkyl radical, an optionally substituted aralkyl radical, an optionally substituted cycloalkyl radical, an aryl or heterocyclyl radical or an optionally substituted alkylsulphonyl radical, or an arylsulphonyl, heterocyclylsulphonyl or aminosulphonyl radical and

$R_6$ denotes an acyl radical, an hydrogen atom, an optionally substituted alkyl radical, an optionally substituted aralkyl radical or an optionally substituted cycloalkyl radical, an aryl or heterocyclyl radical, or

$R_5$ and $R_6$ together with the nitrogen atom denote a 4-membered to 7-membered heterocyclic ring, optionally including further hetero-atoms,

$R_7$ and $R_8$ independently denote a hydrogen atom, an optionally substituted alkyl radical, an aryl radical, an optionally substituted cycloalkyl radical, an aralkyl radical or an optionally substituted amino group or, together with the carbon atom to which they are bonded, denote a 3-membered to 7-membered carbocyclic ring or, including one or more hetero-atoms, a hetero-cyclic ring and

$R_9$ denotes a hydrogen atom, an optionally substituted alkyl radical, an optionally substituted cycloalkyl radical, an aryl, aralkyl or heterocyclyl radical or an optionally substituted alkylsulphonyl radical.

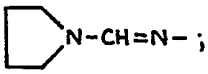
Examples of the ester-forming radicals $R_1$ are optionally substituted alkyl and optionally substituted aralkyl, aryl and heterocyclyl.

The hydrogen atom of $R_2$ and $R_3$ is also to be understood, in particular, as the hydrogen isotope deuterium.

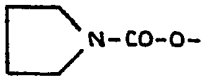
In the general formula (I), optionally substituted alkyl of $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$ and $R_9$, is straightchain or branched alkyl with preferably 1 to 6, especially 1 to 4, carbon atoms. Examples which may be mentioned are optionally substituted methyl, ethyl, n- and i-propyl and n-, i- and t-butyl.

Optionally substituted alkyl of $R_1$ is, for example, $C_1$ to $C_6$ alkyl, preferably $C_1$ to $C_3$ alkyl, which is optionally mono- di- or tri-substituted, preferably mono-substituted, by a substituent or substituents selected from: a

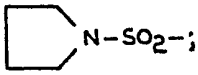
halogen atom (preferably a fluorine, chlorine, bromine or iodine atom, especially a fluorine, chlorine or bromine atom); amino; mono-lower alkylamino (preferably (ethylamino, and, especially, methylamino); di-lower alkylamino (preferably diethylamino, and, especially, dimethylamino); pyrrolidyl; piperidyl; HCO-NH-, lower alkyl-CO-NH- (preferably $CH_3$-CO-NH); H-CO-N(lower alkyl)- (preferably H-CO-N($CH_3$)- or H-CO-N($C_2H_5$)-);lower alkyl-CO-N(lower alkyl), (preferably $CH_3$-CO-N($CH_3$)); (lower alkyl)$_2$C=N-; lower alkyl-$SO_2$-NH-, (preferably $C_2H_5$-$SO_2$-NH- and, especially, $CH_3$-$SO_2$-NH-); lower alkyl- $SO_2$-N(lower alkyl)-, (preferably $CH_3$-$SO_2$-N($CH_3$)-); HO-$SO_2$-NH-; HO-$SO_2$-N(lower alkyl)-, (preferably HO-$SO_2$-N-($CH_3$)- or HO-$SO_2$-N($C_2H_5$)-); amidino; (lower alkyl)$_2$-N-CH=N- (especially $(CH_3)_2$N-CH=N-);




guanido; nitro; azido; hydroxyl; lower alkoxy ($C_2H_5$-O- or, especially, $CH_3O$-), H-CO-O-, lower alkyl-CO-O-, (preferably $CH_3$-CO-O-, $C_2H_5$-CO-O- or $(CH_3)_3$C-CO-O-); lower alkyl-O-CO-O- (preferably $CH_3$-O-CO-O-, $C_2H_5$-O-CO-O- or $(CH_3)_3$C-O-CO-O-); $H_2$N-CO-O-; lower alkyl-NH-CO-O- preferably $CH_3$-NH-CO-O- or $C_2H_5$-NH-CO-O-); (lower alkyl)$_2$N-CO-O- (preferably $(CH_3)_2$N-CO-O- or $(C_2H_5)_2$N-CO-O);




$H_2$N-$SO_2$-O-; lower alkyl-NH-$SO_2$-O-, (preferably $CH_3$-NH-$SO_2$-O- or $C_2H_5$-NH-$SO_2$-O-); (lower alkyl)$_2$N-$SO_2$-O-, (preferably $(CH_3)_2$N-$SO_2$-O- or $(C_2H_5)_2$N-$SO_2$-O-); HOOC-; $H_2$N-CO-; (lower alkyl)$_2$N-CO-(especially $(CH_3)_2$N-CO- or $(C_2H_5)_2$N-CO-); OHC-; HO-$SO_2$-O-; HS-; lower alkyl-S-, (preferably $CH_3$-S-, $CF_3$-S-, $C_2H_5$-S- or $(CH_3)_2$CH-S-); lower alkyl-S- (preferably $CH_3$-S- or $C_2H_5$-S-); $HO_3S$-; lower alkyl-$SO_2$- (preferably $CH_3$-$SO_2$-, $CF_3SO_2$- or $C_2H_5$-$SO_2$-); $H_2$N-$SO_2$-; lower alkyl- NH-$SO_2$- (preferably $CH_3$-NH-$SO_2$- or $C_2H_5$-NH-$SO_2$-); (lower alkyl)$_2$N-$SO_2$- (preferably $(CH_3)_2$N-$SO_2$- or $(C_2H_5)_2$N-$SO_2$);



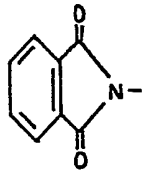

HO-$SO_2$-S-; heterocyclyl (preferably furyl, thienyl, pyridyl or 2-oxo-benzimidazo-linyl); lower alkylcarbonyl (especially acetyl); benzoyl; lower dialkylamino-lower alkoxycarbonyloxy, (especially dimethylamino- or diethylamino-$C_1$ or $C_2$ alkoxycarbonyloxy); morpholino-, piperidino- or pyrrolidino-$C_1$-$C_2$-alkoxy-carbonyloxy; lower alkoxy-carbonylamino; and lower alkylcarbonylthio.

Optionally substituted cycloalkyl of $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$ and $R_9$ is monocyclic, bicyclic or tricyclic and preferably contains 3 to 10, especially 3, 5 or 6, carbon atoms. Examples which may be mentioned are optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, bicyclo-[2.2.1]-heptyl, bicyclo-[2.2.2]-octyl and adamantyl.

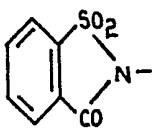
Optionally substituted aryl of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, and $R_9$ is aryl with preferably 6 to 10 carbon atoms in the aryl part. Examples which may be mentioned are optionally substituted phenyl or naphtyl. Substituents in the phenyl ring are in the o-, m- or p- position.

Optionally substituted aralkyl of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$ and $R_9$ is aralkyl which is optionally substituted in the aryl part and/or alkyl part and has preferably 6 or 10, especially 6, carbon atoms in the aryl part and preferably 1 to 4, especially 1 or 2, carbon atoms in the alkyl part, it being possible for the alkyl part to be straight-chain or branched. Examples which may be mentioned are optionally substituted benzyl and phenylethyl.

Optionally substituted heterocyclyl of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ and $R_9$ is a hetero-paraffinic, hetero-aromatic or hetero-olefinic 5-membered to 7-membered, preferably 5-membered or 6-membered, ring with preferably 1 to 3, especially 1 or 2, identical or different betero-atoms. Hetero-atoms are oxygen, sulphur or nitrogen. Examples which may be mentioned are optionally substituted thienyl, furyl, oxazoyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, oxdiazolyl, thiadiazolyl, triazolyl, sydnonyl, oxtriazolyl, thiatriazolyl, tetrazolyl, pyridly, pyrazinyl, pyrimidinyl, tetrahydrofuranyl, dioxanyl, pyrrolidinyl, piperidinyl, morpholinyl, pyron-2-yl and pyron-4-yl, 2-oxo-tetrahydro-fur-5-yl and 2-oxo-2,5-dihydrofur-5-yl. The above-mentioned hetercyclic radicals can be fused to carbocyclic rings or other heterocyclic rings, and in particular they can be benzo-fused. Examples which may be mentioned are




and



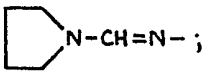

The above-mentioned alkyl, cycloalkyl, aryl and aralkyl radicals can carry one or more, preferably 1 to 3 and especially 1 or 2, identical or different radicals, preferably those defined as $R_{10}$ below.

The radicals mentioned which are unsubstituted or contain one substitutent $R_{10}$ are very particularly preferred.

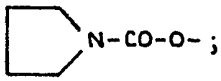
Heterocyclyl can carry one or more, preferably 1 to 3 and especially 1 or 2, identical or different radicals, preferably those defined as $R_{11}$ below. Heterocyclyl which is unsubstituted or contains one substituent $R_{11}$ is very particularly preferred.

In the following explanations, the expression "lower alkyl" denotes straight-chain or branched alkyl with preferably 1 to 6, especially 1 to 4, carbon atoms in all cases, also in association with other atoms or groups (for example lower alkoxy, NCON-(lower alkyl) and the like). Examples which may be mentioned are optionally substituted methyl, ethyl, n- and i- propyl and n-, i- and t-butyl. "Lower alkyl" can be substituted by 1 to 5, especially 1 to 3, identical or different halogen atoms, halogen atoms being, preferably, fluorine, chlorine and bromine, especially fluorine and chlorine. Examples which may be mentioned are tri-fluoromethyl, chloro-difluoromethyl, bromomethyl, 2,2,2-trifluoroethyl and pentafluoroethyl.

$R_{10}$ denotes a halogen atom (preferably a fluorine, chlorine, bromine or iodine atom, especially a fluorine, chlorine or bromine atom); amino; mono-lower alkylamino (preferably ethylamino and, especially, methylamino); di-lower alkylamino (preferably diethylamino and, especially, dimethylamino); pyrrolidyl; piperidyl; HCO-NH-; lower alkyl-CO-NH-, (preferably $CH_3$-CO-NH-); H-CO-N(lower alkyl)- (preferably H-CO-N($CH_3$)- or H-CO-N($C_2H_5$)-); di-lower alkylamino-lower alkyl; lower alkyl-CO-N(lower alkyl)-, (preferably $CH_3$-CO-N($CH_3$)); (lower alkyl)$_2$C=N-; lower alkyl-$SO_2$-NH- (preferably $C_2H_5$-$SO_2$-NH- and, especially, $CH_3$-$SO_2$-NH-); lower alkyl-$SO_2$-N(lower alkyl)-, (preferably $CH_3$-$SO_2$N($CH_3$)-); HO-$SO_2$-NH-; HO-$SO_2$-N(lower alkyl)- (preferably HO-$SO_2$-N-($CH_3$)- or HO-$SO_2$N($C_2H_5$)-); amidino; (lower alkyl)$_2$-N-CH=N-(in particular $(CH_3)_2$N-CH=N-);

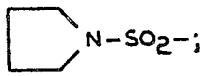



guanido; nitro; azido; hydroxyl; lower alkoxy, (preferably $C_2H_5$-O-, and, especially, $CH_3O$-); H-CO-O-; lower alkyl-CO-O- (preferably $CH_3$-CO-O-, $C_2H_5$-CO-O- or $(CH_3)_3$C-CO-O-): lower alkyl-O-CO-O- (preferably $CH_3$-O-CO-O-, $C_2H_5$-O-CO-O- or $(CH_3)_3$C-O-CO-O-); $H_2$N-CO-O-; lower alkyl-NH-CO-O-, (preferably $CH_3$-NH-CO-O- or $C_2H_5$-NH-CO-O-); (lower alkyl)$_2$N-CO-O-, (preferably $(CH_3)_2$N-CO-O- or $(C_2H_5)_2$N-CO-O-);



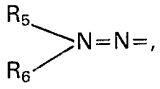

$H_2$N-SO-O-; lower alkyl-NH-$SO_2$-O-, (preferably $CH_3$-NH-$SO_2$-O- or $C_2H_5$-NH-$SO_2$-O-); (lower alkyl)$_2$N-$SO_2$-O- (preferably $(CH_3)_2$N-$SO_2$-O- or $(C_2H_5)_2$N-$SO_2$-O-); HOOC-; $H_2$N-CO-; (lower alkyl)$_2$N-CO-(especially $(CH_3)_2$N-CO- and $(C_2H_5)_2$N-CO-); OHC-; HO-$SO_2$-O-; HS-; lower alkyl-S- (preferably $CH_3$-S-, $CF_3$-S-, $C_2H_5$-S- or $(CH_3)_2$CH-S-); lower alkyl-S- (preferably $CH_3$-S- or $C_2H_5$-S-); $HO_3$S-; lower alkyl-$SO_2$-, (preferably $CH_3$-$SO_2$-,


$CF_3SO_2$- or $C_2H_5$-$SO_2$-); $H_2$N-$SO_2$-); lower alkyl-NH-$SO_2$- (preferably $CH_3$-NH-$SO_2$- or $C_2H_5$-NH-$SO_2$-); (lower alkyl)$_2$N-$SO_2$- (preferably $(CH_3)_2$N-$SO_2$- or $(C_2H_5)_2$N-$SO_2$-);




HO-$SO_2$-S-; straight-chain or branched alkyl with 1 to 6 carbon atoms (preferably ethyl, propyl, isopropyl, n-butyl, sec.-butyl or tert.-butyl, and, especially, methyl); phenyl; or phenoxy.

Possible substituents of the alkyl groups of $R_2$ and $R_3$ are furthermore oxo and groups of the formulae $R_4$-C-N= and



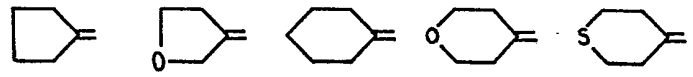

wherein

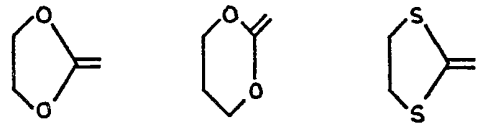
$R_4$, $R_5$ and $R_6$ have the meaning given.

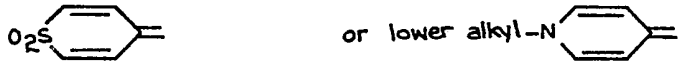
In the case where $R_{11}$ is on one or more carbon atoms in the heterocyclyl radical, $R_{11}$ denotes lower alkyl, (preferably ethyl or isopropyl, and especially, methyl); trifluoromethyl; a halogen atom (preferably a fluorine, chlorine or bromine atom); amino; lower alkylamino (preferably $CH_3$-NH- or $C_2H_5$-NH-); di-lower alkylamino (preferably $(CH_3)_2$N- or $(C_2H_5)_2$N-); formyl-amino; acetylamino; $CH_3$-O-CO-NH-; $C_2H_5$O-CO-NH-; $CH_3$-$SO_2$-NH-; hydroxyl; methoxy; ethoxy; methylthio; ethylthio; $CH_3$-$SO_2$-; $CH_3$-SO-; HOOC-; $HO_3$S-; HCO-; lower alkyl-CO-, (preferably $CH_3$-CO-); lower alkyl-O-CO-, (preferably $CH_3$-O-CO- or $C_2H_5$O-CO-); -CN; the oxo group =O; the thiono group =S; or the imino group =NH.

In the case where $R_{11}$ in a nitrogen-containing heterocyclyl radical is a substitutent on one or more nitrogen atoms, $R_{11}$ denotes lower alkyl, (preferably propyl or isopropyl, and, especially, methyl or ethyl; -C=N; -CHO; -COO-lower alkyl (preferably -COO-$CH_3$, -$COOC_2H_5$, -$COOCH(CH_3)_2$ or -COO-$C(CH_3)_3$); -CO-$NH_2$; -CO-NH-lower alkyl (preferably -CO-NH-$CH_3$, -CO-NH-$C_2H_5$ or -CO-NH-$CH(CH_3)_2$); or -CO-lower alkyl (preferably -CO-$CH_3$, -CO-$C_2H_5$ or -CO-$CH(CH_3)_2$).

The rings which can be formed by $R_7$ and $R_8$, together with the carbon atom to which they are bonded, are saturated or unsaturated. Unsaturated rings preferably contain 1 or 2 double bonds. The rings can contain 1 or more, preferably 1 or 2 and especially 1, hetero-atoms or hetero-groups. Hetero-atoms which may be mentioned are oxygen, sulphur and/or nitrogen. Examples of hetero-groups which may be mentioned are the $SO_2$ group and the lower alkyl-N group, and in the case of 6-rings, one hetero-atom or one hetero-group is preferably in the 4-position (relative to the carbon atom to which $R_7$ and $R_8$ are bonded). Particularly preferred rings which may be mentioned are:






The rings which can be formed by $R_5$ and $R_6$, together with the nitrogen atom to which they are bonded, are saturated or unsaturated; unsaturated rings preferably contain 1 or 2 double bonds. The rings can contain a further 1 or 2 hetero-atoms, in particular 1 further hetero-atom, for example oxygen, sulphur or nitrogen, also in the form of $SO_2$ groups or lower alkyl-N groups. Piperidino, morpholino, pyrrolidino, pyrrolino, piperazino and N'-lower alkyl-piperazino may be mentioned as preferred.

The rings which are formed by $R_7$ and $R_8$ or $R_5$ and $R_6$, together with the carbon atom or nitrogen atom to which they are bonded, can contain one or more, preferably 1 to 3, especially 1 or 2, identical or different substituents preferably selected from, a halogen atom (preferably a fluorine, chlorine or bromine atom); oxo; hydroxyl, lower alkoxy, (preferably methoxy or ethoxy); lower alkylthio, (preferably methylthio or ethylthio); amino; lower alkylamino, (preferably $CH_3$-NH- or $C_2H_5$-NH-); di-lower alkylamino (preferably dimethylamino or diethylamino); -CN; -COOH; -$COOCH_3$; -$COOC_2H_5$; and straight-chain or branched lower alkyl (preferably methyl or ethyl).

Optionally substituted alkoxy of $R_2$ and $R_3$ is, for example, alkoxy which has 1 to 6, especially 1 to 3, carbon atoms and is optionally monosubstituted or polysubstituted, preferably monosubstituted, preferably by $R_{10}$ as defined above.

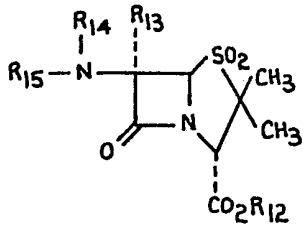
Optionally substituted alkylthio or $R_2$ and $R_3$ and alkylsulphonyl of $R_5$ and $R_6$ are, for example, alkylthio or alkylsulphonyl which has 1 to 6, especially 1 to 3, carbon atoms and can be monosubstituted or polysubstituted, preferably monosubstituted, preferably by $R_{10}$ as defined above.

Acyl of $R_2$, $R_3$ and $R_6$ is, especially, optionally substituted alkylcarbonyl, arylcarbonyl or aralkylcarbonyl, optionally substituted cycloalkylcarbonyl or a corresponding sulphonyl radical, and furthermore optionally substituted alkoxycarbonyl or optionally substituted aminocarbonyl, alkyl, aralkyl, aryl, cycloalkyl, alkoxy and amino corresponding to the above-mentioned definitions.

Optionally substituted amino is $NH_2$ or mono- or di-substituted amino, possible substituents being optionally substituted alkyl or aryl, optionally substituted aralkyl or heterocyclyl or optionally substituted cycloalkyl, the meaning of the substituents on the amino corresponding to the above-mentioned definitions for the individual radicals.

Optionally substituted arylsulphonyl, hetero-cyclylsulphonyl and aminosulphonyl correspond to the above-mentioned definitions with regard to aryl. heterocyclyl and amino.

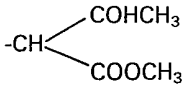
Preferred compounds of the present invention are those of the general formula (II)



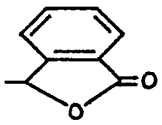
(II)

in which

$R_{12}$ denotes a hydrogen atom, a sodium ion,



, $-CH_2-OCO(CH_3)_3$,



-CH-O-COO-lower alkyl or -CH-OCONH-lower alkyl,
| |
$CH_3$ $CH_3$

$R_{13}$ denotes a hydrogen atom or a methoxy group,
$R_{14}$ denotes a hydrogen atom,
$R_{15}$ denotes a hydrogen atom or $SO_2-R_{17}$ or, $R_{15}$ together with $R_{14}$ denotes $=CH-R_{16}$,

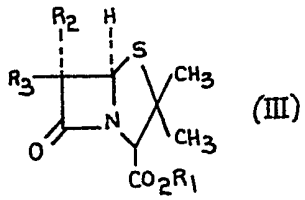
$R_{16}$ denotes 

$R_{17}$ denotes a $C_1$ to $C_4$-alkylsulphonyl radical or a phenyl radical which is optionally substituted by chlorine, bromine, methyl, methoxy, nitro or carboxyl and $R_{18}$ and $R_{19}$ independently denote a hydrogen atom or a $C_1$ to $C_4$ alkyl group, or together denote a $C_4$ to $C_6$ alkylidene radical.

Preferred compounds are, furthermore, 6-β-chloropenicillanic acid S-dioxide, 6-dibromopenicillanic acid S-dioxide, 6-α- and 6-β-(1-hydroxyethyl)-penicillanic acid S-dioxide and the corresponding sulphuric acid half-esters, 6-β-phthalimidopenicillanic acid S-dioxide and 6-β-succinimidopenicillanic acid S-dioxide, 6-β-saccharinyl-penicillanic acid S-dioxide and 6-α-methoxy-6-β-succinimidopenicillanic acid S-dioxide.

Surprisingly, the compounds according to the invention exhibit a considerably more powerful inhibiting action on β-lactamases than the penicillin 1,1-di-oxides known from the state of the art. The compounds according to the invention thus represent an enrichment of the range of medicaments.

According to the present invention we further provide a process for the production of compounds of the invention in which a compound of the general formula



(III)

in which

$R_1$, $R_2$, and $R_3$ have the meaning indicated above, is oxidised in a solvent.

The penicillanic acids of the formula (III) used as starting substances are either already known or they can be prepared by known processes.

Possible solvents are, in particular, polar solvents, for example water, acetic acid and tetrahydro-furan, and mixtures of these three. The reaction temperatures are in general between -20 and +50°C, preferably between 0 and 20°C. The reaction is in general carried out under normal pressure. The pH value of the reaction solution is in general between 2 and 8, preferably between 3.5 and 7.5.

In each case stoichiometric amounts of the reactants are preferably employed in carrying out the reactions. However, it is in all cases possible to add one of the reactants in excess, preferably the oxidising agent. The reaction products are worked up by the methods customary in preparative organic chemistry.

The oxidation is preferably carried out with the following oxidising agents: potassium permanganate, ozone, hydrogen peroxide, hydrogen peroxide in the presence of catalytic amounts of ammonium molybdate, hydrogen peroxide in glacial acetic acid, organic peracids (such as peracetic acid), chromium trioxide, ruthenium tetroxide, nitric acid, or N-chlorosuccinimide in methanol/water.

If the compounds of the formula (III) used as the starting material contain free amino groups, before the oxidation these are in general provided with protective groups, such as benzyloxycarbonyl, tert.-butoxycabronyl or β-dicarbonyl derivatives, by methods customary in peptide chemistry, and after the

oxidation, these groups are split off again in the customary manner.

The compounds of the present invention display an antimicrobial activity, coupled with low toxicity. These properties enable them to be used as chemotherapeutic active compounds in medicine and as substances for preserving inorganic and organic materials, especially organic materials of all kinds, for example polymers, lubricants, paints, fibres, leather, paper and timber, and foodstuffs and water.

Examples of micro-organisms against which the active compounds of the present invention have an action are Micrococcaceae, such as Staphylococci, for example Staphylococcus aureus, Staphylococcus epidermidis and Staphylococcus aerogenes, and Gasskya tetragena; Lactobacteriacea, such as Streptococci, for example Streptococcus pyogenes, and Diplococcus pneumoniae; Neisseriaceae, such as Neisseriae, for example Neisseria gonorrhoeae, Neisseria meningtides, Neisseria catarrhalis and Neisseria flava; and Bacillacea, such as aerobic spore-forming Bacillacea, for example Bacillus anthracis, Bacillus subtilis and Bacillus cereus.

The above list of pathogens is purely illustrative.

As stated above, the invention also relates to the use in human and veterinary medicine in combating bacterial diseases of the compounds of the invention.

The present invention provides a pharmaceutical composition containing as active ingredient a compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile and/or physiologically isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention.

"Medicament" as used in this specification means physically discrete coherent portions suitable for medical administration "Medicament in dosage unit form" as used in this Specification means physically discrete coherent units suitable for medical administration each containing a daily dose or a multiple (up to four times) or submultiple (down to a fortieth) of a daily dose of the compound of the invention in association with a carrier and/or enclosed within an envelope. Whether the medicament contains a daily dose or, for example, a half, a third or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical composition according to the invention may, for example, take the form of ointments, gels, pastes, creams, sprays (including aerosols), lotions, suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granulates or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following: (a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethyl glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters (e.g. $C_{14}$-alcohol with $C_{16}$-fatty acid) or mixtures of these diluents.

The pharmaceutical compositions which are ointments, pastes, creams and gels can, for example, contain the usual diluents, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

The pharmaceutical compositions which are powders and sprays can, for example, contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polyamide powder or mixtures of these substances. Aerosol sprays can, for example, contain the usual propellants, e.g. chlorofluorohydrocarbons.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (for example ground nut oil), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid

esters of sorbitol or mixtures thereof.

For parenteral administration, solutions and emulsions should be sterile, and, if appropriate, blood-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), micro-crystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention generally contain from 0.1 to 99.5%, usually from 0.5 to 95% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention will generally be adapted by virtue of their shape or packaging for medical administration and may be, for example, any of the following: tablets (including lozenges and granulates), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for administration of the medicaments of the invention is 500 mg to 10 g of active ingredient.

The product of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combating (including prevention, relief and cure of) the above-mentioned diseases in human and non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be administered perorally, parenterally (for example intramuscularly, intraperitoneally, subcutaneously and intravenously), rectally or locally, preferably orally or parenterally, especially intravenously or intramuscularly. Preferred pharmaceutical compositions and medicaments are therefore those adapted for administration such as oral or parenteral administration. Administration in the method of the invention is preferably oral or parenteral administration.

In general it has proved advantageous to administer amounts of from 5 mg to 1,000 mg/kg, preferably 10 mg to 200 mg/kg, of body weight per day, optionally in the form of several individual administrations, to achieve effective results. An individual administration preferably contains the active compound or compounds according to the invention in amounts of 1 mg to 250 mg/kg, in particular 10 mg to 100 mg/kg, of body weight. Nevertheless, it can at times be necessary to deviate from those dosage rates, and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subject to the treatment, the type of formulation in which the active ingredient is administered and the mode in which the administration is carried out, and the point in the progress of the disease or interval at which it is to be administered. Thus it may in some case suffice to use less than the above-mentioned minimum dosage rate, whilst other cases the upper limit mentioned must be exceeded to achieve the desired results. Where larger amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

The new penicillanic acid 1,1-dioxide derivatives of the present invention are distinguished by an antibacterial action, which has been tested *in vivo* and by oral resorbability.

In order to broaden the spectrum of action and to achieve a more powerful action, especially in the case of bacteria which form β-lactamase, the penicillanic acid 1,1-dioxide derivatives according to the invention can be combined with other antimicrobial active compounds, for example with β-lactam antibiotics, such as penicillins.

In order to broaden the spectrum of action and to achieve a more powerful action, the penicillanic acid 1,1-dioxide derivatives according to the invention can also be combined with aminoglycoside antibiotics, such as gentamicin, canamicin, sisomicin, amikacin or tobramicin.

The penicillanic acid 1,1-dioxide derivatives according to the invention inactivate, by inhibition or destruction, the bacterial enzymes which split the β-lactam ring (β-lactamases). The degradation of other penicillins, for example of amoxicillin, mezlocillin, ampicillin, azlocillin, penicillin G, carbenicillin and ticarcillin, is thereby prevented and on the one hand they thereby retain their activity and on the other hand their spectrum of action is thereby extended to bacteria which produce β-lactamase. This is demonstrated in

Table 1 with the aid of the improvement in the minimum inhibitory concentrations (MIC).

TABLE 1

| MIC in E/ml<br>Bacteria strain | A | B | C |
|---|---|---|---|
| E. coli T 7 | 256 | 64+64 | 256 |
| Klebsiella pneum. 1852 | 128 | 64+64 | 256 |
| Staphylococcus aureus 1756 | 256 | 64+64 | 256 |

A = mezlocillin; B = mezlocillin + compound according to Example 1; C = compound according to Example 1.

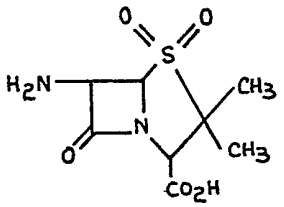
Table 1 shows the improvement (equivalent to lowering) of the minimum inhibitory concentrations (MIC) of mezlocillin in the case of strains which are otherwise resistant towards mezlocillin.

*In vitro experiments*

The compound of Example 1, which can be regarded as a typical representative of the compounds according to the invention, was diluted with Müller-Hinton nutrient broth to a content of 100 µg/ml, 0.1% of glucose being added. The nutrient solution contained in each case one x $10^5$ to two x $10^5$ bacteria per ml. The test-tubes containing this batch were in each case incubated for 24 hours and the degree of turbidity was then determined. Absence of turbidity indicates action. At a dosage of 1 µg/ml, the bacteria cultures inoculated with Staphylococcus aureus 133 were free from turbidity.

The following Examples illustrate processes for the production of compounds of the present invention.

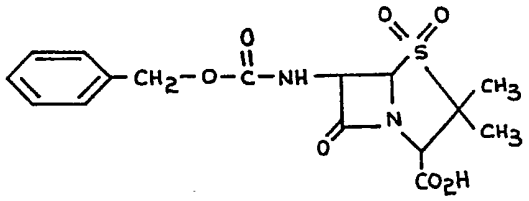
*Example 1*



6-Aminopenicillanic acid 1,1-dioxide

11.7 g of sodium 6-benzyloxycarbonylaminopenicillanate 1,1-dioxide were dissolved in 100 ml of water. The pH was adjusted to 6.5 by adding a little dilute hydrochloric acid and methanol was then added in an amount such that a clear solution is obtained (~40 ml). This solution was added to a suspension of 11.7 g of palladium black in 240 ml of water (pre-hydrogenated for one hour). Hydrogenation was then carried out under normal pressure for 2½ hours. Thereafter, the catalyst was filtered off and the filtrate was adjusted to pH 3.5, concentrated a little on a rotary evaporator in order to remove the methanol and then freeze-dried. The residue was dissolved in a little methanol and re-precipitated by adding ether. The precipitate was filtered off and washed with ether. After purification on an ion exchanger column, 5.8 g of 6-amino-penicillanic acid 1,1-dioxide were obtained.

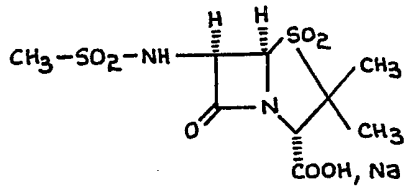
*Example 2*



6-Benzyloxycarbonylaminopenicillanic acid 1,1-dioxide

18.6 g (0.05 mol) of sodium 6-benzyloxycarbonylaminopenicillanate were dissolved in 260 ml of water. A solution of 9.5 g of potassium permanganate in 300 ml of water was added at 0° - 5°C and at pH 6 - 7.5 in the course of one hour. Excess permanganate was then destroyed by adding bisulphite solution and the mixture was filtered over kieselguhr. The filtrate was adjusted to pH 2 and extracted twice with ethyl acetate. The organic phase was dried with anhydrous $Na_2SO_4$ and concentrated. The residue was dissolved in methanol, and an equimolar amount of sodium caprylate solution (ether/methanol) was added. A precipitate formed and was filtered off and washed with ether. 12 g (59% of theory) of sodium 6-benzyloxy-carbonylaminopenicillanate 1,1-dioxide of melting point 168 - 170°C were obtained.

*Example 3*



A solution of 2.05g of $KMnO_4$ in 50 ml of water and 0.68 ml of 58% strength phosphoric acid were added dropwise to a solution, cooled to 0°C, of 3.3 g of sodium 6-mesylaminopenicillanate in 30 ml of water (adjusted to pH 7.0 - 7.5 by means of 1 N NaOH) in the course of about 20 minutes. During this addition, the temperature was kept below 10°C and the pH was kept at 6 - 7.5 by means of 10% strength phosphoric acid. The mixture was then stirred for a further 10 minutes, the excess $KMnO_4$ was removed with a little bisulphite solution and the precipitate was filtered off over celite and washed with water. The combined aqueous solutions were covered with a layer of ethyl acetate, the mixture was acidified to pH 2 with 2 N HCl, whilst stirring, and, after separating off the organic phase, the aqueous phase was extracted a further three times by shaking with ethyl acetate. After distilling off the solvent from the combined dried ethyl acetate extracts, mesylaminopenicillanic acid sulphone was left as as oil, which crystallised, however, on trituration with ether. The needle-shaped crystals were filtered off, washed with ether and dried.

Yield: 1.0 g

NMR ($CD_3OD$;δ; 60 MHz): 5.55 (d, 1H); 5.1 (d, 1H); 4.5 (s, C-3H); 3.1 (s, 3H); 1.6 (s, 3H) and 1.45 (s, 3H) ppm.

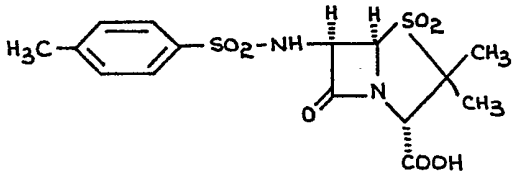
After dissolving the product in methanol and adding sodium 2-ethylhexanoate in methanol-containing ether (about 1 molar), the sodium salt could be precipitated with ether.

NMR ($CD_3OD$; δ; 60MHz): 6.1 (d; 1H); and 5.25 (d; 1H) ppm.

The 6-mesylaminopenicillanic acid used as the starting material was initially obtained as the free acid (foam) from disilylated 6-aminopenicillanic acid and mesyl chloride in chloroform in the presence of triethylamine (1 hour at 0°C; 30 minutes at 20°C). The sodium salt was obtained from the free acid by dissolving in water/sodium hydroxide solution (at pH 7) and freeze-drying the solution.

NMR ($CD_3OD$; δ; 60MHz): 5.4 (d; 1H), 5.1 (d; 1H); 4.0 (s; C-3H); and 2.9 (s; 3H) ppm.

*Example 4*

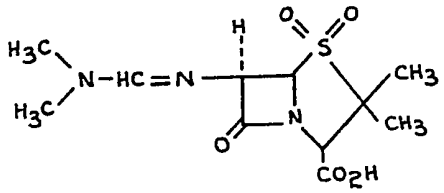


This compound was obtained from 2.2 g of 6-tolylaminopenicillanic acid in the manner described in Example 1.

Yield: 1.6 g

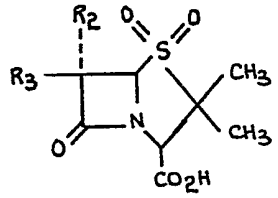
NMR ($CD_3OD$, δ, 60MHz): 7.8 (d; aromatic H); 7.3H (d; aromatic H); 5.5 (d; 1H); 4.85 (d; 1H); 4.4 (s; C-3H); 2.4 (s; 3H); 1.5 (s; 3H); and 1.35 (s; 3H) ppm.

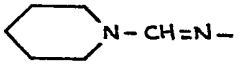
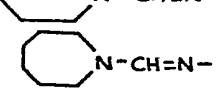
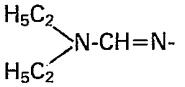
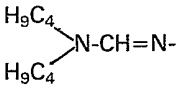
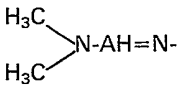
*Example 5*



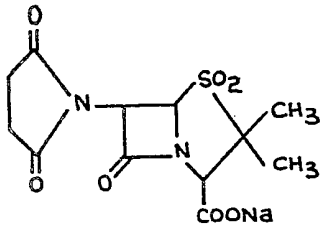
8.3 g of 6-(dimethylaminomethyleneamino)-penicillanic acid were dissolved in 50 ml of water. 180 ml of 0.2 molar $KMnO_4$ solution were added dropwise at 0 to 50°C and at a pH of 6 to 7.5. The reaction mixture was subsequently stirred for 15 minutes and then filtered over kieselguhr. The filtrate was freeze-dried and the residue was purified by chromatography. 5.2 g of 6-(dimethylaminomethyleneamino)-penicillanic acid 1,1-dioxide were obtained.

The following compounds were also obtained in the manner described in Example 5:



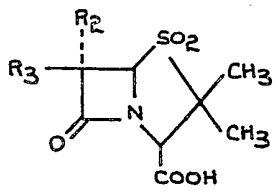
| Example | $R_3$ | $R_2$ |
|---|---|---|
| 6 |  | H |
| 7 |  | H |
| 8 | $H_5C_2$  $H_5C_2$ | H |
| 9 | $H_9C_4$  $H_9C_4$ | H |
| 10 | $H_3C$  $H_3C$ | $OCH_3$ |

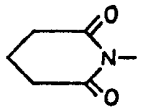
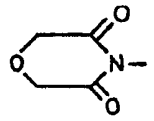
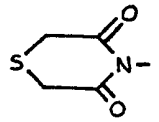
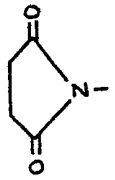
*Example 11*



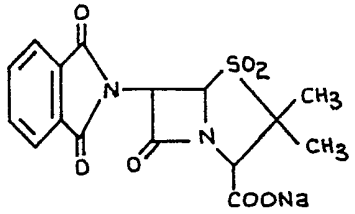
This penicillanic acid S-dioxide was prepared in 54% yield from 2 g of 6-β-pyrrolidine-2,5-dion-1-yl-penicillanic acid in the manner described in Example 2. NMR signals at $\tau$ = 4.1 (1H), 4.9 (1H) , 5.6 (1H), 7.4 (4H) and 8.6 (6H) ppm.

The following compounds were obtained in the manner described Example 2:



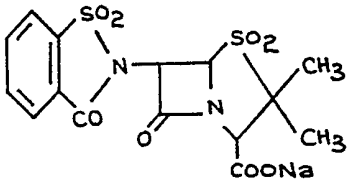
| | $R_3$ | $R_2$ |
|---|---|---|
| 12. |  | H<br>$OCH_3$ |
| 13. | " | |
| 14. |  | H<br>$OCH_3$ |
| 15. | " | |
| 16. |  | H<br>$OCH_3$ |
| 17. | " | |
| 18. |  | $OCH_3$ |

*Example 19*



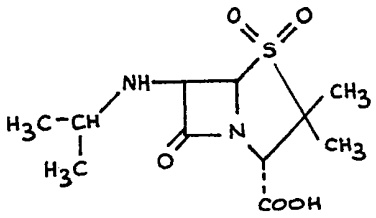
This penicillanic acid S-dioxide was obtained in 48% yield from 3.5 g of 6-β-phthaloyliminopenicillanic acid in the manner described in Example 2.
NMR signals at τ = 2.15 (4H), 4.1 (1H), 4.9 (1H), 5.5 (1H) and 8.6 (6H) ppm.

*Example 20*



This penicillanic acid S-dioxide was obtained on 40% yield from 3 g of 6-β-(4,5-benzoisothiazolin-3-one-S-dioxide-2-yl)-penicillanic acid in the manner described in Example 2.
NMR signals at τ = 1.8 - 2.6 (4H), 4.1 (1H), 4.9 (1H), 5.5 (1H) and 8.6 (6H) ppm.

*Example 21*

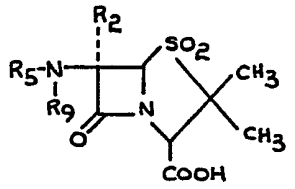


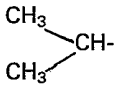
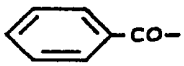
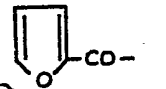
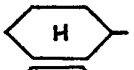
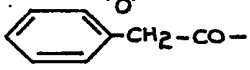
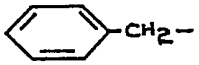
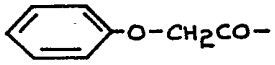
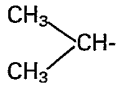
6-β-Isopropylamino-penicillanic acid S-dioxide

The pH of 4.4 g of 6-β-isopropylamino-penicillanic acid in 75 ml of water was adjusted to 7 with 5% strength NaOH and the mixture was cooled to 0°C. 2.4 g of $KMnO_4$ and 0.8 ml of 85% strength phosphoric acid in 60 ml of water were gradually added in a manner such that the internal temperature was kept below 10°C and the pH was kept between 6 and 7.5 (with NaOH or 10% strength $H_3PO_4$). The mixture was subsequently stirred for 10 minutes and filtered over cellite and a further 0.47 g of $KMnO_4$ and 0.15 ml of phosphoric acid in 12 ml of water was added at ≤ 10°C and the mixture was subsequently stirred again for 10

minutes and filtered over celite and the filtrate was adjusted to pH 6 with 1 N HCl. It was then freeze-dried.
Yield: 5.2 g (61% pure according to the analysis, corresponding to a yield of 73%).
NMR signals at $\tau$ = 4.95 (1H), 5.09 (1H), 5.7 (1H) 7.0 (1H), 8.4 (3H), 8.6 (3H) and 8.9 (6H) ppm.

The following penicillanic acid S-dioxides were obtained in the same manner:



| | $R_5$ | $R_9$ | $R_2$ |
|---|---|---|---|
| 22. |  | $CH_3CO$- | H |
| 23. | " |  | H |
| 24. | " |  | H |
| 25. |  |  | H |
| 26. |  | $CH_3SO_2$- | H |
| 27. | $CH_3SO_2$- | $CH_3SO_2$- | H |
| 28. | $CH_3CH_2CO$- | $CH_3CH_2SO_2$- | H |
| 29. |  | $CH_3SO_2$- | H |
| 30. |  | H | $OCH_3$ |

Among the new penicillanic acid 1,1-dioxide salts of the invention, those salts that are pharmaceutically acceptable are particularly important and are preferred.

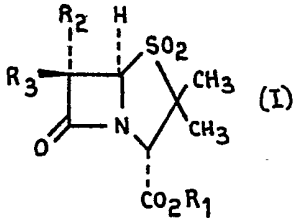
The new free penicillanic acid 1,1-dioxides of the general formula I and their salts can be interconverted in any suitable manner; methods for such interconversion are known in the art.

The present invention also comprises pharmaceutically acceptable biopresursors of the active compounds of the present invention.

For the purposes of this specification the term 'pharmaceutically acceptable bioprecursor' of an active compound of the invention means a compound having a structural formula different from the active compound but which nonetheless, upon administration to an animal or human being is converted in the patient's body to the active compound.

CLAIMS

1. Compounds which are penicillanic acid 1,1-dioxides of the general formula

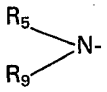


(I)

or a salt thereof,
in which
$R_1$ denotes a hydrogen atom or an ester-forming radical,

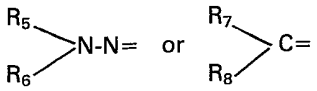
$R_2$ denotes a hydrogen or bromine atom, an optionally substituted alkoxy radical, an optionally substituted alkylthio radical, an azido radical, an optionally substituted alkyl radical, an optionally substituted cycloalkyl radical, an aryl, aralkyl, heterocyclyl or acyl radical or a carboxyl or cyano group and

$R_3$ denotes a hydrogen or halogen atom, an azido radical, an optionally substituted alkyl radical, an optionally substituted alkoxy radical, an optionally substituted cycloalkyl radical, an aralkyl or aryl radical, an optionally substituted alkylthio radical, a heterocyclyl or acyl radical or a radical of the general formula



or

$R_2$ and $R_3$ together represent a radical of the formula O=, $R_4$-O-N=,



in which

$R_2$ and $R_3$ cannot simultaneously be hydrogen, azido or acyl,

$R_4$ denotes an optionally substituted alkyl radical, an optionally substituted cycloalkyl radical, an optionally substituted aralkyl radical or an aryl or heterocyclyl radical,

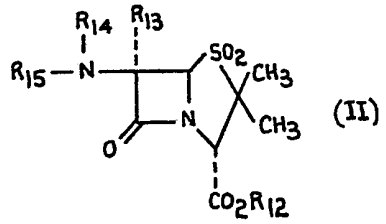
$R_5$ denotes a hydrogen atom, an optionally substituted alkyl radical, an optionally substituted aralkyl radical, an optionally substituted cycloalkyl radical, an aryl or heterocyclyl radical or an optionally substituted alkylsulphonyl radical or an arylsulphonyl, heterocyclylsulphonyl or aminosulphonyl radical, and

$R_6$ denotes an acyl radical, a hydrogen atom, an optionally substituted alkyl radical an optionally substituted aralkyl radical or an optionally substituted cycloalkyl radical, an aryl or heterocyclyl radical, or

$R_5$ and $R_6$ together with the nitrogen atom denote a 4-membered to 7-membered heterocyclic ring, optionally including further heteroatoms,

$R_7$ and $R_8$ independently denote a hydrogen atom, an optionally substituted alkyl radical, an aryl radical, an optionally substituted cycloalkyl radical, an aralkyl radical or an optionally substituted amino group, or, together with the carbon atom to which they are bonded, denote a 3-membered to 7-membered carbocyclic ring or, including one or more hetero-atoms, a heterocyclic ring and $R_9$ denotes a hydrogen atom, an optionally substituted alkyl radical, an optionally substituted cycloalkyl radical, an aryl, aralkyl or heterocyclyl radical or an optionally substituted alkylsulphonyl radical.

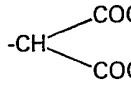
2. Compounds according to claim 1, of the general formula



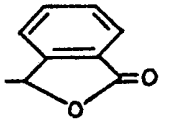
(II)

in which

$R_{12}$ denotes a hydrogen atom, a sodium ion,



, $-CH_2-OCO(CH_3)_3$,



-CH-O-COO-lower alkyl or
|
$CH_3$

-CH-OCONH-lower alkyl,
|
$CH_3$

$R_{13}$ denotes a hydrogen atom or a methoxy group,

$R_{14}$ denotes a hydrogen atom,

$R_{15}$ denotes a hydrogen or $SO_2$-$R_{17}$ or,

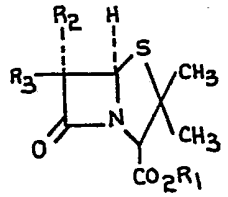
$R_{15}$ together with $R_{14}$ denotes =CH-$R_{16}$,

$R_{16}$ denotes $N\begin{matrix}R_{18}\\R_{19}\end{matrix}$,

$R_{17}$ denotes a $C_1$ to $C_4$ alkylsulphonyl radical or a phenyl radical which is optionally substituted by chlorine, bromine, methyl, methoxy, nitro or carboxyl and

$R_{18}$ and $R_{19}$ independently denote a hydrogen atom or a $C_1$ to $C_4$ alkyl group, or together denote a $C_4$ to $C_6$ alkylidene radical.

3. 6-β-Chloropenicillanic acid S-dioxide.
4. 6-Dibromopenicillanic acid S-oxide.
5. 6-α- and 6-β-(1-hydroxyethyl)-penicillanic acid S-dioxide or the corresponding sulphuric acid half-ester thereof
6. 6-β-Phthalimidopenicillanic acid S-dioxide.
7. 6-β-Succinimidopenicillanic acid S-dioxide.
8. 6-β-Saccharinylpenicillanic acid S-oxide.
9. 6-α-Methoxy-6-β-succinimidopenicillanic acid S-oxide.
10. Compounds according to claim 1 which are hereinbefore specifically mentioned other than those according to claims 3 to 9.
11. A process for the production of a compound according to any of claims 1 to 10 in which a compound of the general formula



(III)

in which

$R_1$, $R_2$ and $R_3$ have the same meaning as in claim 1, is oxidised in a solvent.

12. A process according to claim 11 in which the reaction is carried out in a polar solvent.
13. A process according to claim 11 or 12 in which the reaction is carried out at a temperature between -20 and +50°C.
14. A process according to any of claims 11 to 13 in which the reaction is carried out at a pH value between 2 and 8.
5. A process according to any of claims 11 to 14 in which the oxidising agent is potassium permanganate, ozone, hydrogen peroxide, hydrogen peroxide in the presence of ammonium molybdate, hydrogen peroxide in glacial acetic acid, an organic peracid, chromium trioxide, ruthenium tetroxide, nitric acid or N-chlorosuccinimide in methanol/water.
16. A process for the production of a compound according to claim 1 substantially as hereinbefore described in any of Examples 1 to 30.
17. Compounds according to claim 1 whenever prepared by a process according to any one of claims 11 to 16.
18. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 10 and 17 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent.
19. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 10 and 17 in the form of a sterile or physiologically isotonic aqueous solution.
20. A composition according to claim 18 or 19 containing from 0.5 to 95% by weight of the said active ingredient.
21. A medicament in dosage unit form comprising a compound according to any one of claims 1 to 10 and 17.
22. A medicament in the form of tablets, pills, dragees, capsules, ampoules or suppositories comprising a compound according to any one of claims 1 to 10 and 17.
23. A method of combating bacterial infections in human and non-human animals which comprises administering to the animals an active compound according to any one of claims 1 to 10 and 17 either alone or in admixture with a diluent or in the form of a medicament according to claim 21 or 22.
24. A method according to claim 23 in which the active compound is administered in an amount of 10 to 200 mg per kg body weight per day.
25. A method according to claim 23 or 24 in which the active compound is administered orally or parenterally.
26. A β-lactam antibiotic having had its activity increased by being admixed with a compound according to claim 1.

27. A β-lactam antibiotic which is unstable towards β-lactamase having had its activity increased by being admixed with a compound according to claim 1.

28. A polymer, lubricant, paint, fibre, leather, paper, timber, foodstuff or water preserved against bacterial attach by being treated with a compound according to claim 1.

29. A penicillanic acid 1,1-dioxide as defined in claim 1 for use in combating bacterial infections.

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