

## SPECIFICATION

## Process and intermediates for penicillanic acid 1,1-dioxide and esters thereof

5 This invention relates to a new chemical process, and to new chemical compounds useful as intermediates  
in said process. More particularly, it relates to a new chemical process for the preparation of penicillanic acid  
1,1-dioxide and esters thereof readily hydrolyzable *in vivo*. Said new chemical process comprises  
dehalogenation of a 6-halo or 6,6-dihalo derivative of penicillanic acid 1,1-dioxide or ester thereof readily  
hydrolyzable *in vivo*, or carboxy-protected derivative thereof to the corresponding 1,1-dioxide, followed, if  
10 necessary, by deprotection. Said new chemical compounds useful as intermediates are 6-halo and 6,  
6-dihalo derivatives of penicillanic acid 1,1-dioxides, esters thereof readily hydrolyzable *in vivo*, and  
carboxy-protected derivatives thereof.

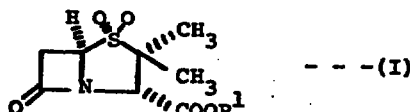
Penicillanic acid 1,1-dioxide and esters thereof readily hydrolyzable *in vivo* are useful as beta-lactamase  
inhibitors and as agents which enhance the effectiveness of certain beta-lactam antibiotics when the latter  
15 are used to treat bacterial infections in mammals, particularly humans. Previously, penicillanic acid  
1,1-dioxide and esters thereof readily hydrolyzable *in vivo* have been prepared from 6-bromopenicillanic  
acid, or ester thereof readily hydrolyzable *in vivo*, by debromination to give penicillanic acid, or ester thereof  
readily hydrolyzable *in vivo*, followed by oxidation to the 1,1-dioxide. It has now been found that, if the  
oxidation step is performed before the dehalogenation step, a better yield of product is obtained. See  
20 Belgian Patent No. 867,859, granted December 6, 1978; and West German Offenlegungsschrift No. 2,824,535  
for details of methods of preparing penicillanic acid 1,1-dioxide and esters thereof readily hydrolyzable *in*  
*vivo*.

6-Halopenicillanic acids have been disclosed by Cignarella *et al.*, *Journal of Organic Chemistry*, 27, 2668  
(1962) and in United States Patent No. 3,206,469; hydrogenolysis of 6-halopenicillanic acids to penicillanic  
25 acid is disclosed in British Patent Specification No. 1,072,108.

Harrison *et al.*, *Journal of the Chemical Society* (London), Perkin I, 1772 (1976) disclose; (a) the oxidation of  
6,6-dibromopenicillanic acid with 3-chloroperbenzoic acid, to give a mixture of the corresponding alpha- and  
beta-sulfoxides; (b) oxidation of methyl 6,6-dibromopenicillanate with 3-chloroperbenzoic acid to give a  
methyl 6,6-dibromopenicillanate 1,1-dioxide; (c) oxidation of methyl 6-alpha-chloropenicillanate with  
30 3-chloroperbenzoic acid, to give a mixture of the corresponding alpha- and beta-sulfoxides; and (d)  
oxidation of methyl 6-bromopenicillanate with 3-chloroperbenzoic acid, to give a mixture of the  
corresponding alpha- and beta-sulfoxides.

Clayton, *Journal of the Chemical Society* (London), (C), 2123, (1969), discloses: (a) the preparation of  
6,6-dibromo- and 6,6-diiodopenicillanic acid; (b) oxidation of 6,6-dibromopenicillanic acid with sodium  
35 periodate, to give a mixture of the corresponding sulfoxides; (c) hydrogenolysis of methyl 6,6-  
dibromopenicillanate to give methyl 6-alpha-bromopenicillanate; (d) hydrogenolysis of 6,6-  
dibromopenicillanic acid, and its methyl ester, to give penicillanic acid and its methyl ester, respectively; and  
(e) hydrogenolysis of a mixture of methyl 6,6-diiodopenicillanate and methyl 6-alpha-iodopenicillanate to  
give pure methyl 6-alpha-iodopenicillanate.

40 This invention provides a process for the preparation of a compound of the formula



45 or a pharmaceutically acceptable base salt thereof, wherein R¹ is hydrogen or an ester-forming residue  
readily hydrolyzable *in vivo*, characterised in that a compound of the formula



50 or a base salt thereof, wherein R is hydrogen, an ester-forming residue readily hydrolyzable *in vivo* or a  
conventional penicillin carboxy protecting group; and X and Y are each hydrogen, chloro, bromo or iodo,  
55 with the proviso that when X and Y are both the same, they must both be bromo; is dehalogenated,  
followed, if necessary, by removal of the conventional penicillin carboxy protecting group.

A preferred way of carrying out the invention comprises contacting the compound of formula (III) with  
hydrogen, in an inert solvent, at a pressure in the range from about 1 to about 100 kg/cm², at a temperature  
60 in the range from about 0 to about 60°C, and at a pH in the range from about 4 to about 9, and in the presence  
of a hydrogenolysis catalyst. The hydrogenolysis catalyst is usually present in an amount from about 0.01 to  
about 2.5 weight-percent, and preferably from about 0.1 to about 1.0 weight-percent, based on the  
compound of formula III.

Preferably X and Y are both bromo or X is bromo and Y is hydrogen.  
65 Preferred values for R and R¹ are hydrogen.

Also embraced within the ambit of this invention are the intermediates of formula III, wherein X, Y and R are as defined above. Preferred intermediates are the compounds of the formula (III) wherein X is bromo and Y is hydrogen or X and Y are both bromo, and wherein R is hydrogen, especially 6- $\alpha$ -bromo and 6,6-dibromopenicillanic acid, 1,1-dioxide.

- 5 This invention relates to the preparation of compounds of the formula I, and to several intermediates therefor. Throughout this specification, these compounds are named as derivatives of penicillanic acid, which is represented by the following structural formula:

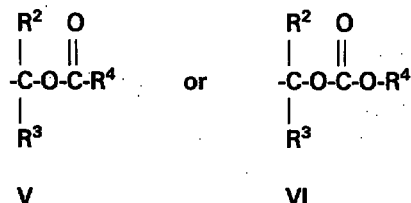


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- 15 In derivatives of penicillanic acid, broken line attachment of a substituent to the bicyclic nucleus indicates that the substituent is below the plane of the nucleus. Such a substituent is said to be in the alpha-configuration. Conversely, solid line attachment of a substituent to the bicyclic nucleus indicates that the substituent is above the plane of the nucleus. This latter configuration is referred to as the beta-configuration. Thus, the group X has the alpha-configuration and the group Y has the beta-

20 configuration in formula III.

- In this specification, when R<sup>1</sup> is an ester-forming residue readily hydrolyzable *in vivo*, it is a grouping which is notionally derived from an alcohol of the formula R<sup>1</sup>-OH, such that the moiety COOR<sup>1</sup> in such a compound of formula I represents an ester grouping. Moreover, R<sup>1</sup> is of such a nature that the grouping COOR<sup>1</sup> is readily cleaved *in vivo* to liberate a free carboxy group (COOH). That is to say, R<sup>1</sup> is a group of the type that when a compound of formula I, wherein R<sup>1</sup> is an ester-forming residue readily hydrolyzed *in vivo*, is exposed to mammalian blood or tissue, the compound of formula I, wherein R<sup>1</sup> is hydrogen, is readily produced. The groups R<sup>1</sup> are well known in the penicillin art. In most instances, they improve the absorption characteristics of the penicillin compound. Additionally, R<sup>1</sup> should be of such a nature that it imparts pharmaceutically-acceptable properties to a compound of formula I, and it liberates pharmaceutically-acceptable fragments when cleaved *in vivo*. The groups R<sup>1</sup> are well known and are readily identified by those skilled in the penicillin art. See, for example, West German Offenlegungsschrift No. 2,517,316. Specific examples of groups for R<sup>1</sup> are 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl and groups of the formula

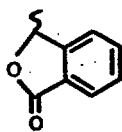


V

VI

- wherein R<sup>2</sup> and R<sup>3</sup> are each selected from the group consisting of hydrogen and alkyl having from 1 to 2 carbon atoms, and R<sup>4</sup> is alkyl having from 1 to 5 carbon atoms. However, preferred groups for R<sup>1</sup> are alkanoyloxymethyl having from 3 to 7 carbon atoms, 1-(alkanoyloxy)ethyl having from 4 to 8 carbon atoms, 1-methyl-1-(alkanoyloxy)ethyl having from 5 to 9 carbon atoms, alkoxy-carboxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-alkoxy-carboxymethyl having from 5 to 8 carbon atoms, 3-phthalidyl, 4-crotonolactonyl and gamma-butyrolacton-4-yl.

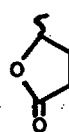
- 50 3-Phthalidyl, 4-crotonolactonyl and gamma-butyrolacton-4-yl refer to structures VII, VIII and IX. The wavy lines are intended to denote either of the two epimers or a mixture thereof.



VII

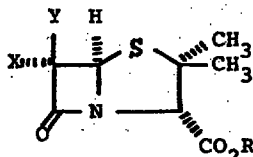


VIII



IX

- The compounds of formula (III) are obtained by a process which involves oxidation of the sulfide grouping in a compound of the formula:



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wherein X, Y and R are as previously defined, to a sulphone grouping, thereby producing a compound of the formula III. A wide variety of oxidants known in the art for the oxidation of sulfides to sulfones can be used for this process. However, particularly convenient reagents are alkali metal permanganates such as sodium and potassium permanganate; alkaline earth metal permanganates, such as calcium and barium

5 permanganates; and organic peroxycarboxylic acids, such as peracetic acid and 3-chloroperbenzoic acid.

When a compound of the formula II, wherein X, Y and R are as defined previously, is oxidized to the corresponding compound of the formula III, using a metal permanganate, the reaction is usually carried out by treating the compound of the formula II with from about 0.5 to about ten molar equivalents, and preferably from about one to about four molar equivalents, of the permanganate in an appropriate, reaction-inert solvent system. An appropriate, reaction-inert solvent system is one that does not adversely interact with either the starting materials or the product, and water is commonly used. If desired, a co-solvent which is miscible with water but will not interact with the permanganate, such as tetrahydrofuran, can be added. The reaction can be carried out at a temperature in the range from about -30° to about 50°C., and it is preferably carried out from about -10 to about 10°C. At about 0°C. the reaction is normally substantially complete within a short period, e.g. within one hour. Although the reaction can be carried out under neutral, basic or acid conditions, it is preferable to operate at a pH in the range from about 4 to about 9, preferably 6-8. However, it is essential to choose conditions which avoid decomposition of the beta-lactam ring system of the compound of the formulae II or III. Indeed, it is often advantageous to buffer the pH of the reaction medium in the vicinity of neutrality. The product is recovered by conventional techniques. Any excess permanganate is usually decomposed using sodium bisulfite, and then if the product is out of solution, it is recovered by filtration. It is separated from manganese dioxide by extracting it into an organic solvent and removing the solvent by evaporation. Alternatively, if the product is not out of solution at the end of the reaction, it is isolated by the usual procedure of solvent extraction.

When a compound of the formula II wherein X, Y and R are as previously defined, is oxidized to the corresponding compound of the formula III using a peroxycarboxylic acid, the reaction is usually carried out by treating the compound of the formula II with from about 1 to about 6 molar equivalents, and preferably about 2.2 molar equivalents of the oxidant in a reaction-inert organic solvent. Typical solvents are chlorinated hydrocarbons, such as dichloromethane, chloroform and 1,2-dichloroethane; and ethers, such as diethyl ether, tetrahydrofuran and 1,2-dimethoxyethane. The reaction is normally carried out at a temperature of from about -30 to about 50°C., and preferably from about 15 to about 30°C. At about 25°C., reaction times of about 2 to about 16 hours are commonly used. The product is normally isolated by removal of the solvent by evaporation *in vacuo*. The reaction product can be purified by conventional methods, well known in the art. Alternatively, it can be used directly in the dehalogenation step without further purification.

The process of the present invention is a dehalogenation reaction. One convenient method of carrying out this transformation is to stir or shake a solution of a compound of the formula III under an atmosphere of hydrogen, or hydrogen mixed with an inert diluent such as nitrogen or argon, in the presence of a hydrogenolysis catalyst. Suitable solvents for this hydrogenolysis reaction are those which substantially dissolve the starting compound of the formula III but which do not themselves suffer hydrogenation or hydrogenolysis. Examples of such solvents include ethers such as diethyl ether, tetrahydrofuran, dioxan and 1,2-dimethoxyethane; low molecular weight esters such as ethyl acetate and butyl acetate; tertiary amides such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide and *N*-methylpyrrolidone; water; and mixtures thereof. Additionally, it is usual to buffer the reaction mixture so as to operate at a pH in the range from about 4 to 9, and preferably from about 6 to 8. Borate and phosphate buffers are commonly used. Introduction of the hydrogen gas into the reaction medium is usually accomplished by carrying out the reaction in a sealed vessel, containing the compound of formula III, the solvent, the catalyst and the hydrogen. The pressure inside the reaction vessel can vary from about 1 to about 100 kg/cm<sup>2</sup>. The preferred pressure range, when the atmosphere inside the reaction vessel is substantially pure hydrogen, is from about 2 to about 5 kg/cm<sup>2</sup>. The hydrogenolysis is generally run at a temperature of from about 0° to about 60°C., and preferably from about 25° to about 50°C. Utilizing the preferred temperature and pressure values, hydrogenolysis generally takes place in a few hours, e.g., from about 2 hours to about 20 hours. The catalysts used in this hydrogenolysis reaction are the type of agents known in the art for this kind of transformation, and typical examples are the noble metals, such as nickel, palladium, platinum and rhodium. The catalyst is usually present in an amount from about 0.01 to about 2.5 weight-percent, and preferably from about 0.1 to about 1.0 weight-percent, based on the compound of formula III. It is often convenient to suspend the catalyst on an inert support; a particularly convenient catalyst is palladium suspended on an inert support such as carbon.

Other methods can be used for reductive removal of the halogen from a compound of formula III.

For example, X and Y can be removed using a dissolving metal reducing system, such as zinc dust in acetic acid, formic acid or a phosphate buffer, according to well-known procedures. Alternatively, the process can be carried out using a tin hydride, for example a trialkyltin hydride such as tri-*n*-butyltin hydride.

As will be appreciated by one skilled in the art, when it is desired to prepare a compound of the formula I, wherein R<sup>1</sup> is hydrogen, a compound of the formula II, wherein R is hydrogen, can be subjected to the dehalogenation process disclosed herein. In other words, the process comprises dehalogenation, of a 6-halo or 6,6-dihalo derivative of penicillanic acid with a free carboxy group at the 3-position. However, in a further aspect of this invention, it is possible to begin with the carboxy group at the 3-position blocked by a conventional penicillin carboxy protecting group. The protecting group can be removed during or after the

- dehalogenation step, with regeneration of the free carboxy group. In this regard, a variety of protecting groups conventionally used in the penicillin art to protect the 3-carboxy group can be employed. The major requirements for the protecting group are that it must be attachable to the particular compound of formula II or III, and removable from the particular compound of formula I or III, using conditions under which the beta-lactam ring system remains substantially intact. For each case preferred typical examples are the tetrahydropyranyl group, trialkylsilyl groups, the benzyl group, substituted benzyl groups (e.g. 4-nitrobenzyl), the benzhydryl group, the 2,2,2-tri-chloroethyl group, the *t*-butyl group and the phenacyl group. Although all protecting groups are not operable in all situations a particular group which can be used in a particular situation will be readily selected by one skilled in the art. See further: United States Patents 3,632,850 and 3,197,466; British Patent No. 1,041,985, Woodward *et al*, *Journal of the American Chemical Society*, 88, 852 (1966); Chauvette, *Journal of Organic Chemistry*, 36, 1259 (1971); Sheehan *et al*, *Journal of Organic Chemistry*, 29, 2006 (1964); and "Cephalosporin and Penicillins, Chemistry and Biology", edited by H.E. Flynn, Academic Press, Inc., 1972. The penicillin carboxy protecting group is removed in conventional manner, having due regard for the lability of the beta-lactam ring system.
- 6-alpha-Chloropenicillanic acid and 6-alpha-bromo-penicillanic acid are prepared by diazotization of 6-aminopenicillanic acid in the presence of hydrochloric acid and hydrobromic acid, respectively (*Journal of Organic Chemistry*, 27, 2668 [1962]). 6-alpha-Iodopenicillanic acid is prepared by diazotization of 6-aminopenicillanic acid in the presence of iodine, followed by hydrogenolysis (Clayton, *Journal of the Chemical Society (C)*, 2123 [1969]). 6-beta-Chloropenicillanic acid, 6-beta-bromopenicillanic acid and 6-iodopenicillanic acid are prepared by reduction of 6-chloro-6-iodopenicillanic acid, 6,6-dibromopenicillanic acid and 6,6-diiodopenicillanic acid, respectively, with tri-*n*-butyltin hydride. 6-Chloro-6-iodopenicillanic acid is prepared by diazotization of 6-aminopenicillanic acid in the presence of iodine chloride; 6,6-dibromopenicillanic acid is prepared by the method of Clayton, *Journal of the Chemical Society (London) (C)* 2123 (1969); and 6,6-diiodopenicillanic acid is prepared by diazotization of 6-aminopenicillanic acid in the presence of iodine.
- The compounds of formula I, II and III, wherein R and R<sup>1</sup> is hydrogen, are acidic and will form salts with basic agents. These salts can be prepared by standard techniques, such as contacting the acidic and basic components, usually in a stoichiometric ratio, in an aqueous, non-aqueous or partially aqueous medium, as appropriate. They are then recovered by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or in the case of aqueous solutions, by lyophilization, as appropriate. Basic agents which are suitably employed in salt formation belong to both the organic and inorganic types, and they include ammonia, organic amines, alkali metal hydroxides, carbonates, bicarbonates, hydrides and alkoxides, as well as alkaline earth metal hydroxides, carbonates, hydrides and alkoxides. Representative examples of such bases are primary amines, such as *n*-propylamine, *n*-butylamine, aniline, cyclohexylamine, benzylamine and octylamine; secondary amines, such as diethylamine, morpholine, pyrrolidine and piperidine; tertiary amines, such as triethylamine, *N*-ethylpiperidine, *N*-methylmorpholine and 1,5-diazabicyclo [4.3.0]non-5-ene; hydroxides, such as sodium hydroxide, potassium hydroxide, ammonium hydroxide and barium hydroxide; alkoxides, such as sodium ethoxide and potassium ethoxide; hydrides, such as calcium hydride and sodium hydride; carbonates, such as potassium carbonate and sodium carbonate; bicarbonates, such as sodium bicarbonate and potassium bicarbonate; and alkali metal salts of long-chain fatty acids, such as sodium 2-ethylhexanoate. Preferred salts of the compound of the formula I are the sodium, potassium and triethylamine salts.
- The compound of formula I, wherein R<sup>1</sup> is hydrogen, and the salts thereof is active as an antibacterial agent of medium potency both *in vitro* and *in vivo*, and the compounds of formula I, wherein R<sup>1</sup> is an ester-forming residue readily hydrolyzable *in vivo*, are active as antibacterial agents of medium potency *in vivo*. Minimum inhibitory concentrations (MIC's) of penicillanic acid 1,1-dioxide against several microorganisms are shown in Table I.

TABLE I

*In Vitro* Antibacterial Activity  
of Penicillanic Acid 1,1-Dioxide

| 5  | Microorganism                   | MIC (mcg./ml.) | 5  |
|----|---------------------------------|----------------|----|
|    | <i>Staphylococcus aureus</i>    | 100            |    |
| 10 | <i>Streptococcus faecalis</i>   | 200            | 10 |
|    | <i>Streptococcus pyogenes</i>   | 100            |    |
|    | <i>Escherichia coli</i>         | 50             |    |
| 15 | <i>Pseudomonas aeruginosa</i>   | 200            | 15 |
|    | <i>Klebsiella pneumoniae</i>    | 50             |    |
| 20 | <i>Proteus mirabilis</i>        | 100            | 20 |
|    | <i>Proteus morgani</i>          | 100            |    |
|    | <i>Salmonella typhimurium</i>   | 50             |    |
| 25 | <i>Pasteurella multocida</i>    | 50             | 25 |
|    | <i>Serratia marcescens</i>      | 100            |    |
| 30 | <i>Enterobacter aerogenes</i>   | 25             | 30 |
|    | <i>Enterobacter cloacae</i>     | 100            |    |
|    | <i>Citrobacter freundii</i>     | 50             |    |
| 35 | <i>Providencia</i>              | 100            | 35 |
|    | <i>Staphylococcus epidermis</i> | 200            |    |
| 40 | <i>Pseudomonas putida</i>       | 200            | 40 |
|    | <i>Hemophilus influenzae</i>    | 50             |    |
| 45 | <i>Neisseria gonorrhoeae</i>    | 0.312          | 45 |

The *in vitro* antibacterial activity of the compound of the formula I, wherein R<sup>1</sup> is hydrogen, and its salts, makes them useful as industrial antimicrobials, for example in water treatment, slime control, paint preservation and wood preservation, as well as for topical application as disinfectants. In the case of use of these compounds for topical application, it is often convenient to admix the active ingredient with a non-toxic carrier, such as vegetable or mineral oil or an emollient cream. Similarly, it can be dissolved or dispersed in liquid diluents or solvents such as water, alkanols, glycols or mixtures thereof. In most instances it is appropriate to employ concentrations of the active ingredient of from about 0.1 percent to about 10 percent by weight, based on total composition.

The *in vivo* activity of the compounds of formula I wherein R<sup>1</sup> is hydrogen or an ester-forming residue readily hydrolyzable *in vivo*, and the salts thereof, makes them suitable for the control of bacterial infections in mammals, including man, by both the oral and parenteral modes of administration. The compounds will find use in the control of infections caused by susceptible bacteria in human subjects, e.g. infections caused by strains of *Neisseria gonorrhoeae*.

When considering therapeutic use of a compound of the formula I, or a salt thereof, in a mammal, particularly man, the compound can be administered alone, or it can be mixed with pharmaceutically acceptable carriers or diluents. It can be administered orally or parenterally, i.e. intramuscularly, subcutaneously or intraperitoneally. The carrier or diluent is chosen on the basis of the intended mode of administration. For example, when considering the oral mode of administration, the compound can be used in the form of tablets, capsules, lozenges, troches, powders, syrups, elixirs, aqueous solutions and

suspensions, and the like, in accordance with standard pharmaceutical practice. The proportional ratio of active ingredient to carrier will depend on the chemical nature, solubility and stability of the active ingredient, as well as the dosage contemplated. However, pharmaceutical compositions containing an antibacterial agent of the formula I will likely contain from about 20% to about 95% of active ingredient. In the case of tablets for oral use, carriers which are commonly used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the active ingredient can be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added. For parenteral administration, which includes intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions are suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic.

The prescribing physician will ultimately determine the appropriate dose of a compound of formula I for a given human subject, and this can be expected to vary according to the age, weight, and response of the individual patient, as well as the nature and the severity of the patient's symptoms. The compound will normally be used orally at dosages in the range from about 10 to about 200 mg. per kilogram of body weight per day, and parenterally at dosages from about 10 to about 400 mg. per kilogram of body weight per day. These figures are illustrative only, however, and in some cases it may be necessary to use dosages outside these limits.

The compounds of the formula I, wherein R<sup>1</sup> is hydrogen or an ester-forming residue readily hydrolyzable *in vivo*, or a salt thereof, enhance the antibacterial effectiveness of beta-lactam antibiotics *in vivo*. They lower the amount of the antibiotic which is needed to protect mice against an otherwise lethal inoculum of certain beta-lactamase producing bacteria. This ability makes them valuable for co-administration with beta-lactam antibiotics in the treatment of bacterial infections in mammals, particularly man. In the treatment of a bacterial infection, said compound of the formula I can be comingled with the beta-lactam antibiotic, and the two agents thereby administered simultaneously. Alternatively, said compound of the formula I can be administered as a separate agent during a course of treatment with a beta-lactam antibiotic. In some instances it is advantageous to pre-dose the subject with the compound of the formula I before initiating treatment with a beta-lactam antibiotic.

When using penicillanic acid 1,1-dioxide, a salt or an ester thereof readily hydrolyzable *in vivo* to enhance the effectiveness of beta-lactam antibiotic, it is administered preferably in formulation with standard pharmaceutical carriers or diluents. The methods of formulation discussed earlier for use of penicillanic acid 1,1-dioxide or an ester thereof readily hydrolyzable *in vivo* as a single-entity antibacterial agent can be used when co-administration with another beta-lactam antibiotic is intended. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier, a beta-lactam antibiotic and penicillanic acid 1,1-dioxide or a readily hydrolyzable ester thereof will normally contain from about 5 to about 80 percent of the pharmaceutically acceptable carrier by weight.

When using penicillanic acid 1,1-dioxide or an ester thereof readily hydrolyzable *in vivo* in combination with another beta-lactam antibiotic, the sulfone can be administered orally or parenterally, i.e. intramuscularly, subcutaneously or intraperitoneally. Although the prescribing physician will ultimately decide the dosage to be used in a human subject, the ratio of the daily dosages of the penicillanic acid 1,1-dioxide or salt or ester thereof and the beta-lactam antibiotic will normally be in the range from about 1:3 to 3:1. Additionally, when using penicillanic acid 1,1-dioxide or salt or ester thereof readily hydrolyzable *in vivo* in combination with another beta-lactam antibiotic, the daily oral dosage of each component will normally be in the range from about 10 to about 200 mg. per kilogram of body weight and the daily parenteral dosage of each component will normally be about 10 to about 400 mg. per kilogram of body weight. These figures are illustrative only, however, and in some cases it may be necessary to use dosages outside these limits.

Typical beta-lactam antibiotics with which penicillanic acid 1,1-dioxide and its esters readily hydrolyzable *in vivo* can be co-administered are:

- 6-(2-phenylacetamido)penicillanic acid,
- 6-(D-2-amino-2-phenylacetamido)penicillanic acid,
- 6-(2-carboxy-2-phenylacetamido)penicillanic acid, and
- 7-(2-[1-tetrazolyl]acetamido)-3-(2-[5-methyl-1,3,4-thiadiazolyl]thiomethyl)-3-desacetoxymethyl-cephalosporanic acid.

Typical microorganisms against which the antibacterial activity of the above beta-lactam antibiotics is enhanced are:

- Staphylococcus aureus*,
- Haemophilus influenzae*,
- Klebsiella pneumoniae* and
- Bacteroides fragilis*.

As will be appreciated by one skilled in the art, some beta-lactam compounds are effective when administered orally or parenterally, while others are effective only when administered by the parenteral route. When penicillanic acid 1,1-dioxide, a salt or an ester thereof readily hydrolyzable *in vivo*, is to be used simultaneously (i.e. co-mingled) with a beta-lactam antibiotic which is effective only on parenteral

administration, a combination formulation suitable for parenteral use will be required. When the penicillanic acid 1,1-dioxide or ester thereof is to be used simultaneously (co-mingled) with a beta-lactam antibiotic which is effective orally or parenterally, combinations suitable for either oral or parenteral administration can be prepared. Additionally, it is possible to administer preparations of the penicillanic acid 1,1-dioxide or salt or ester thereof orally, while at the same time administering a further beta-lactam antibiotic parenterally; and it is also possible to administer preparations of the penicillanic acid 1,1-dioxide or salt or ester thereof parenterally, while at the same time administering the further beta-lactam antibiotic orally.

Further details concerning the use and synthesis of compounds of the formula I are disclosed in West German Offenlegungsschrift No. 2,824,535.

- 10 The following examples and preparations are provided solely for the purpose of further illustration. 10  
Infrared (IR) spectra were measured as potassium bromide discs (KBr discs), and diagnostic absorption bands are reported in wave numbers ( $\text{cm}^{-1}$ ). Nuclear magnetic resonance spectra (NMR) were measured at 60 MHz for solutions in deuteriochloroform ( $\text{CDCl}_3$ ), perdeutero acetone ( $\text{CD}_3\text{COCD}_3$ ), perdeutero dimethyl sulfoxide ( $\text{DMSO}-d_6$ ) or deuterium oxide ( $\text{D}_2\text{O}$ ), and peak positions are expressed in parts per million (ppm) 15  
15 downfield from tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate. The following abbreviations for peak shapes are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. 15

#### EXAMPLE 1

##### 6- $\alpha$ -Bromopenicillanic Acid 1,1-Dioxide

- 20 To a stirred mixture of 560 ml of water, 300 ml of dichloromethane and 56.0 g of 6- $\alpha$ -bromopenicillanic acid was added 4N sodium hydroxide solution until a stable pH of 7.2 was achieved. This required 55 ml of sodium hydroxide. The mixture was stirred at pH 7.2 for 10 minutes and then it was filtered. The layers were separated and the organic phase was discarded. The aqueous phase was then poured rapidly, with stirring, into an oxidizing mixture which had been prepared as follows. 20

- 25 In a 3 liter flask was mixed 63.2 g of potassium permanganate, 1,000 ml of water and 48.0 g of acetic acid. This mixture was stirred for 15 minutes at 20°C. and then it was cooled to 0°C. 25

- After the 6- $\alpha$ -bromopenicillanic acid solution had been added to the oxidizing mixture, a cooling bath at -15°C. was maintained around the reaction mixture. The internal temperature rose to 15°C. and then fell to 5°C. over a 20 minute period. At this point, 30.0 g of sodium metabisulfite was added with stirring over a 10 minute period at about 10°C. After a further 15 minutes, the mixture was filtered, and the pH of the filtrate was lowered to 1.2 by the addition of 170 ml of 6N hydrochloric acid. The aqueous phase was extracted with chloroform, and then with ethyl acetate. Both the chloroform extracts and the ethyl acetate extracts were dried using anhydrous magnesium sulfate and then they were evaporated *in vacuo*. The chloroform solution afforded 10.0 g. (16% yield) of the title compound. The ethyl acetate solution afforded 57 g. of an oil, which was triturated under hexane. A white solid appeared. It was filtered off, giving 41.5 g. (66% yield) of the title compound, mp 134°C. (dec.). 30  
35

*Analysis:* - Calcd. for  $\text{C}_8\text{H}_9\text{BrNO}_5\text{S}$ : C, 30.78; H, 3.23; Br, 25.60; N, 4.49; S, 10.27%. Found: C, 31.05; H, 3.24; Br, 25.54; N, 4.66; S, 10.21%.

- 40 EXAMPLE 2 40  
Oxidation of 6- $\alpha$ -chloropenicillanic acid and 6- $\alpha$ -iodopenicillanic acid with potassium permanganate, according to the procedure of Example 1, affords 6- $\alpha$ -chloropenicillanic acid 1,1-dioxide and 6- $\alpha$ -iodopenicillanic acid 1,1-dioxide, respectively.

- 45 EXAMPLE 3 45  
6- $\beta$ -Chloropenicillanic Acid 1,1-Dioxide

- An oxidizing solution was prepared from 185 mg. of potassium permanganate, 0.063 ml. of 85% phosphoric acid and 5 ml. of water. This oxidizing solution was added dropwise to a solution of 150 mg. of sodium 6- $\beta$ -chloropenicillanate in 5 ml. of water at 0-5°C., until the purple color of the potassium permanganate persisted. Approximately half of the oxidizing solution was required. At this point, the potassium permanganate color was discharged by the addition of solid sodium bisulfite, and then the reaction mixture was filtered. Ethyl acetate was added to the filtrate and the pH was adjusted to 1.8. The layers were separated and the aqueous layer was further extracted with ethyl acetate. The combined ethyl acetate layers were washed with water, dried and evaporated *in vacuo* to give 118 mg. of the title compound. 50  
55 The NMR spectrum (in  $\text{CD}_3\text{COCD}_3$ ) showed absorption at 5.82 (d, 1H), 5.24 (d, 1H), 4.53 (s, 1H), 1.62 (s, 3H) and 1.50 (s, 3H) ppm. 55

- The above product was dissolved in tetrahydrofuran and an equal volume of water was added. The pH was adjusted to 6.8 using dilute sodium hydroxide, the tetrahydrofuran was removed by evaporation *in vacuo*, and the residual aqueous solution was freeze dried. This afforded the sodium salt of the title compound. 60

- 60 EXAMPLE 4 60  
6- $\beta$ -Bromopenicillanic Acid 1,1-Dioxide

- To a solution of 255 mg. of sodium 6- $\beta$ -bromopenicillanate in 5 ml. of water, at 0 to 5°C., was added a solution prepared from 140 mg. of potassium permanganate, 0.11 ml. of 85% phosphoric acid and 5 ml. of water, at 0 to 5°C. The pH was maintained between 6.0 and 6.4 during the addition. The reaction mixture was 65

stirred at pH 6.3 for 15 minutes, and then the purple solution was covered with ethyl acetate. The pH was adjusted to 1.7 and 330 mg. of sodium bisulfite was added. After 5 minutes, the layers were separated and the aqueous layer was further extracted with ethyl acetate. The combined ethyl acetate solutions were washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo*. This afforded 216 mg. of the title compound as 5 white crystals. The NMR spectrum (in  $\text{D}_2\text{O}$ ) showed absorptions at 5.78 (d, 1H,  $J = 4\text{Hz}$ ), 5.25 (d, 1H,  $J = 4\text{Hz}$ ), 4.20 (s, 1H), 1.65 (s, 3H) and 1.46 (s, 3H) ppm.

## EXAMPLE 5

*6-beta-Iodopenicillanic Acid 1,1-Dioxide*

- 10 Oxidation of 6-beta-iodopenicillanic acid with potassium permanganate, according to the procedure of Example 4, affords 6-beta-iodopenicillanic acid 1,1-dioxide.

## EXAMPLE 6

*Pivaloyloxymethyl 6-alpha-Bromopenicillanate 1,1-Dioxide*

- 15 To a solution of 394 mg. of pivaloyloxymethyl 6-alpha-bromopenicillanate in 10 ml. of dichloromethane is added 400 mg. of 3-chloroperbenzoic acid at 0 to 5°C. The reaction mixture is stirred at 0 to 5°C. for 1 hour and then at 25°C. for 24 hours. The filtered reaction mixture is evaporated to dryness *in vacuo* to give the title compound.

## 20 EXAMPLE 7

The procedure of Example 6 is repeated, except that the pivaloyloxymethyl 6-beta-bromopenicillanate acid is replaced by:

- 3-phthalidyl 6-alpha-chloropenicillanate,  
4-crotonolactonyl 6-beta-chloropenicillanate,  
25 gamma-butyrolacton-4-yl 6-alpha-bromopenicillanate,  
acetoxymethyl 6-beta-bromopenicillanate,  
pivaloyloxymethyl 6-beta-bromopenicillanate,  
hexanoyloxymethyl 6-alpha-iodopenicillanate,  
1-(acetoxylethyl 6-beta-iodopenicillanate,  
30 1-(isobutyryloxy)ethyl 6-alpha-chloropenicillanate,  
1-methyl-1-(acetoxylethyl 6-beta-chloropenicillanate,  
1-methyl-1-(hexanoyloxy)ethyl 6-alpha-bromopenicillanate,  
methoxycarbonyloxymethyl 6-alpha-bromopenicillanate,  
propoxycarbonyloxymethyl 6-beta-bromopenicillanate,  
35 1-(ethoxycarbonyloxy)ethyl 6-alpha-bromopenicillanate,  
1-(butoxycarbonyloxy)ethyl 6-alpha-iodopenicillanate,  
1-methyl-1-(methoxycarbonyloxy)ethyl 6-beta-iodopenicillanate and  
1-methyl-1-(isopropoxycarbonyloxy)ethyl 6-alpha-chloropenicillanate,  
respectively. This affords:  
40 3-phthalidyl 6-alpha-chloropenicillanate 1,1-dioxide,  
4-crotonolactonyl 6-beta-chloropenicillanate 1,1-dioxide,  
gamma-butyrolacton-4-yl 6-alpha-bromopenicillanate 1,1-dioxide,  
acetoxymethyl 6-beta-bromopenicillanate 1,1-dioxide,  
pivaloyloxymethyl 6-beta-bromopenicillanate 1,1-dioxide,  
45 hexanoyloxymethyl 6-alpha-iodopenicillanate 1,1-dioxide,  
1-(acetoxylethyl 6-beta-iodopenicillanate 1,1-dioxide,  
1-(isobutyryloxy)ethyl 6-alpha-chloropenicillanate 1,1-dioxide,  
1-methyl-1-(acetoxylethyl 6-beta-chloropenicillanate 1,1-dioxide,  
1-methyl-1-(hexanoyloxy)ethyl 6-alpha-bromopenicillanate 1,1-dioxide,  
50 methoxycarbonyloxymethyl 6-alpha-bromopenicillanate 1,1-dioxide,  
propoxycarbonyloxymethyl 6-beta-bromopenicillanate 1,1-dioxide,  
1-(ethoxycarbonyloxy)ethyl 6-alpha-bromopenicillanate 1,1-dioxide,  
1-(butoxycarbonyloxy)ethyl 6-alpha-iodopenicillanate 1,1-dioxide,  
1-methyl-1-(methoxycarbonyloxy)ethyl 6-beta-iodopenicillanate 1,1-dioxide and  
55 1-methyl-1-(isopropoxycarbonyloxy)ethyl 6-alpha-chloropenicillanate 1,1-dioxide,  
respectively.

## EXAMPLE 8

*Penicillanic Acid 1,1-Dioxide*

- 60 To 100 ml. of water was added 9.4 g. of 6-alpha-bromopenicillanic acid, 1,1-dioxide, at 22°C., followed by sufficient 4N sodium hydroxide solution to achieve a stable pH of 7.3. To the resulting solution was added 2.25 g. of 5% palladium-on-carbon followed by 6.9 g. of dipotassium phosphate trihydrate. This mixture was then shaken under an atmosphere of hydrogen at a pressure varying from 3.5 to 1.8  $\text{kg/cm}^2$ . When hydrogen uptake ceased, the solids were removed by filtration, and the aqueous solution was covered with 100 ml. of  
65 ethyl acetate. The pH was slowly lowered from 5.0 to 1.5 with 6N hydrochloric acid. The layers were

separated, and the aqueous phase was extracted with further ethyl acetate. The combined ethyl acetate layers were washed with brine, dried using anhydrous magnesium sulfate and evaporated *in vacuo*. The residue was triturated under ether and then the solid material was collected by filtration. This afforded 4.5 g. (65% yield) of the title compound.

- 5 **Analysis:**—Calcd. for  $C_8H_{11}NO_5S$ : C, 41.20; H, 4.75; N, 6.00; S, 13.75%. Found: C, 41.16; H, 4.81; N, 6.11; S, 13.51%. 5

#### EXAMPLE 9

##### *Penicillanic Acid 1,1-Dioxide*

- 10 Hydrogenolysis of each of: 10

6-alpha-chloropenicillanic acid 1,1-dioxide,  
6-alpha-iodopenicillanic acid 1,1-dioxide,  
6-beta-chloropenicillanic acid 1,1-dioxide,  
6-beta-bromopenicillanic acid 1,1-dioxide and

- 15 6-beta-iodopenicillanic acid 1,1-dioxide, 15  
according to the procedure of Example 8, affords penicillanic acid 1,1-dioxide.

#### EXAMPLE 10

##### *Pivaloyloxymethyl Penicillanate 1,1-Dioxide*

- 20 To a solution of 1.0 g. of pivaloyloxymethyl 6-alpha-bromopenicillanate in 10 ml. of methanol is added 3 20  
ml. of 1M sodium bicarbonate and 200 mg. of 10% palladium on carbon. The reaction mixture is shaken  
vigorously under an atmosphere of hydrogen, at a pressure of about 5 kg/cm<sup>2</sup>, until hydrogen uptake ceases.  
The mixture is then filtered and the bulk of the methanol is removed by evaporation *in vacuo*. Water and  
ethyl acetate are added to the residue and the pH is adjusted to 8.5. The layers are separated and the organic  
25 layer is washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. This affords the title compound. 25

#### EXAMPLE 11

Hydrogenolysis of the appropriate 6-halopenicillanic acid ester 1,1-dioxide from Example 7, according to the procedure of Example 10, affords the following compounds:

- 30 3-phthalidyl penicillanate 1,1-dioxide, 30  
4-crotonolactonyl penicillanate 1,1-dioxide,  
gamma-butyrolacton-4-yl penicillanate 1,1-dioxide,  
acetoxymethyl penicillanate 1,1-dioxide,  
pivaloyloxymethyl penicillanate 1,1-dioxide,  
35 hexanoyloxymethyl penicillanate 1,1-dioxide, 35  
1-(acetoxymethyl)ethyl penicillanate 1,1-dioxide,  
1-(isobutyryloxy)ethyl penicillanate 1,1-dioxide,  
1-methyl-1-(acetoxymethyl)ethyl penicillanate 1,1-dioxide,  
1-methyl-1-(hexanoyloxy)ethyl penicillanates 1,1-dioxide,  
40 methoxycarbonyloxymethyl penicillanate 1,1-dioxide, 40  
propoxycarbonyloxymethyl penicillanate 1,1-dioxide,  
1-(ethoxycarbonyloxy)ethyl penicillanate 1,1-dioxide,  
1-(butoxycarbonyl)ethyl penicillanate 1,1-dioxide,  
1-methyl-1-(methoxycarbonyloxy)ethyl penicillanate 1,1-dioxide and  
45 1-methyl-1-(isopropoxycarbonyloxy)ethyl penicillanate 1,1-dioxide, 45  
respectively.

#### EXAMPLE 12

##### *Pivaloyloxymethyl 6-Alpha-bromopenicillanate 1,1-Dioxide*

- 50 An oxidizing solution was prepared by combining 4.26 g. of potassium permanganate, 2.65 g. of 85% 50  
phosphoric acid and 40 ml of water. The mixture was stirred for one hour, and then it was added slowly,  
during 20 minutes, at 5 to 10°C., to a stirred solution of 5.32 g. of pivaloyloxymethyl 6-alpha-  
bromopenicillanate in 70 ml. of acetone and 10 ml. of water. The mixture was stirred at 5°C. for 30 minutes,  
and 100 ml. of ethyl acetate was added. After a further 30 minutes, a solution of 3.12 g. of sodium bisulfite in  
55 30 ml. of water was added during 15 minutes at about 10°C. Stirring was continued for another 30 minutes at 55  
5°C., and then the mixture was filtered. The organic phase was separated and washed with saturated sodium  
chloride solution. The dried organic layer was evaporated to give 5.4 g. of the title compound as an oil, which  
slowly crystallized. The NMR spectrum (in CDCl<sub>3</sub>) showed absorptions at 5.80 (q, 2H), 5.15 (d, 1H), 4.75 (d,  
1H), 4.50 (s, 1H), 1.60 (s, 3H), 1.40 (s, 3H) and 1.20 (s, 9H) ppm.

- 60 60

#### EXAMPLE 13

##### *Pivaloyloxymethyl Penicillanate 1,1-Dioxide*

- A solution of 4.4 g. of pivaloyloxymethyl 6-alpha-bromopenicillanate 1,1-dioxide in 60 ml. of tetrahydrofur-  
an was added to 0.84 g. of sodium bicarbonate in 12 ml. of water. The solution was shaken under an  
65 atmosphere of hydrogen in the presence of 2.0 g. of 5% palladium on carbon at 47 to 51 psig. The reaction 65

mixture was then filtered and the residue was washed with 100 ml. of ethyl acetate and 25 ml. of water. The combined filtrate and washes were separated. The organic layer was washed with saturated sodium chloride, and dried ( $\text{MgSO}_4$ ), and evaporated affording the title compound as an oil. This oil was dissolved in ethyl acetate (20 ml.). To the solution was added hexane (100 ml.) slowly, and the precipitate was filtered off.

5 Yield: 2.4 g. The NMR spectrum (in  $\text{DMSO-d}_6$ ) showed absorptions at 5.75 (q, 2H), 5.05 (m, 1H), 4.40 (s, 1H), 3.95 - 2.95 (m, 2H), 1.40 (s, 3H), 1.25 (s, 3H) and 1.10 (s, 9H) ppm.

#### EXAMPLE 14

##### 2,2,2-Trichloroethyl 6- $\alpha$ -Bromopenicillanate 1,1-Dioxide

10 2,2,2-Trichloroethyl 6- $\alpha$ -bromopenicillanate was oxidized with potassium permanganate substantially according to the procedure of Example 12 to give the title compound in 79% yield. The NMR spectrum of the product (in  $\text{CDCl}_3$ ) showed absorptions at 5.30 to 4.70 (m, 4H), 4.60 (s, 1H), 1.70 (s, 3H) and 1.50 (s, 3H) ppm.

#### EXAMPLE 14A

##### 15 Penicillanic Acid 1,1-Dioxide

To a stirred slurry of 6.5 g. of zinc powder in 100 ml. of a 70:30 glacial acetic acid - tetrahydrofuran mixture, was added, portionwise during 5 minutes, 4.0 g. of 2,2,2-trichloroethyl 6- $\alpha$ -bromopenicillanate 1,1-dioxide. The mixture was stirred at ambient temperature for 3 hours, and then it was filtered. The filtrate was concentrated to a volume of 10 ml. and the tan solution was fixed with 50 ml. of water and 100 ml. of ethyl acetate. The pH was adjusted to 1.3 and the layers were separated. The organic phase was washed with saturated sodium chloride solution, dried using magnesium sulfate, and then concentrated to dryness *in vacuo*. The residue was triturated under ether for 20 minutes. This afforded 553 mg. of the title compound as a solid. The NMR spectrum (in  $\text{CDCl}_3/\text{DMSO-d}_6$ ) showed absorptions at 11.2 (broad s, 1H), 4.65 (m, 1H), 4.30 (s, 1H), 3.40 (m, 2H), 1.65 (s, 3H) and 1.50 (s, 3H) ppm.

#### EXAMPLE 15

##### Benzyl 6- $\alpha$ -Bromopenicillanate 1,1-Dioxide

Benzyl 6- $\alpha$ -bromopenicillanate was oxidized with potassium permanganate substantially according to the procedure of Example 12, to give the title compound in 94% yield. The NMR spectrum (in  $\text{CDCl}_3$ ) showed absorptions at 7.35 (s, 5H), 5.10 (m, 3H), 4.85 (m, 1H), 4.40 (s, 1H), 1.50 (s, 3H) and 1.25 (s, 3H) ppm.

#### EXAMPLE 16

##### Penicillanic Acid 1,1-Dioxide

A solution of 4.0 g. of benzyl 6- $\alpha$ -bromopenicillanate 1,1-dioxide in 50 ml. of tetrahydrofuran was combined with a solution of 1.06 g. of sodium bicarbonate in 50 ml. of water. To the mixture was added 2.0 g. of a 50% suspension of 5% palladium-on-carbon in water, then this mixture was shaken under an atmosphere of hydrogen, at a pressure of 46.5 to 50 psig. for 20 minutes. The catalyst was removed by filtration, and then 30 ml. of tetrahydrofuran and 3.0 g. of a 50% suspension of 5% palladium-on-carbon were added. The resulting mixture was shaken under an atmosphere of hydrogen, at pressure of from 42 to 45 psig., for 65 minutes. The reaction mixture was then filtered and the tetrahydrofuran was removed by evaporation. Ethyl acetate was added to the aqueous residue and the pH was adjusted to 7.1. The ethyl acetate layer was removed, and fresh ethyl acetate was added to the remaining aqueous phase. The pH was lowered to 1.5, and the layers were separated. The aqueous phase was further extracted with ethyl acetate, and the combined ethyl acetate solutions were washed with saturated sodium chloride solution and dried ( $\text{MgSO}_4$ ). Evaporation *in vacuo* gave a gum which was triturated under ether. This afforded 31 mg. of penicillanic acid 1,1-dioxide as a yellow solid. The NMR spectrum (in  $\text{CDCl}_3/\text{DMSO-d}_6$ ) showed absorption at 9.45 (broad s, 1H), 4.60 (t, 1H), 4.25 (s, 1H), 3.40 (d, 2H), 1.65 (s, 3H) and 1.30 (s, 3H) ppm.

#### EXAMPLE 17

##### 50 6,6-Dibromopenicillanic Acid 1,1-Dioxide

To the dichloromethane solution of 6,6-dibromopenicillanic acid from Preparation K was added 300 ml. of water, followed by the dropwise addition over a period of 30 minutes of 105 ml. of 3N sodium hydroxide. The pH stabilized at 7.0. The aqueous layer was removed and the organic layer was extracted with water ( $2 \times 100$  ml). To the combined aqueous solutions was added, at  $-5^\circ\text{C}$ , a premixed solution prepared from 59.25 g of potassium permanganate, 18 ml of concentrated phosphoric acid and 600 ml of water, until the pink color of the permanganate persisted. The addition took 50 minutes and 550 ml of oxidant were required. At this point 500 ml of ethyl acetate was added and then the pH was lowered to 1.23 by the addition of 105 ml of 6N hydrochloric acid. Then 250 ml of 1M sodium bisulfite was added during 10-15 minutes at *ca.*  $10^\circ\text{C}$ . During the addition of the sodium bisulfite solution the pH was maintained at 1.25-1.35 using 6N hydrochloric acid. The aqueous phase was saturated with sodium chloride and the two phases were separated. The aqueous solution was extracted with additional ethyl acetate ( $2 \times 150$  ml) and the combined ethyl acetate solutions were washed with brine and dried ( $\text{MgSO}_4$ ). This afforded an ethyl acetate solution of 6,6-dibromopenicillanic acid 1,1-dioxide.

The 6,6-dibromopenicillanic acid 1,1-dioxide can be isolated by removal of the solvent *in vacuo*. A sample so isolated from an analogous preparation had a melting point of  $201^\circ\text{C}$  (dec.). The NMR spectrum

(CDCl<sub>3</sub>/DMSO-d<sub>6</sub>) showed absorptions at 9.35 (s, 1H), 5.30 (s, 1H), 4.42 (s, 1H), 1.63 (s, 3H) and 1.50 (s, 3H) ppm. The IR spectrum (KBr disc) showed absorptions at 3846-2500, 1818, 1754, 1342 and 1250-1110 cm<sup>-1</sup>.

#### EXAMPLE 18

##### 5 6-Chloro-6-iodopenicillanic Acid 1,1-Dioxide

To a solution of 4.9g of 6-chloro-6-iodopenicillanic acid in 50 ml of dichloromethane was added 50 ml of water and then the pH was raised to 7.2 using 3N sodium hydroxide. The layers were separated and the aqueous layer was cooled to 5°C. To this solution was then added, dropwise, over a 20 minute period, a premixed solution prepared from 2.61g of potassium permanganate, 1.75 ml of concentrated phosphoric acid and 50 ml of water. The pH was maintained at 6, and the temperature was maintained below 10°C, during the addition. At this point, 100 ml of ethyl acetate was added and the pH was adjusted to 1.5. To the mixture was then added 50 ml of 10% sodium bisulfite, keeping the temperature below 10°C and the pH at ca 1.5 by the addition of 6N hydrochloric acid. The pH was lowered to 1.25 and the layers were separated. The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate. The combined organic solutions were washed with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give 4.2g of the title compound, mp 143-145°C. The NMR spectrum (CDCl<sub>3</sub>) showed absorptions at 4.86 (s, 1H), 4.38 (s, 1H), 1.60 (s, 3H) and 1.43 (s, 3H) ppm. The IR spectrum (KBr disc) showed absorptions at 1800, 1740 and 1250-1110 cm<sup>-1</sup>.

#### 20 EXAMPLE 19

##### 6-Bromo-6-iodopenicillanic Acid 1,1-Dioxide

To a solution of 6.0 g. of 6-bromo-6-iodopenicillanic acid in 50 ml of dichloromethane was added 50 ml of water. The pH was raised to 7.3 using 3N sodium hydroxide and the aqueous layer was removed. The organic layer was extracted with 10 ml of water. The combined aqueous phases were cooled to 5°C, and a premixed solution of 284g of potassium permanganate in 2 ml of concentrated phosphoric acid and 50 ml of water was added dropwise, between 5 and 10°C. The addition took 20 minutes. At this point, 50 ml of ethyl acetate was added and the pH of the mixture was lowered to 1.5 using 6N hydrochloric acid. To this two-phase system was added, dropwise, 50 ml of 10% sodium bisulfite, maintaining the pH at about 1.5 by the addition of 6N hydrochloric acid. An additional 50 ml of ethyl acetate was added, and then the pH was lowered to 1.23. The layers were separated and the aqueous layer was saturated with sodium chloride. The saturated solution was extracted with ethyl acetate (3 x 50 ml) and the combined ethyl acetate layers were washed with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The residue was dried under high vacuum, leaving 4.2g of the title compound, mp 145-147. The NMR spectrum (CDCl<sub>3</sub>) showed absorptions at 4.90 (s, 1H), 4.30 (s, 1H), 1.60 (s, 3H) and 1.42 (s, 3H) ppm. The IR spectrum (KBr disc) showed absorptions at 1800, 1740, 1330 and 1250-1110 cm<sup>-1</sup>.

#### EXAMPLE 20

##### 6-Chloro-6-bromopenicillanic Acid 1,1-Dioxide

Oxidation of 6-chloro-6-bromopenicillanic acid with potassium permanganate, according to the procedure of Example 19, affords 6-chloro-6-bromopenicillanic acid 1,1-dioxide.

#### EXAMPLE 21

##### Penicillanic Acid 1,1-Dioxide

The ethyl acetate solution of 6,6-dibromopenicillanic acid 1,1-dioxide from Example 17 was combined with 705 ml of saturated sodium bicarbonate solution and 8.88g of 5% palladium-on-carbon catalyst. The mixture was shaken under an atmosphere of hydrogen, at a pressure of about 5 kg/cm<sup>2</sup> for about 1 hour. The catalyst was removed by filtration, and the pH of the aqueous phase of the filtrate was adjusted to 1.2 with 6N hydrochloric acid. The aqueous phase was saturated with sodium chloride. The layers were separated and the aqueous phase was extracted with further ethyl acetate (3 x 200 ml). The combined ethyl acetate solutions were dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to afford 33.5g (58% yield from 6-aminopenicillanic acid) of penicillanic acid 1,1-dioxide. This product was dissolved in 600 ml of ethyl acetate, the solution was decolorized using activated carbon and the solvent was removed by evaporation *in vacuo*. The product was washed with hexane. This afforded 31.0g of pure product.

#### 55 EXAMPLE 22

Hydrogenolysis of each of 6-chloro-6-iodopenicillanic acid 1,1-dioxide, 6-bromo-6-iodopenicillanic acid and 6-chloro-6-bromopenicillanic acid, respectively, according to the procedure of Example 21, affords, in each case, penicillanic acid 1,1-dioxide.

#### 60 EXAMPLE 23

##### Penicillanic Acid 1,1-Dioxide

To a stirred suspension of 786 mg of 6-chloro-6-iodopenicillanic acid 1,1-dioxide in 10 ml of benzene was added 0.3 ml of triethylamine followed by 0.25 ml of trimethylsilyl chloride, at ca 0°C. Stirring was continued for 5 minutes at ca 0°C and then at the reflux temperature of the solvent for 30 minutes. The reaction mixture was cooled to 25°C and the precipitated material was removed by filtration. The filtrate was cooled to ca 0°C

and 1.16g of tri-*n*-butyltin hydride and a few milligrams of azobisisobutyronitrile were added. The reaction mixture was stirred and irradiated with ultraviolet light for 1 hour at *ca* 0°C and then for 3.5 hours at the reflux temperature of the solvent. A further quantity of tri-*n*-butyltin hydride (1.1 ml) and a catalytic amount of azobisisobutyronitrile were added and stirring and irradiation at the reflux temperature were continued for 5 an additional 1 hour. The reaction mixture was then poured into 50 ml of cold 5% sodium bicarbonate and the two-phase system was stirred for 30 minutes. Ethyl acetate (50 ml) was added and the pH was adjusted to 1.5 with 6*N* hydrochloric acid. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined ethyl acetate solutions were washed with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The residue was triturated under hexane and then recovered by filtration. This afforded 0.075 mg of 10 the title.

#### EXAMPLE 24

##### *Penicillanic Acid 1,1-Dioxide*

To a stirred suspension of 0.874g of 6-bromo-6-iodopenicillanic acid 1,1-dioxide in 10 ml of benzene at *ca* 15 5°C, was added 0.3 ml of triethylamine followed by 0.25 ml of trimethylsilyl chloride. Stirring was continued at *ca* 5°C for 5 minutes and then for 30 minutes at the reflux temperature of the solvent. The reaction mixture was cooled to room temperature and the solids were removed by filtration. The filtrate was cooled to *ca* 5°C, and 1.05 ml of tri-*n*-butyltin hydride and a catalytic amount of azobisisobutyronitrile were added. The mixture was irradiated with ultraviolet light for 1 hour at *ca* 5°C, and then it was poured into 30 ml of cold 5% 20 sodium bicarbonate. The mixture was stirred for 30 minutes and then 50 ml of ethyl acetate were added. The mixture was acidified to pH 1.5 and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 25 ml) and the combined ethyl acetate layers were washed with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The residue was dried under high vacuum and the 30 ml of hexane was added. The insoluble material was recovered by filtration, affording 0.035g of the title compound.

#### EXAMPLE 25

##### *Pivaloyloxymethyl 6,6-Dibromopenicillanate 1,1-Dioxide*

To a solution of 4.73g of pivaloyloxymethyl 6,6-dibromopenicillanate in 15 ml of dichloromethane is added 3.80 g of 3-chloroperbenzoic acid at 0 to 5°C. The reaction mixture is stirred at 0 to 5°C for 1 hour and then at 30 25°C for 24 hours. The filtered reaction mixture is evaporated to dryness *in vacuo* and the residue is partitioned between ethyl acetate and water. The pH of the aqueous phase is adjusted to 7.5, and the layers are separated. The ethyl acetate phase is dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to give the title compound.

#### EXAMPLE 26

35 Oxidation of each of the 6,6-dihalopenicillanic acid esters of Preparation P using 3-chloro-perbenzoic acid, according to the procedure of Example 25, affords the following compounds:

- 3-phthalidyl 6,6-dibromopenicillanate 1,1-dioxide,
- 4-crotonolactonyl 6-chloro-6-iodopenicillanate, 1,1-dioxide,
- γ-butyrolactonyl 6-bromo-6-iodopenicillanate 1,1-dioxide,
- 40 acetoxymethyl 6-chloro-6-bromopenicillanate 1,1-dioxide,
- pivaloyloxymethyl 6-chloro-6-iodopenicillanate 1,1-dioxide,
- hexanoyloxymethyl 6,6-dibromopenicillanate 1,1-dioxide,
- 1-(acetoxylethyl) 6,6-dibromopenicillanate 1,1-dioxide,
- 1-(isobutyryloxy)ethyl 6-bromo-6-iodopenicillanate 1,1-dioxide,
- 45 1-methyl-1-(acetoxylethyl) 6,6-dibromopenicillanate 1,1-dioxide,
- 1-methyl-1-(hexanoyloxy)ethyl 6-chloro-6-bromopenicillanate,
- methoxycarbonyloxymethyl 6,6-dibromopenicillanate 1,1-dioxide,
- propoxycarbonyloxymethyl 6-chloro-6-iodopenicillanate 1,1-dioxide,
- 1-(ethoxycarbonyloxy)ethyl 6,6-dibromopenicillanate 1,1-dioxide,
- 50 1-(butoxycarbonyloxy)ethyl 6-bromo-6-iodopenicillanate 1,1-dioxide,
- 1-methyl-1-(methoxycarbonyloxy)ethyl 6,6-dibromopenicillanate 1,1-dioxide and
- 1-methyl-1-(isopropoxycarbonyloxy)ethyl 6,6-dibromopenicillanate 1,1-dioxide, respectively.

#### EXAMPLE 27

##### *Pivaloyloxymethyl Penicillanate 1,1-Dioxide*

To a solution of 1.0g of pivaloyloxymethyl 6,6-dibromopenicillanate 1,1-dioxide in 10 ml of methanol is added 3 ml of 1*M* sodium bicarbonate and 200 mg of 10% palladium on carbon. The reaction mixture is shaken vigorously under an atmosphere of hydrogen, at a pressure of about 5 kg/cm<sup>2</sup>, until hydrogen uptake ceases. The mixture is then filtered and the bulk of the methanol is removed by evaporation *in vacuo*. Water 60 and ethyl acetate are added to the residue and the pH is adjusted to 8.5. The layers are separated and the organic layer is washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. This affords pivaloyloxymethyl penicillanate 1,1-dioxide.

#### EXAMPLE 28

65 Hydrogenolysis of each of the 6,6-dihalo-penicillanic acid ester 1,1-dioxides from Example 26, according to

the procedure of Example 27, affords the following compounds:

- 3-phthalidyl penicillanate 1,1-dioxide,
- 4-crotonolactonyl penicillanate 1,1-dioxide,
- gamma-butyrolacton-4-yl penicillanate 1,1-dioxide,
- 5 acetoxymethyl penicillanate 1,1-dioxide, 5
- pivaloyloxymethyl penicillanate 1,1-dioxide,
- hexanoyloxymethyl penicillanate 1,1-dioxide,
- 1-(acetoxymethyl)ethyl penicillanate 1,1-dioxide,
- 1-(isobutyryloxy)ethyl penicillanate 1,1-dioxide,
- 10 1-methyl-(acetoxymethyl)ethyl penicillanate 1,1-dioxide, 10
- 1-methyl-1-(hexanoyloxy)ethyl penicillanate 1,1-dioxide,
- methoxycarbonyloxymethyl penicillanate 1,1-dioxides,
- propoxycarbonyloxymethyl penicillanate 1,1-dioxide,
- 1-(ethoxycarbonyloxy)ethyl penicillanate 1,1-dioxide,
- 15 1-(butoxycarbonyl)ethyl penicillanate 1,1-dioxide, 15
- 1-methyl-1-(methoxycarbonyloxy)ethyl penicillanate 1,1-dioxide and
- 1-methyl-1-(isopropoxycarbonyloxy)ethyl penicillanate 1,1-dioxide, respectively.

#### EXAMPLE 29

##### 20 Pivaloyloxymethyl 6,6-Dibromopenicillanate 1,1-Dioxide 20

- A stirred solution of 3.92g of 6,6-dibromopenicillanic acid 1,1-dioxide in 20 ml of *N,N*-dimethylformamide was cooled to 0°C and then 1.29g of diisopropylethylamine was added. This was followed by 1.51g of chloromethyl pivalate. This reaction mixture was stirred at 0°C for 3 hours, and then at room temperature for 16 hours. The reaction mixture was then diluted with 25 ml of ethyl acetate and 25 ml of water. The layers 25 were separated and the aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layers 25 were washed with cold 5% sodium bicarbonate solution, water and brine. The ethyl acetate solution was then treated with an activated charcoal, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to a brown oil weighing 2.1g. This oil was chromatographed on 200g of silica gel, using dichloromethane as eluant. The fractions containing the desired product were combined and rechromatographed on silica gel to give 0.025g 30 of the title compound. The NMR spectrum (CDCl<sub>3</sub>) showed absorptions at 6.10 (q, 2H), 5.00 (s, 1H), 4.55 (s, 30 1H), 1.60 (s, 3H), 1.50 (s, 3H), and 1.15 (s, 9H) ppm.

#### EXAMPLE 30

##### Pivaloyloxymethyl Penicillanate 1,1-Dioxide

- 35 To a stirred solution of 60 mg. of pivaloyloxymethyl 6,6-dibromopenicillanate 1,1-dioxide in 5 ml of 35 benzene was added 52 µl of tri-*n*-butyltin hydride followed by a catalytic amount of azobisisobutyronitrile. The reaction mixture was cooled to ca 5°C, and then it was irradiated with ultraviolet light for 1 hour. The reaction mixture was poured into 20 ml of cold 5% sodium bicarbonate and stirred for 30 minutes. Ethyl acetate was added and the pH of the aqueous phase was adjusted to 7.0. The layers were separated, and the 40 aqueous phase was further extracted with ethyl acetate. The combined ethyl acetate solutions were washed 40 with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The residue was dried under high vacuum for 30 minutes. This afforded 70 mg of a yellow oil which was shown by NMR spectroscopy to contain the title compound, together with some impurities containing *n*-butyl groups.

#### 45 EXAMPLE 31 45

##### 6,6-Dibromopenicillanic Acid 1,1-Dioxide

To a solution of 359 mg of 6,6-dibromopenicillanic acid in 30 ml of dichloromethane is added 380 mg of 3-chloroperbenzoic acid at 0-5°C. The reaction mixture is stirred at 0-5°C, for 30 minutes and then at 25°C for 24 hours. The filtered reaction mixture is evaporated *in vacuo* to give the title compound.

50

#### EXAMPLE 32

##### Benzyl 6,6-Dibromopenicillanate 1,1-Dioxide

- A mixture of 10.0g. of 6,6-dibromopenicillanic acid 1,1-dioxide, 2.15 g. of sodium bicarbonate, 3.06 ml. of benzyl bromide and 100 ml. of *N,N*-dimethylformamide was stirred at ambient temperature overnight. Most 55 of the solvent was removed by evaporation *in vacuo* and the residue was partitioned between ethyl acetate 55 and water. The organic layer was removed, washed with 1*N* hydrochloric acid and with saturated sodium chloride, and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation *in vacuo* afforded 11.55 g. of the title compound. The NMR spectrum (in CDCl<sub>3</sub>) showed absorptions at 7.40 (s, 5H), 5.30 (m, 2H), 4.95 (s, 1H), 4.55 (s, 1H), 1.50 (s, 3H) and 1.20 (s, 3H) ppm.

60

#### EXAMPLE 33

##### Penicillanic Acid 1,1-Dioxide

- To a solution of 2.0 g. of benzyl 6,6-dibromopenicillanate 1,1-dioxide in 50 ml. of tetrahydrofuran was added a solution of 0.699 g. of sodium bicarbonate in 50 ml. of water, followed by 2.0 g. of 5% 65 palladium-on-carbon. This mixture was then shaken under an atmosphere of hydrogen, at about 50 psig., for 65

70 minutes. The tetrahydrofuran was removed by evaporation, and the residue was partitioned between ethyl acetate and water at pH 7.37. The aqueous layer was removed and fresh ethyl acetate was added. The pH was lowered to 1.17 and the ethyl acetate was removed and washed with saturated sodium chloride solution. Evaporation *in vacuo* gave 423 mg. of the title product.

#### EXAMPLE 34

##### 2,2,2-Trichloroethyl 6,6-Dibromopenicillanate 1,1-Dioxide

The title compound was prepared from 6,6-dibromopenicillanic acid 1,1-dioxide and 2,2,2-trichloroethyl chloroformate, substantially according to the procedure of Preparation J. The product was purified by chromatography on silica gel. The NMR spectrum of the product (in  $\text{CDCl}_3$ ) showed absorptions at 4.85 (m, 2H), 1.65 (s, 3H) and 1.45 (s, 3H) ppm.

#### EXAMPLE 35

##### Penicillanic Acid 1,1-Dioxide

2,2,2-Trichloroethyl 6,6-dibromopenicillanate 1,1-dioxide was reduced with zinc dust in a mixture of glacial acetic acid and tetrahydrofuran, substantially according to Example 14A. The yield was 27%.

#### EXAMPLE 36

##### 1-(Ethoxycarbonyloxy)ethyl 6,6-Dibromopenicillanate 1,1-Dioxide

A mixture of 2.26 g. of 6,6-dibromopenicillanic acid 1,1-dioxide, 1.02 ml. of 1-(ethoxycarbonyloxy)-ethyl chloride, 1.32 ml. of diisopropylethylamine and 10 ml. of *N,N*-dimethylformamide was stirred at room temperature for 28 hours. The reaction mixture was diluted with 100 ml. of ethyl acetate, and then it was washed sequentially with water, dilute hydrochloric acid, saturated sodium bicarbonate and saturated sodium chloride. The dried ethyl acetate solution was evaporated *in vacuo* to give 1.50 g. of an oil which was chromatographed on silica gel. This afforded 353 mg. of the title compound contaminated with some 1-(ethoxycarbonyloxy)ethyl 6-bromopenicillanate.

#### EXAMPLE 37

##### 1-(Ethoxycarbonyloxy)ethyl Penicillanate 1,1-Dioxide

A portion (230 mg.) of the product of Example 36 was dissolved in 10 ml. of toluene. To this was added 0.4 ml. of tri-*n*-butyltin hydride, followed by 0.164 g. of azobisisobutyronitrile, and the mixture was heated to 70-80°C. for 3.5 hours. The solvent was removed by evaporation *in vacuo*, and the residue was dissolved in 25 ml. of acetonitrile. The acetonitrile solution was washed with hexane several times, and then it was evaporated *in vacuo*. The residue was dissolved in ether, and the ether solution was washed with 5% potassium fluoride and followed by saturated sodium chloride. The dried ( $\text{Na}_2\text{SO}_4$ ) ether solution was evaporated *in vacuo*, and the residue was chromatographed on silica gel, to give 0.043 g. of the title product. The NMR spectrum (in  $\text{CDCl}_3$ ) showed absorptions at 6.75 (m), 4.60 (m), 4.30 (m), 4.15 (s), 4.00 (s), 3.30 (d) and 1.75-1.00 (m) ppm.

#### 40 PREPARATION A

##### 6-Chloro-6-iodopenicillanic Acid

To 3.38 g. of iodine monochloride in 30 ml. of dichloromethane was added, with stirring, at 0-5°C., 11.1 ml. of 2.5N sulfuric acid, followed by 1.92 g. of sodium nitrite. At this point, 3.00 g. of 6-amino-penicillanic acid was added all at once, and stirring was continued for 30 minutes at 0-5°C. To the reaction mixture was then added 22.8 ml. of 1M sodium sulfite solution in portions, and the layers were separated. The aqueous layer was washed with further dichloromethane, and then all the organic phases were washed with saturated sodium chloride. The dichloromethane solution was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated *in vacuo* giving 3.48 g. of the title compound.

The above product was dissolved in 30 ml. of tetrahydrofuran, and then 30 ml. of water were added. The pH was adjusted to 6.8 with dilute sodium hydroxide and the tetrahydrofuran was removed *in vacuo*. The remaining aqueous phase was freeze-dried and the residue was washed with diethyl ether. This afforded 3.67 g. of the title compound as its sodium salt.

#### PREPARATION B

##### 55 6-beta-Chloropenicillanic Acid

A 2.95 g. sample of sodium 6-chloro-6-iodopenicillanic acid was converted to the free acid, and then it was dissolved in 125 ml. of benzene under nitrogen. To the solution was added 1.08 ml. of triethylamine, and the mixture was cooled to 0-5°C. To the cooled mixture was then added 0.977 ml. of trimethylsilyl chloride, and the reaction mixture was stirred at 0-5°C, for 5 minutes, at 25°C, for 60 minutes and at 50°C, for 30 minutes.

The reaction mixture was cooled to 25°C. and the triethylamine hydrochloride was removed by filtration. To the filtrate was added 15 mg. of azobisisobutyronitrile, followed by 2.02 ml. of tri-*n*-butyltin hydride. The mixture was then irradiated with ultraviolet light for 15 minutes with cooling to maintain at temperature of ca. 20°C. The solvent was then removed by evaporation *in vacuo*, and the residue was dissolved in a 1:1 mixture of tetrahydrofuran-water. The pH was adjusted to 7.0 and the tetrahydrofuran was removed by evaporation *in vacuo*. The aqueous phase was washed with ether, and then an equal volume of ethyl acetate was added.

The pH was adjusted to 1.8 and the ethyl acetate layer was removed. The aqueous phase was extracted with further ethyl acetate, and then the combined ethyl acetate solutions were dried and evaporated *in vacuo*. This afforded 980 mg. of 6-beta-chloropenicillanic acid.

The above product was dissolved in tetrahydrofuran, and an equal volume of water was added. The pH was adjusted to 6.8, and the tetrahydrofuran was removed by evaporation *in vacuo*. The aqueous phase remaining was freeze-dried to give 850 mg. of sodium 6-beta-chloropenicillanate. The NMR spectrum (D<sub>2</sub>O) showed absorption at 5.70 (d, 1H, J = 4Hz), 5.50 (d, 1H, J = 4Hz), 4.36 (s, 1H), 1.60 (s, 3H) and 1.53 (s, 3H) ppm.

#### PREPARATION C

##### 10 6-beta-Bromopenicillanic Acid

A mixture of 5.0 g. of 6,6-dibromopenicillanic acid, 1.54 ml. of triethylamine and 100 ml. of benzene was stirred under nitrogen until a solution was obtained. The solution was cooled to 0-5°C., and 1.78 ml. of trimethylsilyl chloride was added. The reaction mixture was stirred at 0-5°C. for 2-3 minutes, and then at 50°C. for 35 minutes. The cooled reaction mixture was filtered and the filtrate was cooled to 0-5°C. A small quantity of azobisisobutyronitrile was added followed by 3.68 ml. of tri-*n*-butyltin hydride. The reaction flask was irradiated with ultraviolet light for 15 minutes, and then the reaction was stirred at *ca.* 25°C. for 1.75 hours. The reaction mixture was irradiated again for 15 minutes and then stirring was continued 2.5 hours. At this point a further small quantity of azobisisobutyronitrile was added, followed by 0.6 ml. of tri-*n*-butyltin hydride (0.6 ml.), added and the mixture was again irradiated for 30 minutes. The solvent was then removed by evaporation *in vacuo*, and to the residue was added 5% sodium bicarbonate solution and diethyl ether. The two-phase system was shaken vigorously for 10 minutes and then the pH was adjusted to 2.0. The ether layer was removed, dried and evaporated *in vacuo* to give 2.33 g. of an oil. The oil was converted into a sodium salt by adding water containing 1 equivalent of sodium bicarbonate followed by freeze drying the solution thus obtained. The afforded sodium 6-beta-bromopenicillanate, contaminated with a small amount of the alpha-isomer.

The sodium salt was purified by chromatography on Sephadex LH-20, combined with some further material of the same quality and re-chromatographed. The NMR spectrum (D<sub>2</sub>O) of the product thus obtained showed absorptions at 5.56 (s, 2H), 4.25 (s, 1H), 1.60 (s, 3H) and 1.50 (s, 3H) ppm.

#### 30 PREPARATION D

##### 6-beta-Iodopenicillanic Acid

The title compound is prepared by reduction of 6,6-diiodopenicillanic acid, with tri-*n*-butyltin hydride, according to the procedure of Preparation B.

#### 35 PREPARATION E

##### Pivaloyloxymethyl 6-alpha-Bromopenicillanate

To a solution of 280 mg. of 6-alpha-bromopenicillanic acid in 2 ml. of *N,N*-dimethylformamide is added 260 mg. of diisopropylethylamine followed by 155 mg. of chloromethyl pivalate and 15 mg. of sodium iodide. The reaction mixture is stirred at room temperature for 24 hours, and then it is diluted with ethyl acetate and water. The pH is adjusted to 7.5, and then the ethyl acetate layer is separated and washed three times with water and once with saturated sodium chloride solution. The ethyl acetate solution is then dried using anhydrous sodium sulfate, and evaporated *in vacuo* to give the title compound.

#### PREPARATION F

Reaction of the appropriate 6-halopenicillanic acid with 3-phthalidyl chloride, 4-crotonolactonyl chloride, gamma-butyrolacton-4-yl chloride or the requisite alkanoyloxymethyl chloride, 1-(alkanoyloxy)ethyl chloride, 1-methyl-1-(alkanoyloxy)ethyl chloride, alkoxycarbonyloxymethyl chloride, 1-(alkoxycarbonyloxy)ethyl chloride or 1-methyl-1-(alkoxycarbonyloxy)ethyl chloride, according to the procedure of Preparation E, affords the following compounds:

- 50 3-phthalidyl 6-alpha-chloropenicillanate,
- 4-crotonolactonyl 6-beta-chloropenicillanate,
- gamma-butyrolacton-4-yl 6-alpha-bromopenicillanate,
- acetoxymethyl 6-beta-bromopenicillanate,
- pivaloyloxymethyl 6-beta-bromopenicillanate,
- 55 hexanoyloxymethyl 6-alpha-iodopenicillanate,
- 1-(acetoxymethyl)ethyl 6-beta-iodopenicillanate,
- 1-(isobutyryloxy)ethyl 6-alpha-chloropenicillanate,
- 1-methyl-1-(acetoxymethyl)ethyl 6-beta-chloropenicillanate,
- 1-methyl-1-(hexanoyloxy)ethyl 6-alpha-bromopenicillanate,
- 60 methoxycarbonyloxymethyl 6-alpha-bromopenicillanate,
- propoxycarbonyloxymethyl 6-beta-bromopenicillanate,
- 1-(ethoxycarbonyloxy)ethyl 6-alpha-bromopenicillanate,
- 1-butoxycarbonyloxyethyl 6-alpha-iodopenicillanate,
- 1-methyl-1-(methoxycarbonyloxy)ethyl 6-beta-iodopenicillanate, and
- 65 1-methyl-1-(isopropoxycarbonyloxy)ethyl 6-alpha-chloropenicillanates,



respectively.

#### PREPARATION G

##### 6,6-Diiodopenicillanic Acid

- 5 A mixture of 15.23 g. of iodine, 10 ml. of 2.5N sulfuric acid, 2.76 g. of sodium nitrite and 75 ml. of dichloromethane was stirred at 5°C., and 4.32 g. of 6-aminopenicillanic acid were added over a period of 15 minutes. Stirring was continued at 5-10°C. for 45 minutes after the addition was complete, and then 100 ml. of 10% sodium bisulfite was added dropwise. The layers were separated, and the aqueous layer was further extracted with dichloromethane. The combined dichloromethane layers were washed with brine, dried 10 (MgSO<sub>4</sub>) and evaporated *in vacuo*. This afforded 1.4 g. of the title compound, contaminated with some 6-iodopenicillanic acid. The product had a melting point of 58-64°C. The NMR spectrum (CDCl<sub>3</sub>) showed absorptions at 5.77 (s, 1H), 4.60 (s, 1H), 1.71 (s, 3H) and 1.54 (s, 3H) ppm.

#### PREPARATION H

##### 15 Pivaloyloxymethyl 6- $\alpha$ -Bromopenicillanate

- To a stirred mixture of 11.2 g. of 6- $\alpha$ -bromopenicillanic acid, 3.7 g. of sodium bicarbonate and 44 ml. of *N,N*-dimethylformamide was added 6.16 g. of chloromethyl pivalate, dropwise, during 5 minutes, at ambient temperature. Stirring was continued for 66 hours and then the reaction mixture was diluted with 100 ml. of ethyl acetate and 100 ml. of water. The layers were separated, and the ethyl acetate layer was washed 20 sequentially with water, saturated sodium chloride, saturated sodium bicarbonate, water and saturated sodium chloride. The decolorized ethyl acetate solution was dried (MgSO<sub>4</sub>) and evaporated to dryness *in vacuo*. This afforded 12.8 g. (80% yield) of the title compound.

#### PREPARATION I

##### 25 Benzyl 6- $\alpha$ -Bromopenicillanate

- The title compound was prepared by esterification of 6- $\alpha$ -bromopenicillanic acid with benzyl bromide, substantially according to the procedure of Preparation H (Yield 83%). The NMR spectrum (in CDCl<sub>3</sub>) showed absorptions at 7.35 (s, 5H), 5.35 (m, 1H), 5.15 (s, 2H), 4.70 (m, 1H), 4.60 (s, 1H), 1.55 (s, 3H) and 1.35 (s, 3H) ppm.

#### 30 PREPARATION J

##### 2,2,2-Trichloroethyl Penicillanate

- To a stirred solution of 11.2 g. of 6- $\alpha$ -bromopenicillanic acid in 50 ml. of tetrahydrofuran, at 0°C., was added 3.48 g. of pyridine over a one-minute period. To the hazy solution so obtained was added, over a 10 35 minute period, 8.47 g. of 2,2,2-trichloroethyl chloroformate, maintaining the temperature between 0 and 2°C. Stirring was continued for 30 minutes, and then the cooling bath was removed. Stirring was continued at ambient temperature overnight. The reaction mixture was then warmed to 35°C. for five minutes and then it was filtered. The filtrate was evaporated and the residue was dissolved in 100 ml. of ethyl acetate. The ethyl acetate solution was washed sequentially with saturated sodium bicarbonate, water and saturated sodium 40 chloride. The ethyl acetate solution was then decolorized, and dried, and then it was concentrated to small volume. To the resulting mixture was added 100 ml. of hexane, and the solids were removed by filtration, giving 10.5 g. of the title compound, m.p. 105-110°C. The NMR spectrum (in CDCl<sub>3</sub>) showed absorptions at 5.50 (d, 1H), 4.95 (d, 1H), 4.90 (s, 2H), 4.65 (s, 1H), 1.70 (s, 3H) and 1.55 (s, 3H) ppm.

#### 45 PREPARATION K

##### 6,6-Dibromopenicillanic Acid

- To 500 ml of dichloromethane cooled to 5°C was added 119.9 g of bromine, 200 ml of 2.5N sulfuric acid and 34.5g of sodium nitrite. To this stirred mixture was then added 54.0g of 6-aminopenicillanic acid, portionwise over 30 minutes, with the temperature maintained from 4 to 10°C. Stirring was continued for 30 minutes at 50 5°C, and then 410 ml of a 1.0M solution of sodium bisulfite was added dropwise at 5 to 10°C during 20 minutes. The layers were separated and the aqueous layer was extracted twice with 150 ml of dichloromethane. The original dichloromethane layer was combined with the two extracts to give a solution of 6,6-dibromopenicillanic acid. This solution was used directly in Example 17.

#### 55 PREPARATION L

##### 6-Chloro-6-iodopenicillanic Acid

- To 100 ml of dichloromethane cooled to 3°C was added 4.87g of iodine chloride, 10 ml of 2.5N sulfuric acid and 2.76g of sodium nitrite. To this stirred mixture was then added 4.32g of 6-amino-penicillanic acid portionwise during a 15 minute period. Stirring was continued for 20 minutes at 0 - 5°C, and then 100 ml of 60 10% sodium bisulfite solution was added dropwise at ca 4°C. Stirring was continued for 5 minutes and then the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 50 ml) and the combined dichloromethane solutions were washed with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give the title compound as a tan solid, mp 148-152°C. The NMR spectrum of the product (CDCl<sub>3</sub>) showed absorptions at 5.40 (s, 1H), 4.56 (s, 1H), 1.67 (s, 3H) and 1.50 (s, 3H) ppm. The IR spectrum (KBr disc) showed 65 absorptions at 1780 and 1715 cm<sup>-1</sup>.

## PREPARATION M

## 6-Bromo-6-iodopenicillanic Acid

- To 100 ml of dichloromethane, cooled to 5°C, was added 10 ml of 2.5*N* sulfuric acid, 6.21g of iodine bromide and 2.76g of sodium nitrite. To this mixture was added, with vigorous stirring, at 0 - 5°C, over 15 minutes, 4.32g of 6-aminopenicillanic acid. Stirring was continued for a further 20 minutes at 0 - 5°C, and then 100 ml of 10% sodium bisulfite was added dropwise between 0 and 10°C. At this point, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 50ml.). The combined dichloromethane layers were washed with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The residue was dried under high vacuum for 30 minutes to give 6.0g (72% yield) of the title compound mp 144-147°C. The NMR spectrum (CDCl<sub>3</sub>) showed absorptions at 5.50 (s,1H), 4.53 (s,1H), 1.70 (s,3H) and 1.53 (s,3H)ppm. The IR spectrum (KBr disc) showed absorptions at 1785 and 1710 cm<sup>-1</sup>. The mass spectrum showed a prominent ion at m/e = 406.

## PREPARATION N

## 15 6-Chloro-6-bromopenicillanic Acid

6-Chloro-6-bromopenicillanic acid is prepared from 6-aminopenicillanic acid *via* diazotization followed by reaction with bromine chloride, according to the procedure of Preparation M.

## PREPARATION O

## 20 Pivaloyloxymethyl 6,6-dibromopenicillanate

- To a stirred solution of 3.59g of 6,6-dibromopenicillanic acid in 20 ml of *N,N*-dimethyl-formamide is added 1.30g of diisopropylethylamine followed by 1.50g of chloromethyl pivalate at ca 0°C. The reaction mixture is stirred at ca 0°C for 30 minutes and then at room temperature for 24 hours. The reaction mixture is then diluted with ethyl acetate and water and the pH of the aqueous phase is adjusted to 7.5. The ethyl acetate layer is separated and washed three times with water and once with saturated sodium chloride solution. The ethyl acetate solution is then dried using anhydrous sodium sulfate, and evaporated *in vacuo* to give the title compound.

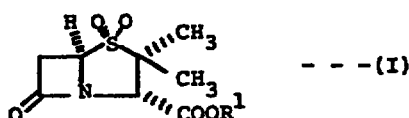
## PREPARATION P

- 30 Reaction of the appropriate 6,6-dihalopenicillanic acid with 3-phthalidyl chloride, 4-crotonlactonyl chloride, gamma-butyrolactone-4-yl chloride or the requisite alkanoyloxymethyl chloride, 1-(alkanyloxy)ethyl chloride, 1-methyl-1-(alkanoyloxy)ethyl chloride, alkoxy-carbonyloxymethyl chloride, 1-(alkoxy-carbonyloxy)ethyl chloride or 1-methyl-1-(alkoxycarbonyloxy)ethyl chloride, according to the procedure of Preparation O, affords the following compounds:

- 35 3-phthalidyl 6,6-dibromopenicillanate,  
4-crotonolactonyl 6-chloro-6-iodopenicillanate,  
gamma-butyrolactonyl 6-bromo-6-iodopenicillanate,  
acetoxymethyl 6-chloro-6-bromopenicillanate,  
pivaloyloxymethyl 6-chloro-6-iodopenicillanate,  
40 hexanoyloxymethyl 6,6-dibromopenicillanate,  
1-(acetoxymethyl) 6,6-dibromopenicillanate,  
1-(isobutyryloxy)ethyl 6-bromo-6-iodopenicillanate,  
1-methyl-1-(acetoxymethyl) 6,6-dibromopenicillanate,  
1-methyl-1-(hexanoyloxy)ethyl 6-chloro-6-bromopenicillanate,  
45 methoxycarbonyloxymethyl 6,6-dibromopenicillanate,  
propoxycarbonyloxymethyl 6-chloro-6-iodopenicillanate,  
1-(ethoxycarbonyloxy)ethyl 6,6-dibromopenicillanate,  
1-(butoxycarbonyloxy)ethyl 6-bromo-6-iodopenicillanate,  
1-methyl-1-(methoxycarbonyloxy)ethyl 6,6-dibromopenicillanate and  
50 1-methyl-1-(isopropoxycarbonyloxy)ethyl 6,6-dibromopenicillanate.

## CLAIMS

1. A process for the preparation of a compound of the formula



- 60 or a pharmaceutically-acceptable base salt thereof, wherein R<sup>1</sup> is hydrogen or an ester-forming residue readily hydrolyzable *in vivo*;



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## PREPARATION M

## 6-Bromo-6-iodopenicillanic Acid

- To 100 ml of dichloromethane, cooled to 5°C, was added 10 ml of 2.5*N* sulfuric acid, 6.21g of iodine bromide and 2.76g of sodium nitrite. To this mixture was added, with vigorous stirring, at 0 - 5°C, over 15 minutes, 4.32g of 6-aminopenicillanic acid. Stirring was continued for a further 20 minutes at 0 - 5°C, and then 100 ml of 10% sodium bisulfite was added dropwise between 0 and 10°C. At this point, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 50ml.). The combined dichloromethane layers were washed with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The residue was dried under high vacuum for 30 minutes to give 6.0g (72% yield) of the title compound mp 144-147°C. The NMR spectrum (CDCl<sub>3</sub>) showed absorptions at 5.50 (s,1H), 4.53 (s,1H), 1.70 (s,3H) and 1.53 (s,3H)ppm. The IR spectrum (KBr disc) showed absorptions at 1785 and 1710 cm<sup>-1</sup>. The mass spectrum showed a prominent ion at m/e = 406.

## PREPARATION N

## 15 6-Chloro-6-bromopenicillanic Acid

6-Chloro-6-bromopenicillanic acid is prepared from 6-aminopenicillanic acid *via* diazotization followed by reaction with bromine chloride, according to the procedure of Preparation M.

## PREPARATION O

## 20 Pivaloyloxymethyl 6,6-dibromopenicillanate

- To a stirred solution of 3.59g of 6,6-dibromopenicillanic acid in 20 ml of *N,N*-dimethyl-formamide is added 1.30g of diisopropylethylamine followed by 1.50g of chloromethyl pivalate at ca 0°C. The reaction mixture is stirred at ca 0°C for 30 minutes and then at room temperature for 24 hours. The reaction mixture is then diluted with ethyl acetate and water and the pH of the aqueous phase is adjusted to 7.5. The ethyl acetate layer is separated and washed three times with water and once with saturated sodium chloride solution. The ethyl acetate solution is then dried using anhydrous sodium sulfate, and evaporated *in vacuo* to give the title compound.

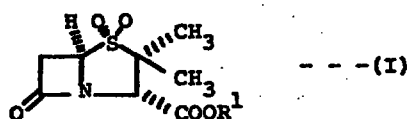
## PREPARATION P

- 30 Reaction of the appropriate 6,6-dihalopenicillanic acid with 3-phthalidyl chloride, 4-crotonlactonyl chloride, gamma-butyrolactone-4-yl chloride or the requisite alkanoyloxymethyl chloride, 1-(alkanyloxy)ethyl chloride, 1-methyl-1-(alkanyloxy)ethyl chloride, alkoxy-carbonyloxymethyl chloride, 1-(alkoxy-carbonyloxy)ethyl chloride or 1-methyl-1-(alkoxy-carbonyloxy)ethyl chloride, according to the procedure of Preparation O, affords the following compounds:

- 35 3-phthalidyl 6,6-dibromopenicillanate,  
4-crotonolactonyl 6-chloro-6-iodopenicillanate,  
gamma-butyrolactonyl 6-bromo-6-iodopenicillanate,  
acetoxymethyl 6-chloro-6-bromopenicillanate,  
pivaloyloxymethyl 6-chloro-6-iodopenicillanate,  
40 hexanoyloxymethyl 6,6-dibromopenicillanate,  
1-(acetoxymethyl) 6,6-dibromopenicillanate,  
1-(isobutyryloxy)ethyl 6-bromo-6-iodopenicillanate,  
1-methyl-1-(acetoxymethyl) 6,6-dibromopenicillanate,  
1-methyl-1-(hexanoyloxy)ethyl 6-chloro-6-bromopenicillanate,  
45 methoxycarbonyloxymethyl 6,6-dibromopenicillanate,  
propoxycarbonyloxymethyl 6-chloro-6-iodopenicillanate,  
1-(ethoxycarbonyloxy)ethyl 6,6-dibromopenicillanate,  
1-(butoxycarbonyloxy)ethyl 6-bromo-6-iodopenicillanate,  
1-methyl-1-(methoxycarbonyloxy)ethyl 6,6-dibromopenicillanate and  
50 1-methyl-1-(isopropoxycarbonyloxy)ethyl 6,6-dibromopenicillanate.

## CLAIMS

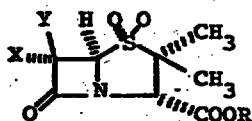
1. A process for the preparation of a compound of the formula



or a pharmaceutically-acceptable base salt thereof, wherein R<sup>1</sup> is hydrogen or an ester-forming residue readily hydrolyzable *in vivo*;

characterized in that a compound of the formula

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--- (III)

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or a base salt thereof, wherein R is hydrogen, an ester-forming residue readily hydrolyzable *in vivo* or a conventional penicillin carboxy protecting group; and X and Y are each hydrogen, chloro, bromo or iodo, with the proviso that when X and Y are both the same, they must both be bromo; is dehalogenated, followed, if necessary, by removal of the conventional penicillin carboxy protecting group.

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2. The process according to claim 1, characterized in that the dehalogenation is carried out by catalytic hydrogenolysis.

3. The process according to claim 2, characterized in that the catalytic hydrogenolysis is carried out in an inert solvent.

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4. The process according to either of claims 2 and 3, characterized in that the catalytic hydrogenolysis is carried out at a pressure in the range from 1 to 100 kg/cm<sup>2</sup> and in the presence of 0.01 to 2.5 weight-percent of a hydrogenolysis catalyst.

5. The process according to any of claims 2 to 4, characterized in that the catalytic hydrogenolysis is carried out at a temperature in the range from 0 to 60°C. and at a pH in the range from 4 to 9.

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6. The process according to any of claims 2 to 5, characterized in that X is bromo and Y is hydrogen.

7. The process according to any of claims 2 to 5, characterized in that X and Y are both bromo.

8. The process according to any of claims 2 to 7, characterized in that R and R<sup>1</sup> are both hydrogen.

9. A compound of the formula

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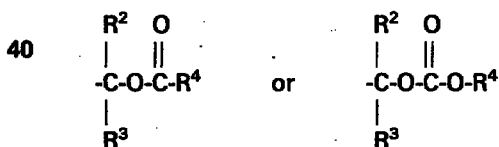
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and the base salts thereof, characterized in that R is hydrogen, an ester-forming residue readily hydrolyzable *in vivo* or a conventional penicillin carboxy protecting group;

10. A compound according to claim 9, characterised in that R is 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolactonyl or a group of the formula:

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wherein R<sup>2</sup> and R<sup>3</sup> are each hydrogen or alkyl having from 1 to 2 carbon atoms, and R<sup>4</sup> is alkyl having from 1 to 5 carbon atoms.

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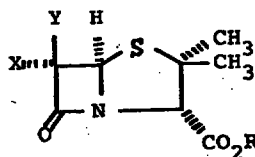
11. A compound according to claim 9, characterised in that R is tetrahydropyranyl, trialkylsilyl having 1 to 3 carbons in each alkyl group, benzyl, 4-nitro-benzyl, benzhydryl, 2,2,2-trichloroethyl, t-butyl or phenacyl.

12. 6,6-Dibromopenicillanic acid 1,1-dioxide.

13. A process as claimed in claim 1 wherein the compound of formula (III) is prepared by contacting a compound of the formula:

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--- (II)

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or a base salt thereof, wherein X, Y and R are as defined in claim 1, with an alkali metal permanganate, an alkaline earth metal permanganate or an organic peroxydicarboxylic acid.

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(11)

ERRATUM

Specification No 2045755B

Page No 18 Formula in claim 9

