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Description

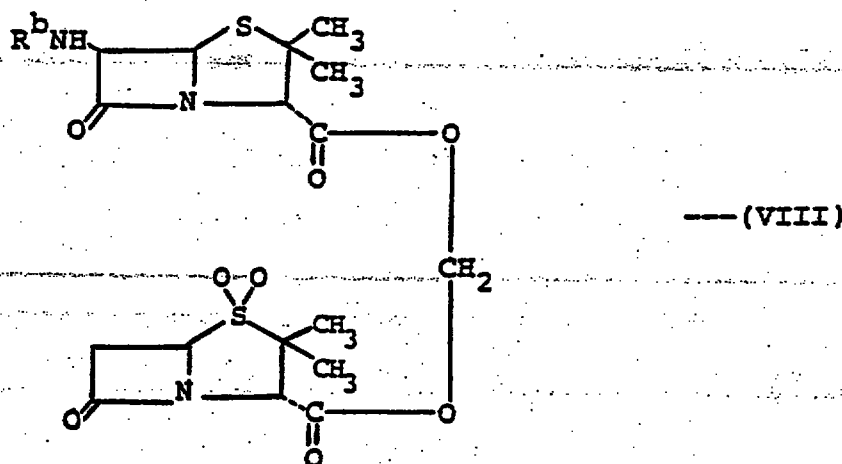
Field of the Invention

The invention relates to novel compounds of formula (I), defined herein and a process for their use in production of 1,1-dioxopenicillanoyloxymethyl 6-(2-amino-2-phenylacetamido)penicillanate antibiotics of formula (II).

Description of the Prior Art

U.S. 4,234,579, issued November 18, 1980, discloses penicillanic acid 1,1-dioxide and esters thereof which are readily hydrolyzable *in vivo*, their use as antibacterial agents and for enhancing the effectiveness of beta-lactam antibiotics against many beta-lactamase producing bacteria.

U.S. 4,244,951, issued January 13, 1981, discloses novel antibacterial agents of formula (VIII) in which penicillanic acid 1,1-dioxide is linked to known penicillin antibiotics via a methylenedioxy group, i.e.,



where R^b is the acyl group of a natural or semisynthetic penicillin. Especially preferred values for R^b include 2-amino-2-phenylacetyl and 2-amino-2-(*p*-hydroxyphenyl)acetyl. The compounds (VIII) are prepared, for example, by reacting a carboxylate salt of the penicillin such as the sodium, potassium or tertiary amine salt with a halomethyl ester (or related ester) of penicillanic acid 1,1-dioxide. The intermediate halomethyl esters are prepared by esterification of penicillanic acid 1,1-dioxide.

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

Belgian Patent 882,028, granted September 9, 1980, discloses a process for preparing penicillanic acid 1,1-dioxide and its readily hydrolyzable *in vivo* esters by oxidation of 6-halopenicillanate or a 6,6-dihalo-penicillanate to the corresponding 1,1-dioxide, then dehalogenation to provide the desired penicillanate 1,1-dioxide.

U.S. 3,293,242 discloses 6-(2-azido-2-phenylacetamido)penicillanic acid and salts thereof.

Japan Kokai 78-37,691; *Chem. Abstr.*, 89, 109466v (1978) discloses 6-[2-azido-2-(*p*-hydroxyphenyl)acetamido]penicillanic acid and its reduction with hydrogen and palladium-on-carbon to give 6-[2-amino-2-(*p*-hydroxyphenyl)acetamido]penicillanic acid.

British Patent Application No. 2,044,255 describes the preparation of certain mutual pro-drugs of beta-lactam antibiotics and beta-lactamase inhibitors including compounds of the formula (VIII). These are also described by Baltzer *et al* in *Journal of Antibiotics*, 1980, 33, 1183 which reports that the esters are relatively stable in acid solution but are rapidly hydrolyzed in neutral solution.

Summary of the Invention

The present invention relates to compounds of the formula

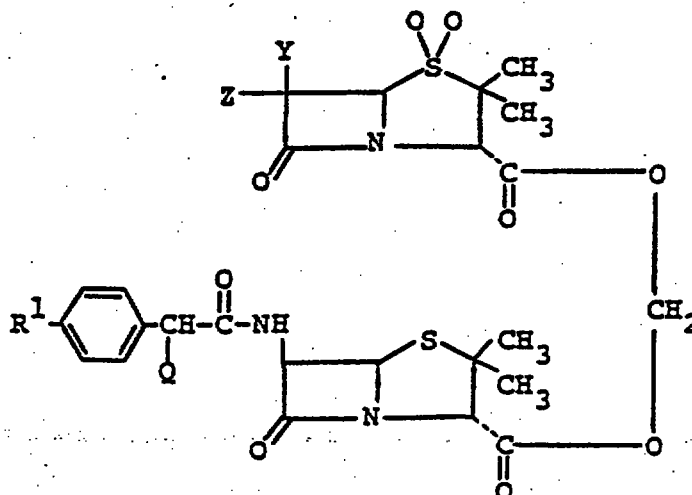
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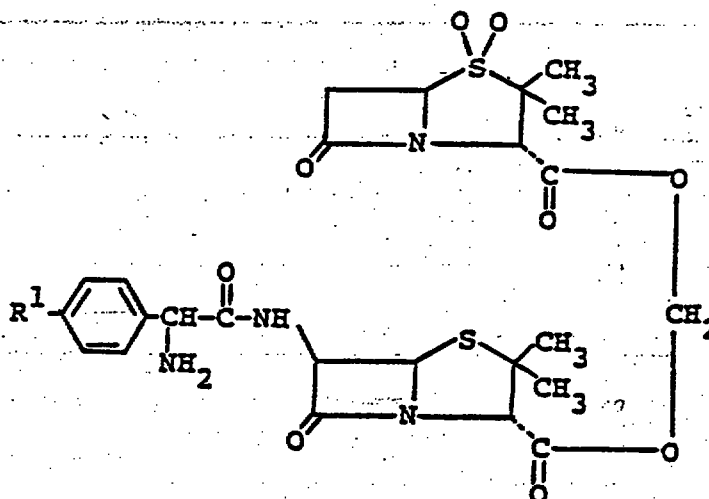
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wherein R^1 is H or OH; Y and Z are each Cl, Br or I, or Y is H and Z is Cl, Br or I; and Q is N_3 or $NHCO_2CH_2C_6H_4R^4$ where R^4 is H, Cl, Br, NO_2 , CH_3 or OCH_3 useful as intermediates for the production of valuable antibiotics of the formula

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In said compounds of formula (I), the particularly preferred value for Q is N_3 . Particularly preferred values for Y and Z are Y is H and Z is Br or Cl, or Y and Z are each Cl or Br; especially Y is H, Z is Br or Y and Z are each Br. Most particularly preferred such compounds are those wherein Q is N_3 , R^1 is H or OH, Y and Z are each Br.

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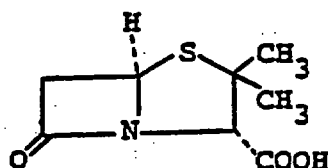
The invention also provides a novel process for production of the antibiotics of formula (II) which is characterized by contacting a compound of formula (I) with hydrogen in the presence of a noble metal catalyst and a reaction inert solvent in the presence of at least two, or when Y is H, at least one molar equivalents of an acid binding agent. The invention process has the advantages over the prior art in that simultaneously the halogen atoms Y and Z are subjected to hydrogenolysis and the group Q is reduced (when Q is N_3) or subjected to hydrogenolysis (when Q is $NHCO_2CH_2C_6H_4R^4$) to produce the antibiotics of formula (II) in a single step. A particularly preferred noble metal catalyst for this process is palladium.

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This invention relates to derivatives of penicillanic acid which is represented by the following structural formula



In derivatives of penicillanic acid, broken line attachment

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15 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, broad line attachment

()

of a substituent to the bicyclic nucleus indicates that the substituent is above the plane of the nucleus. This
20 latter configuration is referred to as the beta-configuration. As used herein a solid line attachment

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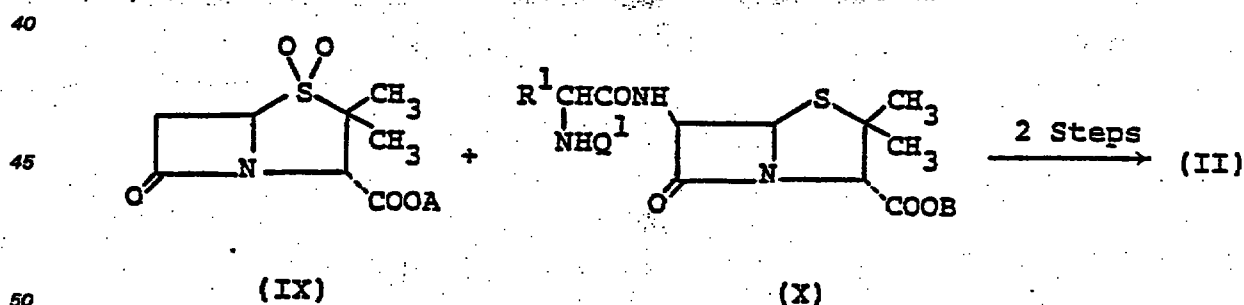
of a substituent to the bicyclic nucleus indicates that the substituent can be in either the alpha-configuration or the beta-configuration.

25 Compounds of the invention of formulae (I) and (II) are named herein as derivatives of penicillanoyloxymethyl penicillanate. Thus, the compound of formula (I) where R¹ is hydrogen and Y and Z are each Br and Q is N₃ is designated as 1,1-dioxo-6,6-dibromopenicillanoyloxymethyl 6-(2-azido-2-phenylacetamido)penicillanate.

30 Additionally, when reference is made herein to a compound which has 2-Q-2-(R¹-substituted phenyl)acetamido or 2-amino-2-(R¹-substituted phenyl)acetamido group at the 6-position of a penicillanic acid derivative, it is understood that this refers to a compound in which said 2-Q-2-(R¹-substituted phenyl)acetamido or 2-amino-2-(R¹-substituted phenyl)acetamido has the D-configuration.

In the invention compounds wherein Y is H and Z is Cl, Br or I the Z substituent can be in the alpha-configuration, the beta-configuration or can be a mixture of the two isomers. All such compounds are included in the scope of the invention.

Methods of preparing penicillanyloxymethyl penicillanates of formula (II) by esterification as illustrated below are disclosed in U.S. 4,244,951 issued January 13, 1981 and Netherlands Patent Application No. 8,000,775 published August 15, 1980, corresponding to British Patent Application No. 2,044,255:



In the above formula one of A and B is $-\text{CH}_2\text{X}^1$ and the other is M^1 , where X^1 is a good leaving group, e.g., Cl, Br, I, $\text{CH}_3\text{SO}_2\text{O}$ or toluenesulfonyloxy; and M^1 is a carboxylate salt forming cation, e.g., sodium, potassium, triethylammonium or tetrabutylammonium ion; and Q^1 is a conventional amino protecting group, e.g., benzyloxycarbonyl. The initial product obtained is the amino-protected derivative of (II) which affords the desired antibiotic compound upon removal of protecting group Q by standard methods known in the art.

The above-mentioned Netherlands and corresponding British patent applications also disclose a process for preparing the compound of formula (II), where R¹ is hydrogen, by coupling chloromethyl 6-(2-azido-2-phenylacetamido)penicillanate and a salt of penicillanic acid 1,1-dioxide, and hydrogenation of the intermediate 1,1-dioxopenicillanoyloxymethyl 6-(2-azido-2-phenylacetamido)penicillanate.

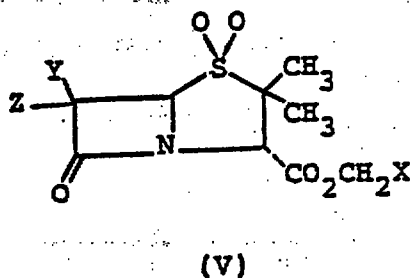
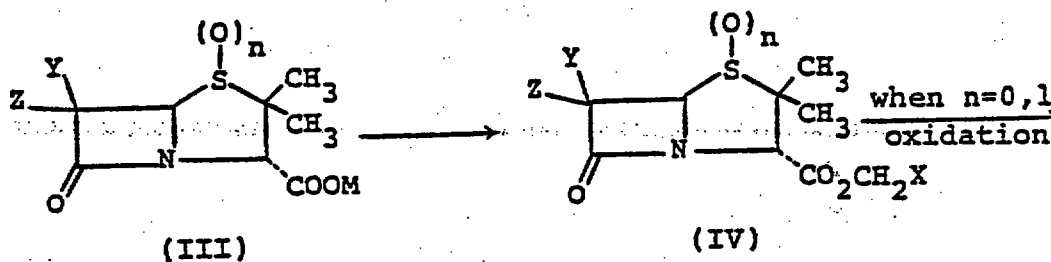
In the prior art methods, the starting 1,1-dioxopenicillanic acid of formula (IX), $A = H$ is obtained e.g. by dehalogenation of the corresponding 6-halo- or 6,6-dihalopenicillanic acid sulfone. The ester (IX), where A is CH_2X^1 , is obtained from the acid by certain esterification techniques.

65 Flow Chart A outlines a preferred method for production of the invention compounds of formula (I) and

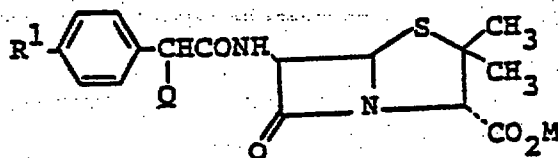
the process of the present invention for their conversion to antibiotic compounds of formula (II) by simultaneous hydrogenolysis of halogen groups Y and Z and reduction of the azido or $\text{NHCO}_2\text{CH}_2\text{C}_6\text{H}_4\text{R}^4$ group to NH_2 by reaction of compound (I) with hydrogen in the presence of a catalyst and an acid binding agent.

The starting halopenicillanic acids of formula (III) where M is hydrogen are prepared e.g., from 6-amino-penicillanic acid or the corresponding sulfoxide or sulfone by reaction with nitrous acid and treatment of the resulting 6-diazo compound with a halogen or hydrohalide of formula Y—Z, where Y and Z are as defined above, by methods known in the art. See, e.g., Clayton *et al.*, *Journal of Chemical Society* (London) (C), 2123 (1969).

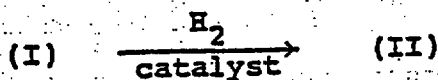
Flow Chart A



(V) +



(VI)



For the esterification step to obtain the compound of formula (IV), the carboxylic acid (III) is converted to a salt wherein M is a cation. A variety of cations can be used to form the carboxylate salt in the compound of formula (III), but salts which are commonly employed include: alkali metal salts, such as sodium and potassium; alkaline earth metal salts, such as calcium and barium salts; tertiary amine salts, such as trimethylamine, triethylamine, tributylamine, N-methylmorpholine and N-methylpyrrolidine; and tetraalkyl ammonium salts, such as tetra-

methyammonium, tetraethylammonium, dimethyl diisopropylammonium, tetrabutylammonium and diethyl di-n-hexylammonium salts. Particularly preferred such salts are the sodium, potassium and tetrabutylammonium salts.

5 The salt of formula (III) is reacted with a compound of the formula X^2CH_2X , wherein X is as defined above and X^2 is X or a better leaving group than X, e.g., when X is Cl, X^2 may be Cl, Br, I, OSO_2Cl , OSO_2CH_3 or $p-CH_3C_6H_4SO_2O$. Particularly preferred values for X^2 are I and OSO_2Cl .

10 The reaction between X^2CH_2X and the salt of formula (III) is usually carried out by contacting approximately equimolar amounts of the reactants in a polar, organic solvent, at a temperature in the range of from about -10 to $80^\circ C$. and preferably from about 0 to $60^\circ C$. The reaction is ordinarily complete in from a few hours to a few days. The desired ester of formula (IV) is isolated by methods well known in the art. For example, by evaporation of solvent and purification of the crude product, if desired, e.g., by column chromatography.

15 Examples of suitable polar solvents which can be employed in this reaction are dimethylformamide, N-methylpyrrolidone, dimethylsulfoxide, ethyl acetate, dichloromethane, acetone and hexamethylphosphoric triamide; alternately, an excess of the reagent X^2CH_2X e.g., ICH_2Cl , can serve as solvent.

20 In the next step of this method, the compounds of formula (IV) where n is zero or one are oxidized to the corresponding sulfone of formula (V). While any of the oxidizing agents known in the art for oxidation of sulfides to sulfones may be employed in this step, preferred oxidizing agents are sodium permanganate, potassium permanganate, calcium permanganate, hydrogen peroxide in the presence of certain transition metal catalysts, peracetic acid or m-chloroperbenzoic acid. The oxidation is carried out in the presence of a reaction inert solvent, preferably at a temperature of from about -30 to $60^\circ C$.

Particularly preferred oxidizing agents are hydrogen peroxide in the presence of certain transition metal catalysts, potassium permanganate and m-chloroperbenzoic acid. Especially preferred are potassium permanganate and m-chloroperbenzoic acid.

25 When a compound of the formula (IV), as defined above, is oxidized to the corresponding compound of the formula (V), using a metal permanganate, the reaction is usually carried out by treating the compound of the formula (IV) with from about two to about ten molar equivalents, and preferably from about two to about four molar equivalents, of the permanganate in an appropriate, reaction-inert solvent system.

30 When said compound of formula (IV) is a sulfoxide wherein n is 1 is employed in this step, approximately half of the above amount of oxidant is ordinarily employed.

35 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 e.g., tetrahydrofuran or acetone can be added. The reaction can be carried out at a temperature in the range from about -30° to about $60^\circ C$, and it is preferably carried out at about 10 to about $30^\circ C$. At about room temperature the reaction is normally substantially complete within a short period, e.g., within two hours. 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. However, it is essential to choose conditions which avoid decomposition of the beta-lactam ring system of the compounds of formulae (IV) or (V). The product is recovered by conventional techniques. Any excess permanganate is usually decomposed using sodium bisulfite, and then if the product is out of solvent, 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.

45 When a compound of the formula (IV) wherein n is zero to oxidized to the corresponding compound of the formula (V) using a peroxy-carboxylic acid, e.g. m-chloroperbenzoic acid, the reaction is usually carried out by treating the compound of the formula (V) with from about 2 to about 6 molar equivalents, and preferably about 2.2 molar equivalents of the oxidant in a reaction-inert organic solvent. As above, only half the amount of oxidant is ordinarily required when sulfoxides of formula (IV) are employed. Preferred reaction-inert solvents are chlorinated hydrocarbons, such as dichloromethane, chloroform and 1,2-dichloroethane; ethers, such as diethyl ether, tetrahydrofuran and 1,2-dimethoxyethane; and ethyl acetate. The reaction is normally carried out at a temperature of from about -30 to about $50^\circ C$, and preferably from about -15 to about $30^\circ C$. At about $0^\circ C$, reaction times of about 4 to about 16 hours are commonly used. The product of formula (V) is isolated by standard methods, e.g., decomposition of excess oxidant by addition of sodium bisulfite, partitioning the reaction mixture between water and water-immiscible solvent and evaporation of solvent from the washed extract. The crude product can be purified, e.g., by chromatography on silica gel.

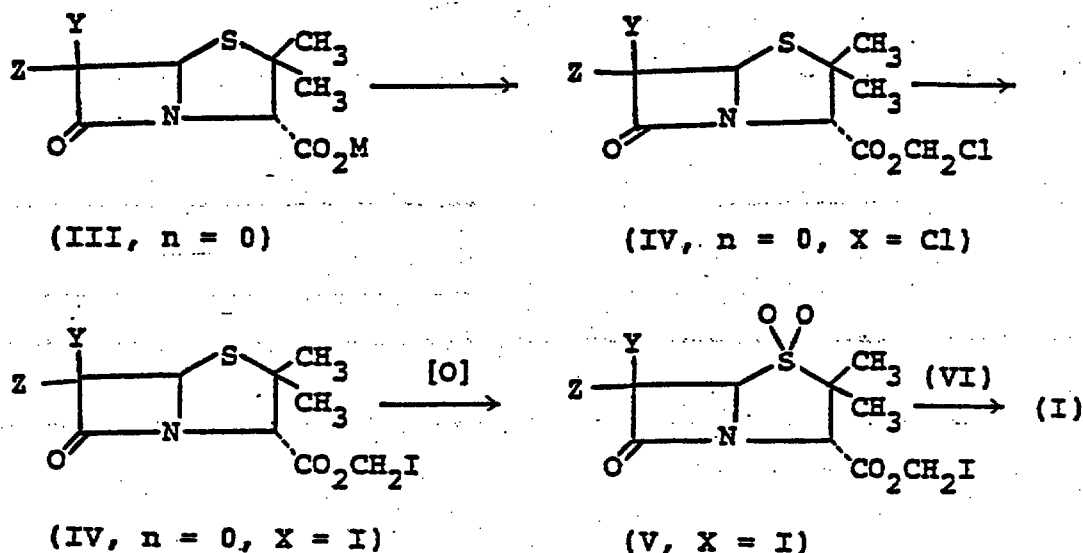
50 When hydrogen peroxide in the presence of certain transition metal catalysts is employed to oxidize a sulfide or sulfoxide such as the compounds of formula (IV) wherein n is zero or 1 to the corresponding sulfone of formula (V), preferred transition metal catalysts are inorganic compounds of tungsten, molybdenum or zirconium in which the metals are in their highest oxidation state. Examples of such compounds are tungstic acid, sodium tungstate, zirconium tetrachloride, molybdic acid and potassium molybdate. The transition metal catalysts can be carried out over a pH range of about 3 to 9, however a pH of from about 4 to 7 is preferred. When the compound to be oxidized is a sulfide, such as that of formula (IV) where n is zero, at least two moles of hydrogen peroxide per mole of said sulfide is required to provide the corresponding sulfone. However, for oxidizing sulfoxides to sulfones or sulfides to sulfoxides, only one

mole of hydrogen peroxide is required to afford the desired product. Preferred reaction inert solvents for the oxidation with hydrogen peroxide/transition metal catalyst include the lower alkanols such as methanol, ethanol and isopropanol; ethylene glycol, ethyl acetate, 1,2-dimethoxyethane, water and mixtures thereof. While the oxidation can be carried out over a wide range of temperature, a preferred temperature is in the range from about 20 to 60°C., at which temperature the oxidation is ordinarily complete in from about two hours to two days, e.g., overnight. The desired product is then isolated and can be purified, if desired, by methods described above and in the Examples.

The reaction of the intermediates (V) with the 6-(2-Q-substituted-2-phenylacetamido)penicillanate salts of formula (VI) where M is as previously defined for compound (III), to provide the invention compounds of formula (I) is usually carried out by contacting the reactants in a polar, organic solvent at a temperature in the range from about 0°C. to about 80°C. and preferably from 25° to 50°C. The compounds of formula (V) and (VI) are usually contacted in substantially equimolar proportions, but an excess of either reagent, for example up to a ten-fold excess can be used. A wide variety of solvents can be used, but it is usually advantageous to use a relatively polar solvent, since this has the effect of speeding up the reaction. Typical solvents which can be used include *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, dimethylsulfoxide, ethyl acetate, dichloromethane, acetone and hexamethylphosphoric triamide. The reaction time varies according to a number of factors, but at about 25°C. reaction times of several hours, e.g. 12 to 24 hours, are commonly used.

The compound of formula (I) is isolated in conventional fashion. When a water-miscible solvent is used, it is usually sufficient simply to dilute the reaction medium with an excess of water. The product is then extracted into a water immiscible solvent such as ethyl acetate, and then the product is recovered by solvent evaporation. When a water immiscible solvent is used, it is usually sufficient to wash the solvent with water, and then recover the product by solvent evaporation. The compound of formula (I) can be purified by well-known methods, such as recrystallization or chromatography, but due regard must be given to the lability of the beta-lactam ring system.

A particularly preferred method for production of compounds of formula (I) from a compound of formula (III) is outlined below.



In the initial step of the particularly preferred method the sulfide, (III, $n = 0$), wherein M, Y and Z are as previously defined, is reacted with a compound of the formula X^2CH_2Cl where X^2 is as defined above, e.g., ICH_2Cl , employing methods and conditions defined previously for the preferred method employing X^2CH_2X .

In the second step of this method the chloromethyl ester is converted to the corresponding iodomethyl ester (IV, $n = 0$, $X = I$), for example by contacting it with at least one equimolar amount of an alkali metal iodide, alkaline earth metal iodide or ammonium iodide in the presence of a reaction inert polar solvent. Examples of suitable solvents for this reaction are dimethylformamide, *N*-methylpyrrolidone, dimethyl sulfoxide, methanol, ethanol, ethyl acetate, acetone and methylethyl ketone. A preferred solvent is acetone. While the reaction can be carried out successfully over a wide range of temperature, a temperature in the range of about 0 to 50°C., and especially 20 to 40°C. is preferred. Within the latter range of temperature the reaction is ordinarily complete in from about 1 to 20 hours. The desired product of formula (IV, $n = 0$, $X = I$), is then isolated and purified by methods well known to those of skill in the art. For example, the solvent is evaporated, the residue partitioned between water and a water-immiscible solvent, e.g. ethyl acetate. Evaporation of solvent then affords the product which can be purified, if desired, e.g., by chromatography on silica gel.

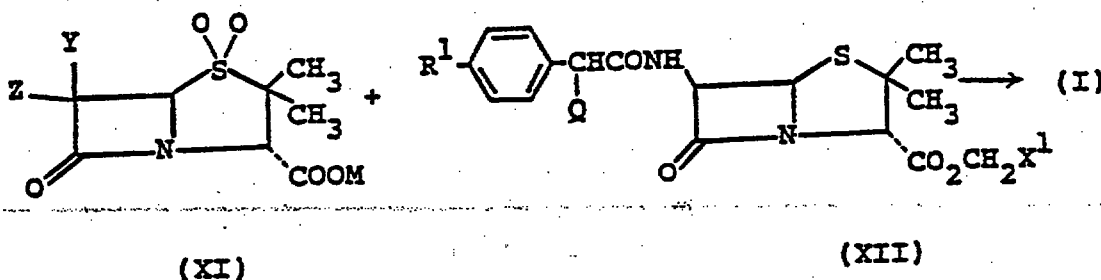
In the next step of this especially preferred method the iodomethyl ester of formula (IV, $n = 0$, $X = I$) is oxidized to the corresponding sulfone of formula (V; $X = I$) employing one of the above preferred oxidizing agents described above, under the preferred conditions, also described above.

The iodomethyl ester (V, $X = I$) is then coupled with a compound of formula (VI) as described above, to provide the invention compounds of formula (I).

At least two moles of hydrogen peroxide per mole of said sulfide is required to provide the corresponding sulfone.

An alternate method for preparation of the iodomethyl sulfone (V, $X = I$) involves oxidation of the chloromethyl ester of formula (IV, $n = 0$, $X = Cl$) or, e.g., the corresponding sulfone employing the above oxidants and conditions; and subsequent conversion of, e.g. the chloromethyl sulfone to the iodomethyl sulfone (V) by reaction with iodide salt, also as described above. However, the latter step with iodide salt, e.g. NaI in acetone, with compounds wherein both of Y and Z are halogen can result in partial dehalogenation at the 6-position of the sulfone to afford a mixture containing iodomethyl 6- α -halo-penicillanate 1,1-dioxide as well as the desired 6,6-dihalo compound of formula (V, $X = I$).

An alternate method for obtaining the valuable intermediates of formula (I) involves reaction of a compound of formula (XI) with a compound of formula (XII) as illustrated below



wherein R^1 , M, Q, X^1 , Y and Z are as previously defined, employing the same procedure and conditions described above for the coupling reaction with compounds of formulae (V) and (VI).

The compounds of formula (I) are useful intermediates for production of the valuable antibiotic compounds of formula (II), disclosed in U.S. 4,244,951.

The process of the present invention provides a particularly convenient method for conversion of intermediates of formula (I) to the antibiotics of formula (II) by the simultaneous hydrogenolysis of halogen groups Y and Z as defined above and reduction of the azido or benzyloxycarbonylamino group Q, as defined above, to NH_2 by means of hydrogen in the presence of a noble metal catalyst and an acid binding agent. A particularly convenient method for carrying out this simultaneous hydrogenolysis and reduction is to stir or shake a solution of a compound of the formula (I) under an atmosphere of hydrogen, or hydrogen mixed with an inert diluent such as nitrogen or argon, in the presence of a noble metal hydrogenation catalyst, and a reaction inert solvent. Suitable solvents for this hydrogenation reaction are those which substantially dissolve the starting compound of the formula (I) but which do not themselves suffer hydrogenation or hydrogenolysis. Examples of such solvents include lower alkanols such as methanol, ethanol and isopropanol; 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; methylene chloride and mixtures thereof.

Additionally, this reaction is carried out in the presence of a sufficient amount of an acid binding agent to bind one (in the case where Y is H), or both molar equivalents of hydrogen halide formed. Examples of suitable acid binding agents include sodium bicarbonate, calcium carbonate, trisodium phosphate, potassium citrate and tertiary amines such as triethylamine, *N,N*-dimethylaniline, *N*-methylmorpholine, *N*-methylpiperidine, *N,N'*-dimethylpiperazine and the like. 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 (I), the solvent, the catalyst and the hydrogen. The pressure inside the reaction vessel can vary from about 1 to about 100 bar. The preferred pressure range, when the atmosphere inside the reaction vessel is substantially pure hydrogen, is from about 2 to about 5 bar. The reaction with hydrogen is generally run at a temperature of from about 0° to about $60^\circ C$., and preferably from about 25° to about $50^\circ C$. Utilizing the preferred temperature and pressure values, hydrogenolysis of halogens and reduction of the group Q generally takes place in a few hours, e.g. from about 2 hours to about 20 hours. The preferred noble metal catalysts used in this hydrogenation reaction are the type of agents known in the art for this kind of transformation, for example, nickel, palladium, platinum and rhodium. Palladium is particularly preferred. The catalyst is usually present in an amount from about 0.1 to about 25 weight-percent, and preferably from about 1 to about 10 weight-percent, based on the compound of formula (I). It is often convenient to suspend the catalyst on an inert support; one particularly convenient catalyst is palladium suspended on an inert support such as carbon. Another convenient catalyst is palladium-on-calcium carbonate in which the calcium carbonate serves as a support for the noble metal and as acid binding agent.

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When the hydrogenolysis and reduction is substantially complete, the desired antibiotic of formula (II) is then isolated by standard methods, e.g., the catalyst is removed by filtration, the solvent evaporated and the product purified, if desired, by well known methods such as crystallization or by chromatography.

Alternatively, the product of formula (II) can be isolated in the form of a pharmaceutically acceptable acid addition salt, for example by treating filtrate obtained upon removal of catalyst or a solution of the isolated free base with an equivalent amount of a pharmaceutically acceptable acid and removal of solvent, e.g. by filtration or evaporation. Examples of pharmaceutically acceptable acids which may be employed include hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, fumaric, succinic, lactic, tartaric, citric, gluconic, saccharic and *p*-toluenesulfonic acids.

As mentioned above the compounds of formula (I) are useful intermediates for preparation of antibacterial agents of formulae (II) and (VIII) disclosed in U.S. Patent 4,244,951 and British Patent Application No. 2,044,255.

The following examples and preparations are provided solely for further illustration. Infrared (IR) spectra were measured neat, as nujol mulls, or as potassium bromide discs (KBr discs) and diagnostic absorption bands are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance spectra (NMR) were measured at 60 MHz for solutions in deuterated chloroform (CDCl_3), D_2O , CD_3SOCD_3 , or deuterated acetone (CD_3COCD_3), and peak positions are reported in parts per million downfield from tetramethylsilane. The following abbreviations for peak shapes are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet.

Example 1

Chloromethyl 6,6-dibromopenicillanate

6,6-Dibromopenicillanic acid (8.0 g., 22 mmole) was stirred with 75 ml. methylene chloride, 35 ml. water was added. To this was added tetrabutylammonium hydroxide to adjust to pH 8. The organic layer was separated, the aqueous phase extracted with 30 ml. methylene chloride. The combined organic layers were evaporated to dryness *in vacuo* to provide the tetrabutylammonium salt of 6,6-dibromopenicillanic acid, 14.2 g., as a light brown oil. To this was added 40 ml. of chloriodomethane, and the resulting mixture stirred under nitrogen for three hours at room temperature. The reaction mixture was concentrated *in vacuo*, the residue stored overnight at room temperature and purified by chromatography on 300 g. silica gel, eluting with 95:5 (by volume) toluene/ethyl acetate. Fractions containing the less polar material were combined and evaporated to afford 5.4 g. (59%) of the desired product, M.P. 105–106°C ^1H -NMR (CDCl_3) ppm (delta): 1.6 (s, 3H), 1.75 (s, 3H), 4.62 (s, 1H), 5.8 (dd, 2H), 5.82 (s, 1H).

When the above procedure is repeated, except that the chloriodomethane used therein is replaced by an equimolar amount of bromiodomethane, diiodomethane, di(methylsulfonyloxy)methane, di(isobutylsulfonyloxy)methane, di(*n*-hexylsulfonyloxy)methane, di(benzenesulfonyloxy)methane or a compound of the formula $(\text{R}^2\text{C}_6\text{H}_4\text{SO}_2\text{O})_2\text{CH}_2$ where R^2 is 4-Cl, 2-Br, 4-I, 3- NO_2 , 4- CH_3 , 3-(CH_3)₂CH, 4- CH_3O , 3- $\text{C}_2\text{H}_5\text{O}$ or 4- $\text{n-C}_3\text{H}_7\text{O}$, this affords, respectively:

bromomethyl 6,6-dibromopenicillanate,
iodomethyl 6,6-dibromopenicillanate,
methylsulfonyloxymethyl 6,6-dibromopenicillanate,
isobutylsulfonyloxymethyl 6,6-dibromopenicillanate,
n-hexylsulfonyloxymethyl 6,6-dibromopenicillanate,
benzenesulfonyloxymethyl 6,6-dibromopenicillanate,
and $\text{R}^2\text{-C}_6\text{H}_4\text{-sulfonyloxymethyl 6,6-dibromopenicillanates}$ where R^2 is as defined above for the di(substituted phenylsulfonyloxy)methane reagent.

Example 1A

Iodomethyl 6,6-dibromopenicillanate

To 25 ml. of acetone was added 4.15 g (10.2 mmole) chloromethyl 6,6-dibromopenicillanic acid and 7.5 g. (50 mmole) sodium iodide. The mixture was stirred overnight at room temperature and the acetone was evaporated to afford a dark residue. This was dissolved in 150 ml. ethyl acetate, washed with water (3 x 25 ml.), saturated brine (25 ml.), dried (MgSO_4) and the solvent evaporated *in vacuo* to yield a residual oil which was purified by chromatography on 100 g. silica gel, eluting with 1:1 (by volume) ethyl acetate/hexane. Thirty milliliter fractions were collected. The product eluted in fractions 4–6, which were combined and evaporated to afford 5.95 g. of colorless oil which crystallized upon standing. M.P. 67–68°C. ^1H -NMR (CDCl_3) ppm (delta): 1.55 (s, 3H), 1.65 (s, 3H), 4.54 (s, 1H), 5.8 (s, 1H), 5.98 (s, 2H).

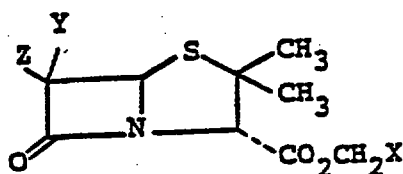
Employing bromomethyl 6,6-dibromopenicillanate, bromomethyl 6,6-dichloropenicillanate, chloromethyl 6,6-dichloropenicillanate, chloromethyl 6-bromo-6-chloropenicillanate, chloromethyl 6-chloro-6-iodopenicillanate, chloromethyl 6-bromo-6-iodopenicillanate or bromomethyl 6-bromo-6-iodopenicillanate in place of chloromethyl 6,6-dibromopenicillanate in the above procedure provides the corresponding iodomethyl ester, in each case.

Example 1B

Employing the appropriate 6-substituted or 6,6-disubstituted penicillanic acid in the procedures of Example 1 and 1A, the following esters are prepared in like manner.

0 061 274

(17)



<u>Y</u>	<u>Z</u>	<u>X</u>
H	alpha-Br	I
H	alpha-Cl	CH ₃ SO ₂ O
H	alpha-I	C ₂ H ₅ SO ₂ O
H	beta-Cl	(CH ₃) ₂ CHCH ₂ SO ₂ O
H	beta-Br	Cl
H	beta-I	C ₆ H ₅ SO ₂ O
Cl	Cl	4-CH ₃ C ₆ H ₄ SO ₂ O
Cl	Cl	Cl
Br	Cl	Cl
Cl	I	<i>n</i> -C ₆ H ₁₃ SO ₂ O
Cl	I	Cl
Br	I	Cl
Br	I	CH ₃ SO ₂ O
Br	Br	Br
I	I	Cl
Br	Br	4-CH ₃ C ₆ H ₄ SO ₂ O
Cl	I	4-ClC ₆ H ₄ SO ₂ O
Br	I	4-CH ₃ OC ₆ H ₄ SO ₂ O
I	I	I
Cl	Cl	2-BrC ₆ H ₄ SO ₂ O
Cl	Br	4-IC ₆ H ₄ SO ₂ O
Cl	Cl	3-NO ₂ C ₆ H ₄ SO ₂ O
Cl	Cl	3-(CH ₃) ₂ CHC ₆ H ₄ SO ₂ O
Br	Br	3-C ₂ H ₅ OC ₆ H ₄ SO ₂ O
Cl	I	4- <i>n</i> -C ₃ H ₇ OC ₆ H ₄ SO ₂ O

Example 2

Chloromethyl 6,6-dibromopenicillanate 1,1-Dioxide

A solution of 7.1 g. (17.4 mmole) chloromethyl 6,6-dibromopenicillanate in 75 ml. ethyl acetate was cooled to 0°C. and 7.3 g (36 mmole) of *m*-chloroperbenzoic acid was added. The mixture was stirred under nitrogen at 0°C. overnight, diluted to 150 ml. with ethyl acetate, and 50 ml. water added at 0°C. Sufficient sodium bisulfite was added to destroy the excess peracid, the mixture adjusted from pH 2 to pH 7.5 with sodium bicarbonate, the organic layer separated and washed with 50 ml. saturated sodium bicarbonate,



50 ml. water and 25 ml. brine. The washed extracts were dried (MgSO_4), concentrated to dryness *in vacuo* and the residue purified by chromatography on 300 g. silica gel, eluting with 9:1 (by volume) toluene/hexane to afford 5.0 g. (65%) of the desired dioxide as a crystalline solid, M.P. 95–96°C. $^1\text{H-NMR}$ (CDCl_3) ppm (delta): 1.5 (s, 3H), 1.7 (s, 3H), 4.58 (s, 1H), 5.04 (s, 1H), 5.8 (dd, 2H).

Analysis: Calculated for $\text{C}_9\text{H}_{10}\text{NO}_5\text{SBr}_2\text{Cl}$:

C, 24.59; H, 2.29; N, 3.18

Found: C, 24.63; H, 2.49; N, 3.31.

A second, more polar component was isolated from the chromatography column, 0.8 g. This was identified as 9:1 mixture of the alpha- and beta-sulfoxides of chloromethyl 6,6-dibromopenicillanate by $^1\text{H-NMR}$.

Example 2A

Iodomethyl 6,6-dibromopenicillanate 1,1-Dioxide

To 40 ml. of acetone was added 0.25 g. (0.5 mmole) iodomethyl 6,6-dibromopenicillanate and the mixture stirred until a solution was obtained, water, 10 ml., was added followed by sufficient concentrated phosphoric acid to adjust the mixture to pH 4.0. Then 158 mg. (1 mmole) powdered potassium permanganate was added and the mixture stirred at room temperature for 1.25 hours. Ethyl acetate, 100 ml. and water, 50 ml., were added. The resulting mixture adjusted to pH 2.0 with 6N hydrochloric acid and sodium bisulfite added to consume the excess oxidizing agent (pH 2.9). The organic layer was separated, the aqueous phase extracted with 50 ml. ethyl acetate and the combined organic layers were washed with saturated brine (3 x 25 ml.). After drying over anhydrous sodium sulfate and evaporation of solvent, 0.29 g. of colorless oil was obtained. The oil was purified by chromatography on 25 g. of silica gel eluting with 1:1 ethyl acetate/hexane taking 15 ml. fractions. Fractions 4 and 5 were combined and evaporated *in vacuo* to yield 0.27 g. (100%) of colorless oil which crystallized upon standing. M.P. 71–73°C. $^1\text{H-NMR}$ (CDCl_3) ppm (delta): 1.5 (s, 3H), 1.62 (s, 3H), 4.49 (s, 1H) 5.02 (s, 1H), 5.98 (dd, 2H).

Use of an equivalent amount of sodium permanganate or calcium permanganate in place of potassium permanganate in the above procedure afforded the same product in like manner.

Attempts to prepare iodomethyl 6,6-dibromopenicillanate 1,1-dioxide from the chloromethyl ester prepared in Example 2, by treatment with sodium iodide in acetone by the procedure of Example 1A gave iodomethyl 6-alpha-bromopenicillanate 1,1-dioxide. $^1\text{H-NMR}$ (CDCl_3) ppm/delta: 1.55 (s, 3H), 1.70 (s, 3H), 4.43 (s, 1H), 5.2 (d, 1H), 5.75 (d, 1H), 6.0 (dd, 2H).

Example 3

Iodomethyl 6-bromo-6-chloropenicillanate 1,1-Dioxide

A solution of 7.6 g. (17.4 mmole) iodomethyl 6-bromo-6-chloropenicillanate in 75 ml. ethyl acetate was cooled to 0°C and 7.3 g. (36 mmole) of *m*-chloroperbenzoic acid was added. The mixture was stirred under nitrogen at 0°C. overnight, diluted to 150 ml. with ethyl acetate, and 50 ml. water added at 0°C. Sufficient sodium bisulfite was added to destroy the excess peracid, the mixture adjusted from pH 2 to pH 7.5 with sodium bicarbonate, the organic layer separated and washed with 50 ml. saturated sodium bicarbonate, 50 ml. water and 25 ml. brine. The washed extracts were dried (MgSO_4), concentrated to dryness *in vacuo* and the residue purified by chromatography on silica gel.

Example 4

Iodomethyl 6,6-dichloropenicillanate 1,1-Dioxide

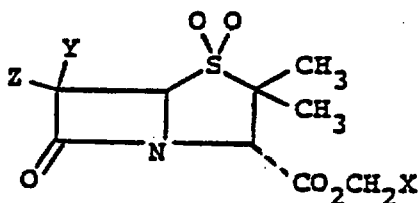
To a solution of 4.09 g (0.01 mole) iodomethyl 6,6-dichloropenicillanate in 50 ml. acetone is added 2.5 ml. (0.24 mole) 30% hydrogen peroxide and 1 ml. of 0.5 M aqueous sodium tungstate. The mixture is heated at reflux for one hour and allowed to stir overnight at room temperature. Evaporation of solvent affords the crude product which is purified by chromatography on silica gel.

When aqueous potassium molybdate or zirconium tetrachloride is used in place of sodium tungstate in the above procedure the result is substantially the same.

When methanol, ethanol, isopropanol, methylethyl ketone or their mixtures with water are employed as solvent in place of acetone and the reaction is carried out at from 25 to 60°C., the title compound is obtained in like manner.

Example 5

Employing the compounds provided in Example 1B as starting materials in the procedures of Example 2 through 4 provides the corresponding compound of the formula below



where Y, Z and X are as defined in Example 1B.

Example 6

Chloromethyl 6-beta-bromopenicillanate 1,1-Dioxide

To a solution of 3.52 g. (8 mmole) chloromethyl 6,6-dibromopenicillanate 1,1-dioxide in dry benzene (100 ml.), under nitrogen, is added at 0°C., 2.32 g. (8 mmole) tri-*n*-butyltin hydride. The resulting mixture is stirred overnight at room temperature, the solvent evaporated *in vacuo* and the residue purified by column chromatography on silica gel to provide the title compound.

Alternately, the same product is obtained by employing chloromethyl 6,6-dibromopenicillanic acid in the above procedure and oxidizing the resulting sulfide, chloromethyl 6-beta-bromopenicillanate, to the sulfone by the procedures of Example 2, 2A, 3 or 4.

Example 7

Iodomethyl 6-beta-bromopenicillanate 1,1-Dioxide

A solution of 0.12 g. (0.33 mmole) chloromethyl 6-beta-bromopenicillanate 1,1-dioxide and 0.25 g. (1.66 mmole) sodium iodide in 5 ml. of acetone was stirred 30 hours at room temperature. The resulting pale yellow suspension was evaporated to dryness and the residue taken up in 50 ml. of ethyl acetate, washed successively with 2 x 10 ml. water, 10 ml. saturated brine and dried over anhydrous sodium sulfate. The resulting solution was evaporated at reduced pressure to obtain the title compound, as a solid, 0.14 g. ¹H-NMR (CDCl₃) ppm (delta): 1.45 (s, 3H), 1.65 (s, 3H), 4.5 (s, 1H), 4.83 (d, 1H), 5.42 (d, 1H), 6.0 (dd, 2H).

Example 8

6-alpha-Bromopenicillanic Acid 1,1-Dioxide

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.

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.

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, M.P. 134°C. (dec.).

Analysis: Calculated for C₈H₁₀BrNO₅S:

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%

Oxidation of 6-alpha-chloropenicillanic acid and 6-alpha-iodopenicillanic acid with potassium permanganate, according to the above procedure, affords 6-alpha-chloropenicillanic acid 1,1-dioxide and 6-alpha-iodopenicillanic acid 1,1-dioxide, respectively.

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Example 9

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. The NMR spectrum (in CD₃COCD₃) 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.

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.

Example 10

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 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 (MgSO₄) and evaporated *in vacuo*. This afforded 216 mg. of the title compound as white crystals. The NMR spectrum (in D₂O) showed absorptions at 5.78 (d, 1H, J = 4 Hz), 5.25 (d, 1H, J = 4 Hz), 4.20 (s, 1H), 1.65 (s, 3H) and 1.46 (s, 3H) ppm.

Example 11

6-beta-Iodopenicillanic Acid 1,1-Dioxide

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

Example 12

Chloromethyl 6-alpha-bromopenicillanate 1,1-Dioxide

6-alpha-Bromopenicillanic acid 1,1-dioxide is esterified by the procedure of Example 1 to provide the title compound.

The above procedure is repeated but the chloriodomethane used therein is replaced by an equimolar amount of bromiodomethane, diiodomethane, di(methylsulfonyloxy)methane, di(isopropylsulfonyloxy)methane, di(isovaleryl sulfonyloxy)methane or a compound of the formula (R²C₆H₄SO₂O)₂CH₂ where R² is H, 3-Cl, 4-Br, 4-NO₂, 4-CH₃, 3-*n*-C₃H₇, 4-CH₃O, 4-C₂H₅O or 3-(CH₃)₂CH₂ to provide, respectively:

bromomethyl 6-alpha-bromopenicillanate 1,1-dioxide,
iodomethyl 6-alpha-bromopenicillanate 1,1-dioxide,
methylsulfonyloxymethyl 6-alpha-bromopenicillanate 1,1-dioxide,
isopropylsulfonyloxymethyl 6-alpha-bromopenicillanate 1,1-dioxide,
isovaleryl sulfonyloxymethyl 6-alpha-bromopenicillanate 1,1-dioxide,
and R²C₆H₄-sulfonyloxymethyl 6-alpha-bromopenicillanate 1,1-dioxides where R² is as defined above.

The corresponding esters of 6-alpha-chloropenicillanic acid 1,1-dioxide; 6-alpha-iodopenicillanic acid 1,1-dioxide; 6-beta-chloropenicillanic acid 1,1-dioxide and 6-beta-iodopenicillanic acid 1,1-dioxide are prepared in like manner.

Example 13

Chloromethyl 6-alpha-Chloropenicillanate

A mixture of 2.35 g. (0.01 mole) 6-alpha-chloropenicillanic acid and 5.0 ml. water is treated with 5.0 ml. 2N potassium hydroxide. Potassium bicarbonate (6.0 g.), tetrabutylammonium hydrogen sulfate (0.34 g., 0.001 mole), dichloromethane (20 ml.) and chloromethyl chlorosulfate (1.64 g., 0.011 mole) is added and the resulting mixture stirred at 25 to 30°C. for two hours. The reaction mixture is filtered, the layers separated. The organic phase is dried (Na₂SO₄) and evaporated to dryness to afford the title compound.

The following compounds are made in like manner from the appropriate 6-substituted penicillanic acid:

chloromethyl 6-alpha-bromopenicillanate,
chloromethyl 6-alpha-iodopenicillanate,
chloromethyl 6-beta-chloropenicillanate,
chloromethyl 6-beta-bromopenicillanate,

chloromethyl 6-beta-iodopenicillanate,
 chloromethyl 6,6-dibromopenicillanate,
 chloromethyl 6,6-dichloropenicillanate,
 chloromethyl 6,6-diiodopenicillanate,
 chloromethyl 6-chloro-6-iodopenicillanate,
 chloromethyl 6-bromo-6-iodopenicillanate,
 chloromethyl 6-bromo-6-chloropenicillanate.

Example 14

Chloromethyl 6-alpha-chloropenicillanate 1-Oxide

To a stirred solution of 8.49 g. (0.03 mole) chloromethyl 6-alpha-chloropenicillanate in 200 ml. chloroform is added at 0°C. a solution of 6.12 g. (0.03 mole) 3-chloroperbenzoic acid in 100 ml. chloroform. Stirring is continued for 1.5 hours at 0—5°C. The reaction mixture is then filtered, washed with sodium bicarbonate solution, water and dried (Na₂SO₄). Evaporation of solvent *in vacuo* affords the crude title compound as a mixture of alpha- and beta-sulfoxides which can be purified, if desired, by chromatography on silica gel.

Alternately, the title compound is prepared by oxidation of 6-alpha-chloropenicillanic acid by oxidation with one equivalent of 3-chloroperbenzoic acid in tetrahydrofuran at 0—25°C. for about one hour, according to the procedure of Harrison *et al.*, *Jour. Chem. Soc. (London)*, Perkin I, 1772 (1976). The resulting 6-alpha-chloropenicillanic acid 1-oxide is then esterified by the procedure of Example 1 to provide the desired chloromethyl ester.

The remaining 6-substituted penicillanate esters and 6,6-dihalopenicillanate esters provided in Examples 1, 1B and 13 are converted to the corresponding 1-oxides by the above procedure.

The same compound is obtained by reaction of 0.1 mole chloromethyl 6-alpha-chloropenicillanate in 150 ml. isopropanol containing 0.8 ml. of 0.5 M sodium tungstate (Na₂WO₄) or an equivalent amount of potassium molybdate (K₂MoO₄) with 0.1 mole of hydrogen peroxide (30%). The peroxide is added slowly to the other reagents at 60°C., after which the mixture is allowed to cool while stirring overnight. The product is isolated as described above.

Example 15

Chloromethyl 6-alpha-chloropenicillanate 1,1-Dioxide

To a solution of 2.83 g., 0.01 mole chloromethyl 6-alpha-chloropenicillanate in 50 ml. of chloroform is added 4.32 g. (0.025 mole) *m*-chloroperbenzoic acid and the mixture is stirred under a nitrogen atmosphere for 36 hours at room temperature. The solvent is evaporated *in vacuo*, the residue partitioned between ethyl acetate and water at pH 6.0 and sodium bisulfite is added until a test for the presence of peroxides is negative. The pH is adjusted to 8.0, the layers separated and the organic phase is washed with brine, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to provide the title compound.

Alternatively, the title compound is obtained by oxidation of the same starting material in methanol or ethanol containing a catalytic amount of sodium tungstate and addition of 2 molar equivalents of hydrogen peroxide at temperatures of from 20 to 60°C.

In like manner the remaining penicillanate esters provided in Example 13 are converted to the corresponding 1,1-dioxides by the above procedures.

Similarly, the remaining chloromethyl-6-substituted (and 6,6-disubstituted) penicillanate 1-oxides provided in Example 14 are converted to 1,1-dioxides by the above procedure employing one half the amount of *m*-chloroperbenzoic acid, or by employing an equimolar amount of peracetic acid.

Example 16

1,1-Dioxo-6,6-dibromopenicillanoyloxymethyl 6-(D-2-azido-2-phenylacetamido)penicillanate

To a mixture of 0.232 g. (0.37 mmole) tetrabutylammonium 6-(D-2-azido-2-phenylacetamido)-penicillanate* and 10 ml. acetone was added 0.20 g. (0.37 mmole) iodomethyl 6,6-dibromopenicillanate 1,1-dioxide and the mixture stirred at room temperature for 30 minutes. An additional 50 mg. of tetrabutylammonium D-(2-azido-2-phenylacetamido)penicillanate was added and stirring continued for 30 minutes. The reaction mixture was concentrated to dryness and the residue placed on a column of silica gel (50 g.). Elution with 1:1 (v/v) ethyl acetate/hexane was carried out taking 7 ml. fractions. Fractions 17-24 were combined and evaporated *in vacuo* to afford 0.14 g. (49%) of the desired product as a light yellow oil. ¹H-NMR (CDCl₃) ppm (delta): 1.4 (s, 3H), 1.5 (s, 3H), 1.59 (s, 3H), 1.62 (s, 3H), 4.4 (s, 1H), 4.5 (s, 1H), 4.97 (s, 1H), 5.04 (s, 1H), 5.4-5.70 (m, 2H), 5.85 (s, 2H), 7.05 (d, 1H), 7.35 (s, 5H); Infrared (neat) cm⁻¹: 1810, 1775.

*The tetrabutylammonium salt was prepared as follows:

One gram of sodium d-2-azido-2-phenylacetamido penicillanate, 50 ml. ethyl acetate and 25 ml. water, were combined and adjusted to pH 2.0 (2N HCl). The organic layer was separated, washed with brine (10 ml.) and the solvent evaporated *in vacuo*. The residual foam was dissolved in 30 ml. methylene chloride, 15 ml. water was added and 40% tetrabutylammonium hydroxide solution was added until the aqueous phase reached pH 8.0. The organic layer was separated, the aqueous layer extracted again with methylene chloride (2 x 20 ml.) and the combined extracts were dried (Na₂SO₄) and concentrated to dryness to afford a hard gum. This was triturated with ethyl acetate (2 x 10 ml.) and ethyl ether

(2 x 10 ml.). The resulting off-white solid was air dried to afford 1.25 g. of the desired tetrabutylammonium salt.

Example 17

5 1,1-Dioxo-6,6-dibromopenicillanoyloxymethyl 6-(D-2-benzyloxycarbonylamino-2-phenylacetamido)-penicillanate

The title compound is obtained by employing tetrabutylammonium 6-(D-2-benzyloxycarbonylamino-2-phenylacetamido)penicillanate in place of the corresponding azidocillin salt in the procedure of Example 10.

Example 18

10 1,1-Dioxo-6-bromo-6-chloropenicillanoyloxymethyl 6-[D-2-azido-2-(p-hydroxyphenyl)acetamido]-penicillanate

15 To a stirred solution of 4.29 g. (0.01 mole) potassium 6-(D-2-azido-2-p-hydroxyphenylacetamido)-penicillanate in 75 ml. dimethylsulfoxide is added 4.86 g. (0.01 mole) iodomethyl 6-bromo-6-chloropenicillanate 1,1-dioxide and the mixture stirred at ambient temperature for 18 hours. The reaction mixture was poured into water, extracted with ethyl acetate, the extracts washed with water and saturated sodium chloride solution, then dried (Na₂SO₄). Evaporation of solvent affords the crude product which can be purified if desired by chromatography on silica gel.

20 When the above reaction is carried out in dimethylformamide, N-methylpyrrolidone, ethyl acetate, dichloromethane or hexamethylphosphoric acid triamide as solvent in place of dimethylsulfoxide at temperatures of from 25 to 50°C., the results are substantially the same.

Example 19

25 1,1-Dioxo-6,6-dichloropenicillanoyloxymethyl 6-(D-2-azido-2-phenylacetamido)penicillanate

A mixture of 3.08 g. (5 mmole) tetrabutylammonium 6-(D-2-azido-2-phenylacetamido)penicillanate, ethyl acetate 25 ml. and methylene chloride 10 ml. is stirred and a solution of 2.21 g. (5 mmole) iodomethyl 6,6-dichloropenicillanate 1,1-dioxide in 20 ml. ethyl acetate is added. The resulting mixture is stirred at room temperature for one hour, the methylene chloride evaporated *in vacuo* and the precipitate of tetrabutylammonium iodide is removed by filtration. Evaporation of the filtrate affords the desired product.

Example 20

35 1,1-Dioxo-6-bromo-6-iodopenicillanoyloxymethyl 6-(D-2-benzyloxycarbonylamino-2-phenylacetamido)-penicillanate

Sodium 6-(D-2-benzyloxycarbonylamino-2-phenylacetamido)penicillanate (4.05 g., 0.01 mole), 4-toluenesulfonyloxymethyl 6-bromo-6-iodopenicillanate 1,1-dioxide and 50 ml. dimethylformamide are combined and stirred at 30°C. for 24 hours. The mixture is poured into water (125 ml.), the pH adjusted to 8.5 with sodium hydroxide solution and extracted with ethyl acetate. The extract is washed with water, 40 brine, dried (Na₂SO₄) and the solvent evaporated *in vacuo* to afford the crude title compound. It is purified by column chromatography on silica gel.

Example 21

45 1,1-Dioxo-6,6-dibromopenicillanoyloxymethyl 6-[D-2-benzyloxycarbonylamino-2-(p-hydroxyphenyl)-acetamido]penicillanate

To a mixture of 101.3 g. (0.25 mole) 6-[D-2-benzyloxycarbonylamino-2-(p-hydroxyphenyl)acetamido]-penicillanic acid, 250 ml. water, 500 ml. methylene chloride and 84.8 g. (0.25 mole) tetrabutylammonium bisulfate at 5°C. is added 125 ml. 2N sodium hydroxide while maintaining the mixture at 5-10°C. The organic layer is separated and the aqueous phase extracted with methylene chloride. The combined 50 organic layers are dried (Na₂SO₄) and solvent evaporated *in vacuo*. The residue is dissolved in 1000 ml. ethyl acetate, evaporated *in vacuo* to about 300 ml. and refrigerated overnight. The precipitated tetrabutylammonium 6-[D-2-benzyloxycarbonylamino-2-(p-hydroxyphenyl)acetamido]penicillanate is collected by filtration and dried *in vacuo*.

To 74.1 g. (0.10 mole) tetrabutylammonium 6-[D-2-benzyloxycarbonylamino-2-(p-hydroxyphenyl)-acetamido]penicillanate in 1000 ml. methylethyl ketone is added 49.8 g. (0.10 mole) methylsulfonyloxymethyl 6,6-dibromopenicillanate 1,1-dioxide and the resulting mixture stirred at 50°C. for one hour. The solvent is evaporated *in vacuo* and the residue partitioned between ethyl acetate and water. The aqueous layer is separated, washed with ethyl acetate and the combined organic layers washed with brine and dried (Na₂SO₄). Evaporation of ethyl acetate *in vacuo* affords the title compound.

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Example 22

1,1-Dioxo-6-beta-bromopenicillanoyloxymethyl 6-(D-2-azido-2-phenylacetamido)penicillanate

65 To a mixture of 0.152 g. (0.25 mmole) tetrabutylammonium (D-2-azido-2-phenylacetamido)penicillanate and 5.0 ml. acetone was added 0.14 g. (0.25 mmole) iodomethyl 6-beta-bromopenicillanate 1,1-dioxide. The resulting colorless mixture was stirred at room temperature for 30 minutes, the solvent

evaporated *in vacuo* and the residue chromatographed on a column of silica gel (25 g.), eluting with 1:1 (v/v) ethyl acetate/hexane. Fractions of 6 ml. were taken at about 30 second intervals. Fractions 13—17 were combined and concentrated *in vacuo* to afford 0.125 g. of the desired product as a foam. ¹H—NMR (CDCl₃) ppm (delta): 1.4 (s, 3H), 1.5 (s, 3H), 1.6 (s, 3H), 1.65 (s, 3H), 4.42 (s, 1H), 4.5 (s, 1H), 4.75 (d, 1H), 5.07 (s, 1H), 5.3 (d, 1H), 5.4—5.75 (m, 2H), 5.85 (s, broad, 2H), 7.1 (d, 1H), 7.35 (s, 5H); Infrared (neat) cm⁻¹: 1800, 1775.

Example 23

1,1-Dioxo-6- α -bromopenicillanoyloxymethyl 6-(D-2-azido-2-phenylacetamido)penicillanate

A mixture of 0.308 g. (0.5 mmole) tetrabutylammonium (D-2-azido-2-phenylacetamido)penicillanate, 0.219 g. (0.485 mmole) iodomethyl 6- α -bromopenicillanate 1,1-dioxide and 10 ml. acetone was stirred for 30 minutes at room temperature. The solvent was evaporated *in vacuo* and the residue chromatographed on a column of 50 g. silica gel, eluting with 1:1 (v/v) ethyl acetate/hexane. The product-containing fractions were combined and the solvent evaporated *in vacuo* to afford 0.125 g. (38%) of the title compound as an oil. ¹H—NMR (CDCl₃) ppm (delta): 1.43 (s, 3H), 1.5 (s, 3H), 1.6 (s, 3H), 1.66 (s, 3H), 4.4 (s, 2H), 4.64 (d, 1H), 5.05 (s, 1H), 5.1 (d, 1H), 5.4—5.7 (m, 2H), 5.85 (s, 2H), 7.08 (d, 1H), 7.35 (s, 5H); Infrared (neat) cm⁻¹: 1795, 1775.

Example 24

Employing the halomethyl, alkylsulfonyloxymethyl or arylsulfonyloxymethyl esters of 6,6-dihalopenicillanic acid 1,1-dioxides or the corresponding 6-halo compounds provided in Examples 2 through 8, 12, 13 and 15 as starting material, the following compounds are prepared by the methods of Examples 16 through 23.

24

evaporated *in vacuo* and the residue chromatographed on a column of silica gel (25 g.), eluting with 1:1 (v/v) ethyl acetate/hexane. Fractions of 6 ml. were taken at about 30 second intervals. Fractions 13—17 were combined and concentrated *in vacuo* to afford 0.125 g. of the desired product as a foam. ¹H—NMR (CDCl₃) ppm (delta): 1.4 (s, 3H), 1.5 (s, 3H), 1.6 (s, 3H), 1.65 (s, 3H), 4.42 (s, 1H), 4.5 (s, 1H), 4.75 (d, 1H), 5.07 (s, 1H), 5.3 (d, 1H), 5.4—5.75 (m, 2H), 5.85 (s, broad, 2H), 7.1 (d, 1H), 7.35 (s, 5H); Infrared (neat) cm⁻¹: 1800, 1775.

Example 23

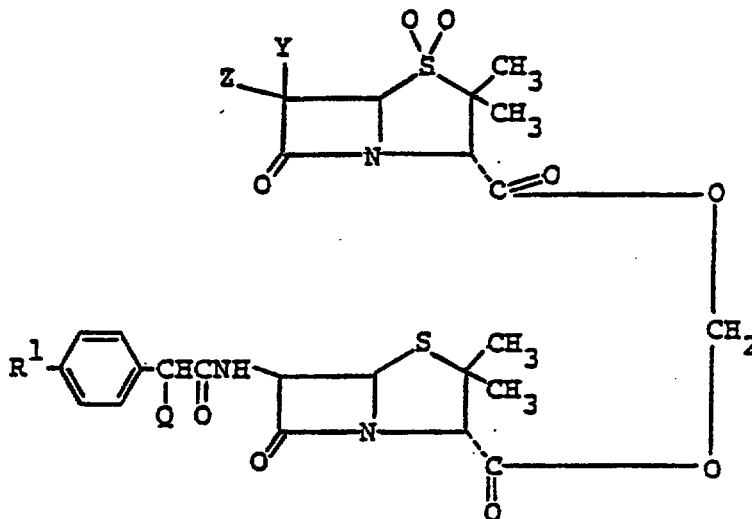
1,1-Dioxo-6- α -bromopenicillanoyloxymethyl 6-(D-2-azido-2-phenylacetamido)penicillanate

A mixture of 0.308 g. (0.5 mmole) tetrabutylammonium (D-2-azido-2-phenylacetamido)penicillanate, 0.219 g. (0.485 mmole) iodomethyl 6- α -bromopenicillanate 1,1-dioxide and 10 ml. acetone was stirred for 30 minutes at room temperature. The solvent was evaporated *in vacuo* and the residue chromatographed on a column of 50 g. silica gel, eluting with 1:1 (v/v) ethyl acetate/hexane. The product-containing fractions were combined and the solvent evaporated *in vacuo* to afford 0.125 g. (38%) of the title compound as an oil. ¹H—NMR (CDCl₃) ppm (delta): 1.43 (s, 3H), 1.5 (s, 3H), 1.6 (s, 3H), 1.66 (s, 3H), 4.4 (s, 2H), 4.64 (d, 1H), 5.05 (s, 1H), 5.1 (d, 1H), 5.4—5.7 (m, 2H), 5.85 (s, 2H), 7.08 (d, 1H), 7.35 (s, 5H); Infrared (neat) cm⁻¹: 1795, 1775.

Example 24

Employing the halomethyl, alkylsulfonyloxymethyl or arylsulfonyloxymethyl esters of 6,6-dihalopenicillanic acid 1,1-dioxides or the corresponding 6-halo compounds provided in Examples 2 through 8, 12, 13 and 15 as starting material, the following compounds are prepared by the methods of Examples 16 through 23.

25



where Q, R¹, Y and Z are as defined below.

	<u>Q</u>	<u>R¹</u>	<u>Y</u>	<u>Z</u>
25	4-Cl-C ₆ H ₅ CH ₂ OCONH-	H	Cl	Cl
	C ₆ H ₅ CH ₂ OCONH-	H	Cl	Br
	3-Br-C ₆ H ₄ CH ₂ OCONH-	H	Br	Br
30	4-NO ₂ -C ₆ H ₄ CH ₂ OCONH-	H	Br	I
	2-CH ₃ -C ₆ H ₄ CH ₂ OCONH-	H	I	I
35	4-CH ₃ OC ₆ H ₄ CH ₂ OCONH-	HO	Cl	Cl
	C ₆ H ₅ CH ₂ OCONH-	HO	Cl	Br
	3-CH ₃ OC ₆ H ₄ CH ₂ OCONH-	HO	Br	Br
40	2-Cl-C ₆ H ₄ CH ₂ OCONH-	HO	Br	I
	C ₆ H ₅ CH ₂ OCONH-	HO	H	alpha-I
45	N ₃	HO	H	alpha-Br
	C ₆ H ₅ CH ₂ OCONH-	H	H	alpha-Cl
	4-NO ₂ -C ₆ H ₄ CH ₂ OCONH-	HO	H	beta-I
50	N ₃	HO	H	beta-Br
	N ₃	H	H	beta-Cl

Example 25

1,1-Dioxopenicillanoyloxymethyl 6-(D-2-amino-2-phenylacetamido)penicillanate

A mixture of 1.2 g. 5% palladium-on-calcium carbonate and 30 ml. 1:1 by volume isopropanol/methylene chloride was hydrogenated at 50 psi (3.45 bar) for 30 minutes. To this was added 0.25 g. (0.32 mmole) 1,1-dioxo 6,6-dibromopenicillanoyloxymethyl 6-(D-2-azido-2-phenylacetamido)penicillanate dissolved in 3 ml. methylene chloride. The resulting mixture was hydrogenated at 50 psi for one hour. The catalyst was removed by filtration, washing with 30 ml. 1:1 isopropanol/methylene chloride. The filtrate was concentrated *in vacuo* to afford a tan solid. This was triturated with 15 ml. ethyl ether, filtered, washed with 10 ml. ether and air dried to afford 0.195 g. of product. ¹H-NMR (CDCl₃) ppm (delta): 1.5 (d, 6H), 1.6 (d, 6H), 3.55 (d, 2H), 4.45 (s, 1H), 4.55 (s, 1H), 4.6-4.75 (m, 2H), 5.5-5.7 (m, 2H), 5.9 (q, 2H), 7.4 (s, 4H), 8.1 (d, 1H).



Example 26

1,1-Dioxopenicillanoyloxymethyl 6-[D-2-amino-2-(*p*-hydroxyphenyl)acetamido]penicillanate

A mixture of 1.0 g. 1,1-dioxo-6-bromo-6-chloro-penicillanoyloxymethyl 6-[D-2-azido-2-(*p*-hydroxyphenyl)acetamido]penicillanate, 50 ml. methylene chloride, 50 ml. isopropanol, 270 mg. triethylamine and 1 g. 5% P palladium-on-carbon catalyst is shaken with hydrogen at 60 psi (4.1 bar) for two hours. The catalyst is removed by filtration and the filtrate washed with 3 x 50 ml. water. The washings are combined, adjusted to pH 7.5 and extracted with methylene chloride. The combined organic layers are dried (MgSO₄) and the solvent evaporated *in vacuo* to afford the crude title compound which is purified by chromatography on silica gel.

Example 27

1,1-Dioxopenicillanoyloxymethyl 6-(D-2-amino-2-phenylacetamido)penicillanate

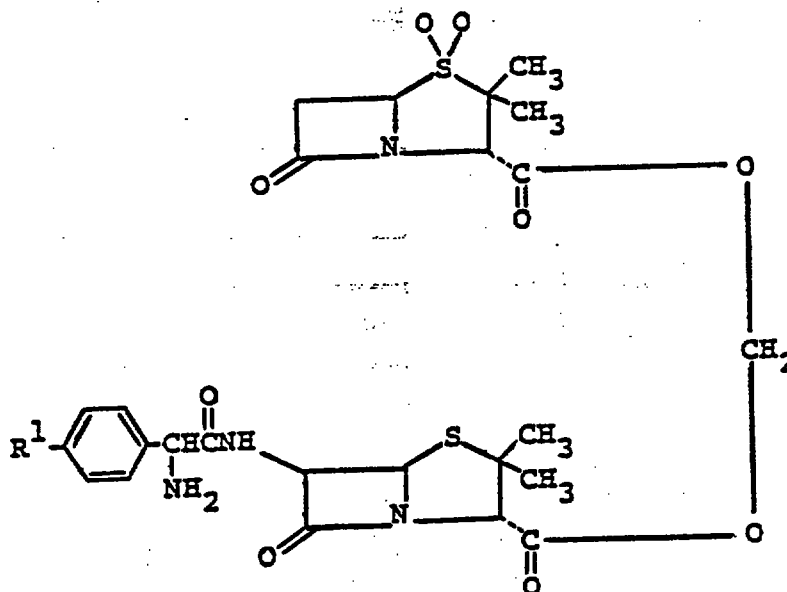
A. A mixture of 2.5 g. 1,1-dioxo-6,6-dichloropenicillanoyloxymethyl 6-(D-2-azido-2-phenylacetamido)penicillanate, 60 ml. ethyl acetate, 20 ml. 5% (w/v) sodium bicarbonate solution and 2.5 g. of 10% palladium-on-carbon catalyst is hydrogenated with agitation at 50 psi (3.5 bar) until hydrogen uptake ceases. The catalyst is removed by filtration, the layers separated and the aqueous phase extracted with ethyl acetate. The combined organic layers are dried (Na₂SO₄) and evaporated *in vacuo* to provide the desired product. It is purified by chromatography on silica gel.

When the palladium catalyst employed above is replaced by a similar amount of nickel, platinum or rhodium catalyst similar results are obtained.

B. Hydrogenation of 1,1-dioxo-6,6-dibromopenicillanoyloxymethyl 6-(D-2-benzyloxycarbonylamino-2-phenylacetamido)penicillanate by the above procedures affords the same product.

Example 28

Hydrogenation of the compounds provided in Examples 16—24 by the procedures of Examples 25 through 27 affords compounds of the formula below in like manner



where R¹ is as defined in Examples 16 through 24.

Preparation A

6-[D-2-azido-2-(*p*-hydroxyphenyl)acetamido]penicillanic Acid

The method is that of Japanese Kokai 78—37, 691; *Chem. Abstr.*, 89, 109466v (1978).

To a mixture of 10 g. 6-aminopenicillanic acid and 100 ml. acetone is added dropwise at 0°C. 10 g. D-2-azido-2-(*p*-hydroxyphenyl)acetic acid chloride while simultaneously adding powdered potassium bicarbonate to maintain the mixture at pH 7—8. After the addition is complete the mixture is stirred at room temperature and pH 7—8 for five hours. The reaction mixture is filtered and the filtrate evaporated *in vacuo*. the residue is purified by chromatography on silica gel to afford the title compound.

Preparation B

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 34.5 g. of sodium nitrate. To this stirred mixture was then added 54.0 g. of 6-aminopenicillanic acid, portionwise over 30 minutes, with the temperature maintained from 4 to 10°C. Stirring was continued

for 30 minutes at 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 preparation of esters or evaporated to dryness to provide the desired product.

Preparation C

6-Chloro-6-iodopenicillanic Acid

To 100 ml. of dichloromethane cooled to 3°C. was added 4.87 g. of iodine chloride, 10 ml. of 2.5N sulfuric acid and 2.76 g. of sodium nitrite. To this stirred mixture was then added 4.32 g. of 6-aminopenicillanic acid portionwise during a 15 minute period. Stirring was continued for 20 minutes at 0—5°C., and then 100 ml. of 10% sodium bisulfite solution was added dropwise at ca. 4°C. Stirring was continued for 5 minutes and 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 (MgSO₄) and evaporated *in vacuo* to give the title compound as a tan solid, m.p. 148—152°C. The NMR spectrum of the product (CDCl₃) 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 absorptions at 1780 and 1715 cm⁻¹.

Preparation D

6-Bromo-6-iodopenicillanic Acid

To 100 ml. of dichloromethane, cooled to 5°C., was added 10 ml. of 2.5N sulfuric acid, 6.21 g. of iodine bromide and 2.76 g. of sodium nitrite. To this mixture was added, with vigorous stirring, at 0—5°C., over 15 minutes, 4.32 g. 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 x 50 ml.). The combined dichloromethane layers were washed with brine, dried (MgSO₄) and evaporated *in vacuo*. The residue was dried under high vacuum for 30 minutes to give 6.0 g. (72% yield) of the title compound m.p. 144—147°C. The NMR spectrum (CDCl₃) 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⁻¹. The mass spectrum showed a prominent ion at m/e = 406.

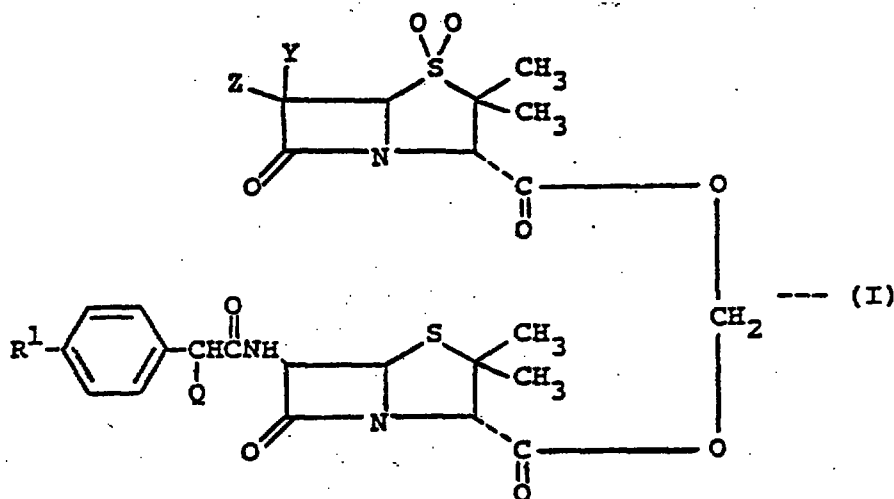
Preparation E

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 D.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula



wherein R¹ is H or OH;

Y and Z are each Cl, Br or I, or Y is H and Z is Cl, Br or I and

Q is N₃ or NHCO₂CH₂C₆H₄R⁴ where R⁴ is H, Cl, Br, NO₂, CH₃ or OCH₃.

2. A compound according to claim 1 wherein Y and Z are each Cl or Br, or Y is H and Z is Cl or Br; and Q is N₃ or NHCO₂CH₂C₆H₅.

3. A compound according to claim 2 wherein Y and Z are each Br or Y is H and Z is Br; and Q is N₃.

4. A process for preparing a compound of the formula

for 30 minutes at 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 preparation of esters or evaporated to dryness to provide the desired product.

Preparation C

6-Chloro-6-iodopenicillanic Acid

To 100 ml. of dichloromethane cooled to 3°C. was added 4.87 g. of iodine chloride, 10 ml. of 2.5N sulfuric acid and 2.76 g. of sodium nitrite. To this stirred mixture was then added 4.32 g. of 6-aminopenicillanic acid portionwise during a 15 minute period. Stirring was continued for 20 minutes at 0–5°C., and then 100 ml. of 10% sodium bisulfite solution was added dropwise at ca. 4°C. Stirring was continued for 5 minutes and 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 (MgSO₄) and evaporated *in vacuo* to give the title compound as a tan solid, m.p. 148–152°C. The NMR spectrum of the product (CDCl₃) 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 absorptions at 1780 and 1715 cm⁻¹.

Preparation D

6-Bromo-6-iodopenicillanic Acid

To 100 ml. of dichloromethane, cooled to 5°C., was added 10 ml. of 2.5N sulfuric acid, 6.21 g. of iodine bromide and 2.76 g. of sodium nitrite. To this mixture was added, with vigorous stirring, at 0–5°C., over 15 minutes, 4.32 g. 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 x 50 ml.). The combined dichloromethane layers were washed with brine, dried (MgSO₄) and evaporated *in vacuo*. The residue was dried under high vacuum for 30 minutes to give 6.0 g. (72% yield) of the title compound m.p. 144–147°C. The NMR spectrum (CDCl₃) 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⁻¹. The mass spectrum showed a prominent ion at m/e = 406.

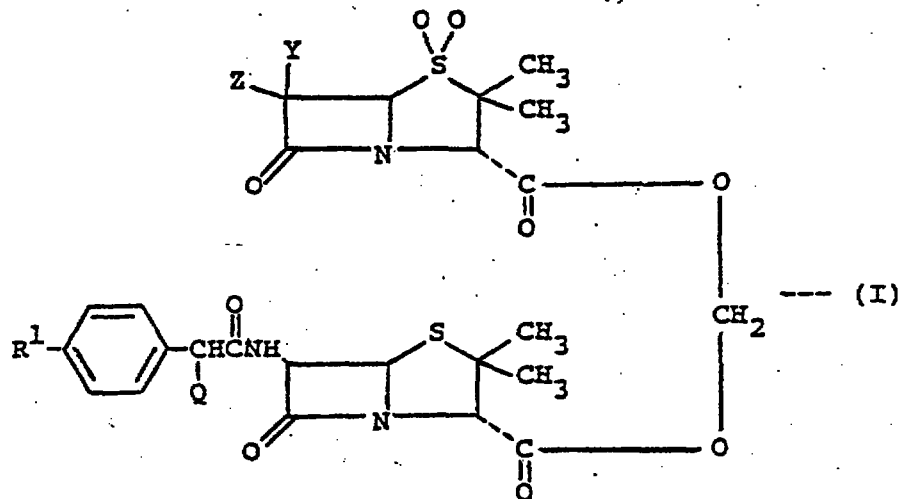
Preparation E

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 D.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula



wherein R¹ is H or OH;

Y and Z are each Cl, Br or I, or Y is H and Z is Cl, Br or I and

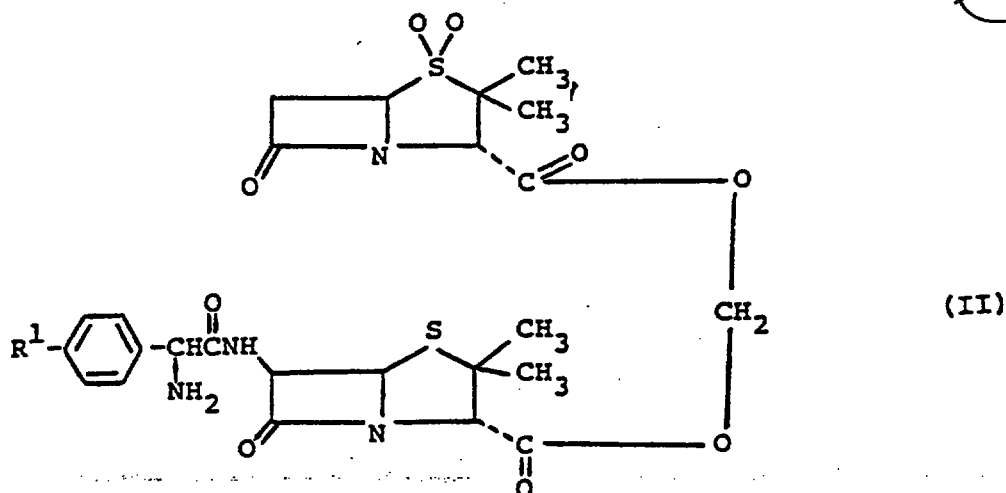
Q is N₃ or NHCO₂CH₂C₆H₄R⁴ where R⁴ is H, Cl, Br, NO₂, CH₃ or OCH₃.

2. A compound according to claim 1 wherein Y and Z are each Cl or Br, or Y is H and Z is Cl or Br; and Q is N₃ or NHCO₂CH₂C₆H₅.

3. A compound according to claim 2 wherein Y and Z are each Br or Y is H and Z is Br; and Q is N₃.

4. A process for preparing a compound of the formula





20 or a pharmaceutically acceptable acid addition salt thereof; wherein R¹ is H or OH, characterized in that a compound of the formula (I) wherein R¹, Y, Z and Q are as defined in Claim 1, in a reaction inert solvent, is contacted with hydrogen in the presence of a noble metal catalyst and at least two, or when Y is H, at least one molar equivalents of an acid binding agent.

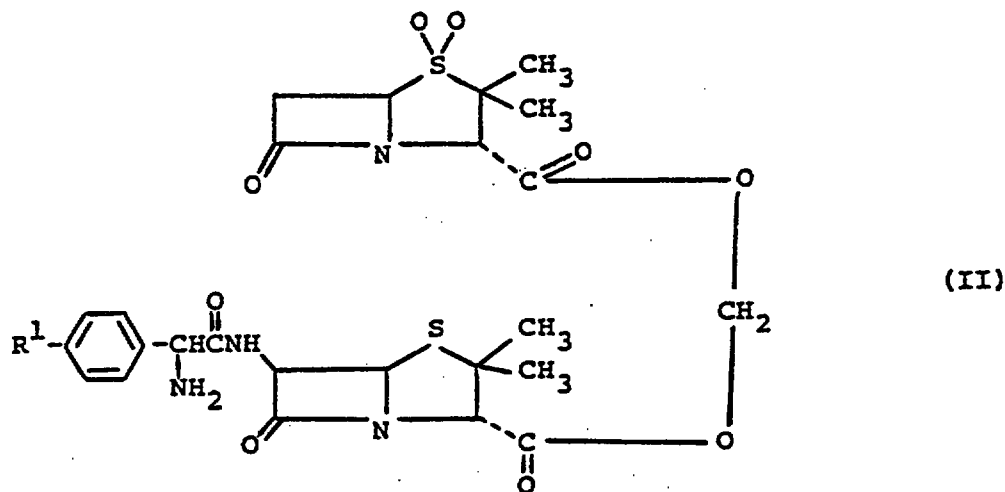
25 5. A process according to claim 4 wherein Q is N₃ or NHCO₂CH₂C₆H₅, Y and Z are each Cl or Br or Y is H and Z is Cl or Br.

30 6. A process according to claim 5 wherein Q is N₃, Y and Z are each Br.

7. A process according to claim 4 wherein the acid binding agent is sodium bicarbonate, calcium carbonate, trisodium phosphate, potassium citrate triethylamine, N,N-dimethylaniline, N-methylmorpholine, N-methyl-piperidine or N,N'-dimethylpiperazine.

30 Claims for the Contracting State: AT

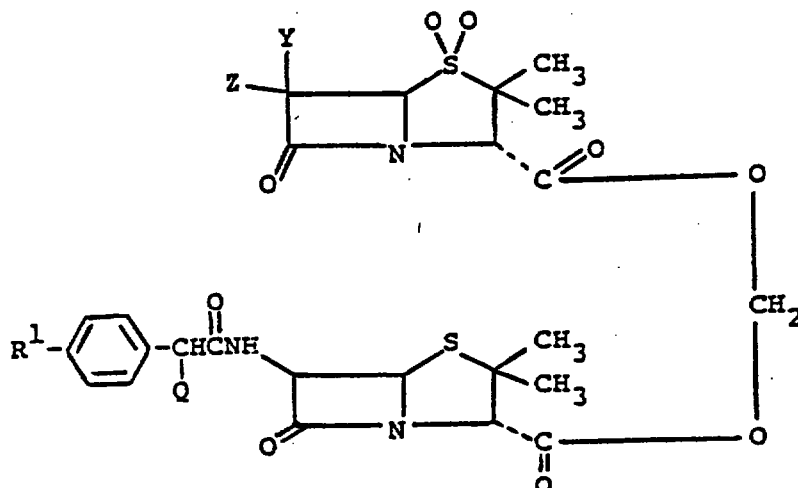
1. A process for preparing a compound of the formula



55 or a pharmaceutically acceptable acid addition salt thereof; wherein R¹ is H or OH, characterized in that a compound of the formula

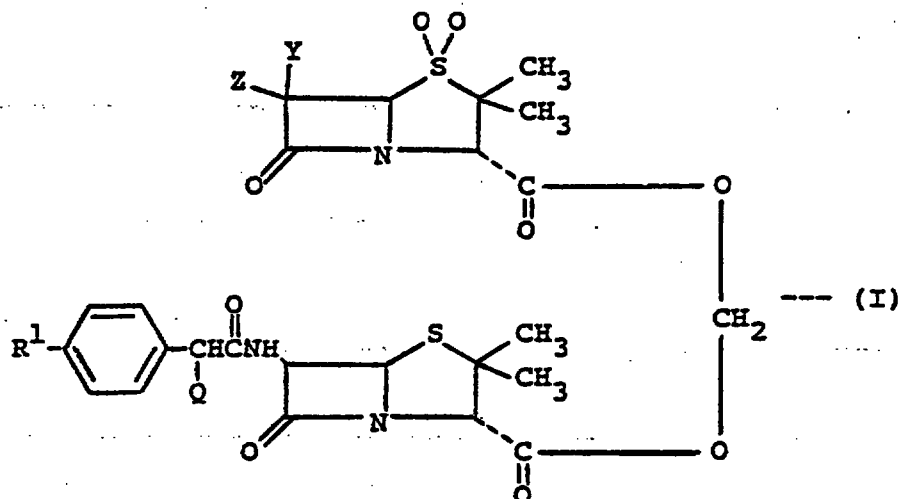


29



wherein R^1 is as defined above, Q is N_3 or $NHCO_2CH_2C_6H_4R^4$ where R^4 is H, Cl, Br, NO_2 , CH_3 or OCH_3 ; Y and Z are each Cl, Br or I, or Y is H and Z is Cl, Br or I; in a reaction inert solvent, is contacted with hydrogen in the presence of a noble metal catalyst and at least two, or when Y is H, at least one molar equivalents of an acid binding agent.

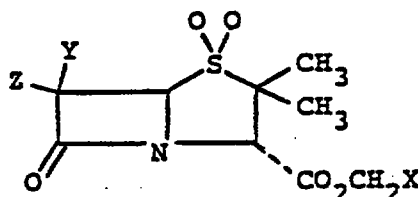
2. A process for preparing a compound of the formula



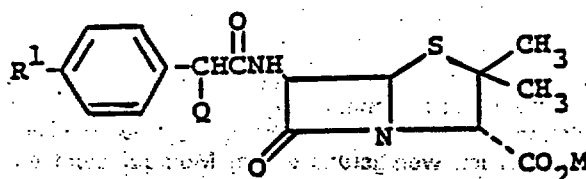
wherein R^1 is H or OH;

Y and Z are each Cl, Br or I, or Y is H and Z is Cl, Br or I and

Q is N_3 or $NHCO_2CH_2C_6H_4R^4$ where R^4 is H, Cl, Br, NO_2 , CH_3 or OCH_3 ; characterized in that a compound of the formula



where X is Cl, Br, I or OSO_2R^2 where R^2 is alkyl having from one to six carbon atoms or $C_6H_4R^3$ and R^3 is Cl, Br, I, NO_2 alkyl or alkoxy having from one to three carbon atoms; is contacted with an equimolar amount of a compound of the formula



where M is an alkali metal, alkaline earth, tertiary amine or tetraalkylammonium cation; in a polar organic solvent at a temperature of from 0 to 80°C.

3. A process according to claims 1 or 2 wherein Q is N₃ or NHCO₂CH₂C₆H₅.

4. A process according to claim 3 wherein Q is N₃, Y and Z are each Cl or Br, or Y is H and Z is Cl or Br.

5. A process according to claim 4 wherein Y and Z are each Br or Y is H and Z is Br.

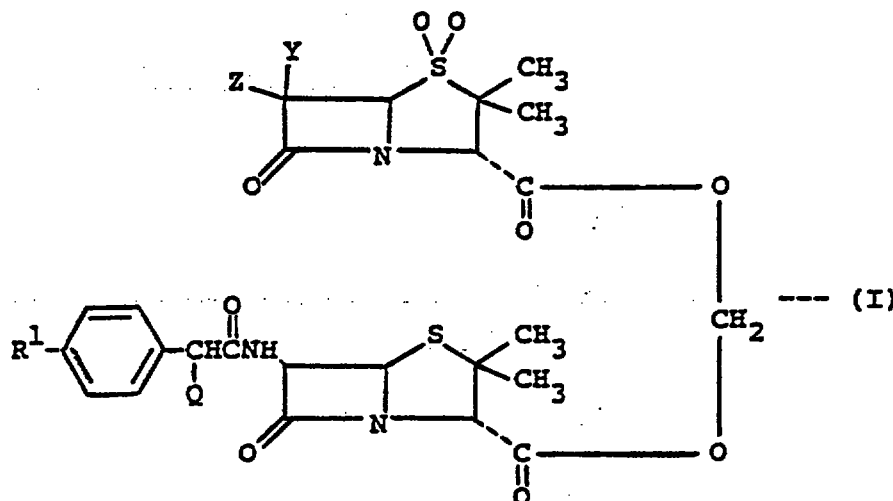
6. A process according to claim 5 wherein Y and Z are each Br and R¹ is H.

7. A process according to claim 2 wherein X is Cl, Br, I, CH₃SO₂O or 4-CH₃C₆H₄SO₂O and M is a sodium, potassium or tetrabutylammonium cation.

8. A process according to claim 7 wherein X is I and M is tetrabutylammonium.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der Formel



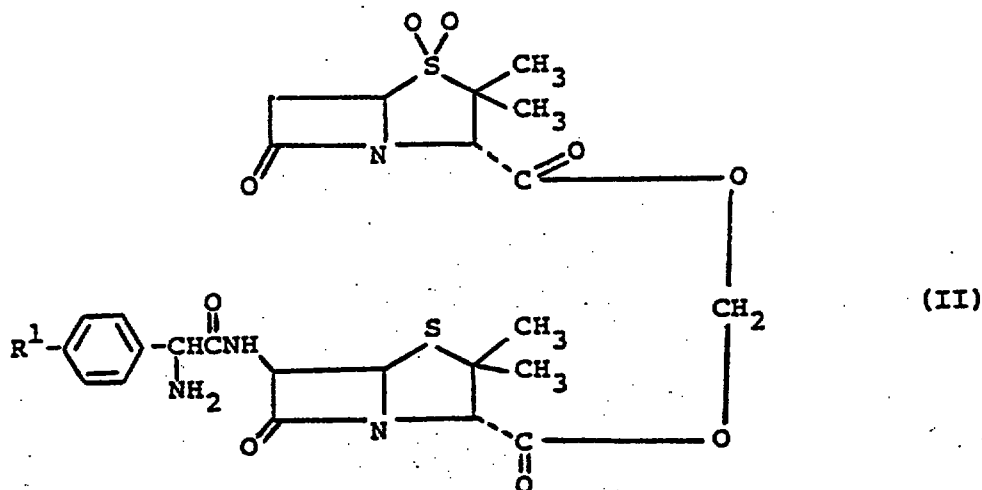
worin R¹ H oder OH ist;

Y und Z jeweils Cl, Br oder J sind oder Y H und Z Cl, Br oder J ist, und Q N₃ oder NHCO₂CH₂C₆H₄R⁴ ist, worin R⁴ H, Cl, Br, NO₂, CH₃ oder OCH₃ ist.

2. Verbindung nach Anspruch 1, worin Y und Z jeweils Cl oder Br sind oder Y H und Z Cl oder Br ist; und Q N₃ oder NHCO₂CH₂C₆H₅ ist.

3. Verbindung nach Anspruch 2, worin Y und Z jeweils Br sind oder Y H und Z Br ist; und Q N₃ ist.

4. Verfahren zur Herstellung einer Verbindung der Formel



odereines pharmazeutisch annehmbaren Säureadditionssalzes hiervon, worin R¹ H oder OH ist, dadurch gekennzeichnet, daß eine Verbindung der Formel (I), worin R¹, Y Z und Q wie in Anspruch 1 definiert sind, in einem reaktionsinerten Lösungsmittel mit Wasserstoff in Gegenwart eines Edelmetallkatalysators und wenigstens zwei, oder, wenn Y H ist, wenigstens einem Moläquivalent eines säurebindenden Mittels zusammengebracht wird.



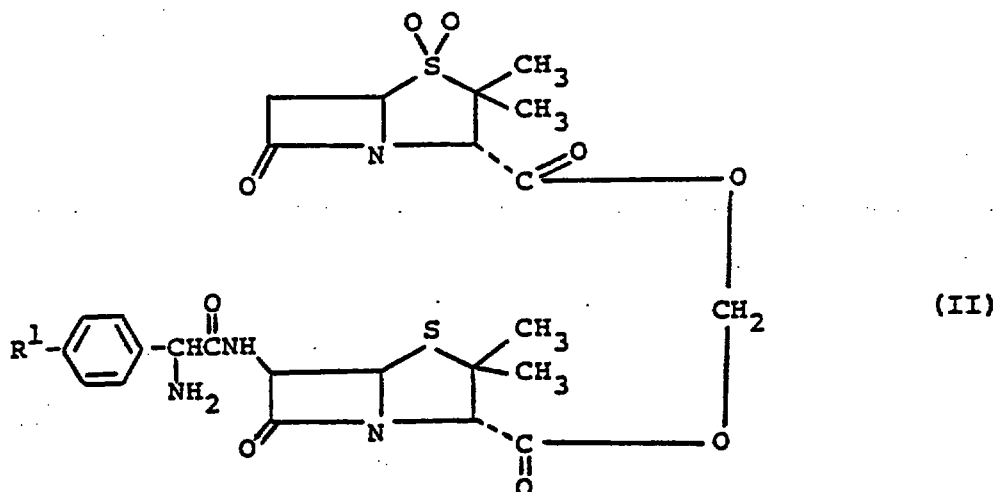
5. Verfahren nach Anspruch 4, worin Q N₃ oder NHCO₂CH₂—C₆H₅ ist, Y und Z jeweils Cl oder Br sind oder Y H und Z Cl oder Br ist.

6. Verfahren nach Anspruch 5, worin Q N₃ ist, Y und Z jeweils Br sind.

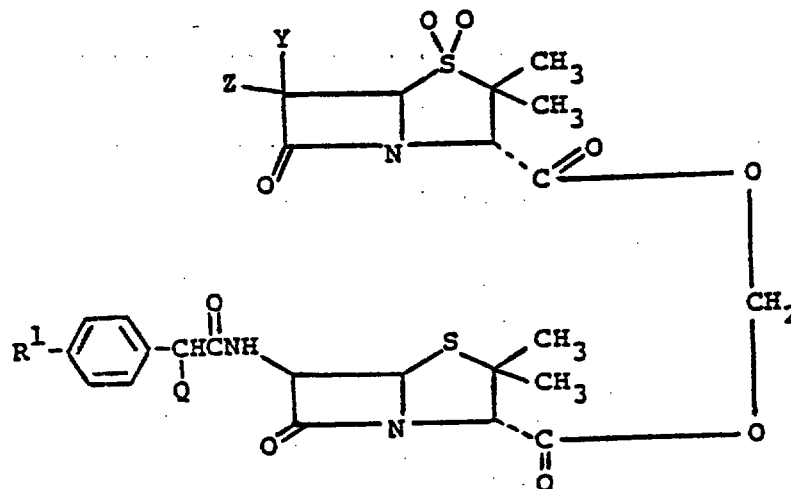
7. Verfahren nach Anspruch 4, worin das säurebindende Mittel Natriumbicarbonat, Calciumcarbonat, Trinatriumphosphat, Kaliumcitrat, Triethylamin, N,N-Dimethylanilin, N-Methylmorpholin, N-Methylpiperidin oder N,N'-Dimethylpiperazin ist.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel



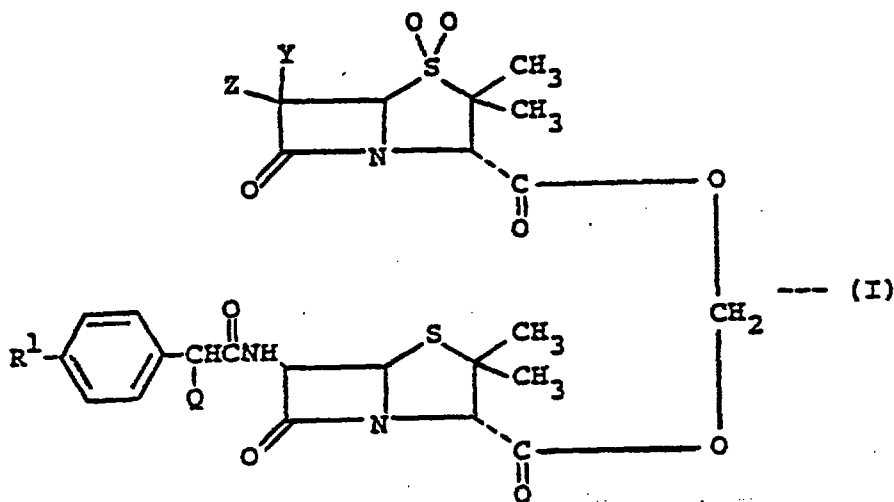
oder eines pharmazeutisch akzeptablen Säureadditionssalzes hiervon, worin R¹ H oder OH ist, dadurch gekennzeichnet, daß eine Verbindung der Formel



worin R¹ wie oben definiert ist, Q N₃ oder NHCO₂CH₂C₆H₄R⁴ ist, worin R⁴ H, Cl, Br, NO₂, CH₃ oder OCH₃ ist; Y und Z jeweils Cl, Br oder J sind oder Y H ist und Z Cl, Br oder J ist; in einem reaktionsinerten Lösungsmittel mit Wasserstoff in Gegenwart eines Edelmetallkatalysators und wenigstens zwei oder, wenn Y H ist, wenigstens einem Moläquivalent eines säurebindenden Mittels zusammengebracht wird.

2. Verfahren zur Herstellung einer Verbindung der Formel

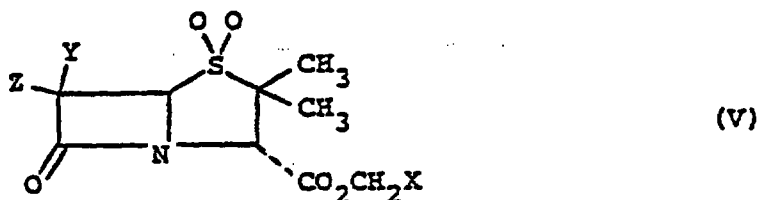




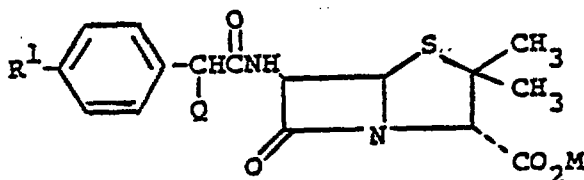
worin R^1 H oder OH ist;

Y und Z jeweils Cl, Br oder J sind oder Y H ist und Z Cl, Br oder J ist und

Q N_3 oder $NHCO_2CH_2C_6H_4R^4$ ist, worin R^4 H, Cl, Br, NO_2 , CH_3 oder OCH_3 ist; dadurch gekennzeichnet, daß eine Verbindung der Formel



worin X Cl, Br, J oder OSO_2R^2 ist, worin R^2 Alkyl mit 1 bis 6 Kohlenstoffatomen oder $C_6H_4R^3$ ist und R^3 Cl, Br, J, NO_2 oder Alkyl oder Alkoxy mit 1 bis 3 Kohlenstoffatomen ist, mit einer äquimolaren Menge einer Verbindung der Formel



worin M ein Alkalimetall-, Erdalkali-, tert.-Amin- oder Tetraalkylammoniumkation ist; in einem polaren organischen Lösungsmittel bei einer Temperatur von 0 bis $80^\circ C$ zusammengebracht wird.

3. Verfahren nach den Ansprüchen 1 oder 2, worin Q N_3 oder $NHCO_2CH_2C_6H_5$ ist.

4. Verfahren nach Anspruch 3, worin Q N_3 ist, Y und Z jeweils Cl oder Br sind oder Y H ist und Z Cl oder Br ist.

5. Verfahren nach Anspruch 4, worin Y und Z jeweils Br sind oder Y H ist und Z Br ist.

6. Verfahren nach Anspruch 5, worin Y und Z jeweils Br sind und R^1 H ist.

7. Verfahren nach Anspruch 2, worin X Cl, Br, J, CH_3SO_2O oder $4-CH_3C_6H_4SO_2O$ ist und M ein Natrium-, Kalium- oder Tetrabutylammoniumkation ist.

8. Verfahren nach Anspruch 7, worin X J und M Tetrabutylammonium ist.



1. Composé de formule



Y et Z représentent chacun Cl, Br ou I, ou bien Y représente

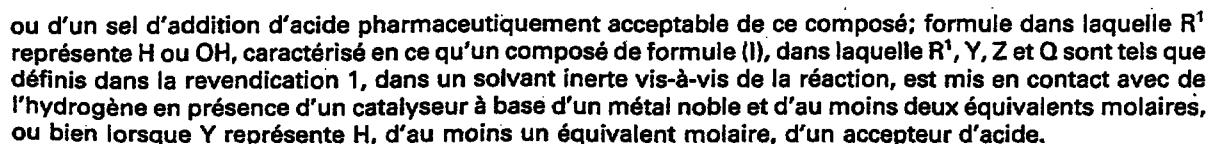
H et Z représente Cl, Br ou I et

Q représente N₃ ou un groupe NHCO₂CH₂C₆H₄R⁴, dans lequel R⁴ représente H, Cl, Br, NO₂, CH₃ ou

2. Composé suivant la revendication 1, dans lequel Y et Z représentent chacun Cl ou Br, ou bien Y représente H et Z représente Cl ou Br; et Q représente N₃ ou le groupe NHCO₂CH₂C₆H₅.

3. Composé suivant la revendication 2, dans lequel Y et Z représentent chacun Br, ou bien Y représente H et Z représente Br; et Q représente N_3 .

4. Procédé de préparation d'un composé de formule



5. Procédé suivant la revendication 4, dans lequel Q représente N₃ ou le groupe NHCO₂CH₂C₆H₅, Y et Z représentent chacun Cl ou Br ou bien Y représente H et Z représente Cl ou Br.

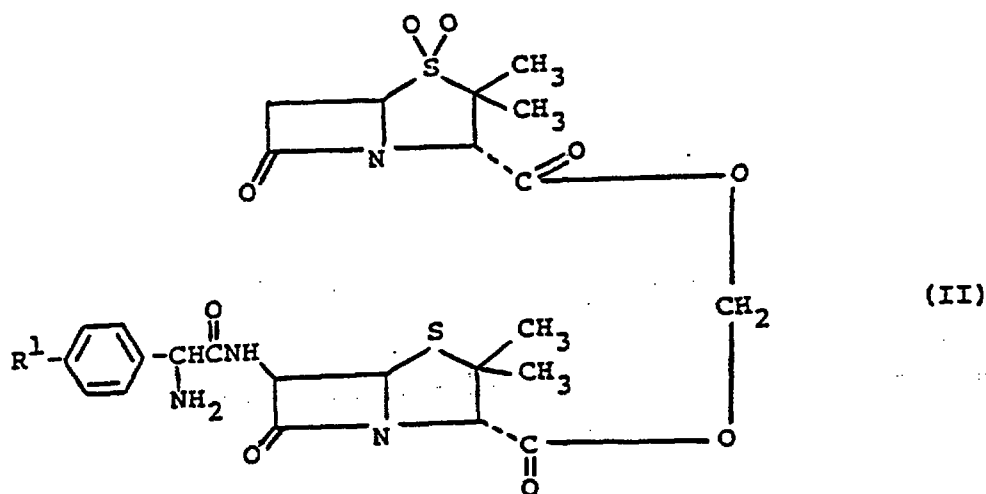
6. Procédé suivant la revendication 5, dans lequel Q représente N_3 , Y et Z représentant chacun Br.

7. Procédé suivant la revendication 4, dans lequel l'accepteur d'acide est le bicarbonate de sodium, le carbonate de calcium, le phosphate trisodique, le citrate de potassium, la triéthylamine, la N,N-diméthylaniline, la N-méthylmorpholine, le N-méthylpipéridine ou la N,N'-diméthylpipérazine.

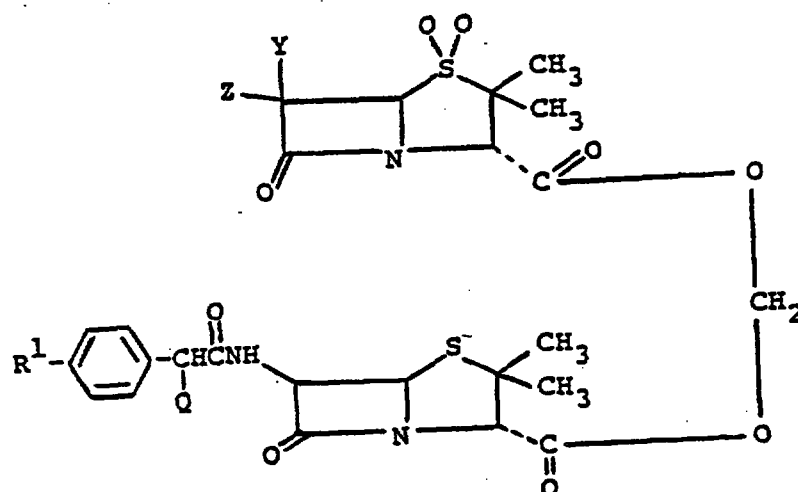
Revendications pour l'Etat contractant: AT

3A

1. Procédé de préparation d'un composé de formule



ou d'un sel d'addition d'acide pharmaceutiquement acceptable de ce composé; formule dans laquelle R¹ représente H ou OH, caractérisé en ce qu'un composé de formule

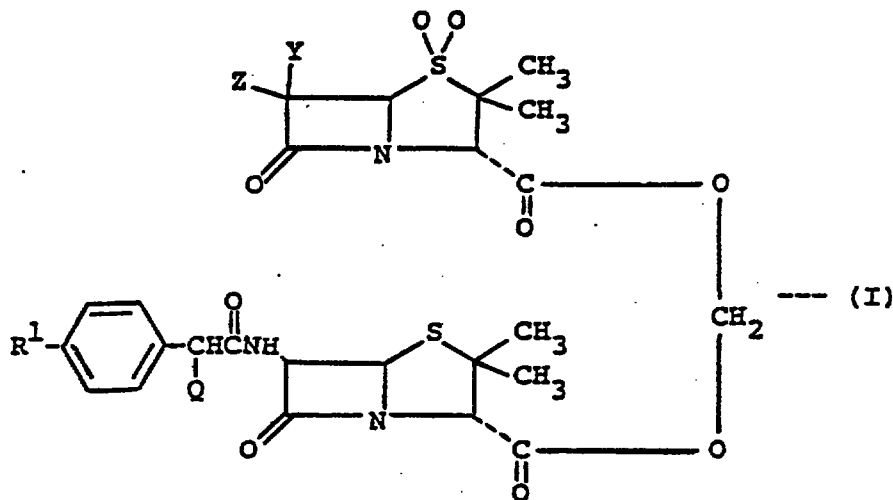


dans laquelle R¹ est tel que défini ci-dessus, Q représente N₃ ou un groupe NHCO₂CH₂C₆H₄R⁴, dans lequel R⁴ représente H, Cl, Br, NO₂, CH₃ ou OCH₃; Y et Z représentent chacun Cl, Br ou I, ou bien Y représente H et Z représente Cl, Br ou I; dans un solvant inerte vis-à-vis de la réaction, est mis en contact avec de l'hydrogène en présence d'un catalyseur à base d'un métal noble et d'au moins deux équivalents molaires, ou bien lorsque Y représente H, d'au moins un équivalent molaire, d'un accepteur d'acide.

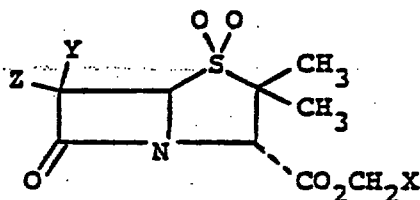
2. Procédé de préparation d'un composé de formule



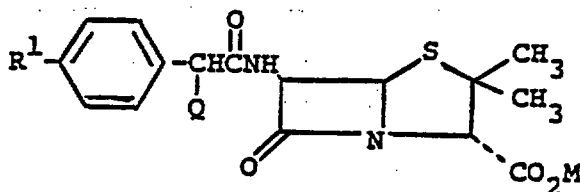
(35)



- 20 dans laquelle R^1 représente H ou OH;
 Y et Z représentent chacun Cl, Br ou I, ou bien Y représente H et Z représente Cl, Br ou I et
 Q représente N_3 ou un groupe $NHCO_2CH_2C_6H_4R^4$ dans lequel R^4 représente H, Cl, Br, NO_2 , CH_3 ou OCH_3 ;
 caractérisé en ce qu'un composé de formule



- 35 dans laquelle X représente Cl, Br, I ou un groupe OSO_2R^2 , dans lequel R^2 est un radical alkyle ayant 1 à 6
 atomes de carbone ou un groupe $C_6H_4R^3$ et R^3 représente Cl, Br, I, NO_2 ou un radical alkyle ou alkoxy ayant
 un à trois atomes de carbone;
 est mis en contact avec une quantité équimolaire d'un composé de formule



- 40 dans laquelle M est un métal alcalin, un métal alcalinoterreux, une amine tertiaire ou un cation tétraalkyl-
 ammonium; dans un solvant organique polaire à une température de 0 à 80°C.
 3. Procédé suivant la revendication 1 ou 2, dans lequel Q représente N_3 ou le groupe $NHCO_2CH_2C_6H_5$.
 4. Procédé suivant la revendication 3, dans lequel Q représente N_3 , Y et Z représentent chacun Cl ou Br,
 ou bien Y représente H et Z représente Cl ou Br.
 5. Procédé suivant la revendication 4, dans lequel Y et Z représentent chacun Br ou bien Y représente H
 et Z représente Br.
 6. Procédé suivant la revendication 5, dans lequel Y et Z représentent chacun Br et R^1 représente H.
 7. Procédé suivant la revendication 2, dans lequel X représente Cl, Br, I, CH_3SO_2O ou $4-CH_3C_6H_4SO_2O$
 et M est un cation sodium, potassium ou tétrabutylammonium.
 8. Procédé suivant la revendication 7, dans lequel X représente I et M est le cation tétrabutyl-
 ammonium.

