

PATENT SPECIFICATION

(11) 1291052

1291052

NO DRAWINGS

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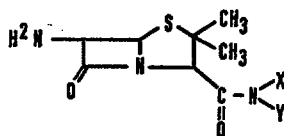


(54) PENICILLIN DERIVATIVES AND THEIR PREPARATION

(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America or 685 Third Avenue, New York City 17, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the preparation of 6-aminopenicillanic acid by hydrolysis of 2-amido-6-amino-penicillanic acids.

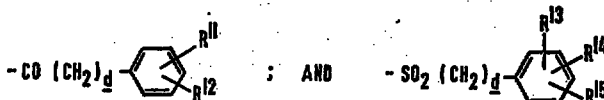
The 2-amido-6-aminopenicillanic acids have the formula



in which X and Y when taken separately are both electron withdrawing groups, or when taken with the nitrogen atom to which they are attached, complete a cyclic electron withdrawing group.

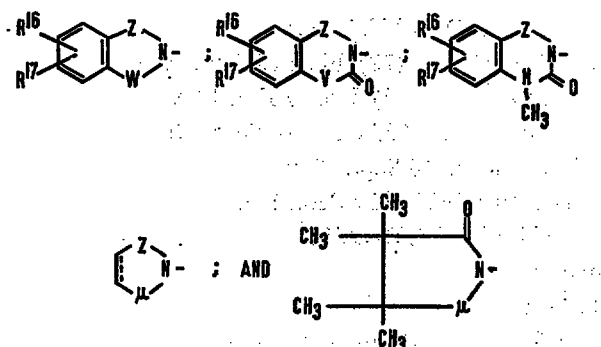
The compounds of this formula are described and claimed in our patent application No. 45514/69 (Serial No. 1291053).

As known to those skilled in the chemical art, included in those groups which are electron withdrawing when X and Y are taken separately are, for example: cyano, nitro, trifluoromethylsulphonyl, 2,4,6-trimethylbenzoyl, 2,3,5,6-tetramethylbenzoyl; carb(lower)alkoxy; di(lower)alkylcarbonyl, loweralkylsulphonyl; di(lower)alkylsulphamyl, di(lower)alkylamino(lower)alkylsulphonyl; lower alkanoyl, e.g. tert.-butyryl; cyclo(lower)alkanoyl, aryl, e.g. naphthoyl and furyl; substituted aroyl; arylsulphonyl, e.g. naphthylsulphonyl, pyridylsulphonyl, furylsulphonyl; substituted arylsulphonyl;



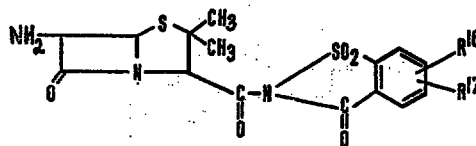
wherein R¹¹ and R¹² are hydrogen, lower alkyl, halogen, trifluoromethyl, lower alkoxy, phenyl, phenoxy, nitro, loweralkylsulphonyl, di(lower)alkylsulphamyl; R¹³, R¹⁴ and R¹⁵ can be hydrogen, nitro, halogen, trifluoromethyl, lower alkyl, lower alkoxy, lower alkylsulphonyl, lower alkylthio, di(lower)alkylsulphamyl, di(lower)alkylcarbonyl, cyano and carb(lower)alkoxy; and the integer d is from 0 to 6.

As is also known to those skilled in the chemical art, included in those cyclic electron withdrawing groups when X and Y are taken together are, for example:



wherein R^{16} and R^{17} when taken separately can be hydrogen, lower alkyl, lower alkoxy, halogen, phenyl, phen(lower)alkyl, loweralkoxyphenyl, aryl, heterocyclyl, e.g. 2-pyridyl, 4-pyridyl, trihalomethyl, e.g. trifluoromethyl, nitro, di(lower)alkylamino, sulphamido, carb(lower)alkoxy, cyano, loweralkylthio or loweralkylsulphonyl, and when R^{16} and R^{17} are joined, they complete a benzene ring fused to the existing benzene ring to form thereith a naphthalene ring; Z is sulphonyl or carbonyl; W is sulphonyl, carbonyl or methylene; Y is oxygen, sulphur or methylene; μ is carbonyl or methylene; and the broken line indicates the presence of a single or double bond between these to positions.

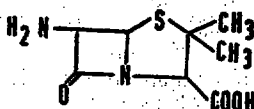
The preferred starting compounds for the process are those compounds wherein X and Y are concatenated to form a saccharyl or substituted saccharyl group. These compounds are designated by the following formula:



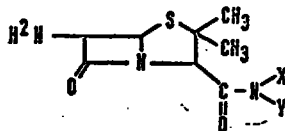
and the acid-addition salts thereof, wherein R^{16} and R^{17} are defined as above.

The term "lower alkyl" as employed herein, alone or in conjunction with the other designated groups, means straight chain or branched chain alkyl groups containing from one to six carbon atoms, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, 2-ethylpropyl, hexyl, 2-propylpropyl, and the like. Similarly, the terms "lower alkoxy" and "lower alkanoyl" as used herein, alone or in conjunction with other designated groups, mean straight chain or branched chain groups also containing from one to six carbon atoms. The term "halogen" as used herein, alone or attached to other designated groups, may be illustrated by chlorine, bromine, iodine or fluorine. As will also be understood the ringed substituents, whether carbocyclic, e.g. phenyl, benzyl, etc. or heterocyclic, e.g. 2-pyridyl, 4-pyridyl, and the like may also be substituted by one or more of such usual substituents as those set forth for R^{16} and R^{17} above. Similarly, the naphthalene ring resulting when R^{16} and R^{17} are joined as referred to above may also carry one or more of the same substituents as mentioned above. By the phrase "electron withdrawing group" is meant an electrophilic group which will inductively withdraw electrons from the carbonyl portion of the 2-amido groups of the starting products thereby making these groups more liable to cleavage by a nucleophilic agent, e.g. water, alkali metal, hydroxides, tertiary amines, quinoline and the like, to afford a carboxylic acid group.

The invention provides a process of preparation of 6-aminopenicillanic acid whose formula is



which comprises contacting a 2-amido derivative of 6-amino penicillanic acid of formula



wherein X and Y are defined above with water, in the presence of a hydrolytic catalyst, until the hydrolysis is complete. As used herein the term "hydrolytic catalyst" refers to substances which will assist in the hydrolysis of the 2-amido moiety of the 2-amido amine starting compounds of this invention. Many such substances will readily suggest themselves to those skilled in the art of chemistry, for example, quinoline, pyridine, imidazole and alkali metal acetates, such as, sodium acetate. The hydrolysis is preferably carried out with treatment of the 2-amido derivative at a pH of from about 1.5 to about 9, in water or a mixture of water and a water-miscible solvent until hydrolysis is complete to afford 6-aminopenicillanic acid.

6-Aminopenicillanic acid may be acylated to prepare synthetic penicillins. For example, 6-aminopenicillanic acid may be acylated with an acid chloride by the procedures described in United States Patent Number 3,248,386 to afford 2-ethoxy naphthyl penicillin or nafcillin, or an N-carboxy anhydride as described in United States Patent Number 3,206,455 to obtain D(-)- α -aminobenzylpenicillin or ampicillin. Both of these penicillins have potent antibiotic activity in warm-blooded animals. Employing these same procedures many synthetic penicillins are prepared which possess valuable activity against both gram-positive and gram-negative bacteria.

The following examples illustrate the invention in which temperatures where not indicated are in $^{\circ}\text{C}$.

Example 1

6-Aminopenicillanic Acid

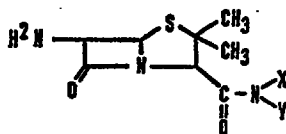
2 - (6 - Amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]hept-2 - ylcarbonyl) - 1,2 - benzisothiazol - 3(2H) - one 1,1 - dioxide (the saccharimide of 6-aminopenicillanic acid) (7.64 g., 0.02 mole) is dissolved in tetrahydrofuran (60 ml.) and a solution of sodium bicarbonate (3.36 g., 0.04 mole) in water (40 ml.) is added all at once. The mixture is stirred for $3\frac{1}{2}$ hours at room temperature giving a solution. Then the tetrahydrofuran is stripped off at 30°C under vacuum, and the resulting mixture is washed with methylene chloride. The aqueous fraction is then placed on a rotary evaporator at 30°C and the dissolved methylene chloride is removed. The solution is filtered and the pH adjusted to 3.8 with glacial acetic acid. The mixture is stirred in ice water for 20 minutes and then filtered, giving white crystals of 6-aminopenicillanic acid.

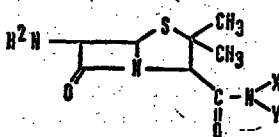
Example 2

2 - [(6 - Amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]hept-2-yl)carbonyl] - 1,2 - benzisothiazol - 3(2H) - one 1,1 - dioxide hydrobromide, also described as the saccharimide of 6-aminopenicillanic acid hydrobromide (0.02 mole) is dissolved in tetrahydrofuran (60 ml.) and a solution of sodium bicarbonate (3.36 g., 0.04 mole) in water (40 ml.) are added all at once. The mixture is stirred for three and a half hours at room temperature giving a solution. Then the tetrahydrofuran is stripped off at 30°C . under vacuum, and the resulting mixture is washed with methylene chloride. The aqueous fraction is then placed on a rotary evaporator at 30°C . and the methylene chloride is removed. The solution is filtered and the pH adjusted to 3.8 with glacial acetic acid. The mixture is stirred in ice-water for twenty minutes and then filtered, giving white crystals of 6-amino-3,3-dimethyl-7-oxo-4-thia-azabicyclo[3.2.0]heptane-2-carboxylic acid, also known as 6-aminopenicillanic acid.

WHAT WE CLAIM IS:—

1. A process of preparation of 6-aminopenicillanic acid, in which a 2-amido-6-aminopenicillanic acid of general formula





wherein X and Y are defined above with water, in the presence of a hydrolytic catalyst, until the hydrolysis is complete. As used herein the term "hydrolytic catalyst" refers to substances which will assist in the hydrolysis of the 2-amido moiety of the 2-amido amine starting compounds of this invention. Many such substances will readily suggest themselves to those skilled in the art of chemistry, for example, quinoline, pyridine, imidazole and alkali metal acetates, such as, sodium acetate. The hydrolysis is preferably carried out with treatment of the 2-amido derivative at a pH of from about 1.5 to about 9, in water or a mixture of water and a water-miscible solvent until hydrolysis is complete to afford 6-aminopenicillanic acid.

6-Aminopenicillanic acid may be acylated to prepare synthetic penicillins. For example, 6-aminopenicillanic acid may be acylated with an acid chloride by the procedures described in United States Patent Number 3,248,386 to afford 2-ethoxy naphthyl penicillin or nafcillin, or an N-carboxy anhydride as described in United States Patent Number 3,206,455 to obtain D(-)- α -aminobenzylpenicillin or ampicillin. Both of these penicillins have potent antibiotic activity in warm-blooded animals. Employing these same procedures many synthetic penicillins are prepared which possess valuable activity against both gram-positive and gram-negative bacteria.

The following examples illustrate the invention in which temperatures where not indicated are in °C.

Example 1

6-Aminopenicillanic Acid

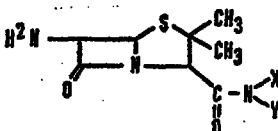
2 - (6 - Amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]hept-2 - ylcarbonyl) - 1,2 - benzisothiazol - 3(2H) - one 1,1 - dioxide (the saccharimide of 6-aminopenicillanic acid) (7.64 g., 0.02 mole) is dissolved in tetrahydrofuran (60 ml.) and a solution of sodium bicarbonate (3.36 g., 0.04 mole) in water (40 ml.) is added all at once. The mixture is stirred for 3½ hours at room temperature giving a solution. Then the tetrahydrofuran is stripped off at 30°C under vacuum, and the resulting mixture is washed with methylene chloride. The aqueous fraction is then placed on a rotary evaporator at 30°C and the dissolved methylene chloride is removed. The solution is filtered and the pH adjusted to 3.8 with glacial acetic acid. The mixture is stirred in ice water for 20 minutes and then filtered, giving white crystals of 6-aminopenicillanic acid.

Example 2

2 - [(6 - Amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]hept-2-yl)carbonyl] - 1,2 - benzisothiazol - 3(2H) - one 1,1 - dioxide hydrobromide, also described as the saccharimide of 6-aminopenicillanic acid hydrobromide (0.02 mole) is dissolved in tetrahydrofuran (60 ml.) and a solution of sodium bicarbonate (3.36 g., 0.04 mole) in water (40 ml.) are added all at once. The mixture is stirred for three and a half hours at room temperature giving a solution. Then the tetrahydrofuran is stripped off at 30°C. under vacuum, and the resulting mixture is washed with methylene chloride. The aqueous fraction is then placed on a rotary evaporator at 30°C. and the methylene chloride is removed. The solution is filtered and the pH adjusted to 3.8 with glacial acetic acid. The mixture is stirred in ice-water for twenty minutes and then filtered, giving white crystals of 6-amino-3,3-dimethyl-7-oxo-4-thia-azabicyclo[3.2.0]heptane-2-carboxylic acid, also known as 6-aminopenicillanic acid.

WHAT WE CLAIM IS:—

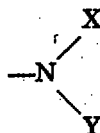
1. A process of preparation of 6-aminopenicillanic acid, in which a 2-amido-6-aminopenicillanic acid of general formula



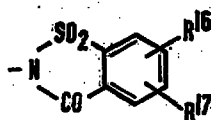
wherein X and Y, when taken separately, are both electron withdrawing groups or, when taken together with the nitrogen atom to which they are attached, X and Y complete a cyclic electron withdrawing group, is hydrolysed with water in the presence of a hydrolytic catalyst until hydrolysis is complete.

5 2. A process as claimed in Claim 1 wherein the 2-amido-6-aminopenicillanic acid is treated with water or a mixture of water and a water miscible organic solvent at a pH of from 1.5 to 9.

3. A process as claimed in Claim 1 or 2, wherein the group

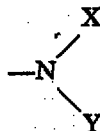


10 constitutes a saccharyl residue or a substituted saccharyl residue of general formula



15 wherein R¹⁶ and R¹⁷ taken separately are hydrogen, lower alkyl, lower alkoxy, halo, phenyl, benzyl, loweralkoxyphenyl, 2-pyridyl, 4-pyridyl, trihalomethyl, nitro, dilower-alkylamino, sulphamido, carboloweralkoxy, cyano, loweralkylthio or loweralkylsulphonyl or when joined together complete a benzene ring fused to the existing benzene ring to form a naphthalene ring.

4. A process as claimed in Claim 1 or 2, wherein the group



20 stands for an unsubstituted saccharyl group.

5. A process as claimed in Claim 1, substantially as described herein with reference to either of the Examples herein.

6. 6-Aminopenicillanic acid whenever prepared according to a process as claimed in any one of Claims 1 to 5.

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