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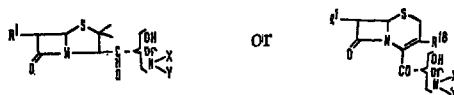


(54) PENICILLIN AND CEPHALOSPORIN DERIVATIVES AND THEIR PREPARATION

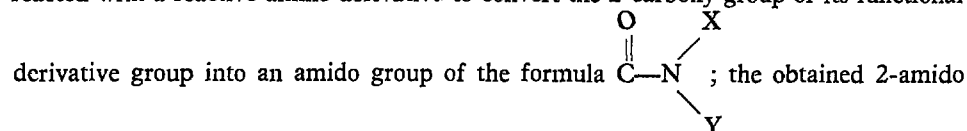
(71) **We, AMERICAN HOME PRODUCTS CORPORATION**, a corporation organised and existing under the laws of the State of Delaware, United States of America, and having a place of business at 685 Third Avenue, New York City 17, New York, United States of America, do hereby declare the invention for which 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 penicillins and cephalosporins and particularly to the preparation of and provides novel 2-amidopenicillins and 2-amidocephalosporins having antibiotic activity and hydrolysis of these to their corresponding acid forms. The invention further relates to the preparation of these 2-amido compounds by amidation of penicillins or cephalosporins or by acylation of a 2-amido-6-aminopenicillanic acid or a 2-amido-7-aminocephalosporin acid. The invention also concerns the preparation of and provides the aforesaid 2-amido-6-amidopenicillanic acids and 2-amido-7-amino acids via 2-amido-6-haloimido pencillins, 2-amido-6-alkoxyimido-penicillins, 2-amido-7-haloimidocephalosporins and 2-amido-7-alkoxyimidocephalosporins also provided and also concerns the preparation of 7-aminocephalosporin acids by hydrolysis of 2-amido-7-aminocephalosporin acids.

The invention provides, therefore, a process for the preparation of a penicillin or cephalosporin or a 2-amido derivative thereof of general formulae:



in which R¹ is a penicillin or cephalosporin amide group, X and Y when taken separately are both electron withdrawing groups or when taken together with the nitrogen atom to which they are attached complete a cyclic electron withdrawing group and R¹⁵ is a methyl, hydroxymethyl, N-pyridiniumylmethyl or alkanoyloxymethyl group; in which a penicillin or cephalosporin, or a functional derivative thereof is reacted with a reactive amine derivative to convert the 2-carboxy group or its functional



penicillin or 2-amidocephalosporin is reacted in a reaction inert aprotic solvent with a phosphorus pentahalide in the presence of a base to afford a corresponding 2-amido-6-haloimidopenicillin or 2-amido-7-haloimidocephalosporin which is reacted with an alkanol to afford the hydrohalide of a corresponding 2-amido-6-alkoxyimidopenicillin or 2-amido-7-alkoxyimidocephalosporin which in turn is hydrolysed with water to afford a 2-amido-6-aminopenicillanic acid or 2-amido-7-aminoccephalosporin acid hydrohalide which, if desired, is neutralised and the 2-amido-6-aminopenicillanic acid

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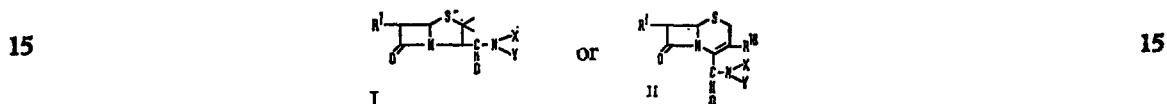
or 2-amido-7-aminocephalosporin acid or an acid addition salt thereof is reacted with an acylating agent to afford the 2-amidopenicillin or 2-amidocephalosporin which, if desired, is hydrolysed to the corresponding penicillin or cephalosporin.

5 The novel 2-amidopenicillins and 2-amidocephalosporins provided by the invention are the antibiotically active 2-amidopenicillins and 2-amidocephalosporins and their pharmacologically acceptable acid addition salts in which the amido group is 5

represented by the formula $\begin{array}{c} \text{X} \\ | \\ -\text{C}-\text{N} \\ || \quad | \\ \text{O} \quad \text{Y} \end{array}$ wherein X is an electron withdrawing group,

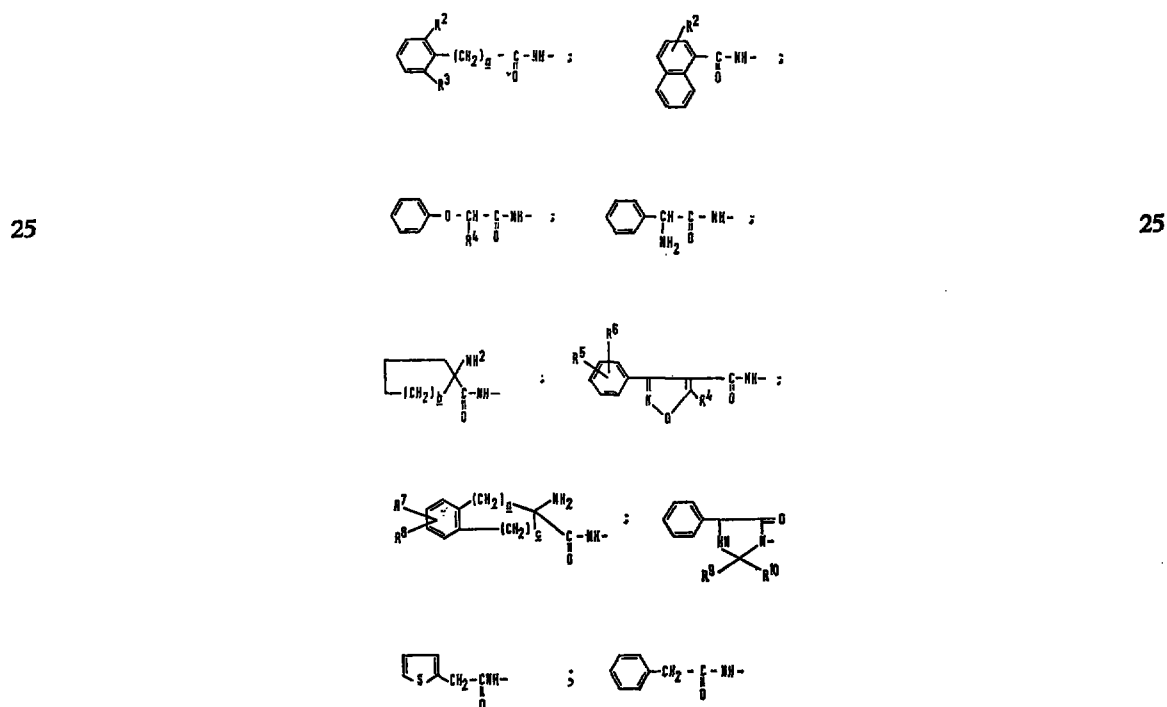
10 Y is an electron withdrawing group or X and Y are joined together to form an electron withdrawing cyclic group (taken together with the nitrogen atom to which they are attached). The invention also provides the corresponding 6 or 7 respectively 10

Thus the invention provides a 2-amidopenicillin or 2-amidocephalosporin or its 6 or 7 respectively amino, haloimido or alkoxyimido derivative having the general formulae



wherein R¹ is a penicillin or cephalosporin amide group, an amino group or a haloimido or alkoxyimido group derived from a penicillin or cephalosporinamide group, R^{1a} is 20 methyl, hydroxymethyl, N-pyridiniumylmethyl or alkanoylmethyl, X is an electron withdrawing group, Y is an electron withdrawing group or X and Y are joined together to form an electron withdrawing cyclic group; or an acid addition salt thereof. 20

Penicillin or cephalosporin amide groups are well known to those skilled in the art in both natural and synthetic penicillins and cephalosporins and include for example those selected from the following general formulae:



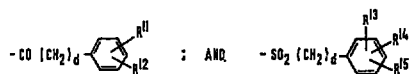
wherein R^2 and R^3 are hydrogen or lower alkoxy; R^4 is hydrogen, lower alkyl or phenyl; R^5 and R^6 are hydrogen or halogen; R^7 and R^8 are hydrogen, halogen, lower alkyl, lower alkoxy, phenyl or phenoxy; R^9 and R^{10} when taken separately are hydrogen or lower alkyl, and when taken together with the carbon atom to which they are attached complete a ring selected from the group consisting of cycloalkyl containing from 4 to 8 carbon atoms and piperidine; a is an integer from 0 to 1; b is an integer from 0 to 5; c is an integer from 1 to 3, with the provisos that when a is 0, c is greater than 1, and when a is 1, c is less than 3; and X and Y are defined as set forth above.

As employed herein the term "natural penicillins" includes those which are produced by fermentation as well as those that are biosynthetically prepared by the addition of certain precursors to the fermentation broth. Examples of these types of penicillins are: Penicillin O, which is designated by the 2-carboxy derivative of the compound of formula (VI) hereafter where R^{20} is allylmercaptomethyl; Penicillin S, wherein R^{20} is γ -chlorocrotylmercaptomethyl; Penicillin V, wherein R^{20} is phenoxy-methyl; Penicillin G, wherein R^{20} is benzyl; Penicillin F, wherein R^{20} is 2-pentenyl; Dihydropenicillin F, wherein R^{20} is amyl; Penicillin K, wherein R^{20} is heptyl; and Penicillin X, wherein R^{20} is p -hydroxybenzyl. The term "synthetic penicillins" is used to include any penicillin which may be prepared by the acylation of 6-aminopenicillanic acid. Examples of these types of penicillins are: Ampicillin, which is designated by the 2-carboxy derivative of the compound of formula (VI), wherein R^{20} is α -aminobenzyl; Nafcillin, wherein R^{20} is 2-ethoxynaphthyl and Dicloxacillin, wherein R^{20} is 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazole. It should be noted that although it is most desirable to use "natural penicillins" as starting materials in the process of this invention, the process is not limited in operability to these starting material and will operate equally well utilising "synthetic penicillins" as reactants.

As known to those skilled in the cephalosporin art, to be included as compounds provided by this invention are those compounds of formula (II) wherein the 3-position "acetoxymethyl" group R^{18} is modified by known chemical procedures to afford compounds which are substituted at the 3-position with other R^{18} substituents, for example N-pyridiniumylmethyl, methyl, hydroxymethyl or alkanoyloxymethyl groups other than acetoxymethyl.

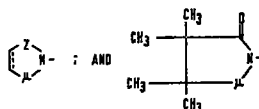
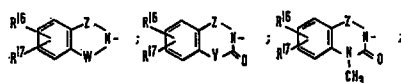
By the term "cephalosporins" is meant known derivatives of cephalosporanic acid, such as, cephalothin, as well as, those compounds wherein the 3-position "acetoxymethyl" group has been modified as aforesaid.

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.-butryl; cyclo(lower)alkanoyl, aroyl, e.g. naphthoyl and furyl; substituted aroyl; arylsulphonyl, e.g. naphthylsulphonyl, pyridylsulphonyl, furylsulphonyl; substituted arylsulphonyl;



wherein R^{11} and R^{12} can be hydrogen, lower alkyl, halogen, trifluoromethyl, lower alkoxy, phenyl, phenoxy, nitro, loweralkylsulphonyl, di(lower)alkylsulphamyl; R^{13} , R^{14} and R^{15} 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 about 6.

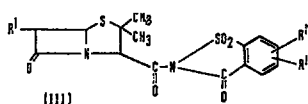
As is also known to those skilled in the chemical art, included in those cyclic electron withdrawing groups when X and Y are taken together are, for example:



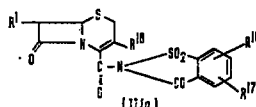
wherein R^{16} and R^{17} when taken separately can be hydrogen, lower alkyl, lower alkoxy, halogen, phenyl, phen(lower)alkyl, loweralkoxyphenyl, aryl, heterocyclyl, e.g. 2-pyridyl, 4-pyridyl, trihalomethyl, e.g. trifluoromethyl, nitro, di(lower)alkylamino, sulphamido, carb(lower)alkoxy, cyano, loweralkylthio or loweralkylsulphonyl, and when R^{16} and R^{17} are joined, they complete a benzene ring fused to the existing benzene ring to form therewith a naphthalene ring; Z is sulphonyl or carbonyl; W is sulphonyl, carbonyl or methylene; V 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 two positions.

As is well known to those skilled in the art, included in those groups that are defined as "haloimido" (such as chloroimido and bromoimido) are those haloimido substituents which are derived from natural and synthetic penicillins and cephalosporins, for example, R^1 as employed in the penicillin formula (I) may be defined as 2-allyl-mercapto - 1 - haloethylideneamino, 1 - halo - 2 - (γ - chlorocrotylmercapto) - ethylideneamino, 1 - halo - 2 - phenoxyethylideneamino, α -halophenethylideneamino, 1-halo-3-hexenylideneamino, 1-halohexylideneamino, 1-halo-octylideneamino and α -chloro-*p*-hydroxyphenethylideneamino and R^1 as employed in the cephalosporin formula (II) may be 1-halo-2-(2-thienyl)ethylideneamino. As will also be known to this skilled in the art, included in those groups that are defined as "alkoxyimido" are those lower alkoxyimido substituents which are derived from natural and synthetic penicillins and cephalosporins. Examples thereof, when R^1 is employed in the penicillin formula I are: 1 - (lower)alkoxy - 2 - allylmercaptoethylideneamino, 1 - (lower)alkoxy - 2 - (γ - chlorocrotylmercapto)ethylideneamino, 1 - (lower)alkoxy - 2 - phenoxyethylideneamino, α - (lower)alkoxyphenethylideneamino, 1 - (lower)alkoxy - 3 - hexenylideneamino, 1 - (lower)alkoxyhexylideneamino, 1 - (lower)alkoxyoctylideneamino and α - (lower)alkoxy-*p*-hydroxyphenethylideneamino and R^1 as employed in the cephalosporin formula (II) may be 1 - (lower)alkoxy - 2 - (2 - thienyl)ethylideneamino.

The preferred compounds provided by this invention are those compounds of formula (III) wherein X and Y are concatenated to form a saccharyl or substituted saccharyl group. These compounds are designated by the following formula:



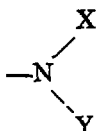
and the acid-addition salts thereof; wherein R^1 , R^{16} and R^{17} are defined as above. Among the cephalosporins corresponding 2-saccharyl or substituted saccharyl cephalosporins (IIIa) are similarly preferred.



By the term "lower alkyl" as employed herein, alone or in conjunction with the other designated groups, we mean 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. As halogens alone or attached to other designated groups, there may be used chlorine, bromine, iodine and 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 also referred to 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 compounds of this invention thereby making these groups more liable to

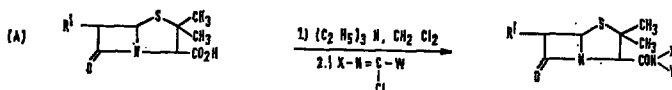
cleavage by a nucleophilic agent, e.g. water, alkali metal hydroxides, tertiary amines, quinoline and the like, to afford a carboxylic acid group.

- 5 The novel 2-amidopenicillins and 2-amidocephalosporins provided by the invention may be prepared by reacting a starting penicillin or cephalosporin, e.g. a 6-acylated penicillanic acid or a 7-acylated cephalosporanic acid with a suitable reactive nitrogen compound which will replace the hydroxy moiety of the carboxyl group of the penicillin or cephalosporin with a group of the formula:



- 10 wherein X and Y have the same meaning as hereinbefore defined. Such reactions are well known to those skilled in the art and several thereof are hereinafter schematically illustrated for the preparation of the 2-amidopenicillins of this invention. It should be noted that the new and novel 2-amidocephalosporins of this invention may also be prepared by these reactions merely by replacing the starting penicillin with an appropriate cephalosporin.

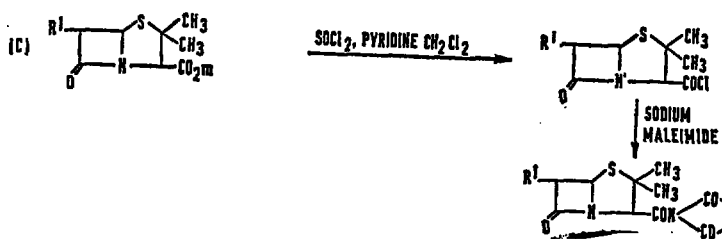
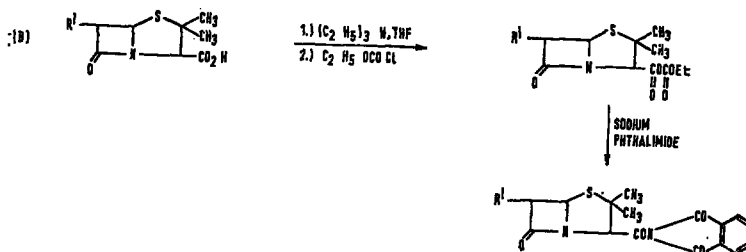
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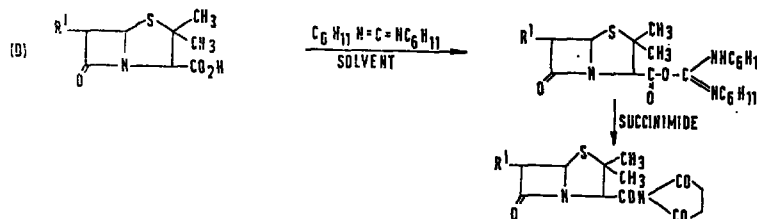
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where C.COOH is an organic carboxylic acid

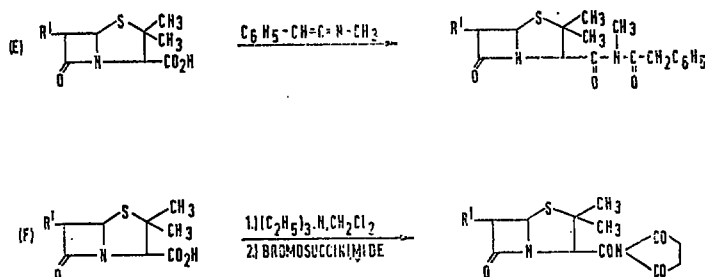


where m = hydrogen or alkali metal



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Thus, for example, the preferred compound (III) of this invention may be prepared generally by reacting, preferably in the cold, a 3-halosaccharin derivative, e.g. 3-chloro-1,2-benzisothiazole 1,1-dioxide or an appropriately substituted derivative thereof, with a penicillin or an alkali metal salt thereof in an organic solvent, such as, anhydrous methylene chloride which contains an acid acceptor, e.g. triethylamine when the starting penicillin is in its acid form. When the condensation reaction is complete, the 2-saccharimidopenicillin may be recovered by standard procedures, for example the reaction mixture is washed, dried and concentrated, e.g. under vacuum at above ambient temperatures. The residue may then be redissolved and crystallised from a suitable organic solvent system for instance ether (e.g. 25%) in benzene.

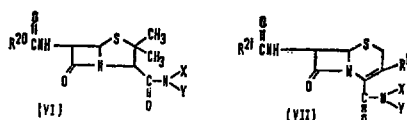
The 3-chloro-1,2-benzisothiazole 1,1-dioxide starting material is commercially available, while the R^{16} and R^{17} substituents on the benzo moiety of the saccharin derivatives may be introduced by well known conventional procedures. The penicillins and cephalosporins are either obtainable commercially or may be prepared by procedures well known in the literature. Merely by way of example, there may be noted: United States Patent No. 2,996,501 issued August 15, 1961, to Doyle *et al*, entitled "Synthetic Penicillins"; United States Patent No. 3,157,639 issued November 17, 1963, to Doyle *et al*, entitled "Synthetic Penicillins"; United States Patent No. 3,159,617 issued December 1, 1964, to John C. Sheehan, entitled "Production of Penicillins" and United States Patent No. 3,239,507 issued March 8, 1966, to Nayler *et al*, entitled "Isoxazolylpenicillin Derivatives" which describe conventional methods for preparing the various penicillins employed as starting material. Similarly, the reactive nitrogen compounds employed for providing the aforesaid amido groups are also obtainable commercially or, in those instances where they are not available, they may be synthesised readily by standard organic procedures described in the chemical literature and known to those skilled in the art. The preferred 2-saccharyl or substituted saccharyl cephalosporins (IIIa) may be prepared similarly.

The invention further provides a process for the preparation of 2-amido-6- amino-penicillanic acids (IV) or 2-amido-7-aminocephalosporin acids (V) having the general formulae:



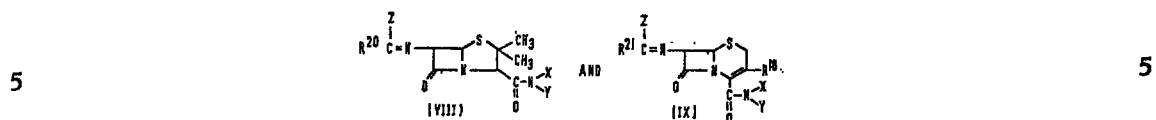
(IV)

wherein R^{18} is defined above, X and Y are as defined above; which comprises: contacting a phosphorus pentahalide, such as, phosphorus pentachloride and phosphorus pentabromide, with a 2-amido derivative of a natural or synthetic penicillin (VI) or cephalosporin (VII) having the general formulae:



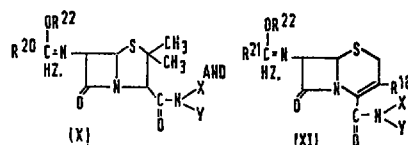
wherein R^{18} , X and Y are defined as above; R^{20} is substituent selected from those contained in natural and synthetic penicillins, for example, allylmercaptomethyl, γ -chlorocrotylmercaptomethyl, phenoxyethyl, benzyl, 2-pentenyl, amyl, heptyl and

and *p*-hydroxybenzyl; and R^{21} is a substituent selected from those contained in natural and synthetic cephalosporins, e.g. 2-thienylmethyl; in a reaction-inert aprotic solvent, in the presence of a base to afford a 2-amido haloimido compound having one of the respective general formulae:



wherein R^{20} , R^{21} , X and Y are defined as above and Z is a halogen, e.g. chloro and bromo. The new and novel 2-amidohaloimido compounds of this invention, in particular, the 2-amido-6-haloimidopenicillins (VIII) and 2-amido-6-haloimido-cephalosporins (IX) prepared by the above reaction may be separated by conventional recovery procedures, e.g. the reaction mixture is filtered and the collected solid is dried to afford the product (VIII or IX). Alternatively, the unseparated product is employed directly in the following reaction.

The above prepared 2-amidohaloimido compound (VIII) or (IX) is contacted with an alkanol to afford the corresponding 2-amidoalkoxyimido hydrohalide compound, e.g. the hydrochloride or the hydrobromide having one of the respective general formulae:

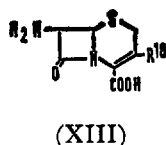


wherein R^{20} , R^{21} , X, Y and Z are defined as above; and R^{22} is lower alkyl. The new and novel 2-amido alkoxyimido hydrohalide compounds of this invention, in particular, the 2-amido-6-alkoxyimidopenicillin hydrohalides (X) and the 2-amido-7-alkoxy-imidocephalosporin hydrohalides (XI), prepared by the above-described substitution reaction may be employed directly in the subsequent reaction or may be recovered by standard separation procedures, e.g. filtration and drying the collected precipitate.

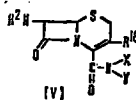
The 2-amido-alkoxyimido hydrohalide compound (X or XI) as prepared above, is then hydrolysed by routine procedures, e.g. contact with water to afford the corresponding hydrohalide of the 2-amido amine compound. This hydrohalide, e.g. the hydrochloride or hydrobromide is then readily converted to its corresponding basic form (IV or V) by neutralisation processes which are well-known to those skilled in the art of chemistry. For example, the hydrohalide is treated for a short time with water containing a base, such as, triethylamine, sodium bicarbonate or the like, preferably in the presence of a water-miscible solvent.

The expression "reaction-inert, aprotic solvent" encompasses those liquids which do not yield protons and will dissolve the reactants without interfering with their interaction, such as, methylene chloride, chloroform, dioxane, tetrahydrofuran, ether, dimethoxyethane, benzene, xylene and toluene. The term "base" is meant to include both organic and inorganic proton acceptors which are capable of taking up protons, e.g. quinoline, dimethylaniline, pyridine, N-ethylmorpholine and potassium carbonate. Since many of the compounds (I and II) provided by the invention are basic, advantage may be taken of the water solubility of salts of those compounds formed with acids in the isolation and purification of the above compounds and in the preparation of aqueous solutions thereof. Such acids are well-known in the art, for example, hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, benzenesulphonic, toluenesulphonic, methylsulphonic, ethylsulphonic acids and the like. These salts may be prepared by procedures commonly employed in the art, for example, reacting the compound with an equivalent of the selected acid in aqueous solution and concentration of the solution. Other known procedures may also be employed.

A further process according to the invention concerns the preparation of 7-amino-cephalosporanic acid (XIII) having the general formula:



which comprises contacting a 2-amido amine compound (V) of the formulae:



wherein R^{18} , 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 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.

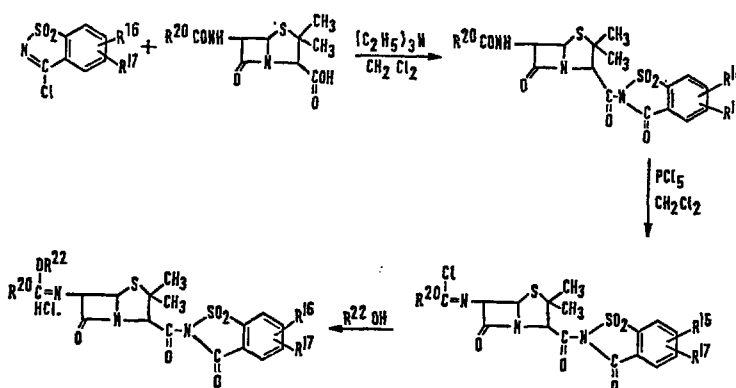
The starting diamide compounds, e.g. 2-amidopenicillins and 2-amidocephalosporins can be prepared by reacting imido yl halides with natural or synthetic penicillins and cephalosporins. Thus, for example, the starting 2-saccharimido penicillins for the preparation of the preferred compounds (III) where R^1 is an amino group are synthesised by reacting a penicillin with a 3-halosaccharin derivative, or an appropriately substituted derivative as noted above. The natural or synthetic penicillins and cephalosporins employed in the synthesis of the above-described starting materials are commercially available or are readily prepared by well-known procedures. Similarly, the imido yl halides are commercially available or, in those instances where they are not available, they may be synthesised readily by standard organic procedures described in the chemical literature and known to those skilled in the art.

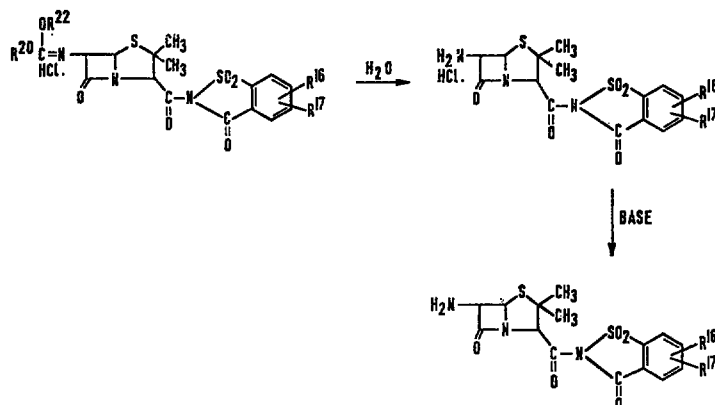
A preferred process provided by the invention concerns the preparation of the above designated 2-saccharimido amine compounds, such as, 2-saccharimido-6-aminopenicillanic acids (III). These compounds (III) are synthesised by first preparing the saccharimide of a natural or synthetic penicillin, e.g. benzyl penicillin, phenoxymethyl penicillin and the like as described above.

The 2-saccharimido amido compound is dissolved in a reaction-inert aprotic solvent, e.g. methylene chloride, in the presence of a base, e.g. quinoline and then admixed with phosphorus pentachloride to afford the corresponding 2-saccharimido chloroimido compounds, e.g. 2-saccharimido-6-chloroimidopenicillin, which is then reacted with an alkanol, e.g. methyl alcohol, ethyl alcohol, propyl alcohol, butyl alcohol and the like, so that the chlorine atom of the imido chloride moiety is replaced by the alkoxy group supplied by the alkanol employed to afford an appropriate hydrochloride salt of a 2-saccharimido alkoxyimido compound, e.g. 2-saccharimido-6-alkoxyimidopenicillin hydrochloride.

Thereafter, water is added to the reaction mixture to hydrolyse the above-described salt, so that there is obtained a hydrochloride of a 2-saccharimido amine compound, such as the hydrochloride of 2-saccharimido-6-aminopenicillanic acid which may then be converted to its corresponding base by treatment with an aqueous base, e.g. triethylamine, sodium bicarbonate and the like, preferably in the presence of a water-miscible solvent.

The preferred method of the present invention to prepare the 2-saccharimido-6-aminopenicillanic acids (III) which has hereinbefore been described may be represented by the following reaction scheme:





There is also available an alternative method for preparing the new and novel 2-amidopenicillins and 2-amidocephalosporins of the present invention. This new and novel alternative method is especially useful for preparing the new compounds of this invention which are derivatives of synthetic α -amino and 1-amino penicillins and cephalosporins, which contain an additional reactive group to which the haloimino derivatives of other reactants might also attach. In this method, the 2-amido moiety is already present on the 6-amino-penicillanic acid starting material, which is then acylated in the 6-position in the usual manner. Generally, this method comprises first preparing a 2-amido derivative of a penicillin, e.g. benzyl penicillin, phenoxy penicillin, penicillin K, and the like. This is accomplished by admixing a particular starting penicillin with a suitable organic solvent, e.g. methylene chloride followed by addition of an acid acceptor, such as triethylamine, trimethylamine and the like to form a solution. Thereafter, this solution is admixed, preferably in the cold, with an appropriate imino halide derivative. When the amidation is complete, the solution is washed, dried and concentrated under vacuum to afford a residue of the 2-amido derivative of the starting penicillin which may then be crystallised from a suitable organic solvent system, e.g. ether in benzene. Thereafter, the 2-amido derivative of the penicillin either as the residue or in the crystallised form is dissolved in methylene chloride containing an organic base, e.g. N,N-dimethylaniline, quinoline, N-ethylmorpholine and the like and then reacted with a phosphorus pentahalide, such as phosphorus pentachloride or phosphorus pentabromide to afford the corresponding 6-haloimide. Alternatively, the organic base is preferably added directly to the original reaction mixture after the addition of the imino halide derivative thereby circumventing the above-described isolation and crystallisation procedure. This 2-amido-6-haloimido derivative of the penicillin is then admixed with a lower alkanol, e.g. methyl alcohol, ethyl alcohol, propyl alcohol, butyl alcohol, and the like to form a hydrohalide acid addition salt of the 6-alkoxyimido-2-amido derivative of the penicillin wherein the halogen atom of the 6-imido moiety has been replaced by the alkoxy portion of the lower alkanol employed. Thereafter, the reaction mixture is subjected to aqueous hydrolysis to afford the corresponding 2-amido-6-aminopenicillanic acid as the hydrohalide salt. The basic form of this salt is obtained by treating the hydrohalide for a short time with the acid acceptor, such as triethylamine, sodium bicarbonate and the like, in a solvent, preferably water.

Acylation of this 2-amido-6-aminopenicillanic acid may then be undertaken by conventional procedures, as referred to hereinbefore, to afford the antibiotically active 2-amido penicillins of the present invention.

These conventional procedures generally concern the reaction of the 6-amino group of 2-amino 6-aminopenicillanic acid or correspondingly in the cephalosporin series with an acylating agent to form the desired penicillin or cephalosporin amide group and in this specification the terms reaction with an acylating agent or "acylation" include and imply all such reaction. It will also be appreciated by those skilled in the peptide and penicillin arts that if the penicillin amide residue contains another reactive functional group, this is conveniently protected in the acylating agent and the protecting group is removed by methods well known in the art, for instance an amino group can be protected by protonation as an acid addition salt or as an N-carboxyanhydride and such conventional steps are also included within and implied where necessary by the above terms. For example, a 2-amido-6-amino-penicillanic acid may be reacted with an acid chloride to obtain the 2-amido derivatives of 2-ethoxy naphthyl penicillin,

or an N-carboxy anhydride to obtain the 2-amido derivatives of D(-)- α -aminobenzylpenicillin both having potent and sustained antibiotic activity in warm-blooded animals. Employing these same procedures synthetic 2-amido penicillins and cephalosporins are obtained which possess valuable sustained activity against both gram-positive and gram-negative bacteria. In those instances where it is deemed desirable to obtain the acid forms of the penicillins *per se*; i.e., without the 2-amido substituent, said acid forms may be obtained by simple hydrolysis. For example, the 2-amidopenicillin upon treatment for a sufficient length of time with water or a mixture of water and a miscible organic solvent, for example at a pH of from about 1.5 to about 9 affords the deamidated penicillin. For example, the amido derivatives of nafcillin may be treated with water or with a mixture of water and a miscible organic solvent at a pH of from about 1.5 to 9 for a sufficient period of time. By similar procedures, ampicillin may be prepared from the amido derivatives of ampicillin. It should be noted that, although the above-described process has been described in terms of 2-amido penicillins, it is equally applicable to the 2-amidocephalosporins of this invention.

Thus the novel 2-amido-7-aminocephalosporanic acid, 2-amido-7-haloimidocephalosporins and 2-amido-7-alkoxyimidocephalosporins and their acid addition salts are extremely useful intermediates in the preparation of 6-aminocephalosporanic acid which by procedures which are now conventional in the art may be acylated to prepare synthetic cephalosporins.

Employing these same procedures many synthetic cephalosporins are prepared which possess valuable activity against both gram-positive and gram-negative bacteria. They are also useful in preparing new synthetic 2-amidocephalosporins using conventional acylation procedures as noted above.

The antibiotically active 2-amidopenicillins and 2-amidocephalosporins of the present invention possess valuable biological activity. In particular, in standard and accepted biological tests these compounds exhibit activity against gram-positive and gram-negative bacteria. In this regard these compounds are, therefore, of value as antibacterial agents, nutritional supplements in animal feeds; agent for the treatment of mastitis in cattle; and as therapeutical agents in poultry and animals, in the treatment of infectious diseases caused by gram-positive and gram-negative bacteria, upon either parenteral or oral administration. Further, upon the parenteral administration, e.g. intramuscular of the compounds of this invention a sustained antibacterial activity is effected by the slow *in situ* hydrolysis thereof to afford the corresponding deamidated penicillins which are then readily absorbed.

As will be understood by those skilled in the art, the 2-amidopenicillins and 2-amidocephalosporins of this invention may be utilised as such, or in the cases of those compounds of the α -amino or 1-amino type, they may be in the form of the pharmacologically acceptable, acid addition salts thereof prepared by the reaction of the selected antibiotically active compound with a suitable organic or inorganic acid, e.g. hydrochloric, hydrobromic, furaric, citric, and the like, as is conventional in this art.

As will also be understood by those skilled in the art, the antibiotically active synthetic penicillins and cephalosporins, 2-amidopenicillins and 2-amidocephalosporins provided by this invention may be utilised in pharmacological compositions in association with pharmacologically acceptable carriers, e.g. in suitable injectable form, including solutions and suspensions, or orally as tablets, capsules, and the like, utilising conventional solvents, suspensoids, excipients, and the like. As previously indicated, when the compounds of this invention are employed, they may be administered orally or parenterally. Naturally, the dosage of these compounds will vary somewhat with the form of administration and the particular compound chosen. Further, it will vary with the particular subject under treatment. In general, the compounds of this invention are most desirably administered at dosage levels corresponding to those of commercially available penicillins and cephalosporins. Although variations from these dosages will occur, these dosages will generally afford effective results without causing any harmful or deleterious side effects.

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

Example 1

The Saccharimide of Phenoxymethyl penicillin

3,3 - Dimethyl - 7 - oxo - 6 - (2 - phenoxyacetamido) - 4 - thia - 1 - azabicyclo [3.2.0]heptane-2-carboxylic acid(phenoxymethyl penicillin) (17.5 g., 0.05 mole) is added to anhydrous methylene chloride (750 ml.) followed by triethylamine (5.5 g., 0.05 mole), giving a solution. The magnetically stirred solution is cooled to 3° in

- ice-water. 3-Chloro-1,2-benzisothiazole 1,1-dioxide (10.05 g., 0.05 mole) is added all at once, giving a light yellow solution. After stirring for $\frac{1}{2}$ hour in ice-water the solution is kept over night at room temperature. The solution is washed with cold water (700 ml.), cold 0.13 M/pH7.4/(K₂HPO₄/KH₂PO₄) (500 ml.), and dried through sodium sulphate. The filtrate is dried over calcium sulphate, and then concentrated at 40° under vacuum, giving a foam (24.2 g.). The foam is dissolved in 25% ether in benzene (approx. 80 ml.), giving the title compound as crystals (18.6 g., 70%), m.p. 171° dec. (uncorr.).
- Analysis: Calcd. for C₂₃H₂₁N₃O₇S₂·0.7H₂O C, 72.30; H, 4.27; N, 7.96; S, 12.14; H₂O, 2.38. Found: C, 52.22; H, 3.91; N, 7.89; S, 12.18; H₂O, 2.35.

Example 2

- The Saccharimide of 6-(2,2-Dimethyl-5-oxo-4-phenylimidazolidin-1-yl) Penicillin 6 - (2,2 - Dimethyl - 5 - oxo - 4 - phenylimidazolidin - 1 - yl) - 3,3 - dimethyl-7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]heptane - 2 - carboxylic acid [6-(2,2-dimethyl-5 - oxo - 4 - phenylimidazolidin - 1 - yl)penicillin] (3.90 g., 0.01 mole) is added to anhydrous methylene chloride (150 ml.) followed by triethylamine (1.01 g., 0.01 mole), giving a solution. The magnetically stirred solution is cooled to 3° in ice-water. 3-Chloro-1,2-benzisothiazole 1,1-dioxide (2.02 g., 0.01 mole) is added all at once, and the resulting solution is reacted and worked-up in a manner similar to Example 1, giving the title compound as a light yellow solid (3.7 g., 67%), m.p. 182° dec. (uncorr.).
- Analysis: Calcd. for C₂₆H₂₆N₄O₆S₂: C, 56.30; H, 4.72; N, 10.10; S, 11.57. Found: C, 56.08; H, 4.52; N, 10.21; S, 11.78.

Example 3

- Following the procedure described in Example 1, a series of penicillins are reacted with various saccharin chloride derivatives to obtain the corresponding saccharimides of penicillins having potent antibiotic activity. The reactants and resulting saccharimides of penicillins are set forth in Table A below:

TABLE A

Penicillins	Saccharin Chloride Derivatives	Saccharimides of Penicillins
phenoxymethyl penicillin	3-chloro-4-ethyl-1,2-benzisothiazole 1,1-dioxide	4-ethyl-saccharimide of phenoxymethyl penicillin
6-(2,2-dimethyl-5-oxo-4-phenylimidazolidin-1-yl) penicillin	3,5-dichloro-4-propyl-1,2-benzisothiazole 1,1-dioxide	4-propyl-5-chloro-saccharimide of 6-(2,2-dimethyl-5-oxo-4-phenylimidazolidin-1-yl)penicillin
2,6-dimethoxy-phenyl penicillin	3-chloro-5,6-diamino-1,2-benzisothiazole 1,1-dioxide	5,6-diamino-saccharimide of 2,6-dimethoxy-phenyl penicillin
2-ethoxy-naphthyl penicillin	3-chloro-4-nitro-1,2-benzisothiazole 1,1-dioxide	4-nitro-saccharimide of 2-ethoxy-naphthyl penicillin
phenoxyprop-1-yl penicillin	3-chloro-4,5-dibromo-1,2-benzisothiazole 1,1-dioxide	4,5-dibromo-saccharimide of phenoxyprop-1-yl penicillin
3-(2,6-dichloro-phenyl)-5-methyl-4-isoxazolyl penicillin	3-chloro-4-hexyl-1,2-benzisothiazole 1,1-dioxide	4-hexyl-saccharimide of 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin

TABLE A (Continued)

Penicillin	Saccharin Chloride Derivatives	Saccharimides of Penicillins
3-phenyl-5-methyl-4-isoxazolyl penicillin	3-chloro-4-butoxy-5-phenyl-1,2-benzisothiazole 1,1-dioxide	4-butoxy-5-phenyl-saccharimide of 3-phenyl-5-methyl-4-isoxazolyl penicillin
3-p-chlorophenyl-5-methyl-4-isoxazolyl penicillin	3-chloro-5-(p-methoxy)-phenyl-1,2-benzisothiazole 1,1-dioxide	5-(p-methoxy)-phenyl-saccharimide of 3-p-chlorophenyl-5-methyl-4-isoxazolyl penicillin
benzyl penicillin	3-chloro-4-phenyl-1,2-benzisothiazole 1,1-dioxide	4-phenyl-saccharimide of benzyl penicillin
phenoxyethyl penicillin	3-chloro-5-benzyl-1,2-benzisothiazole 1,1-dioxide	5-benzyl-saccharimide of phenoxyethyl penicillin
2-methoxy-naphthyl penicillin	3-chloro-7-(m-propoxyphenyl)-1,2-benzisothiazole 1,1-dioxide	7-(m-propoxyphenyl)-saccharimide of 2-methoxy-naphthyl penicillin
3-o-chlorophenyl-5-methyl-4-isoxazolyl penicillin	3-chloro-4-butyl-5-fluoro-1,2-benzisothiazole 1,1-dioxide	4-butyl-5-fluoro-saccharimide of 3-o-chlorophenyl-5-methyl-4-isoxazolyl penicillin
3,5-diphenyl-4-isoxazolyl penicillin	3-chloro-4,5-dimethyl-1,2-benzisothiazole 1,1-dioxide	4,5-dimethyl-saccharimide of 3,5-diphenyl-4-isoxazolyl penicillin
α -phenoxybenzyl penicillin	3-chloro-4-(2-pyridyl)-1,2-benzisothiazole 1,1-dioxide	4-(2-pyridyl)-saccharimide of α -phenoxybenzyl penicillin
α -phenoxyethyl penicillin	3-chloro-5-dimethyl-amino-1,2-benzisothiazole 1,1-dioxide	5-dimethylamino-saccharimide of α -phenoxyethyl penicillin
2,6-dimethoxybenzyl penicillin	3-chloro-6-trifluoromethyl-1,2-benzisothiazole 1,1-dioxide	6-trifluoromethyl-saccharimide of 2,6-dimethoxybenzyl penicillin

Example 4

The Saccharimide of Ampicillin

2 - (6 - Amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]heptan-2-ylcarbonyl)-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, p-toluenesulphonic acid salt (the saccharimide of 6-aminopenicillanic acid, p-toluenesulphonic acid salt) (5.5 g., 0.01 mole) is dissolved in 80% acetone-water (230 ml.) at 0°, giving a solution of pH 2.2. Then D-(-)- α -aminophenylacetyl chloride hydrochloride (3.1 g., 0.015 mole) is added to the magnetically stirred solution in about ten lots over $\frac{1}{2}$ hour at 0°, keeping the pH at 2—3 with 50% sodium hydroxide. The solution is stirred an additional 15 minutes at 0° and the pH is adjusted to 4.5 with 50% sodium hydroxide. Then the acetone is removed at 0° under vacuum and the volume of the residual water is adjusted to 100 ml. The pH is adjusted at 0° to 6.8 with 50% sodium hydroxide, giving the title compound as a light yellow solid (3.2 g., 62%), m.p. 170° dec. (uncorr.)

5

10

10

Example 5

Following the procedure of Example 4, in this instance, a series of saccharimides of 6-aminopenicillanic acid are reacted with various acylating agents to obtain the saccharimides of penicillins having antibiotic activity. The reactants and resulting saccharimides of penicillins are given in Table B below:

TABLE B

Saccharimides of 6-Aminopenicillanic Acid	Acylating Agents	Saccharimides of Penicillins
4-(4-(pyridyl)-5-methyl-saccharimide of 6—APA	N-carboxyanhydride of 1-aminocyclopentane carboxylic acid	4-(4-pyridyl)-5-methyl-saccharimide of 1-amino-cyclopentane penicillin
5-trichloromethyl-saccharimide of 6—APA	N-carboxyanhydride of 1-aminocyclohexane carboxylic acid	5-trichloromethyl-saccharimide of 1-aminocyclohexane penicillin
6-dimethylamino-7-methyl-saccharimide of 6—APA	phenylglycine chloride, hydrochloride	6-dimethylamino-7-methyl-saccharimide of 1-aminobenzylpenicillin
6-sulphamido-saccharimide of 6—APA	N-carboxyanhydride of 1-amino-1-indane carboxylic acid	6-sulphamido-saccharimide of 1-amino-1-indane penicillin
4-carbethoxy-saccharimide of 6—APA	N-carboxyanhydride of 1-amino-1,2,3,4-tetrahydro-naphthoic acid	4-carbethoxy-saccharimide of 1-amino-1,2,3,4-tetrahydro-naphthyl penicillin
4-cyano-saccharimide of 6—APA	N-carboxyanhydride of 1-amino-1,2,3,4-tetrahydro-7-ethoxy-1-naphthoic acid	4-cyano-saccharimide of 1-amino-1,2,3,4-tetrahydro-7-ethoxy-1-naphthyl penicillin
4-(prop-2-yl)-thio-saccharimide of 6—APA	N-carboxyanhydride of 1-amino-4-phenyl-1-indane carboxylic acid	4-(prop-2-yl)-thio-saccharimide of 1-amino-4-phenyl-1-indane-penicillin
5-ethylsulphonyl-saccharimide of 6—APA	N-carboxyanhydride of 2-amino-3-phenoxy-2-indane carboxylic acid	5-ethylsulphonyl-saccharimide of 2-amino-3-phenoxy-2-indane penicillin
4,5-benzo-saccharimide of 6—APA	N-carboxyanhydride of 1-amino-1,2,3,4-tetrahydro-3,6-dimethyl-1-naphthoic acid	4,5-benzo-saccharimide of 1-amino-1,2,3,4-tetrahydro-3,6-dimethyl-1-naphthyl penicillin

Example 6

The Dimethylcarbamoyl Dimethylsulphamoyl Imide of Ampicillin

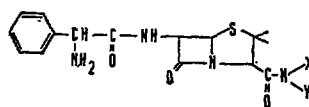
6 - Amino - 3,3 - dimethyl - N - dimethylcarbamoyl - N - dimethyl - sulphamoyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]heptane - 2 - carboxamide (the N - dimethylcarbamoyl N-dimethylsulphamoyl imide of 6-aminopenicillanic acid) 7.81 g., 0.02 mole) is dissolved in 60% water-tetrahydrofuran (200 ml.) containing N-carboxy-D-phenylglycine anhydride (5.32 g., 0.03 mole) at 0—5°, and the pH is adjusted to 5 with glacial acetic acid. The solution is stirred for 3 hours at 0.5° and filtered. The

tetrahydrofuran is removed at 0° under vacuum, and the pH of the aqueous residue is adjusted to approximately 7 at 0°. The mixture is filtered, giving the title compound as a light yellow solid.

Example 7

Utilising the general procedure of Example 6, but employing a series of amides of 6-aminopenicillanic acid other than that employed in said Example 6, for acylation by the N-carboxy anhydride of phenyl glycine, the corresponding amido derivatives of ampicillin are obtained as indicated in Table C below wherein the substituents X and Y of said amido derivative are as set forth therein:

TABLE C



X	Y
—CN	—CN
—CN	—NO ₂
—CN	—SO ₂ CF ₃
—CN	—CO ₂ C ₅ H ₁₁
—CN	—CON(CH ₃) ₂
—CN	—SO ₂ C ₂ H ₅
—CN	—SO ₂ N(C ₂ H ₅) ₂
—NO ₂	—SO ₂ CF ₃
—NO ₂	—CO ₂ C ₂ H ₅
—NO ₂	—CON(C ₃ H ₇) ₂
—NO ₂	—SO ₂ CH ₃
—NO ₂	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{—SO}_2\text{N} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array}$
—SO ₂ CF ₃	—SO ₂ CF ₃
—SO ₂ CF ₃	—CO ₂ CH ₂ H ₁₃
—SO ₂ CF ₃	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \diagup \\ \text{—CON} \\ \diagdown \\ \text{CH}_3 \end{array}$
—SO ₂ CF ₃	—SO ₂ C ₃ H ₇
—SO ₂ CF ₃	—SO ₂ N(CH ₃) ₂
—CO ₂ CH ₃	—CON(C ₅ H ₁₁) ₂
—CO ₂ CH ₃	—SO ₂ CH ₃

TABLE C Continued

	X	Y	
	$-\text{CO}_2\text{CH}_3$	$-\text{SO}_2\text{N}(\text{CH}_3)_2$	
	$-\text{CON}(\text{CH}_3)_2$	$-\text{CON}(\text{C}_2\text{H}_5)_2$	
5	$-\text{CON}(\text{CH}_3)_2$	$-\text{SO}_2\text{C}_6\text{H}_{11}$	5
	$-\text{CON}(\text{CH}_3)_2$	$-\text{SO}_2\text{N}(\text{CH}_3)_2$	
	$-\text{CON}(\text{CH}_3)_2$	$-\text{CON}(\text{CH}_3)_2$	
	$-\text{SO}_2\text{N}(\text{CH}_3)_2$	$-\text{SO}_2\text{N}(\text{CH}_3)_2$	
	$-\text{CN}$	$-\text{CO}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_5$	
10	$-\text{CN}$	$-\text{CO}-\text{C}_6\text{H}_4-\text{CH}_3$	10
	$-\text{CN}$	$-\text{CO}-\text{C}_6\text{H}_4-\text{OC}_6\text{H}_5$	
	$-\text{SO}_2\text{CH}_3$	$-\text{CO}-\text{C}_6\text{H}_4-\text{Cl}$	
	$-\text{SO}_2\text{CH}_3$	$-\text{CO}-\text{C}_6\text{H}_2(\text{Br})_2$	
	$-\text{CO}_2\text{C}_2\text{H}_5$	$-\text{CO}-\text{C}_6\text{H}_4-\text{Cl}-\text{CH}_3$	
15	$-\text{CO}_2\text{C}_2\text{H}_5$	$-\text{CO}-\text{C}_6\text{H}_4-\text{I}$	15
	$-\text{CON}(\text{CH}_3)_2$	$-\text{CO}-\text{C}_6\text{H}_4-\text{C}_2\text{H}_5$	
	$-\text{CO}_2\text{C}_4\text{H}_9$	$-\text{CO}-\text{C}_6\text{H}_4-\text{OCN}_3$	
	$-\text{NO}_2$	$-\text{CO}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_5$	
	$-\text{SO}_2\text{CF}_3$	$-\text{CO}-\text{C}_6\text{H}_4-\text{SO}_2\text{N}(\text{CH}_3)_2$	
20	$-\text{SO}_2\text{N}(\text{C}_2\text{H}_5)_2$	$-\text{CO}-\text{C}_6\text{H}_4-\text{CF}_3$	20
	$-\text{CO}_2\text{CH}_3$	$-\text{CO}-\text{C}_6\text{H}_4-\text{CF}_3$	

Example 8

The Maleimide of 1-aminocyclohexyl Penicillin

1 - (6 - Amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]heptan-2-ylcarbonyl)- $\Delta^{3,4}$ -pyrroline-2,5-dione (the maleimide of 6-aminopenicillanic acid) (5.90 g., 0.02 mole) is dissolved in 60% water-tetrahydrofuran (200 ml.) containing N-carboxyl-1-aminocyclohexane carboxylic anhydride (5.07 g., 0.03 mole) at 0—5°, and the pH is adjusted to 5 with glacial acetic acid. The solution is stirred for 3 hours at 0—5° and filtered. The tetrahydrofuran is removed at 0° under vacuum, and the pH of the aqueous residue is adjusted to approximately 7 at 0°. The mixture is filtered, giving the title compound as a light yellow solid.

Example 9

Following the general procedure of Example 8, but now employing a series of amides of 6-aminopenicillanic acid having cyclic amido moieties thereon, said amides are acylated with the N-carboxy anhydride of 1-aminocyclohexane carboxylic acid to obtain the corresponding amido penicillin derivatives indicated in Table D below:

TABLE D

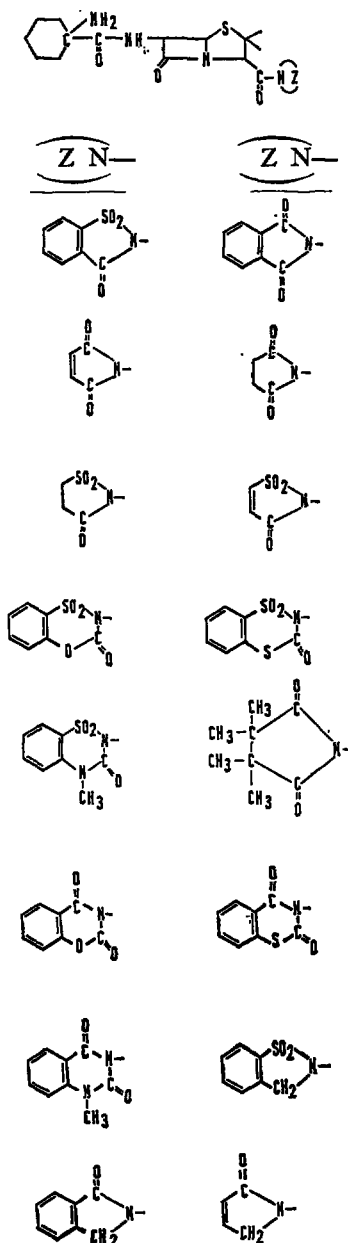
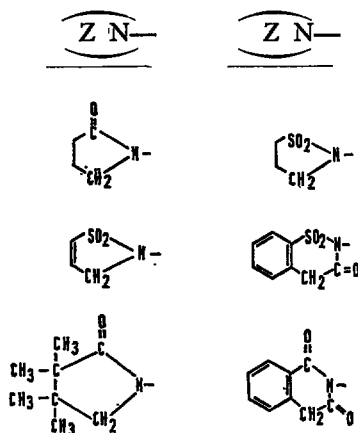


TABLE D (continued)



Example 10

Saccharimide of 1-Aminocyclohexyl Penicillin

- 5 6 - (α - aminocyclohexanecarboxamido) - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1-azabicyclo[3.2.0]heptane-2-carboxylic acid (1-amino-cyclohexyl penicillin) (23.4 g., 0.0685 mole) is added to methylene chloride (1 l.) followed by triethylamine (6.93 g., 0.0685 mole) giving a solution. The magnetically stirred solution is cooled to 3° in ice water. 3-Chloro-1,2-benzisothiazole 1,1-dioxide (13.8 g., 0.0685 mole) is added all at once, and the resulting solution is reacted and worked up in a manner similar to example 1, giving the title compound as a light yellow solid (16.5 g., 48%), m.p. 174° dec. (uncorr.).
- 10 Analysis: Calcd. for $C_{22}H_{26}N_4O_6S_2$: C, 52.16; H, 5.17; N, 11.06; S, 12.66. Found: C, 51.12, 51.06; H, 5.06, 4.90; N, 10.82; S, 11.28.

Example 11

Saccharimide of Dicloxacillin

- 15 6 - [3 - (2,6 - dichlorophenyl) - 5 - methylisoxazol - 4 - carboxamido] - 3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (dicloxacillin) (47.03 g., 0.1 mole) is added to anhydrous methylene chloride (1.5 l.) followed by triethylamine (10.1 g., 0.1 mole), giving a solution. The magnetically stirred solution is cooled to 3° in ice water, and 3-chloro-1,2-benzisothiazole 1,1-dioxide (20.2 g., 0.1 mole) is added all at once. The resulting solution is reacted and worked up in a manner similar to example 1, giving a crude light yellow foam. The foam is crystallised from ethyl acetate giving white crystals of title compound (10 g., 16%), m.p. 192° dec. (uncorr.).
- 20 Analysis: Calcd. for $C_{26}H_{20}Cl_2N_4O_6S_2$: C, 49.14; H, 3.17; N, 8.81; S, 10.09; Cl, 11.16. Found: C, 49.15; H, 3.30; N, 8.72; S, 9.83; Cl, 11.15.
- 25

Example 12

Saccharimide of Benzyl Penicillin

- 30 Triethylammonium 3,3 - dimethyl - 7 - oxo - 6 - (2 - penhnylacetamido) - 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (benzyl penicillin) (105 g., 0.222 mole) is dissolved in methylene chloride (2.5 l.) and the solution is cooled to 3° in ice water. Then 3-chloro-1,2-benzisothiazole 1,1-dioxide (44.8 g., 0.222 mole) is added to the magnetically stirred solution all at once. The resulting solution is reacted and worked up in a manner similar to example 1. The resulting solution is concentrated at 40° under vacuum, giving white crystals of title compound (70 g., 63%), m.p. 198° dec. (uncorr.), that are washed with cold methylene chloride and anhydrous ether. The filtrate of the crystals yields an additional amount of crude yellow solid (19.5 g.).
- 35 Analysis: Calcd. for $C_{23}H_{22}N_4O_6S_2$: C, 55.30; H, 4.23; N, 8.41; S, 12.84. Found: C, 55.21; H, 4.12; N, 8.41; S, 12.65; H_2O , 0.16.
- 40

Example 13

Saccharimide of Phenoxymethyl Penicillin

2 - (6 - amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]heptan-2-ylcarbonyl)-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, *p*-toluenesulphonic acid salt

- (saccharimide of 6-aminopenicillanic acid *p*-toluenesulphonic acid salt) (2.21 g., 0.004 mole) is added to a mixture of ethanol (15 ml.), methylene chloride (15 ml.), water (8 ml.) and sodium bicarbonate (1.01 g., 0.012 mole) stirred at 0—3°. Then phenoxyacetyl chloride (1.36 g., 0.008 mole) in methylene chloride (3 ml.) is added over a few minutes, followed by more sodium bicarbonate (1.01 g., 0.012 mole), and the mixture is stirred at 0—3° for 1 hour. Water (25 ml.) is added and the mixture is extracted twice with methylene chloride. Then the methylene chloride solution is washed twice with water, once with saturated salt, and dried over sodium sulphate. The solution is then evaporated under vacuum at 20° to a small volume, and anhydrous ether (approx. 25 ml.) is added, giving a white solid of title compound (0.75 g., 35%). The infra-red spectrum is identical to that of the authentic title compound of example 1.

Example 14

Phenoxymethyl Penicillin

- 2 - [3,3 - dimethyl - 7 - oxo - 6 - (2 - phenoxyacetamido) - 4 - thia - 1 - azabicyclo[3.2.0]heptan - 2 - ylcarbonyl] - 1,2 - benzisothiazol - 3(2H) - one 1,1-dioxide (saccharimide of phenoxymethyl penicillin) (5.16 g., 0.01 mole) is dissolved in tetrahydrofuran (30 ml.), and then a solution of sodium bicarbonate (1.68 g., 0.02 mole) in water (20 ml.) is added. The mixture is magnetically stirred at room temperature for 2½ hours under nitrogen and water (15 ml.) is added. Some of the tetrahydrofuran is removed at 30° under vacuum until a cloudy solution is obtained. The solution is stirred an additional ½ hour, and then all of the tetrahydrofuran is removed at 30° under vacuum. The mixture is washed twice with methylene chloride and all of the methylene chloride is removed at 30° under vacuum. Then glacial acetic acid (2.4 ml.) is added, and the mixture is stirred in ice for 20 minutes and a brown gum is filtered off and washed with water (15 ml.). After sitting at room temperature for approx. 2 hours, white crystals formed in the mother liquor (1.2 g., 34%). The infrared spectrum is identical to one of authentic phenoxymethyl penicillin acid.

Example 15

The Saccharimide of 6-Aminopenicillanic Acid, Hydrochloride

- 2 - [3,3 - Dimethyl - 7 - oxo - 6 - (2 - phenoxyacetamido) - 4 - thia - 1 - azabicyclo[3.2.0]heptan - 2 - ylcarbonyl] - 1,2 - benzisothiazol - 3(2H) - one 1,1-dioxide (the saccharimide of phenoxymethyl penicillin) (10.3 g., 0.02 mole) is dissolved in anhydrous methylene chloride (75 ml.) and *N,N*-dimethylaniline (8.5 g., 0.07 mole) is added. The solution is cooled to -40° by an acetone-dry ice bath, and phosphorous pentachloride (4.54 g., 0.218 mole) is added over a few minutes under nitrogen. The solution is kept at -35 to -40° for 3 hours, while mechanically stirring. After approximately ½ to 1 hour at this temperature the saccharimide of 6-chlorimido-phenoxymethyl penicillin forms as a white crystalline material. Then 1-butanol (75 ml.) is added over approximately 5 minutes at -35 to -40° and this temperature is maintained for 3 hours to afford the saccharimide of 6-butoxyimidophenoxymethyl penicillin hydrochloride. Then water (40 ml.) is added to the rapidly stirred mixture allowing the temperature to go to 0—5°. The mixture is stirred at 0—5° for 1 hour and then kept at 0° overnight, without stirring. The mixture is filtered and the solid is washed with anhydrous ether giving a white solid of title compound (2.5 g., 29%), m.p. 172° dec. (uncorr.).
- Analysis: Calcd. for $C_{18}H_{15}N_3O_5S_2 \cdot HCl \cdot 1/2H_2O$: C, 42.20; H, 4.01; N, 9.84; S, 15.02; H_2O , 2.10. Found: C, 42.57; H, 3.99; N, 9.14; S, 13.40; H_2O , 1.99.

Example 16

- Following the procedure of Example 15, a series of saccharimide derivatives of phenoxymethyl penicillin are utilized as precursors to obtain the corresponding saccharimides of 6-aminopenicillanic acid as set forth in Table E below. The saccharin chloride per se (e.g., 3-chloro-1,2-benzisothiazole 1,1-dioxide required to obtain the saccharimides of the penicillin) is obtainable commercially. The benzene ring substituents R^2 and R^3 are introduced into the fused benzene moiety of the saccharin chloride by conventional procedures known for such purpose.

TABLE E

Saccharimide Derivative of Phenoxymethyl Penicillin	Saccharimide Derivative of 6-Aminopenicillanic Acid
4-ethyl-saccharimide of phenoxymethyl penicillin	4-ethyl-saccharimide of 6- aminopenicillanic acid
4-propyl-5-chloro-saccharimide of phenoxymethyl penicillin	4-propyl-5-chloro-saccharimide of 6-aminopenicillanic acid
4-nitro-saccharimide of phenoxymethyl penicillin	4-nitro-saccharimide of 6- aminopenicillanic acid
4,5-dibromo-saccharimide of phenoxymethyl penicillin	4,5-dibromo-saccharimide of 6-aminopenicillanic acid
4-hexyl-saccharimide of phenoxymethyl penicillin	4-hexyl-saccharimide of 6-aminopenicillanic acid
4-butoxy-5-phenyl-saccharimide of phenoxymethyl penicillin	4-butoxy-5-phenyl-saccharimide of 6-aminopenicillanic acid
5-(p-methoxy)-phenyl-sacchar- imide of phenoxymethyl penicillin	5-(p-methoxy)-phenyl-sacchar- imide of 6-aminopenicillanic acid
4-phenyl-saccharimide of phenoxymethyl penicillin	4-phenyl-saccharimide of 6-aminopenicillanic acid
5-benzyl-saccharimide of phenoxymethyl penicillin	5-benzyl-saccharimide of 6-aminopenicillanic acid
7-(m-propoxy)-phenyl-sacchar- imide of phenoxymethyl penicillin	7-(m-propoxy)-phenyl-sacchar- imide of 6-aminopenicillanic acid
4-butyl-5-fluoro-saccharimide of phenoxymethyl penicillin	4-butyl-5-fluoro-saccharimide of 6-aminopenicillanic acid

Example 17

Again following the procedure of Example 15, but in this instance utilising a series of saccharimide derivatives of benzyl penicillin as precursors, the corresponding saccharimide derivatives of 6-aminopenicillanic acid are obtained as set forth in Table F below:

TABLE F

Saccharimide Derivative of Benzyl Penicillin	Saccharimide Derivative of 6-Aminopenicillanic Acid
4-(2-pyridyl)-5-methyl-saccharimide of benzyl penicillin	4-(2-pyridyl)-5-methyl-saccharimide of 6-aminopenicillanic acid
5-trifluoromethyl-saccharimide of benzyl penicillin	5-trifluoromethyl-saccharimide of 6-aminopenicillanic acid
6-(dimethylamino)-7-methyl-saccharimide of benzyl penicillin	6-(dimethyl)-amino-7-methyl-saccharimide of 6-amino-penicillanic acid
7-(diethylamino)-saccharimide of benzyl penicillin	7-(dimethyl)-amino-saccharimide of 6-aminopenicillanic acid
4-carbamoyl-saccharimide of benzyl penicillin	4-carbamoyl-saccharimide of 6-aminopenicillanic acid
6-sulphamido-saccharimide of benzyl penicillin	6-sulphamido-saccharimide of 6-aminopenicillanic acid
4-carbethoxy-saccharimide of benzyl penicillin	4-carbethoxy-saccharimide of 6-aminopenicillanic acid
4-cyano-saccharimide of benzyl penicillin	4-cyano-saccharimide of 6-aminopenicillanic acid
4-(propyl-2)-thio-saccharimide of benzyl penicillin	4-(propyl-2)-thio-saccharimide of 6-aminopenicillanic acid
5-ethylsulphonyl-saccharimide of benzyl penicillin	5-ethylsulphonyl-saccharimide of 6-aminopenicillanic acid
4-(4-pyridyl)-saccharimide of benzyl penicillin	4-(4-pyridyl)-saccharimide of 6-aminopenicillanic acid
4,5-benzo-saccharimide of benzyl penicillin	4,5-benzo-saccharimide of 6-aminopenicillanic acid

Example 18

Utilising the general procedure of Example 15, but employing a series of amido phenoxymethyl penicillins other than the saccharimides thereof, the corresponding 2-amide derivatives of 6-aminopenicillanic acid are obtained as indicated in formula (I) wherein separate substituents X and Y are set forth in Table C and cyclic substituents

$\text{—N} < \begin{matrix} \text{X} \\ \text{Y} \end{matrix}$; are set forth in Table D in Examples 7 and 9 above respectively.

Example 19

Saccharimide of Cephalothin

Triethylammonium 3 - acetoxymethyl - 8 - oxo - 5 - thia - 7 - (thiophene - 2 - acetamido)-1-azabicyclo[4.2.0]oct-2-en-2-carboxylate (3.3 g., 0.00663 mole) is dissolved in methylene chloride (100 ml.) and the solution is cooled to 3°C. Then 3-chloro-1,2-benzisothiazole 1,1-dioxide (1.33 g., 0.00663 mole) is added to the magnetically stirred solution all at once. The solution is allowed to warm to room temperature overnight to afford 2-[(3-hydroxymethyl-8-oxo-7-[2-thiopheneacetamido] - 5 - thia - 1 - azabicyclo[4.2.0]oct - 2 - en - 2 - yl)carbonyl] - 1,2 - benzisothiazol-3(2H)-one 1,1-dioxide, acetate, also designated as the saccharimide of cephalothin.

Repeating the above procedure to react the triethylammonium salt of cephalothin with an appropriate substituted saccharimide, the following compounds are obtained:

- | | | |
|----|---|----|
| 5 | 5-methoxysaccharimide of cephalothin;
5,6-dichlorosaccharimide of cephalothin;
4-chloro-6-iodosaccharimide of cephalothin;
7-fluoro-5-phenethylsaccharimide of cephalothin;
5-ethoxyphenylsaccharimide of cephalothin;
5-(<i>N</i> -ethyl- <i>N</i> -methylamino)saccharimide of cephalothin;
6-carbomethoxysaccharimide of cephalothin; | 5 |
| 10 | 5-chloro-6-methylthiosaccharimide of cephalothin;
6-carbethoxysaccharimide of cephalothin; and
5-methylsulphonylsaccharimide of cephalothin. | 10 |

Example 20

Saccharimide of 2-Ethoxynaphthyl Penicillin

- | | | |
|----|--|----|
| 15 | 6 - (2 - Ethoxy - 1 - naphthamido) - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]heptane-2-carboxylic acid (20.7 g., 0.050 mole), also known as 2-ethoxynaphthyl penicillin, is added to methylene chloride (750 ml.) followed by triethylamine (5.05 g., 0.050 mole) 3-Chloro-1,2-benzisothiazole 1,1-dioxide (10.1 g., 0.050 mole) is added to the cooled solution (about 3°C.) in a single portion with stirring, and the reaction mixture processed in a manner similar to that of Example 1. | 15 |
| 20 | The product is obtained as a foam which is converted to a gummy solid on heating with absolute ethanol (about 300 ml.) and cooling and scratching. The crude product is recrystallised from ethyl acetate-hexane (charcoal), giving white crystals of 2-[(6-[2 - ethoxy - 1 - naphthamido] - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]hept-2-yl)carbonyl]-1,2-benzisothiazolin-3-one 1,1-dioxide, also designated as the saccharimide of 2-ethoxynaphthyl penicillin, (1.5 g.) m.p. 180°C. dec. (uncorr.). | 20 |
| 25 | Analysis: Calcd. for C ₂₈ H ₂₂ N ₂ O ₇ S ₂ : C, 58.02; H, 4.34; N, 7.25; S, 11.07. Found: C, 58.17; H, 4.51; N, 7.50; S, 10.90. | 25 |

Example 21

- | | | |
|----|---|----|
| 30 | Following the procedures described in Examples 1, 2, 19 and 20 a series of penicillins are reacted with various saccharin chloride derivatives to obtain the corresponding saccharimides of penicillins having potent antibiotic activity. The reactants and resulting saccharimides of penicillins are set forth in Table G below: | 30 |
|----|---|----|

TABLE G

Penicillins	Saccharin Chloride Derivatives	Saccharimides of Penicillins
phenoxymethyl penicillin	3-chloro-5-ethyl-1,2-benzisothiazole 1,1-dioxide	5-ethylsaccharimide of phenoxymethyl penicillin
6-(2,2-dimethyl-5-oxo-4-phenylimidazolidin-1-yl)-penicillanic acid	3,5-dichloro-6-propyl-1,2-benzisothiazole 1,1-dioxide	4-propyl-6-chloro-saccharimide of 6-(2,2-dimethyl-5-oxo-4-phenylimidazolidin-1-yl)penicillanic acid
2-ethoxynaphthyl penicillin	3-chloro-5-nitro-1,2-benzisothiazole 1,1-dioxide	5-nitrosaccharimide of 2-ethoxynaphthyl penicillin
phenoxyprop-1-yl penicillin	4,5-dibromo-3-chloro-1,2-benzisothiazole 1,1-dioxide	4,5-dibromosaccharimide of phenoxyprop-1-yl penicillin
3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin	3-chloro-5-hexyl-1,2-benzisothiazole 1,1-dioxide	5-hexylsaccharimide of 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin

TABLE G (Continued)

Penicillins	Saccharin Chloride Derivatives	Saccharimides of Penicillins
3-phenyl-5-methyl-4-isoxazolyl penicillin	6-butoxy-3-chloro-5-phenyl-1,2-benzisothiazole 1,1-dioxide	6-butoxy-5-phenyl-saccharimide of 3-phenyl-5-methyl-4-isoxazolyl penicillin
3-(<i>p</i> -chlorophenyl)-5-methyl-4-isoxazolyl penicillin	3-chloro-5-(<i>p</i> -methoxyphenyl)-1,2-benzisothiazole 1,1-dioxide	5-(<i>p</i> -methoxyphenyl)-saccharimide of 3-(<i>p</i> -chlorophenyl)-5-methyl-4-isoxazolyl penicillin
benzyl penicillin	3-chloro-6-phenyl-1,2-benzisothiazole 1,1-dioxide	6-phenylsaccharimide of benzyl penicillin
phenoxyethyl penicillin	5-benzyl-3-chloro-1,2-benzisothiazole 1,1-dioxide	5-benzylsaccharimide of phenoxyethyl penicillin
2-methoxynaphthyl penicillin	3-chloro-7-(<i>m</i> -propoxyphenyl)-1,2-benzisothiazole 1,1-dioxide	7-(<i>m</i> -propoxyphenyl)-saccharimide of 2-methoxynaphthyl penicillin
3-(<i>o</i> -chlorophenyl)-5-methyl-4-isoxazolyl penicillin	6-butyl-3-chloro-5-fluoro-1,2-benzisothiazole 1,1-dioxide	6-butyl-5-fluoro-saccharimide of 3-(<i>o</i> -chlorophenyl)-5-methyl-4-isoxazolyl penicillin
3,5-diphenyl-4-isoxazolyl penicillin	3-chloro-5,6-dimethyl-1,2-benzisothiazole 1,1-dioxide	5,6-dimethylsaccharimide of 3,5-diphenyl-4-isoxazolyl penicillin
α -phenoxybenzyl penicillin	3-chloro-4-(2-pyridyl)-1,2-benzisothiazole 1,1-dioxide	4-(2-pyridyl)-saccharimide of α -phenoxybenzyl penicillin
α -phenoxyethyl penicillin	3-chloro-5-dimethylamino-1,2-benzisothiazole 1,1-dioxide	5-dimethylamino-saccharimide of α -phenoxyethyl penicillin
2,6-dimethoxybenzyl penicillin	3-chloro-6-trifluoromethyl-1,2-benzisothiazole 1,1-dioxide	6-trifluoromethyl-saccharimide of 2,6-dimethoxybenzyl penicillin

Example 22

Saccharimide of 1-Aminocyclohexane Penicillin

- 5 2 - [(6 - Amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]hept-2-yl)carbonyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (1.91 g., 0.005 mole) is dissolved in methylene chloride (100 ml.) and the stirred solution is cooled at -5°C . in an ice-salt bath. Pyridine (0.403 ml., 0.005 mole) is added, followed by 1-aminocyclohexane carboxylic acid chloride hydrochloride (1.02 g., 0.005 mole), and the mixture is stirred at -5°C . for twenty minutes. The resulting solution is allowed to warm to room temperature, and then stirred for two hours, giving a white solid precipitate. The mixture is divided in half and one-half is filtered and washed with methylene chloride, giving 2 - [(6 - (1 - aminocyclohexanecarboxamido) - 3,3 - dimethyl - 7 - oxo - 4-
- 5
- 10
- 10

thia - 1 - azabicyclo[3.2.0]hept - 2 - yl)carbonyl] - 1,2 - benzisothiazol - 3(2*H*)-one 1,1-dioxide hydrochloride, also designated as the saccharimide of 1-aminocyclohexane penicillin hydrochloride, as a white solid (1.15 g., 85% based on one-half the total yield), m.p. 153°C. dec. (uncorr.).

5 Analysis: Calcd. for $C_{22}H_{26}N_4O_6S_2 \cdot HCl$: C, 48.65; H, 5.01; N, 10.32; S, 11.81; Cl, 5.01. Found: C, 48.71; H, 5.12; N, 10.14; S, 10.25; Cl, 9.83.

The other half of the mixture is evaporated to dryness under vacuum at 30°C., giving a white solid (1.7 g.). The solid is powdered and added to water (15 ml.) at 3°C. which is kept constantly at pH 9.4 with 1 N sodium hydroxide. The mixture is filtered ten minutes after the final addition and washed with water, giving 2-[(6-[1-aminocyclohexanecarboxamido] - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]hept-2-yl)carbonyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide, also described as the saccharimide of 1-aminocyclohexane penicillin, as a white solid (1.25 g., 99% based on one-half the total yield), m.p. 145°C. dec. (uncorr.).

15 Analysis: Calcd. for $C_{22}H_{26}N_4O_6S_2 \cdot H_2O$: C, 50.37; H, 5.38; N, 10.68; S, 12.23; H_2O , 3.44. Found: C, 49.78; H, 5.54; N, 11.11; S, 12.59; H_2O , 3.34.

Example 23

Following the procedures of Examples 4 and 22, a series of saccharimides of 6-aminopenicillanic acid (6—APA) are reacted with various acylating agents to obtain the saccharimides of penicillins having potent antibiotic activity. The reactants and resulting saccharimide of penicillins are set forth in Table H below:

20

20

TABLE H

Saccharimides of 6-Aminopenicillanic Acid (6-APA)	Acylating Agents	Saccharimide Penicillins
5-methyl-4-(4-pyridyl)saccharimide of 6-APA	N-carboxyanhydride of 1-aminocyclopentane carboxylic acid	5-methyl-4-(4-pyridyl)saccharimide of 1-aminocyclopentane penicillin
5-trifluoromethylsaccharimide of 6-APA	N-carboxyanhydride of 1-aminocyclohexane carboxylic acid	5-trifluoromethylsaccharimide of 1-aminocyclohexane penicillin
dimethylamino-7-methylsaccharimide of 6-APA	phenylglycine chloride hydrochloride	6-dimethylamino-7-methylsaccharimide of 1-aminobenzyl penicillin
6-sulphamido-saccharimide of 6-APA	N-carboxyanhydride of 1-amino-1-indane carboxylic acid	6-sulphamidossaccharimide of 1-amino-1-indane penicillin
5-carbethoxy-saccharimide of 6-APA	N-carboxyanhydride of 1-amino-1,2,3,4-tetrahydronaphthoic acid	5-carbethoxy-saccharimide of 1-amino-1,2,3,4-tetrahydronaphthyl penicillin
5-cyanosaccharimide of 6-APA	N-carboxyanhydride of 1-amino-7-ethoxy-1,2,3,4-tetrahydro-1-naphthoic acid	5-cyanosaccharimide of 1-amino-7-ethoxy-1,2,3,4-tetrahydro-1-naphthyl penicillin
6-(prop-2-yl)thio-saccharimide of 6-APA	N-carboxyanhydride of 1-amino-4-phenyl-1-indane carboxylic acid	6-(prop-2-yl)thio-saccharimide of 1-amino-4-phenyl-1-indane penicillin

TABLE H (Continued)

Saccharimides of 6-Aminopenicillanic Acid (6-APA)	Acylating Agents	Saccharimide Penicillins
5-ethylsulphonyl-saccharimide of 6-APA	N-carboxyanhydride of 2-amino-3-phenoxy-2-indane carboxylic acid	5-ethylsulphonyl-saccharimide of 2-amino-3-phenoxy-2-indane penicillin
5,6-benzosaccharimide of 6-APA	N-carboxyanhydride of 1-amino-1,2,3,4-tetrahydro-3,6-dimethyl-1-naphthoic acid	5,6-benzosaccharimide of 1-amino-1,2,3,4-tetrahydro-3,6-dimethyl-1-naphthyl penicillin

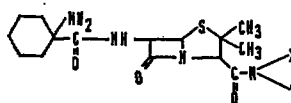
Example 24

Repeating the procedure of Examples 6 and 7, to acylate 2-amido-6-aminopenicillanic acid and 2-amido-7-aminocephalosporanic acids by reaction with appropriate N-carboxyanhydrides, the compounds of Tables I, J, K, L and M are obtained:

5

5

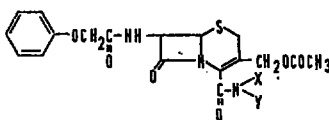
TABLE I



wherein X and Y when taken separately are defined as follows:

X	Y
<i>p</i> -nitrophenylsulphonyl	<i>m</i> -nitrobenzoyl
<i>p</i> -trifluoromethylphenylsulphonyl	<i>p</i> -methylsulphonylbenzoyl
2,4-dinitrophenylsulphonyl	<i>p</i> -toluyl
<i>p</i> -chlorophenylsulphonyl	<i>p</i> -methoxybenzoyl
trifluoromethylsulphonyl	<i>p</i> -(N,N-dimethylsulphamyl)benzoyl
<i>m</i> -(N,N-diethylsulphamyl)benzoyl	<i>p</i> -trifluoromethylbenzoyl
carbomethoxy	<i>p</i> -trifluoromethylbenzoyl
cyano	<i>o</i> -chlorophenylsulphonyl
cyano	<i>m</i> -trifluoromethylphenylsulphonyl
trifluoromethylsulphonyl	<i>p</i> -nitrophenylsulphonyl
N,N-dimethylcarbamyl	2-bromo-4-chlorophenylsulphonyl

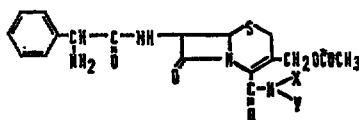
TABLE J



wherein X and Y when taken separately are defined as follows:

X	Y
methylsulphonyl	2-bromo-4-nitrophenylsulphonyl
N,N-dimethylsulphamyl	<i>m</i> -(N,N-dimethylcarbamyl)phenylsulphonyl
carbohexoxy	<i>p</i> -methylsulphonylphenylsulphonyl
carbethoxy	<i>p</i> -(N,N-diethylsulphamyl)phenylsulphonyl
trifluoromethylsulphonyl	4-cyano-2-iodophenylsulphonyl
cyano	2-fluoro-4-nitrophenylsulphonyl
pentylsulphonyl	<i>p</i> -carbobutoxyphenylsulphonyl

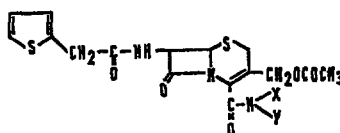
TABLE K



wherein X and Y when taken separately are defined as follows:

X	Y
propionyl	<i>p</i> -iodobenzylsulphonyl
acetyl	butyryl
propionyl	benzoyl
cyano	phenylsulphonyl
2,4,6-trimethylbenzoyl	phenethylsulphonyl
2,4,6-trimethylbenzoyl	<i>p</i> -methoxyphenylsulphonyl
N,N-dimethylcarbamyl	N,N-dimethylaminoethylsulphonyl
2,3,5,6-tetramethylbenzoyl	<i>p</i> -methylthiophenylsulphonyl
cyclovaleryl	<i>m</i> -nitrophenethylsulphonyl

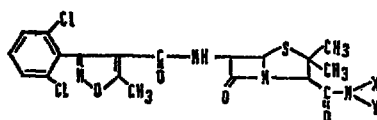
TABLE L



wherein X and Y when taken separately are defined as follows:

X	Y
N,N-dipropylaminobutyl sulphonyl	2-naphthoyl
cyano	2,4-dimethylbenzoyl
cyclobutyryl	<i>p</i> -fluorophenacetyl
cyclocaproyl	trifluoromethylsulphonyl
furoyl	cyano
N,N-dimethylsulphamylphenpropionyl	carbopropoxy
<i>p</i> -propylphenylsulphonyl	acetyl
2-naphthylsulphonyl	<i>p</i> -butoxybenzoyl
phenbutyryl	nitro
2-furylsulphonyl	caproyl

TABLE M



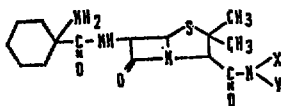
wherein X and Y when taken separately are defined as follows:

X	Y
2-pyridylsulphonyl	methylsulphonyl
phencaproyl	cyano
phenpropylsulphonyl	trifluoromethylsulphonyl
<i>p</i> -propylsulphonylphenylsulphonyl	cyano
nitro	<i>p</i> -(N,N-dibutylcarbamyl)phenylsulphonyl
<i>m</i> -carbomethoxyphenylsulphonyl	carbethoxy
<i>p</i> -propoxyphenylsulphonyl	methylsulphonyl
cyano	<i>p</i> -pentylthiophenylsulphonyl

Example 25

Following the general procedure of Example 8, to acylate a series of 2-cycloamido-6-aminopenicillanic acid by reaction with the *N*-carboxyanhydride of 1-aminocyclohexane carboxylic acid, there is obtained the corresponding 2-cycloamido penicillin derivatives indicated in Table N below:

TABLE N



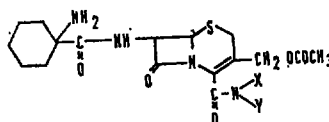
wherein X and Y when taken together with the nitrogen atom to which they are attached form the following cyclic electron withdrawing groups:

- 5-ethyl-3-oxo-1,2-benzisothiazolin-2-yl 1,1-dioxide;
- 4-methoxyphthalimido;
- 6,7-dichloro-3-oxo-4,1,2-benzoxathiazin-2(3*H*)-yl 1,1-dioxide;
- 3-oxo-6-nitro-1,4,2-benzodithiazin-2(3*H*)-yl 1,1-dioxide;
- 6-cyano-3,4-dihydro-4-methyl-3-oxo-2*H*-1,2,4-benzothiadiazin-2-yl 1,1-dioxide;
- 3,3,4,4-tetramethyl-2-oxo-1-pyrrolidinyl;
- 6-bromo-3,4-dihydro-2,4-dioxo-2*H*-1,3-benzoxazin-3-yl;
- 7-trifluoromethyl-3,4-dihydro-2,4-dioxo-2*H*-1,3-benzothiazin-3-yl;
- 7-ethylsulphonyl-1,4-dihydro-1-methyl-2,4-dioxo-3(2*H*)-quinazolinyl;
- 6-fluoro-1,2-benzisothiazolin-2-yl 1,1-dioxide;
- 5-benzyl-1-oxo-2-isoindolinyl;
- 2-isothiazolidinyl 1,1-dioxide;
- 6-chloro-3,4-dihydro-7-methyl-3-oxo-2*H*-1,2-benzothiazin-2-yl 1,1-dioxide;
- 7-carbomethoxy-3,4-dihydro-1,3-dioxo-2(1*H*)-isoquinolyl;
- o*-benzenedisulphonimido; and
- o*-(3-bromobenzene)disulphonimido.

Example 26

Repeating the general procedure of Example 8, to acylate a series of 2-cycloamido-7-aminocephalosporins by reaction with the *N*-carboxyanhydride of 1-aminocyclohexane carboxylic acid, there is obtained the corresponding 2-cycloamidocephalosporin derivatives indicated in Table O below:

TABLE O



wherein X and Y when taken together with the nitrogen atom to which they are attached form the following cyclic electron withdrawing groups:

- 5-ethyl-3-oxo-1,2-benzisothiazolin-2-yl 1,1-dioxide;
- phthalimido;
- succinimido;
- 3-oxo-2-isothiazolidinyl 1,1-dioxide;
- 3-oxo-4-isothiazolin-2-yl 1,1-dioxide;
- 6,7-dichloro-3-oxo-4,1,2-benzoxathiazin-2(3*H*)-yl 1,1-dioxide;
- 3-oxo-1,4,2-benzodithiazin-2(3*H*)-yl 1,1-dioxide;
- 6-cyano-3,4-dihydro-4-methyl-3-oxo-2*H*-1,2,4-benzothiadiazin-2-yl 1,1-dioxide;
- tetramethylsuccinimido;
- 3,4-dihydro-2,4-dioxo-2*H*-1,3-benzoxazin-3-yl;
- 7-trifluoromethyl-3,4-dihydro-2,4-dioxo-2*H*-1,3-benzothiazin-3-yl;
- 1,4-dihydro-1-methyl-2,4-dioxo-3(2*H*)-quinazolinyl;
- 1,2-benzisothiazolin-2-yl 1,1-dioxide;
- 5-benzyl-1-oxo-2-isoindolinyl;
- 2-isothiazolidinyl 1,1-dioxide;
- 2-oxo-1-pyrrolidinyl;
- 3,4-dihydro-3-oxo-2*H*-1,2-benzothiazin-2-yl 1,1-dioxide;
- 7-carbomethoxy-3,4-dihydro-1,3-dioxo-2(1*H*)-isoquinolyl; and
- o*-benzenedisulphonimido.

Example 27

Saccharimides of 1-Aminocycloaliphatic Penicillins

In a similar manner to example 10, reacting appropriate 1-aminocycloalkane penicillins with 3-chloro-1,2-benzisothiazole 1,1-dioxide, the following compounds are prepared:

- 1-aminocycloheptane penicillin saccharimide;
1-aminocyclooctane penicillin saccharimide; and
1-aminocyclononane penicillin saccharimide.

Example 28

Saccharimides of Various Penicillins

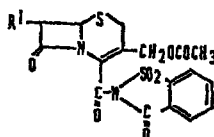
When the procedure of example 13 is repeated using appropriate reactants the following compounds are prepared:

- 2,6-dipropoxybenzyl penicillin saccharimide;
4-butoxynaphthyl penicillin saccharimide;
naphthyl penicillin saccharimide;
3-(2,6-dibromophenyl)-4-isoxazolyl penicillin saccharimide;
3-(2-fluoro-4-iodophenyl)-5-propyl-4-isoxazolyl penicillin saccharimide;
5-ethyl-3-(*p*-fluorophenyl)-4-isoxazolyl penicillin saccharimide;
1-amino-4-chloro-1,2,3,4-tetrahydronaphthyl penicillin saccharimide;
1-amino-4-bromo-5-methoxy-1,2,3,4-tetrahydronaphthyl penicillin saccharimide;
6-(2,2-dibutyl-5-oxo-4-phenylimidazolidin-1-yl)penicillanic acid saccharimide;
6-(2-ethyl-5-oxo-4-phenylimidazolidin-1-yl)penicillanic acid saccharimide;
6-[5-oxo-4-phenyl-2-(4-piperidine)imidazolidin-1-yl]penicillanic acid saccharimide;
6-(2-cyclobutyl-5-oxo-4-phenylimidazolidin-1-yl)-penicillanic acid saccharimide; and
6-(2-cyclohexyl-5-oxo-4-phenylimidazolidin-1-yl)penicillanic acid saccharimide.

Example 29

When the procedure of Example 13 is repeated to react 2[(7-amino-3-hydroxy-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-en-2-yl)carbonyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide acetate with an appropriate acyl chloride, the compounds listed in Table P are prepared:

TABLE P



wherein R¹ is defined as follows:

- 2-phenoxyacetamido;
2,2-dimethyl-5-oxo-4-phenylimidazolidin-1-yl;
thiophene-2-acetamido;
2-ethoxy-1-naphthamido;
2-amino-2-phenylacetamido;
1-aminocyclohexanecarboxamido;
2-phenylacetamido;
1-aminocyclopentanecarboxamido;
1-naphthamido; and
3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarboxamido.

Example 30

Various Penicillins and Cephalosporins

When the procedure of Example 14 is conducted substituting as starting materials the saccharimides of Examples 1 to 5, 10 to 13, 19 to 23, 25 to 29, 36 and 40 the corresponding 3-acetoxymethyl-8-oxo-5-thia-7-substituted-1-azabicyclo[4.2.0]oct-en-2-carboxylic acids and 3,3-dimethyl-7-oxo-6-substituted-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acids are afforded.

Example 31

1-Aminocyclohexane Penicillin

- 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 hydrochloride (80 g., 0.1725 mole on the basis of 98% purity) is added to a solution of acetonitrile (1200 ml.) and water (300 ml.) that had previously been warmed to 35°C. The mixture is rapidly stirred for approximately thirty seconds, causing the solid to dissolve. The solution is stirred and cooled in an ice-salt bath, and at 11°C. the pH is adjusted to 2.5—3.0 with 35% sodium hydroxide. 1-Aminocyclohexanecarboxylic acid chloride hydrochloride (43.6 g., 0.22 mole) is added in approximately ten portions over a period of about fifteen minutes. The temperature is maintained at 8—10°C. and, simultaneously, with the addition of the acid chloride, there is added 35% sodium hydroxide to maintain the pH at 2.5 to 3. After adding all the acid chloride the mixture is stirred at pH 2.75 at 0—10°C. for twenty minutes and the pH adjusted to 2.0 with concentrated hydrochloric acid. The stirring is stopped and the top layer is removed by decantation. Anhydrous ether (2.4 litres) is added to the top layer and the mixture cooled to 5°C. in ice-salt and stirred for one hour. The solid is filtered and the organic solvents are removed by evaporation. The resulting solid is powdered, stirred with cold water (140 ml.), filtered and washed once with cold water. The pasty filter cake is spread on filter paper, air-dried until solid, powdered and dried over P₂O₅ in vacuum, giving a white powder which is 2-[(6-[1-aminocyclohexanecarboxamido]-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 hydrochloride, also described as the saccharimide of 1-aminocyclohexane penicillin hydrochloride (21 g., 22%).
- Cold water (130 ml.) is added to the lower layer and the solid is filtered using a funnel. The filter cake is washed twice with cold water, and the pasty filter cake is spread on filter paper and dried. The solid is powdered and dried over P₂O₅ in vacuum giving a white powder which is also the saccharimide of 1-aminocyclohexane penicillin hydrochloride (50 g., 52%).
- The above prepared saccharimide of 1-aminocyclohexane penicillin hydrochloride (4.0g. 0.00737 mole) is mixed with water (20 ml.) until completely suspended. Quinoline (4 ml.) is dripped in over approximately three minutes, giving a thick white paste. Mixing is continued for one hour causing most of the solid to dissolve, but leaving a gum on the sides of the flask that is scraped into the solution. The mixture is filtered and washed with water (5 ml.). The filtrate is cooled to 0°C. and the pH brought to 7.6 with 25% NaOH. The mixture is washed twice with ether, and antipyrine (1.2 g., 0.0064 mole) is added. The solution is cooled to -3 to -5°C. and the pH adjusted to 1.5 while crystals form. After ten minutes the mixture is filtered and the filtrate washed with ethyl acetate. The pH of the aqueous phase is raised to 5.2 with 25% sodium hydroxide, and the solution concentrated at 30°C. to 7.5 ml. The solution is seeded with a few crystals of 1-aminocyclohexane penicillin dihydrate and a few crystals of anhydrous 1-aminocyclohexane penicillin. Isopropanol (about one millilitre) is added, and after scratching crystals form. The crystals are kept at 0°C. overnight, filtered, and washed with a minimum of cold water, giving white crystals of 6 - (1 - aminocyclohexanecarboxamido) - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]heptane-2-carboxylic acid, dihydrate (1.37 g., 51%).

Example 32

- 3,3 - Dimethyl - 7 - oxo - 6 - (2 - phenoxyacetamido) - 4 - thia - 1 - azabicyclo[3.2.0]heptane-2-carboxylic acid, also described as phenoxymethyl penicillin, (15.1 g., 0.043 mole) is added to anhydrous methylene chloride (150 ml.) contained in a dry 500 ml. three neck round bottom flask equipped with a stirrer, a drying tube and a thermometer through a U-tube nitrogen inlet. Then triethylamine (4.34 g., 0.043 mole) is added, and the solution is cooled to 5°C. in ice. Pseudosaccharin chloride (8.7 g., 0.043 mole) is added all at once, giving a canary yellow solution. The solution is stirred for one-half hour at 5°C., and kept at room temperature overnight. The solution is then brought to the boiling point for five minutes, and allowed to cool to room temperature to afford 2-[(3,3-dimethyl-7-oxo-6-[2-phenoxyacetamido]-4-thia-1-azabicyclo[3.2.0]hept-2-yl)carbonyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, also named as the saccharimide of phenoxymethyl penicillin.
- Thereafter, quinoline (14.5 g., 0.112 mole) is added and the stirred solution containing said saccharimide and the mixture is cooled to -30°C. and phosphorus pentachloride (11.6 g., 0.056 mole) is added over a few minutes, keeping the temperature at -30°C. The mixture is stirred for three hours at -30°C. to yield 2-[(6-[1-chloro-2-phenoxyethylideneamino]-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, also known as the saccharimide of 6-chloroimidophenoxymethyl penicillin. A small portion of this mixture is separated and the 6-chloroimide isolated.

5 Analysis: Calcd. for $C_{27}H_{26}ClN_3O_6S_2$: C, 51.73; H, 3.78; Cl, 6.64; N, 7.87; S, 12.01. Found: C, 51.92; H, 3.91; Cl, 6.16; N, 7.76; S, 11.69. 5

To the remainder of above-described mixture containing said 6-chloroimide, quinoline (6.6 ml., 0.056 mole) is added followed by absolute ethanol (100 ml.) over a few minutes, keeping the temperature at $-30 \pm 3^\circ\text{C}$. After stirring the mixture for one hour at -30°C ., the temperature is rapidly raised to $+20^\circ\text{C}$. with hot water, 10 and immediately brought back to -30°C . and stirred for another hour. Then the temperature is brought up to $+20^\circ\text{C}$. with hot water and immediately back to -10°C . and stirred for one more hour to afford 2-[(6-[1-ethoxy-2-phenoxyethylideneamino]-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 hydrochloride, also described as the saccharimide 15 of 6-ethoxyimidophenoxymethyl penicillin hydrochloride. 15

Subsequently, water (75 ml.) is added to above-described mixture containing said 6-ethoxyimide hydrochloride and the temperature is lowered to 0°C . and then stirred for twenty minutes. The mixture is kept at 0°C . overnight and filtered. The solid is washed with cold (5°C .) water (30 ml.), without slurrying the solid in the water, and 20 sucked dry. The solid is then washed with cold (5°C .) methylene chloride (2×30 ml.), slurrified in absolute ether and sucked dry on the funnel, dried over P_2O_5 in a vacuum, giving white crystals of 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 hydrochloride, also 25 known as the saccharimide of 6-aminopenicillanic acid hydrochloride (11.1—12.6 g., 62—75%), m.p. 176°C . dec. (uncorr.). 25

Analysis: Calcd. for $C_{15}H_{15}N_3O_5S_2 \cdot HCl \cdot 1/2H_2O$: C, 42.40; H, 4.01; N, 9.84; S, 15.02; Cl, 8.30. Found: C, 42.25; H, 3.83; N, 9.73; S, 15.11; Cl, 11.40.

Example 33

2 - [(6 - Amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]- 30 hept - 2 - yl)carbonyl] - 1,2 - benzisothiazol - 3(2H) - one 1,1 - dioxide hydrochloride (8.6 g., 0.0206 mole) as prepared in Example 32, is powdered, added to water (75 ml.) in four portions, and stirred at 0°C . Adjustment of the pH to 6.9 after each addition is done with a 60°C . saturated sodium bicarbonate solution. After the second 35 addition some ether is added to control the foaming. After the final adjustment of the pH to 6.9 the mixture is stirred at $0-2^\circ\text{C}$. for ten minutes, and the pH slowly goes to 7.1. The solid is filtered and washed with cold water (2x), and dried in a desiccator over P_2O_5 under vacuum at 5°C ., giving a white solid which is 2-[(6-amino - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]hept - 2 - yl)- 40 carbonyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, also described as the saccharimide of 6-aminopenicillanic acid (7.0 g., 90%), m.p. 158°C . dec. (uncorr.). 40

Analysis: Calcd. for $C_{15}H_{15}N_3O_5S_2$: C, 47.23; H, 3.97; N, 11.02; S, 16.81. Found: C, 47.43; H, 3.94; N, 11.21; S, 16.60.

Example 34

Following the procedure of Examples 15, 32 and 33, phenoxymethyl penicillin 45 is reacted with a series of saccharimide derivatives to afford the hereinafter listed saccharimide derivatives of phenoxymethyl penicillin, which are contacted with phosphorus pentachloride to afford the corresponding saccharimides of 6-chloroimido-phenoxymethyl penicillin which are contacted with an alkanol to yield appropriate 50 saccharimides of 6-alkoxyimidophenoxymethyl penicillin hydrohalides, which are then hydrolysed and neutralised to produce the following saccharimides of 6-amino-penicillanic acid: 50

TABLE Q

Saccharimide Derivatives of Phenoxymethyl Penicillin	Saccharimide Derivatives of 6-Aminopenicillanic Acid
5-ethylsaccharimide of phenoxymethyl penicillin	5-ethylsaccharimide of 6- aminopenicillanic acid
5-chloro-6-propylsaccharimide of phenoxymethyl penicillin	5-chloro-6-propylsaccharimide of 6-aminopenicillanic acid
6-nitrosaccharimide of phenoxymethyl penicillin	6-nitrosaccharimide of 6- aminopenicillanic acid
5,6-dibromosaccharimide of phenoxymethyl penicillin	5,6-dibromosaccharimide of 6-aminopenicillanic acid
5-hexylsaccharimide of phenoxymethyl penicillin	5-hexylsaccharimide of 6- aminopenicillanic acid
5-butoxy-6-phenylsaccharimide of phenoxymethyl penicillin	5-butoxy-6-phenylsaccharimide of 6-aminopenicillanic acid
5-(<i>p</i> -methoxyphenyl)saccharimide of phenoxymethyl penicillin	5-(<i>p</i> -methoxyphenyl)saccharimide of 6-aminopenicillanic acid
5-phenylsaccharimide of phenoxymethyl penicillin	5-phenylsaccharimide of 6-aminopenicillanic acid
6-benzylsaccharimide of phenoxymethyl penicillin	6-benzylsaccharimide of 6-aminopenicillanic acid
7-(<i>m</i> -propoxyphenyl)saccharimide of phenoxymethyl penicillin	7-(<i>m</i> -propoxyphenyl)saccharimide of 6-aminopenicillanic acid
4-butyl-5-fluorosaccharimide of phenoxymethyl penicillin	4-butyl-5-fluorosaccharimide of 6-aminopenicillanic acid

Example 35

Repeating the procedure of Examples 15, 32 and 33 to react a series of saccharimide derivatives with benzyl penicillin there is produced the hereafter set forth saccharimide derivatives of benzyl penicillin which are contacted with phosphorus pentabromide to afford the corresponding saccharimides of 6-bromoimidobenzyl penicillin which are contacted with an alkanol to yield appropriate saccharimides of 6-alkoxyimidobenzyl penicillin hydrobromide which are then hydrolysed and neutralised to produce the following saccharimides of 6-aminopenicillanic acid:

TABLE R

Saccharimide Derivatives of Benzyl Penicillin	Saccharimide Derivatives of 6-Aminopenicillanic acid
5-methyl-6-(2-pyridyl)- saccharimide of benzyl penicillin	5-methyl-6-(2-pyridyl)saccharimide of 6-aminopenicillanic acid
5-trifluoromethylsaccharimide of benzyl penicillin	5-trifluoromethylsaccharimide of 6-aminopenicillanic acid

TABLE R (Continued)

Saccharimide Derivatives of Benzyl Penicillin	Saccharimide Derivatives of 6-Aminopenicillanic Acid
6-dimethylamino-7-methyl saccharimide of benzyl penicillin	6-dimethylamino-7-methyl saccharimide of 6-aminopenicillanic acid
7-diethylaminosaccharimide of benzyl penicillin	7-diethylaminosaccharimide of 6-aminopenicillanic acid
5-carbomethoxysaccharimide of benzyl penicillin	5-carbomethoxysaccharimide of 6-aminopenicillanic acid
6-sulphamidossaccharimide of benzyl penicillin	6-sulphamidossaccharimide of 6-aminopenicillanic acid
5-carbethoxysaccharimide of benzyl penicillin	5-carbethoxysaccharimide of 6-aminopenicillanic acid
6-cyanosaccharimide of benzyl penicillin	6-cyanosaccharimide of 6-aminopenicillanic acid
5-propylthiosaccharimide of benzyl penicillin	5-propylthiosaccharimide of 6-aminopenicillanic acid
5-ethylsulphonylsaccharimide of benzyl penicillin	5-ethylsulphonylsaccharimide of 6-aminopenicillanic acid
6-(4-pyridyl)saccharimide of benzyl penicillin	6-(4-pyridyl)saccharimide of 6-aminopenicillanic acid
5,6-benzosaccharimide of benzyl penicillin	5,6-benzosaccharimide of 6-aminopenicillanic acid

Example 36

- 6 - (3 - Hexenamido) - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]-
heptane-2-carboxylic acid, also described as 2-pentenyl penicillin, (0.040 mole) is added
5 to anhydrous methylene chloride (150 ml.) contained in a dry 500 ml. three neck round
bottom flask equipped with a stirrer, a drying tube and a thermometer through a U-
tube nitrogen inlet. Then triethylamine (0.040 mole) is added, and the solution is
cooled to 5°C. in ice. Pseudosaccharin chloride (0.040 mole) is added all at once,
giving a yellow solution. The solution is stirred for one-half hour at 5°C., and kept
10 at room temperature overnight. The solution is then brought to the boiling point for
five minutes, allowed to cool to room temperature, filtered and the collected solid is
2 - [(6 - [2 - hexenamido] - 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, also named as
the saccharimide of 2-pentenyl penicillin.
- 15 Repeating the above procedure, to react appropriate penicillins with various
saccharin chloride derivatives, the following penicillin saccharimides are obtained:
- 2 - [(6 - [2 - allylmercaptoacetamido] - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1-
azabicyclo[3.2.0]hept-2-yl)carbonyl] - 5 - chloro- 1,2 - benzisothiazol - 3(2H) - one
1,1-dioxide, also known as the 5-chlorosaccharimide of allylmercaptomethyl penicillin;
- 20 2 - [(6 - [2 - (γ - chlorocrotylmercapto)acetamido] - 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, also described as the saccharimide of γ -chlorocrotylmercaptomethyl
penicillin;
- 25 2 - [(3,3 - dimethyl - 7 - oxo - 6 - [2 - phenylacetamido] - 4 - thia - 1 - aza-
bicyclo[3.2.0]hept - 2 - yl)carbonyl] - 1,2 - benzisothiazol - 3(2H) - one 1,1-
dioxide, also named as the saccharimide of benzyl penicillin;
- 2 - [(6 - hexenamido - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]-

hept-2-yl)carbonyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide, also defined as the saccharimide of amyl penicillin;

- 5 2 - [(3,3 - dimethyl - 6 - octanamido - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]-hept-2-yl)carbonyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide, also named as the saccharimide of heptyl penicillin; and
- 5 2 - [(6 - [2 - (*p* - hydroxyphenyl)acetamido] - 3,3 - dimethyl - 7 - oxo - 4 - thia-1 - azabicyclo[3.2.0]hept - 2 - yl)carbonyl] - 1,2 - benzisothiazol - 3(2*H*) - one 1,1-dioxide, also described as the saccharimide of hydroxybenzyl penicillin.

Example 37

- 10 The saccharimide of 2-pentenyl penicillin, as prepared in Example 36, is admixed with methylene chloride (150 ml.) quinoline (0.110 mole), the stirred mixture is cooled to -10°C . and phosphorus pentachloride (0.055 mole) is added over a few minutes. The resulting mixture is stirred at -10°C ., thereafter the precipitate is separated by filtration to yield the saccharimide of the 6-chloroimido-2-pentenyl penicillin.
- 15

In a similar manner, the other penicillin saccharimides of Example 36 are reacted with phosphorus pentahalides to afford:

- 5-chlorosaccharimide of 6-chloroimidoallyl-mercaptopmethyl penicillin;
saccharimide of 6-bromoimido- γ -chlorocrotyl-mercaptopmethyl penicillin;
20 saccharimide of 6-chloroimidobenzyl penicillin;
saccharimide of 6-chloroimidoamyl penicillin;
saccharimide of 6-chloroimidoheptyl penicillin; and
saccharimide of 6-chloroimidohydroxybenzyl penicillin.
- 20

Example 38

- 25 The saccharimide of the 6-chloroimido-2-pentenyl penicillin, as prepared in Example 37, is admixed with methylene chloride (150 ml), quinoline (0.055 mole) and absolute methanol (100 ml.), keeping the temperature at $-30^{\circ}\text{C} \pm 3^{\circ}\text{C}$. After stirring the mixture for one hour at -30°C ., the temperature is rapidly raised to $+20^{\circ}\text{C}$. with hot water, and brought back to -30°C . and stirred for another hour.
- 30 Then the temperature is brought up to $+20^{\circ}\text{C}$. with hot water and quickly back to -10°C . and stirred for one more hour to produce the saccharimide of 6-methoxyimido-2-pentenyl penicillin hydrochloride which is separated by filtration.
- 30

In like manner, the 6-haloimido penicillin saccharimides of Example 37 are reacted with various alkanols to yield:

- 35 saccharimide of 6-ethoxyimido-2-pentenyl penicillin, hydrochloride;
saccharimide of 6-pentoxyimido-2-pentenyl penicillin hydrochloride;
5-chlorosaccharimide of 6-methoxyimidoallylmercaptopmethyl penicillin hydrochloride;
5-chlorosaccharimide of 6-ethoxyimidoallylmercaptopmethyl penicillin hydrochloride;
40 5-chlorosaccharimide of 6-butoxyimidoallylmercaptopmethyl penicillin hydrochloride;
saccharimide of 6-methoxyimido- γ -chlorocrotylmercaptopmethyl penicillin hydrobromide;
45 saccharimide of 6-ethoxyimido- γ -chlorocrotylmercaptopmethyl penicillin hydrobromide;
saccharimide of 6-hexoxyimido- γ -chlorocrotylmercaptopmethyl penicillin hydrobromide;
saccharimide of 6-ethoxyimidobenzyl penicillin hydrochloride;
50 saccharimide of 6-butoxyimidobenzyl penicillin hydrochloride;
saccharimide of 6-ethoxyimidoamyl penicillin hydrochloride;
saccharimide of 6-propoxyimidoamyl penicillin hydrochloride;
saccharimide of 6-methoxyimidoamyl penicillin hydrochloride;
55 saccharimide of 6-methoxyimidoheptyl penicillin hydrochloride;
saccharimide of 6-ethoxyimidoheptyl penicillin hydrochloride;
saccharimide of 6-butoxyimidoheptyl penicillin hydrochloride;
saccharimide of 6-methoxyimidohydroxybenzyl penicillin hydrochloride; and
saccharimide of 6-butoxyimidohydroxybenzyl penicillin hydrochloride.
- 60

Example 39

The saccharimide of 6-methoxyimido-2-pentenyl penicillin hydrochloride, as prepared in Example 38, is added to methanol (100 ml.), water (75 ml.) and the tem-

perature is lowered to 0°C. with stirring for one-half hour. The mixture is kept at 0°C. overnight and filtered. The solid is washed with cold (5°C.) water (30 ml.), without slurring the solid in the water, and dried. The solid is then washed with cold (5°C.) methylene chloride (2 × 30 ml.), slurried in absolute ether and dried on the funnel, dried over P₂O₅ in a vacuum, giving crystals of the saccharimide of 6-aminopenicillanic acid hydrochloride.

In the same manner, the other 6-alkoxyimido penicillin saccharimide hydrohalides of Example 38 are converted to the corresponding saccharimide of 6-aminopenicillanic acid hydrohalides.

When the above-prepared hydrohalides are neutralised by the procedure of Example 33, the appropriate saccharimides of 6-aminopenicillanic acid are obtained.

Example 40

Triethylammonium 3 - acetoxymethyl - 8 - oxo - 5 - thia - 7 - (thiophene - 2 - acetamido) - 1 - azabicyclo[4.2.0]oct-2-en-2-carboxylate (0.040 mole) is added to anhydrous methylene chloride (150 ml.) contained in a dry 500 ml. three neck round bottom flask equipped with a stirrer, a drying tube and a thermometer. Thereafter, the solution is cooled to 5°C. in ice and pseudosaccharin chloride (0.040 mole) is added all at once, giving a yellow solution. The solution is stirred for one-half hour at 5°C., and kept at room temperature overnight. The solution is then brought to the boiling point for five minutes, and allowed to cool to room temperature to afford 2 - [3 - hydroxymethyl - 8 - oxo - 7 - (2 - thiopheneacetamido) - 5 - thia - 1 - azabicyclo[4.2.0]oct - 2 - en - 2 - yl - carbonyl] - 1,2 - benzisothiazol - 3(2H) - one 1,1-dioxide acetate, also designated as the saccharimide of cephalothin.

Thereafter, quinoline (0.110 mole) is added to the stirred solution containing said saccharimide. The mixture is cooled to -30°C. and phosphorus pentachloride (11.6 g., 0.056 mole) is added over a few minutes, keeping the temperature at -30°C. The mixture is stirred for three hours at -30°C. to yield 2 - [7 - (1-chloro-2-[2-thienyl]ethylideneamino) - 3 - hydroxymethyl - 8 - oxo - 5 - thia - 1 - azabicyclo[4.2.0]oct-2-en-2-ylcarbonyl] - 1,2-benzisothiazol-3(2H)-one 1,1-dioxide acetate, also known as the saccharimide of 7-chloroimidocephalothin.

To the above-described mixture containing said 7-chloroimide, quinoline (0.055 mole) is added followed by absolute ethanol (100 ml.) over a few minutes, keeping the temperature at -30°C. + 3°C. after stirring the mixture for one hour at -30°C., the temperature is rapidly raised to +20°C. with hot water, and immediately brought back to -30°C. and stirred for another hour. Then the temperature is brought up to +20°C. with hot water and immediately back to -10°C. and stir for one more hour to afford 2 - [7 - (1 - ethoxy - 2 - [2 - thienyl]ethylideneamino) - 3 - hydroxymethyl - 8 - oxo - 5 - thia - 1 - azabicyclo[4.2.0]oct - 2 - en - 2 - ylcarbonyl] - 1,2-benzisothiazol-3(2H)-one 1,1-dioxide acetate hydrochloride, also described as the saccharimide of 7-ethoxyimidocephalothin hydrochloride.

Subsequently, water (75 ml.) is added to above-described mixture containing said 7-ethoxyimide hydrochloride and the temperature is lowered to 0°C. and then stirred for twenty minutes. The mixture is kept at 0°C. overnight and filtered. The solid is washed with cold (5°C.) water (30 ml.), without slurring the solid in the water, and sucked dry. The solid is then washed with cold (5°C.) methylene chloride (2 × 30 ml.), slurried in absolute ether and dried on the funnel, dried over P₂O₅ in a vacuum, giving crystals of 2 - [7 - amino - 3 - hydroxymethyl - 8 - oxo - 5 - thia - 1 - azabicyclo[4.2.0]oct-2-en-2-ylcarbonyl] - 1,2-benzisothiazol-3(2H)-one 1,1-dioxide acetate hydrochloride, also known as the saccharimide of 7-aminocephalosporanic acid hydrochloride.

Example 41

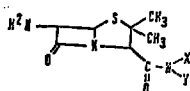
2 - [7 - Amino - 3 - hydroxymethyl - 8 - oxo - 5 - thia - 1 - azabicyclo[4.2.0]oct - 2 - en - 2 - ylcarbonyl] - 1,2 - benzisothiazol - 3(2H) - one 1,1 - dioxide acetate hydrochloride (0.02 mole), as prepared in Example 40, is powdered and added to water (75 ml.) in four portions, stirred at 0°C. Adjustment of the pH to 6.9 after each addition is done with a 60°C. saturated sodium bicarbonate solution. After the second addition some ether is added to control the foaming. After the final adjustment of the pH to 6.9 the mixture is stirred at 0—2°C. for ten minutes, and the pH slowly goes to 7.1. The solid is filtered and washed with cold water (2 x), and dried in a desiccator over P₂O₅ under vacuum at 5°C., giving a white solid which is 2 - [7 - amino - 3 - hydroxymethyl - 8 - oxo - 5 - thia - 1 - azabicyclo[4.2.0]oct - 2 - en - 2 - ylcarbonyl] - 1,2-benzisothiazol-3(2H)-one 1,1-dioxide acetate, also described as the saccharimide of 7-aminocephalosporanic acid.

Example 42

2 - [7 - Amino - 3 - hydroxymethyl - 8 - oxo - 5 - thia - 1 - azabicyclo[4.2.0] - oct - 2 - en - 2 - ylcarbonyl] - 1,2 - benzisothiazol - 3(2H) - one 1,1 - dioxide acetate as prepared in Example 41, is dissolved in tetrahydrofuran (60 ml.) and a solution of sodium bicarbonate (0.04 mole) in water (40 ml.) is added all at once. The mixture is stirred for three hours at room temperature giving a solution. Then the tetrahydrofuran is removed 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 one-half hour and then filtered, giving crystals of 7-amino-3-(hydroxymethyl) - 8 - oxo - 5 - thia - 1 - azabicyclo[4.2.0]oct - 2 - en - 2 - carboxylic acid, acetate, also known as 7-aminocephalosporanic acid.

Example 43

Utilising the general procedures of Examples 36 to 39, a series of 2-amido derivatives of natural penicillins are prepared which are reacted with phosphorus pentachloride to yield their corresponding 2-amido-6-chloroimidopenicillins which are then reacted with an alkanol to afford appropriate 2-amido-6-alkoxyimidopenicillin hydrochlorides which are then hydrolysed and neutralised to afford 2-amido-6-amino-penicillanic acids having the formula:



wherein X and Y when taken separately are defined as follows:

TABLE S

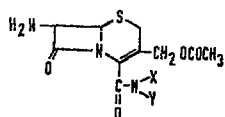
X	Y
cyano	cyano
cyano	nitro
cyano	trifluoromethylsulphonyl
cyano	carbopentoxy
cyano	N,N-dimethylcarbamyl
cyano	ethylsulphonyl
cyano	N,N-diethylsulphamyl
nitro	trifluoromethylsulphonyl
nitro	carbethoxy
nitro	N,N-dipropylcarbamyl
nitro	methylsulphonyl
nitro	N-ethyl-N-methylsulphamyl
trifluoromethylsulphonyl	trifluoromethylsulphonyl
trifluoromethylsulphonyl	carbohexoxy
trifluoromethylsulphonyl	N-ethyl-N-methylcarbamyl
trifluoromethylsulphonyl	propylsulphonyl

TABLE S (Continued)

X	Y
trifluoromethylsulphonyl	N,N-dimethylsulphamyl
carbomethoxy	N,N-dipentylcarbamyl
carbomethoxy	methylsulphonyl
carbomethoxy	N,N-dimethylsulphamyl
N,N-dimethylcarbamyl	pentylsulphonyl
N,N-dimethylcarbamyl	N,N-dimethylsulphamyl
N,N-dimethylcarbamyl	N,N-dimethylcarbamyl
N,N-dimethylsulphamyl	N,N-dimethylsulphamyl
cyano	<i>p</i> -butylbenzoyl
cyano	<i>m</i> -toluyl
cyano	<i>p</i> -phenoxybenzoyl
methylsulphonyl	<i>o</i> -chlorobenzoyl
methylsulphonyl	2,4-dibromobenzoyl
carbethoxy	<i>p</i> -chloro- <i>m</i> -toluyl
carbethoxy	<i>p</i> -iodobenzoyl
N,N-dimethylcarbamyl	<i>p</i> -ethylbenzoyl
carbobutoxy	<i>p</i> -methoxybenzoyl
nitro	<i>p</i> -phenylbenzoyl
<i>p</i> -nitrophenylsulphonyl	<i>m</i> -nitrobenzoyl
<i>p</i> -trifluoromethylphenylsulphonyl	<i>p</i> -methylsulphonylbenzoyl
2,4-dinitrophenylsulphonyl	<i>p</i> -toluyl
<i>p</i> -chlorophenylsulphonyl	<i>p</i> -methoxybenzoyl
trifluoromethylsulphonyl	<i>p</i> -(N,N-dimethylsulphamyl)benzoyl
<i>m</i> -(N,N-diethylsulphamyl)benzoyl	methylsulphonyl
carbomethoxy	<i>p</i> -trifluoromethylbenzoyl
cyano	<i>o</i> -chlorophenylsulphonyl
cyano	<i>m</i> -trifluoromethylphenylsulphonyl
trifluoromethylsulphonyl	<i>p</i> -nitrophenylsulphonyl
N,N-dimethylcarbamyl	2-bromo-4-chlorophenylsulphonyl

Example 44

When the procedures of Examples 40 to 42 are repeated, a series of 2-amido derivatives of cephalothin are prepared which are reacted with a phosphorus pentahalide to yield their corresponding 2-amido-7-haloimidocephalothins which are reacted with an alkanol to afford appropriate 2-amido-7-alkoxyimidocephalothin hydrohalides which are then hydrolysed and neutralised to produce 2-amino-7-amino-cephalosporanic acids having the formula:



wherein X and Y when taken separately are defined as follows:

TABLE T

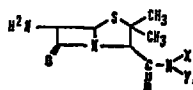
X	Y
methylsulphonyl	2-bromo-4-nitrophenylsulphonyl
N,N-dimethylsulphamyl	<i>m</i> -(N,N-dimethylcarbamyl)phenylsulphonyl
carbohexoxy	<i>p</i> -methylsulphonylphenylsulphonyl
carbethoxy	<i>p</i> -(N,N-diethylsulphamyl)phenylsulphonyl
trifluoromethylsulphonyl	4-cyano-2-iodophenylsulphonyl
cyano	2-fluoro-4-nitrophenylsulphonyl
pentylsulphonyl	<i>p</i> -carbobutoxyphenylsulphonyl
cyano	<i>p</i> -iodobenzylsulphonyl
cyano	butyryl
nitro	acetyl
cyano	benzoyl
propionyl	phenylsulphonyl
2,4,6-trimethylbenzoyl	phenethylsulphonyl
2,4,6-trimethylbenzoyl	<i>p</i> -methoxyphenylsulphonyl
N,N-dimethylcarbamyl	N,N-dimethylaminoethylsulphonyl
2,3,5,6-tetramethylbenzoyl	<i>p</i> -methylthiophenylsulphonyl
cycloaleryl	<i>m</i> -nitrophenethylsulphonyl
N,N-dipropylaminobutylsulphonyl	2-naphthoyl
cyano	2,4-dimethylbenzoyl
nitro	<i>p</i> -fluorophenacetyl
cyclopropyl	trifluoromethylsulphonyl

TABLE T (Continued)

X	Y
furoyl	cyano
N,N-dimethylsulphamylphenpropionyl	carbopropoxy
<i>p</i> -propylphenylsulphonyl	cyclobutyryl
2-naphthylsulphonyl	<i>p</i> -butoxybenzoyl
phenbutyryl	nitro
2-furylsulphonyl	caproyl
2-pyridylsulphonyl	methysulphonyl
phencaproyl	cyano
phenpropylsulphonyl	trifluoromethylsulphonyl
<i>p</i> -propylsulphonylphenylsulphonyl	cyano
nitro	<i>p</i> -(N,N-dibutylcarbamyl)phenylsulphonyl
<i>m</i> -carbomethoxyphenylsulphonyl	carbethoxy
<i>p</i> -propoxyphenylsulphonyl	methysulphonyl
cyano	<i>p</i> -pentylthiophenylsulphonyl

Example 45

When the procedures of Examples 36 to 39 are repeated, a series of 2-cycloamido derivatives of natural penicillins are prepared which are reacted with phosphorus pentachloride to yield their corresponding 2-cycloamido-6-chloroimidopenicillins which are then reacted with an alkanol to afford appropriate 2-cycloamido-6-alkoxyimido-penicillin hydrochlorides which are then hydrolysed and neutralised to afford 2-cycloamido-6-aminopenicillanic acids having the formula:



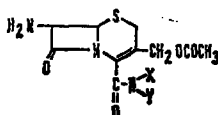
wherein X and Y when taken together are defined as:

Table U

3-oxo-1,2-benzisothiazolin-2-yl 1,1-dioxide;	
4-methoxyphthalimido;	
maleimido;	
succinimido;	
3-oxo-4,1,2-benzoxathiazin-2(3 <i>H</i>)-yl 1,1-dioxide;	
3-oxo-6-nitro-1,4,2-benzodithiazin-2(3 <i>H</i>)-yl 1,1-dioxide;	
3,4-dihydro-4-methyl-3-oxo-2 <i>H</i> -1,2,4-benzothiadiazin-2-yl 1,1-dioxide;	
3,3,4,4-tetramethyl-2-oxo-1-pyrrolidinyl;	
6-bromo-3,4-dihydro-2,4-dioxo-2 <i>H</i> -1,3-benzoxazin-3-yl;	
3,4-dihydro-2,4-dioxo-2 <i>H</i> -1,3-benzothiazin-3-yl;	
7-ethylsulphonyl-1,4-dihydro-1-methyl-2,4-dioxo-3(2 <i>H</i>)-quinazolinyl;	
6-fluoro-1,2-benzisothiazolin-2-yl 1,1-dioxide;	
1-oxo-2-isindolinyl;	
2-oxo-3-pyrrolin-1-yl;	
4-isothiazolin-2-yl 1,1-dioxide;	
6-chloro-3,4-dihydro-7-methyl-3-oxo-2 <i>H</i> -1,2-benzothiazin-2-yl 1,1-dioxide;	
3,4-dihydro-1,3-dioxo-2(1 <i>H</i>)-isoquinolyl; and	
<i>o</i> -(3-bromobenzene)disulphonimido.	

Example 46

When the procedures of Examples 40 to 42 are repeated, a series of 2-cycloamido derivatives of cephalothin are prepared which are reacted with phosphorus pentabromide to yield their corresponding 2-cycloamido-7-bromoimidocephalothins which are reacted with an alkanol to afford appropriate 2-cycloamido-7-alkoxyimidocephalothin hydrobromides which are then hydrolysed and neutralised to produce 2-cycloamido-7-aminocephalosporanic acids having the formula:



wherein X and Y when taken together are defined as:

Table V

10	5-ethyl-3-oxo-1,2-benzisothiazolin-2-yl 1,1-dioxide; phthalimido; succinimido; 3-oxo-2-isothiazolidinyl 1,1-dioxide;	10
15	3-oxo-4-isothiazolin-2-yl 1,1-dioxide; 6,7-dichloro-3-oxo-4,1,2-benzoxathiazin-2(3H)-yl 1,1-dioxide; 3-oxo-1,4,2-benzodithiazin-2(3H)-yl 1,1-dioxide; 6-cyano-3,4-dihydro-4-methyl-3-oxo-2H-1,2,4-benzothiadiazine-2-yl 1,1-dioxide; tetramethylsuccinimido;	15
20	3,4-dihydro-2,4-dioxo-2H-1,3-benzoxazin-3-yl; 7-trifluoromethyl-3,4-dihydro-2,4-dioxo-2H-1,3-benzothiazin-3-yl; 1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl; 1,2-benzisothiazolin-2-yl 1,1-dioxide;	20
25	5-benzyl-1-oxo-2-isoindolinyl; 2-isothiazolidinyl 1,1-dioxide; 2-oxo-1-pyrrolidinyl; 3,4-dihydro-3-oxo-2H-1,2-benzothiazin-2-yl 1,1-dioxide; 7-carbomethoxy-3,4-dihydro-1,3-dioxo-2(1H)-isoquinolyl; and o-benzenedisulphonimido.	25

Example 47

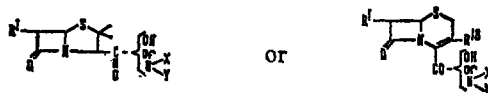
30	3,3 - Dimethyl - 7 - oxo - 6 - (2 - phenoxyacetamido) - 4 - thia - 1 - azabicyclo-[3.2.0]heptane-2-carboxylic acid, also described as phenoxymethyl penicillin (256 g., 0.73 mole) is added to anhydrous methylene chloride (2 litres) and the mixture is stirred and cooled in ice to 6°C. Then triethylamine (78.8 g., 0.73 mole) is added and washed in with anhydrous methylene chloride (250 ml.), causing the solid to dissolve. The solution is cooled to 5°C. and ψ-saccharin chloride (147 g., 0.73 mole) is added and washed in with anhydrous methylene chloride (250 ml.). The light yellow solution is stirred at 5—10°C. for one-half hour, and then kept at room temperature overnight. Quinoline (213 ml., 1.8 mole) is added to the stirred solution, the internal temperature is quickly lowered to -30°C. As soon as the temperature reached -30°C. powdered phosphorus pentachloride (187 g., 0.90 mole) is added over about three minutes while the temperature is maintained at -28 to -30°C. The mixture is stirred for three hours at -30°C. and a solution of quinoline (105 ml., 0.90 mole) in absolute ethanol (850 ml.) is added over about ten minutes, while maintaining the temperature at -27 to -30°C. After stirring for one hour at -30°C. the temperature is rapidly raised to +20°C., and then immediately lowered to -30°C. After stirring another hour at -30°C. the temperature is rapidly raised to +20°C. and then immediately lowered to -10°C. The temperature is maintained at -10°C. for one hour, water (650 ml.) is added and the mixture stirred at 0°C. for twenty minutes. The mixture is stored at 0°C. overnight and filtered through a coarse sintered funnel. The off-white solid is slurried three times with cold (5°C.) methylene chloride, three times with cold water (just enough to cover the solid), and two times with anhydrous ether. The resulting white solid is spread out on paper in a hood and air-dried overnight, giving a powdery white solid which is 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 hydrochloride, as named as the saccharimide of 6-amino-penicillanic acid hydrochloride (189 g., 62%).	30
35		35
40		40
45		45
50		50
55		55

Example 48

2 - [(D - [2 - amino - 2 - phenylacetamido] - 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, also described as the saccharimide of ampicillin, (0.02 mole) is dissolved in
anhydrous methylene chloride (75 ml.) and N,N-dimethylaniline (0.07 mole) is added.
The solution is cooled to -40°C. by an acetone-dry ice bath, and phosphorus penta-
bromide (0.218 mole) is added over a few minutes under nitrogen. The solution is
kept at -35 to -40°C. for three hours with mechanical stirring. After approxi-
mately one-half to one hour at this temperature, a white crystalline material forms
which is 2[(D - [2 - amino - 1 - bromo - 2 - phenylethylideneamino] - 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, also known as the saccharimide of 6-bromo-
imidoampicillin. Then 1-butanol (75 ml.) is added over approximately five minutes
at -35 to -40°C. and this temperature is maintained for three hours to afford 2-
[(D - [2 - amino - 1 - butoxy - 2 - phenylethylideneamino] - 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 named as the saccharimide of 6-butoxyimido-
ampicillin hydrobromide. Then water (40 ml.) is added to the rapidly stirred mixture
allowing the temperature to cool to 0-5°C. The mixture is stirred at 0-5°C. for
one hour and then kept at 0°C. overnight, without stirring. The mixture is filtered
and the solid is washed with anhydrous ether giving a white solid which is the hydro-
bromide of 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, also described
as the saccharimide of 6-aminopenicillanic acid hydrobromide.

WHAT WE CLAIM IS:—

1. A process for the preparation of a penicillin or cephalosporin or a 2-amido
derivative thereof of general formulae:

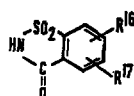


in which R¹ is a penicillin or cephalosporin amide group, X and Y when taken
separately are both electron withdrawing groups or when taken with the nitrogen
atom to which they are attached complete a cyclic electron withdrawing group and
R¹⁸ is a methyl, hydroxymethyl, N-pyridiniumylmethyl or alkanoyloxymethyl group;
in which a penicillin or cephalosporin, or a functional derivative thereof is reacted with
a reactive amine derivative to convert the 2-carboxy group or its functional derivative

group to an amido group of the formula $\text{—}\overset{\text{O}}{\parallel}\text{C—N}\begin{matrix} \text{X} \\ \text{Y} \end{matrix}$, the obtained 2-amido penicillin
or 2-amidocephalosporin is reacted in a reaction inert aprotic solvent with a

phosphorus pentahalide in the presence of a base to afford a corresponding 2-amido-
6-haloimidopenicillin or 2-amido-7-haloimidocephalosporin which is reacted with an
alkanol to afford the hydrohalide of a corresponding 2-amido-6-alkoxyimidopenicillin
or 2-amido-7-alkoxyimidocephalosporin which in turn is hydrolysed with water to
afford a 2-amido-6-aminopenicillanic acid or 2-amido-7-aminocephalosporin acid
hydrohalide which, if desired, is neutralised and the 2-amido-6-aminopenicillanic acid
or 2-amido-7-aminocephalosporin acid or an acid addition salt thereof is reacted with
an acylating agent to afford the 2-amidopenicillin or 2-amidocephalosporin which, if
desired, is hydrolysed to the corresponding penicillin or cephalosporin.

2. A process according to Claim 1, wherein the reactive amine derivative used is
a saccharin or substituted saccharin of general formula



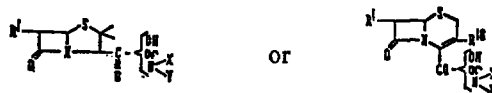
or its functional derivative wherein R¹⁶ and R¹⁷ when taken separately are hydrogen,
lower alkyl, lower alkoxy, halogen, phenyl, phen(lower)alkyl, loweralkoxyphenyl, aryl,
heterocyclyl, trihalomethyl, nitro, diloweralkylamino, sulphamido, carbloweralkoxy,

Example 48

2 - [(D - [2 - amino - 2 - phenylacetamido] - 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, also described as the saccharimide of ampicillin, (0.02 mole) is dissolved in anhydrous methylene chloride (75 ml.) and N,N-dimethylaniline (0.07 mole) is added. The solution is cooled to -40°C. by an acetone-dry ice bath, and phosphorus pentabromide (0.218 mole) is added over a few minutes under nitrogen. The solution is kept at -35 to -40°C. for three hours with mechanical stirring. After approximately one-half to one hour at this temperature, a white crystalline material forms which is 2[(D - [2 - amino - 1 - bromo - 2 - phenylethylideneamino] - 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, also known as the saccharimide of 6-bromo-imidoampicillin. Then 1-butanol (75 ml.) is added over approximately five minutes at -35 to -40°C. and this temperature is maintained for three hours to afford 2-[(D - [2 - amino - 1 - butoxy - 2 - phenylethylideneamino] - 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 named as the saccharimide of 6-butoxyimido-ampicillin hydrobromide. Then water (40 ml.) is added to the rapidly stirred mixture allowing the temperature to cool to 0-5°C. The mixture is stirred at 0-5°C. for one hour and then kept at 0°C. overnight, without stirring. The mixture is filtered and the solid is washed with anhydrous ether giving a white solid which is the hydrobromide of 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, also described as the saccharimide of 6-aminopenicillanic acid hydrobromide.

WHAT WE CLAIM IS:—

1. A process for the preparation of a penicillin or cephalosporin or a 2-amido derivative thereof of general formulae:

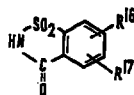


in which R¹ is a penicillin or cephalosporin amide group, X and Y when taken separately are both electron withdrawing groups or when taken with the nitrogen atom to which they are attached complete a cyclic electron withdrawing group and R¹⁸ is a methyl, hydroxymethyl, N-pyridiniumylmethyl or alkanoyloxymethyl group; in which a penicillin or cephalosporin, or a functional derivative thereof is reacted with a reactive amine derivative to convert the 2-carboxy group or its functional derivative

group to an amido group of the formula $\text{—}\overset{\text{O}}{\parallel}\text{C—N}\begin{matrix} \text{X} \\ \text{Y} \end{matrix}$, the obtained 2-amido penicillin

or 2-amidocephalosporin is reacted in a reaction inert aprotic solvent with a phosphorus pentahalide in the presence of a base to afford a corresponding 2-amido-6-haloimidoampicillin or 2-amido-7-haloimidocephalosporin which is reacted with an alcohol to afford the hydrohalide of a corresponding 2-amido-6-alkoxyimidoampicillin or 2-amido-7-alkoxyimidocephalosporin which in turn is hydrolysed with water to afford a 2-amido-6-aminopenicillanic acid or 2-amido-7-aminocephalosporin acid hydrohalide which, if desired, is neutralised and the 2-amido-6-aminopenicillanic acid or 2-amido-7-aminocephalosporin acid or an acid addition salt thereof is reacted with an acylating agent to afford the 2-amidoampicillin or 2-amidocephalosporin which, if desired, is hydrolysed to the corresponding penicillin or cephalosporin.

2. A process according to Claim 1, wherein the reactive amine derivative used is a saccharin or substituted saccharin of general formula



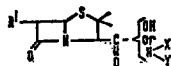
or its functional derivative wherein R¹⁶ and R¹⁷ when taken separately are hydrogen, lower alkyl, lower alkoxy, halogen, phenyl, phen(lower)alkyl, loweralkoxyphenyl, aryl, heterocyclyl, trihalomethyl, nitro, diloweralkylamino, sulphamido, carbloweralkoxy,



cyano, loweralkylthio or loweralkylsulphonyl or when joined complete a benzene ring fused to the existing benzene ring to form therewith a naphthalene ring.

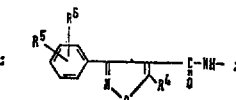
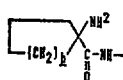
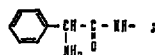
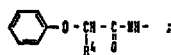
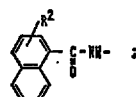
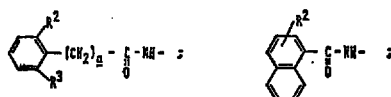
3. A process for the preparation of a penicillin or a 2-amido derivative thereof having the general formula

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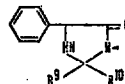
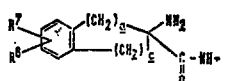


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wherein R^1 is a group selected from one of the following formulae

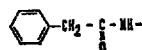


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and



wherein R^2 and R^3 are hydrogen or lower alkoxy, R^4 is hydrogen, loweralkyl or phenyl, R^5 and R^6 are hydrogen or halogen; R^7 and R^8 are hydrogen, loweralkyl, loweralkoxy, phenyl or phenoxy; R^9 and R^{10} when taken separately are hydrogen or lower alkyl or when taken together with the carbon atom to which they are attached complete a cycloalkyl ring of from 4 to 8 carbon atoms or a piperidine ring; a is 0 or 1; b is an integer from 1 to 5; c is an integer from 1 to 3 with the provisos that when a is 0, c is greater than 1, and when a is 1, c is less than 3, and where 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, in which a penicillin whose penicillin amide group is R^1 as defined above or a functional derivative thereof is reacted with a reactive amine derivative to replace the 2-carboxy group

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or its functional derivative group with an amido group of the formula $\text{C}(=\text{O})-\text{N}(\text{X})(\text{Y})$, the

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obtained 2-amidopenicillin is reacted in an inert organic solvent containing an organic base with phosphorus pentachloride to afford the chloroimide of the penicillin amide (2-amido-6-chloroimidopenicillin), a lower alcohol is added to replace the chlorine atom on the imino chloride moiety by a lower alkoxy residue and water is added to hydrolyse the imide moiety and afford the hydrochloride of a 2-amido-6-aminopenicillanic acid and if desired this is treated with water at neutrality or in the presence of an acid acceptor to give the free 2-amido-6-aminopenicillanic acid and this or an acid addition salt thereof is reacted with an acylating agent to introduce the desired group R^1 to afford the 2-amidopenicillin which if desired can be hydrolysed to the corresponding penicillin.

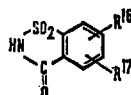
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4. A process according to Claim 3, in which the reactive amine derivative used is a saccharin or substituted saccharin of general formula



or its functional derivative wherein R^{16} and R^{17} taken separately are hydrogen, lower alkyl, lower alkoxy, halo, phenyl, benzyl, loweralkoxyphenyl, 2-pyridyl, 4-pyridyl, trihalomethyl, nitro, diloweralkylamino, sulphamido, carbloweralkoxy, cyano, loweralkylthio or loweralkylsulphonyl or when joined together complete a benzene ring fused to the existing benzene ring to form a naphthalene ring.

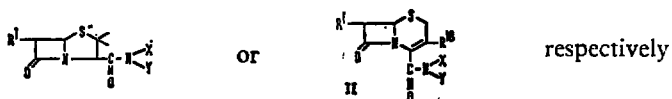
5. A process according to Claim 3 or Claim 4 in which either the penicillin acid is reacted with a reactive amine derivative to replace the penicillin acid carboxy group

with the amido group of formula $\text{—C(=O)—N} \begin{smallmatrix} \text{X} \\ \text{Y} \end{smallmatrix}$ or the penicillin acid is converted to

a mixed anhydride by reaction with ethylchloroformate or to an acyl halide by reaction with thionyl chloride or to a dicyclohexylcarbodiimide derivative by reaction with dicyclohexylcarbodiimide and then reacted with the reactive amine derivative.

6. A process according to Claim 5 in which the reaction with phosphorus pentachloride is carried out in methylene chloride.

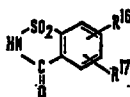
7. A process for the preparation of a 2-amidopenicillin or 2-amidocephalosporin of the general formulae



wherein R^1 is a penicillin or cephalosporin amide group, R^{18} is a methyl, hydroxymethyl, N-pyridiniummethyl or alkanoyloxymethyl group, 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, in which a penicillin or cephalosporin or a functional derivative thereof is reacted with a reactive amine derivative to convert the 2-carboxy group or its functional derivative

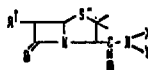
group into an amido group of formula $\text{—C(=O)—N} \begin{smallmatrix} \text{X} \\ \text{Y} \end{smallmatrix}$.

8. A process according to Claim 7, wherein the reactive amine derivative is a saccharin or substituted saccharin of general formula

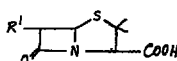


or its functional derivative where R^{16} and R^{17} are as defined in Claim 2.

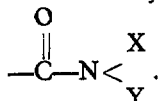
9. A process according to Claim 7 for the preparation of a 2-amidopenicillin of general formula



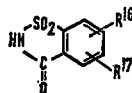
in which R^1 , X and Y are as defined in Claim 3 in which a penicillin having the general formula



or a functional derivative thereof is reacted with a reactive amine derivative to convert the 2-carboxy group or its functional derivative to an amido group of the formula



10. A process according to Claim 9, wherein the reactive amine derivative used is saccharine or a substituted saccharine of general formula

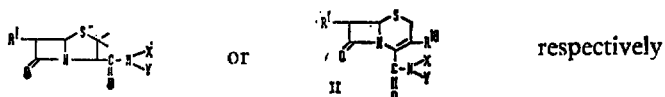


where R^{16} and R^{17} are as defined in Claim 4 or its functional derivative.

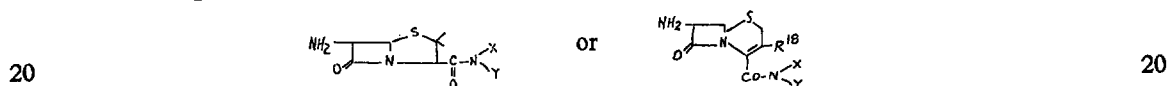
5 11. A process according to Claim 9 or Claim 10 in which either the penicillin acid is reacted with a reactive amine derivative to replace the penicillin acid carboxy group with the amido group of formula $\text{—C(=O)—N} \begin{smallmatrix} \text{X} \\ \text{Y} \end{smallmatrix}$ or the penicillin acid is con-

verted to a mixed anhydride by reaction with ethylchloroformate or to an acyl halide by reaction with thionyl chloride or to a dicyclohexylcarbodiimide by reaction with dicyclohexylcarbodiimide and then reacted with the reactive amine derivative.

10 12. A process for the preparation of a 2-amidopenicillin or 2-amidocephalosporin of the general formulae

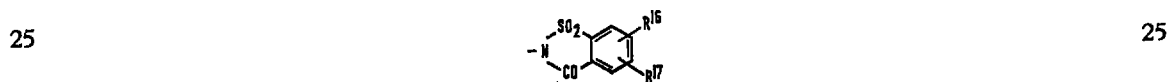


15 wherein R^1 is a penicillin or cephalosporin amide group, R^{18} is a methyl, hydroxymethyl, N-pyridiniumylmethyl or alkanoyloxymethyl group, X and Y when taken separately are both electron withdrawing groups or when taken with the nitrogen atom to which they are attached complete a cyclic electron withdrawing group, in which a corresponding 2-amido-6-aminopenicillanic acid or 7-aminocephalosporin acid of general formula



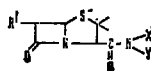
or an acid addition salt thereof is reacted with an acylating agent to form the desired group R^1 .

13. A process according to Claim 12, wherein in the formulae $\text{—N} \begin{smallmatrix} \text{X} \\ \text{Y} \end{smallmatrix}$ stands for a saccharyl or substituted saccharyl group of the general formula

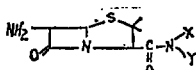


where R^{16} and R^{17} are as defined in Claim 2.

14. A process for the preparation of a 2-amidopenicillin of general formula



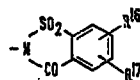
30 wherein R^1 , X and Y are as defined in Claim 3, in which a 2-amido-6-aminopenicillanic acid of general formula



or an acid addition salt thereof is reacted with an acylating agent to form the desired group R^1 .

15. A process according to Claim 14, wherein in the formulae $-\text{N} \begin{smallmatrix} \text{X} \\ \text{Y} \end{smallmatrix}$ stands for a saccharyl or substituted saccharyl group of the general formula

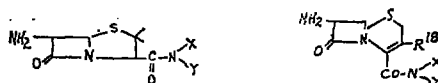
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in which R^{16} and R^{17} are as defined in Claim 4.

16. A process for the preparation of a 2-amido-6-aminopenicillanic acid or 2-amido-7-aminocephalosporin acid of general formulae



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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, in which a 2-amidopenicillin or 2-amidocephalosporin of general formulae

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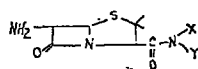
where R^1 is a penicillin or cephalosporinamide group, R^{18} is a methyl, hydroxymethyl, N-pyridiniummethyl or alkanoyloxymethyl group and X and Y are as defined above, is reacted in a reaction inert aprotic solvent with a phosphorus pentahalide in the presence of a base to afford a corresponding 2-amido-6-haloimidoyl penicillin or 2-amido-7-haloimidoylcephalosporin which is reacted with an alkanol to afford the hydrohalide of a corresponding 2-amido-6-iminoether penicillin or 2-amido-7-iminoether cephalosporin which in turn is hydrolysed with water to afford a 2-amido-6-aminopenicillanic acid or 2-amido-7-aminocephalosporin acid hydrohalide which, if desired is neutralised.

15

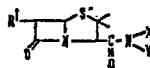
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17. A process according to Claim 16 for the preparation of a 2-amido-6-aminopenicillanic acid having the general formula

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in which X and Y are as defined in claim 16, in which a 2-amidopenicillin of general formula



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where R^1 is as defined in Claim 3 and X and Y are as defined above, is reacted in an inert organic solvent containing an organic base with phosphorus pentachloride to afford the chloroimide of the penicillin amide (a 2-amido-6-chloroimidoyl penicillin) which is reacted with a lower alcohol to replace the chlorine atom on the imino chloride moiety by a lower alkoxy residue to afford a 2-amido-6-loweralkoxyimidoyl penicillin hydrochloride which is hydrolysed by water to afford the hydrochloride of 2-amido-6-aminopenicillanic acid; and if desired this is treated with water at neutrality or in the presence of an acid acceptor to give the free 2-amido-6-aminopenicillanic acid.

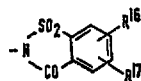
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18. A process according to Claim 17, wherein in the formula $-\text{N} \begin{smallmatrix} \text{X} \\ \text{Y} \end{smallmatrix}$ stands



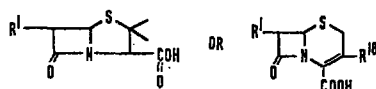
for saccharyl or substituted saccharyl group having the general formula



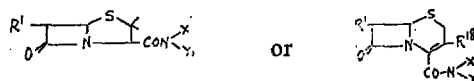
in which R^{16} and R^{17} are as defined in Claim 4.

19. A process according to Claim 17 or Claim 18 in which the reaction with phosphorus pentachloride is carried out in methylene chloride.

20. A process for the preparation of a penicillin or cephalosporin having the general formula



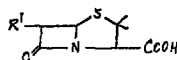
- 10 in which R^1 is a penicillin or cephalosporin amide group and R^{18} is methyl, hydroxymethyl, N-pyridiniummethyl or alkanoyloxymethyl; in which a 2-amido penicillin or cephalosporin having the general formula



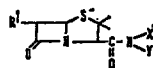
- 15 where R^1 and R^{18} are as defined above, X and Y when taken separately are both electron withdrawing groups or when taken with the nitrogen atom to which they are attached complete a cyclic electron withdrawing group, is hydrolysed with water.

21. A process according to Claim 20 in which the hydrolysis is carried out by treatment with water or a mixture of water and a water miscible organic solvent at a pH of about 1.5 to about 9.

- 20 22. A process according to Claim 20 for the preparation of a penicillin having the general formula



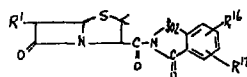
where R^1 is as defined in Claim 3 in which a 2-amidopenicillin having the general formula



- 25 where R^1 is as defined above, X and Y are as defined in Claim 20 is hydrolysed with water.

23. A process according to Claim 22 in which the hydrolysis is carried out by treatment with water or a mixture of water and a water miscible organic solvent at a pH of about 1.5 to about 9.

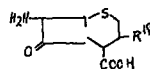
- 30 24. A process according to Claim 23, in which a 2-saccharyl or substituted saccharyl penicillin having the general formula



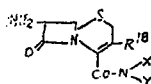
where R^1 is as defined in Claim 3 and R^{16} and R^{17} are as defined in Claim 4, is hydrolysed.



25. A process for the preparation of a 7-aminocephalosporin acid of general formula

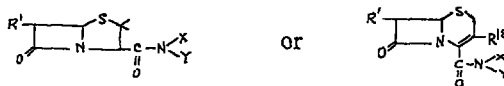


5 where R¹⁸ is methyl, hydroxymethyl, N-pyridiniumylmethyl or alkanoyloxymethyl which comprises reacting a 2-amido-7-aminocephalosporin acid of general formula 5



10 wherein X and Y when taken separately are both electron withdrawing groups and when taken together with the nitrogen atom to which they are attached complete a cyclic electron withdrawing group, with water in the presence of a hydrolytic catalyst until hydrolysis is complete. 10

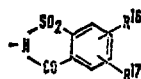
26. A 2-amidopenicillin or 2-amidocephalosporin or its 6 or 7 respectively amino, haloimido or alkoxyimido derivative having the general formula



15 wherein R¹ is a penicillin or cephalosporin amide group, an amino group or a haloimido or alkoxyimido group derived from a penicillin or cephalosporinamide group, R¹⁸ is methyl, hydroxymethyl, N-pyridiniumylmethyl or alkanoyloxymethyl, 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; or an acid addition salt thereof. 15

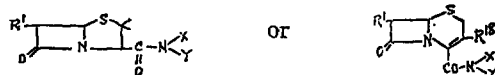
20 27. A 2-saccharyl or substituted saccharyl penicillin or cephalosporin or its 6 or 7 respectively amino, haloimido or alkoxyimido derivative having the general formula 20

given in Claim 26, in which —N— stands for



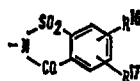
wherein R¹⁶ and R¹⁷ are as defined in Claim 2.

25 28. A 2-amidopenicillin or 2-amidocephalosporin having the general formula 25



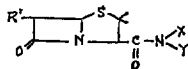
30 in which R¹ is a penicillin or cephalosporin amide group, R¹⁸ is methyl, hydroxymethyl, N-pyridiniumylmethyl or alkanoyloxymethyl X and Y when taken separately are both electron withdrawing groups or when taken with the nitrogen atom to which they are attached complete a cyclic electron withdrawing group; or a pharmaceutically acceptable acid addition salt thereof. 30

29. A 2-saccharyl or substituted saccharyl penicillin or cephalosporin having the general formula given in Claim 28, in which —N— stands for



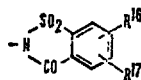
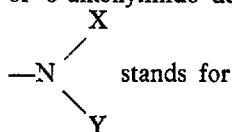
where R^{16} and R^{17} are as defined in Claim 4.

30. A 2-amidopenicillin or a 6-amino, 6-haloimido or 6-alkoxyimido derivative having the general formula



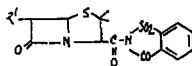
5 wherein R^1 is a penicillin amide group selected from the penicillin amide groups defined in Claim 3 or a chloroimido or loweralkoxyimido group derived therefrom or an amido group; and X and Y when taken separately are both electron withdrawing groups or when taken together with the nitrogen atom to which they are attached complete a cyclic electron withdrawing group; or an acid addition salt thereof. 5

10 31. A 2-saccharyl or substituted saccharyl penicillin or a 6-amino, 6-haloimido or 6-alkoxyimido derivative having the general formula given in Claim 30, wherein 10



where R^{16} and R^{17} are as defined in Claim 4.

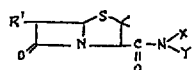
15 32. A 2-saccharyl penicillin or a 6-amino, 6-haloimido or 6-alkoxyimido derivative having the general formula 15



where R^1 is as defined in Claim 30; or an acid addition salt thereof.

33. A 2-amidopenicillin having the general formula

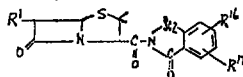
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where R^1 is as defined in Claim 30, X and Y when taken separately are both electron withdrawing groups or when taken with the nitrogen atom to which they are attached complete an electron withdrawing group; or an acid addition salt thereof.

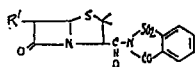
34. A 2-saccharyl or substituted saccharyl penicillin of general formula

25 25



where R^1 is as defined in Claim 30 and R^{16} and R^{17} are as defined in Claim 4; or a pharmaceutically acceptable acid addition salt thereof.

35. A 2-saccharyl penicillin of general formula



30 where R^1 is as defined in Claim 30; or a pharmaceutically acceptable acid addition salt thereof. 30





36. The saccharimide of phenoxymethyl penicillin.
37. The saccharimide of 6 - (2,2 - dimethyl - 5 - oxo - 4 - phenylimidazolidin-1-yl)penicillin or its pharmacologically acceptable acid addition salt.
- 5 38. The saccharimide of ampicillin or its pharmaceutically acceptable acid addition salt. 5
39. The dimethylcarbamoyl dimethylsulphamoyl imide of ampicillin or its pharmacologically acceptable acid addition salt.
40. The maleimide of 1-aminocyclohexyl penicillin or its pharmacologically acceptable acid addition salt.
- 10 41. The saccharimide of 1-aminocyclohexyl penicillin or its pharmacologically acceptable acid addition salt. 10
42. The saccharimide of dicloxacillin or its pharmacologically acceptable acid addition salt.
43. The saccharimide of benzyl penicillin.
- 15 44. The saccharimide of 6-aminopenicillanic acid or its acid addition salt. 15
45. The saccharimide of cephalothin.
46. The saccharimide of 2-ethoxynaphthyl penicillin.
47. The saccharimide of 2-pentenyl penicillin.
48. The saccharimide of 7-aminocephalosporanic acid or its acid addition salt.
- 20 49. The saccharimide of 6-chloroimidophenoxymethyl penicillin. 20
50. The saccharimide of 6-loweralkoxyimidophenoxymethyl penicillin or its acid addition salt.
51. The saccharimide of 6-chloroimido-2-pentenyl penicillin.
52. The saccharimide of 6-loweralkoxyimido-2-pentenyl penicillin or its acid addition salt.
- 25 53. The saccharimide of 7-chloroimidocephalothin. 25
54. The saccharimide of 7-loweralkoxyimidocephalothin or its acid addition salt.
55. The saccharimide of 6-haloimidoampicillin.
- 30 56. The saccharimide of 6-loweralkoxyimidoampicillin or its acid addition salt. 30
57. A 2-amido penicillin substantially as described herein and shown with reference to Examples 1 to 13 and 15 to 18.
58. A 2-amido penicillin or 2-amido cephalosporin substantially as described herein and shown with reference to Examples 19 to 29, 31 to 40 and 43 to 48.
- 35 59. A process for the preparation of 2-amido penicillins substantially as described herein and shown with reference to Examples 1 to 13 and 15 to 18. 35
60. A process for the preparation of 2-amido penicillins or 2-amido cephalosporins substantially as described herein and shown with reference to Examples 19 to 29, 31 to 40 and 43 to 48.
- 40 61. A process for the preparation of 2-amido-6-aminopenicillanic acid or of a haloimido or loweralkoxyimido derivative of a penicillin substantially as described herein and shown with reference to Examples 15 to 18. 40
62. A process for the preparation of 2-amido-6-aminopenicillanic acid, 2-amido-7-aminocephalosporin acids or haloimido or alkoxyimido derivatives of penicillins or cephalosporins substantially as described herein and shown with reference to Examples 32 to 35, 37 to 41, and 43 to 48.
- 45 63. A process for the preparation of a penicillin substantially as described herein and shown with reference to Example 14. 45
64. A process for the preparation of penicillins or cephalosporins substantially as described herein and shown with reference to Examples 30 and 31.
- 50 65. A process for the preparation of a 7-aminocephalosporin acid substantially as described herein and shown with reference to Example 42. 50
66. A 2-amido penicillin or 2-amido cephalosporin prepared by a process according to any one of Claims 1, 2, 7, 8, 12 and 13.
- 55 67. A 2-amido penicillin prepared by a process according to any one of Claims 3 to 6, 9 to 11, 14 and 15. 55
68. A 2-amido-6-aminopenicillanic acid or 7-aminocephalosporin acid prepared by a process according to Claim 16.
69. A 2-amido-6-aminopenicillanic acid prepared by a process according to any one of Claims 17 to 19.
- 60 70. A penicillin or cephalosporin prepared by a process according to Claim 20 or Claim 21. 60
71. A penicillin prepared by a process according to any one of Claims 22 to 24.
72. A 7-aminocephalosporin acid prepared by a process according to Claim 25.
- 65 73. A pharmaceutical composition comprising a 2-amido penicillin or 2-amido. 65

cephalosporin according to Claim 28 in association with a pharmacologically acceptable carrier.

5 74. A pharmaceutical composition comprising a 2-amido penicillin of 2-amido cephalosporin according to Claim 29 in association with a pharmacologically acceptable carrier. 5

75. A pharmaceutical composition comprising a 2-amido penicillin according to Claim 33 in association with a pharmacologically acceptable carrier.

76. A pharmaceutical composition comprising a 2-amido penicillin according to Claim 34 in association with a pharmacologically acceptable carrier.

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