

PATENT SPECIFICATION

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Int. Cl.:—C 07 d 99/24

COMPLETE SPECIFICATION

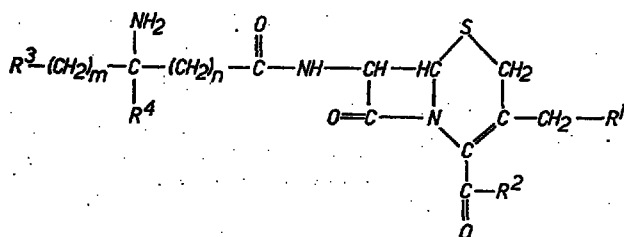
Cephalosporin Compounds

We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 740 South Alabama Street, City of Indianapolis, State of Indiana, 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:—

The present invention concerns an improved process for preparing 7-aminoacyl cephalosporin compounds having antibiotic activity, and certain new intermediate compounds useful in the preparation of said cephalosporin compounds.

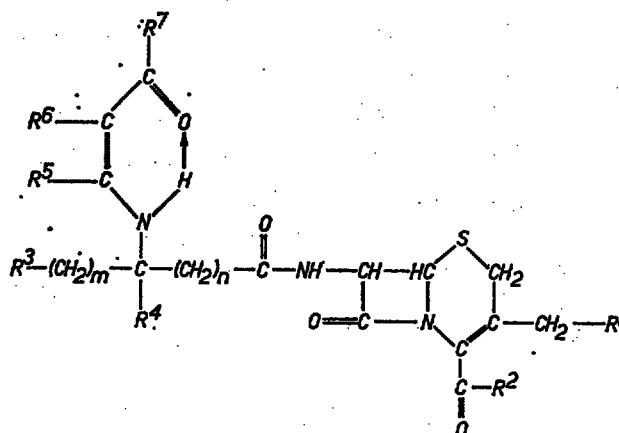
More particularly, this invention is concerned with an improved process for preparing cephalosporanic acid derivatives with an aminoacylamido linkage in the 7 position on the cephalosporin nucleus, which demonstrate unexpected activity against Gram-negative as well as against Gram-positive bacteria.

In accordance with one embodiment of the invention there is provided a process for preparing 7-aminoacyl cephalosporin compounds represented by the formula:



(I)

in which R¹ is acetoxy or pyridino; R² is OH when R¹ is acetoxy; R² is O⁻ when R¹ is pyridino; R³ is C₁—C₄ alkyl, C₃—C₆ cycloalkyl, phenyl, naphthyl, thienyl, benzo-thienyl, furyl, benzofuryl, indolyl, or pyridyl; R⁴ is hydrogen, methyl, or ethyl; and m and n are 0 or 1; which comprises hydrolyzing at a pH below 5 an N-protected, aminoacyl cephalosporin compound represented by the formula:



(II)

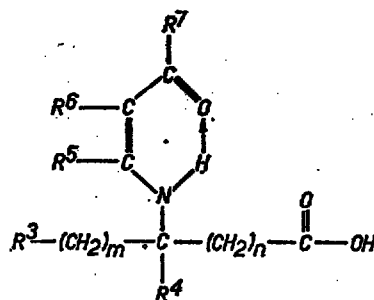
wherein R¹, R², R³, R⁴ and m and n are as defined above; R⁵, taken alone, is hydrogen, C₁-C₄ alkyl, or phenyl; R⁶, taken alone, is hydrogen, C₁-C₄ alkyl, or phenyl; R⁷, taken alone, is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, or phenyl; R¹ and R², when taken together with the carbon atoms to which they are attached, complete a carbocyclic ring having the structure of benzene or naphthalene; and R⁵ and R⁷, when taken together with the interconnecting carbon atoms, complete a C₅-C₇ cycloaliphatic ring; and wherein R¹ when pyridino and each of R³ to R⁷ when other than hydrogen may optionally be substituted; to thereby remove the amine protecting group, and recovering the desired 7-aminoacylcephalosporin compound.

The present invention further provides a pharmaceutical composition comprising a cephalosporin compound whenever prepared by the process of the invention, and a pharmaceutical carrier.

The compounds represented by formula II employed in the process of this invention are new compounds. Accordingly, a further provision of this invention are such new compounds as are represented by formula II; such compounds are useful as intermediates in organic syntheses.

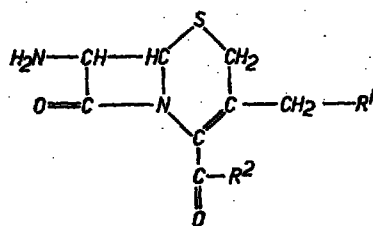
These new intermediate compounds can be prepared by reacting an N'-protected amino acid, as defined hereinafter, with the desired cephalosporin nucleus. The novel intermediates can be isolated and purified, if desired. However, substantially pure aminoacyl cephalosporins of formula I can be obtained without isolating the novel intermediates, by acidifying the product mixture containing the intermediate.

Accordingly, a further provision of the invention is a process for preparing antibiotic compounds represented by the formula I above, which comprises reacting an N'-protected amino acid of the formula:



(III)

wherein R³, R⁴, R⁵, R⁶, R⁷, m and n have the same meaning as above, with a cephalosporin nucleus represented by the formula:



(IV)

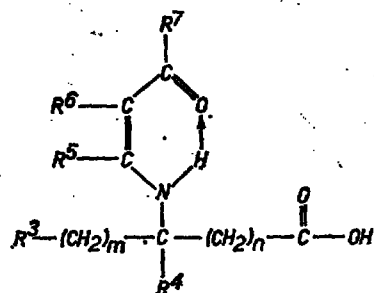
wherein R^1 and R^2 are as defined above, then acidifying the reaction product mixture to below pH 5, and recovering therefrom the desired derivative of cephalosporanic acid.

Compounds represented by formula I above have been heretofore prepared by the reaction of the appropriate cephalosporin nucleus with an acylating agent comprising the appropriate aminoacyl moiety, whereby the derived aminoacyl structure was attached to the 7-amino group. In order for this reaction to be carried out successfully, it was necessary to protect the aminoacyl moiety at the amino function with a protecting group in such a way as to prevent a side reaction from occurring between two or more of these aminoacyl groups, which would produce a mixture of the desired aminoacyl cephalosporin with other di-, tri-, and polypeptides. It was necessary also for the protecting group to be removable quantitatively, after acylation had been carried out, without degrading the other desired portions of the molecule.

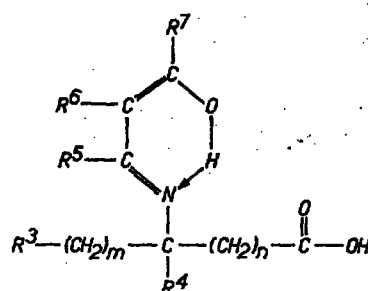
To accomplish this purpose, many protecting groups have been devised by prior workers. Examples of those groups include carbobenzoxy, carbo-*tert*-butoxy, carballyloxy and trityl. These are more or less successful generally, but when applied to the reaction used to prepare the defined aminoacyl cephalosporins, they lead to a rather poor yield of difficultly separable products.

However, it will be understood from the foregoing, that in accordance with this invention, the 7-aminoacyl cephalosporins may be easily prepared from the said novel intermediate compound or, in a further embodiment, by a process in which an aminoacylating agent, protected on the amino moiety by reaction with a β -dicarbonyl compound, as hereinafter defined, is reacted with the cephalosporin nucleus. The N' -protected aminoacyl cephalosporin thus formed is then hydrolysed in a known manner to remove the protecting group, thus yielding the desired end product. Thus, this invention makes it possible to obtain substantially pure 7-aminoacyl cephalosporins of the defined class and as represented by formula I above in improved yield on a large scale, without any need for isolating and purifying any intermediate materials.

In accordance with the present invention the protected amino acids (formula III above) can be represented by the formulae:



V(a)



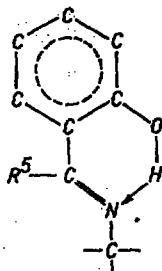
V(b)

wherein R^3 , R^4 , R^5 , R^6 , R^7 , m and n are as defined above.

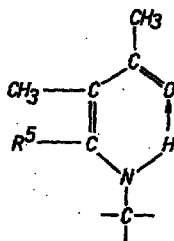
Formulae V(a) and V(b) demonstrate two different electronic representations of the hybrid system as defined for the structure by Dane et al., *Angew. Chem.* 74, 873 (1962). It is well known that structural formulas cannot represent the true picture of the resonant hybrid. The presence of resonance stabilization through some other portion of the molecule will, of course, allow the structure to be represented more precisely by one of the formulas, although the molecule will exist at all times in a hybrid form represented in part by the other structural formula. It will be seen that when R^6 and R^7 form a ring with resonance stabilization, structure V(b) will more



nearly represent the predominating species. When R^6 and R^7 do not form such a ring, it is believed that the structure of the compound is more nearly represented by V(a). For example, when R^6 , taken together with R^7 and the carbon atoms to which they are respectively attached, form benzene, the preferred structural representation would be:



whereas when R^6 and R^7 are methyl, the preferred species is thought to be represented more correctly by:



It should be understood, however, that the true species cannot be accurately represented by a single structure, but only by a hybrid of the written structures. For the sake of simplicity, the formula of the compound defined by either V(a) or V(b), or a hybrid structure thereof, will be written as the structure V(a) as obtained from a noncyclic di-ketone, although it is to be understood this is not a limiting notation.

In the above structural formulae representing the compounds with which this invention is concerned, the following should be noted.

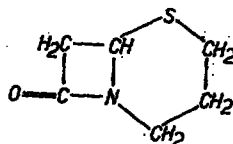
" C_1-C_4 alkyl" when used herein refers to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, and tert.-butyl.

" C_1-C_4 alkoxy" refers to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy, and tert.-butoxy.

" C_3-C_6 cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The compounds wherein R^6 and R^7 , taken together with the interconnecting carbon atoms, complete a C_5-C_7 cycloaliphatic ring are prepared from such cyclic structures as 1,3-cyclopentanedione, 1,3-cyclohexanedione, 5,5-dimethyl-1,3-cyclohexanedione or 1,3-cycloheptanedione.

In naming the novel compounds provided by the process of the invention, it is convenient to designate the basic, saturated, fused-ring, β -lactam thiazine structure as "cepham", VI,



(VI)

and to name the compounds as derivatives thereof, the term "cephem" referring to the basic structure with a single olefinic bond.

The compounds provided by the process of the present invention have been defined in terms of a structural formula including the organic radicals R' when pyridino and R^3 to R^7 when other than hydrogen. Such radicals may bear one or more substituents without requiring any significant modification of the process of the invention. Among such substituents are halo, hydroxy, nitro, lower alkyl, trifluoromethyl, methoxy, methylmercapto, cyano, hydroxymethyl, β -hydroxyethyl, acetyl and acetamido.



The protected amino acids (formula III) which ultimately form the substituent at position 7 of the cephalosporin nucleus are conveniently prepared by condensing an appropriately substituted amino acid, as the salt thereof, with a β -diketone, β -keto-ester, or other β -dioxo-compound, one method of effecting such as condensation being that described by Dane et al., *supra*. Either optical isomer of the amino acid, or the racemic mixture, may be employed.

Examples of β -dicarbonyl compounds which can be used to condense with the amine function of the amino acid include acetylacetone, formylacetone (as an alkali metal salt), propionylacetone, butyrylacetone, isobutyrylacetone, 3,5-diketo-2,6-dimethylheptane, acetylacetophenone, benzoylbenzophenone, 3-methyl-2,4-diketopentane, 3-phenyl-2,4-diketopentane, α -acetylpropionophenone, α -benzoylpropionophenone, 3-(β -phenethyl)-2,4-diketopentane, salicylaldehyde, 2-hydroxy-1-naphthaldehyde, 2-hydroxyacetophenone and 2-hydroxypropionophenone.

The thus prepared N-protected amino carboxylic acid can be caused to react with the cephalosporin nuclei (formula IV) if the amino-acid is first converted into a mixed anhydride, suitably by reacting the protected acid, or a salt thereof, in a nonaqueous, nonhydroxylic, water-miscible solvent with an alkyl chlorocarbonate such as ethyl chlorocarbonate, isobutyl chlorocarbonate, benzyl chlorocarbonate, p-methoxybenzyl chlorocarbonate or adamantyl chlorocarbonate. The mixed anhydride formation is carried out at or below ambient room temperature. Suitable solvents in which to carry out this reaction include acetone, methyl ethyl ketone, dioxane, tetrahydrofuran, acetonitrile, ethyl acetate and dimethylacetamide.

Alternatively, the protected amino carboxylic acid can be used directly in conjunction with an equimolar proportion or more of a carbodiimide to acylate the 7-amino group. In this method, the acylation proceeds at ordinary temperatures. Any of the carbodiimides are effective for this purpose, the active moiety being the —N=C=N— structure. Illustrative examples include N,N'-diethylcarbodiimide, N,N'-di-n-propylcarbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N,N'-diallylcarbodiimide, N,N'-bis(p-dimethylaminophenyl)carbodiimide and N-ethyl-N'-(4'-ethyl-2''-oxazinyl)carbodiimide, other suitable carbodiimides being disclosed in U.S. Patents Nos. 2,938,892 and 3,065,224.

As a further alternative, an equimolar proportion or more of carbonyl diimidazole can be used in the acylation procedure to activate the reaction with the protected amino carboxylic acid.

The resulting N'-protected aminoacyl cephalosporanic acid (formula II) may be isolated in the form of the free acid or may be converted, by known methods, to a salt with a pharmaceutically acceptable cation.

For the purpose of illustration, there can be mentioned several types of cationic salts which can be prepared from said compounds, including for example, water soluble salts as the sodium, potassium, ammonium, and substituted ammonium salts, as well as less water soluble salts such as the calcium, barium, procaine, quinine, and dibenzylethylenediamine salts.

The hydrolysis of the N'-protected cephalosporanic acid derivative is carried out in aqueous solution, acidified to below about pH 5, preferably around pH 2, and at ambient room temperature. In a preferred embodiment, the hydrolysis is effected by adding a small quantity of an aqueous solution of a strong acid to a solution of the N'-protected cephalosporanic acid, or a salt thereof, dissolved or suspended in water, an organic solvent, or mixture thereof. Suitable acids include hydrochloric acid, hydrobromic acid, hydriodic acid, formic acid and trifluoroacetic acid.

Enhanced yields of the N-protected 7-aminoacyl cephalosporin compound can be obtained by reacting a cephalosporin nucleus with a mixed anhydride prepared from a salt obtained by the reaction of a tertiary amine with the N'-protected aminocarboxylic acid, or an alkali metal salt of the mixed anhydride in the presence of a small quantity of a tertiary amine.

"Tertiary amine" as used herein refers to any tertiary amine of ionic strength great enough to form an ionic bond with the acid function of the amino acid reactant; it may include trimethylamine, triethylamine, N-methyldiallylamine, N-methoxymethyl-dimethylamine, N,N,N',N'-tetramethylethylenediamine, dimethylbenzylamine, diethylbenzylamine, N-methylmorpholine or N-ethylmorpholine.

"Alkali metal" refers to sodium, potassium.

The overall process afforded by one embodiment of this invention can illustratively be carried out in the following manner:

The amino carboxylic acid in the form of its anionic salt, by the basic primary nitrogen by reaction with a β -dicarbonyl compound, is dissolved at ambient tempera-



ture in an anhydrous, nonhydroxylic, water-miscible, organic solvent. If the salt is any other than an amine salt, a catalytic amount of an amine (such as dimethylbenzylamine) is added and the solution is cooled to about 0 to -10°C . or lower if desired. As the solution is stirred, an alkyl chlorocarbonate is added in at least about equimolar ratio to the amino acid. The solution thus formed is stirred for the length of time necessary for the intermediate anhydride to be formed. To the resulting intermediate is then added an aqueous solution of 7-aminocephalosporanic acid in the form of an amine salt, which can be prepared by dissolving 7-aminocephalosporanic acid in water with trimethylamine, triethylamine, dimethylethylamine, di-n-propylamine or di-isopropylamine.

The whole mixture is stirred at or below ambient room temperature and allowed to react for about one hour, after which it can be filtered to remove solid by-products and/or evaporated to a smaller volume if desired.

It is at this point that the N'-protected 7-aminoacyl cephalosporin can be isolated. One method of isolation is to overlay the aqueous solution with a non-miscible organic solvent capable of extracting the desired product therefrom, then to acidify to about pH 3, separate the organic layer and isolate the desired product therefrom, as by precipitation or crystallizing via addition of a diluent liquid, for example, ether or petroleum ether, in which the product is insoluble. Alternatively, the nonaqueous solution can be evaporated to dryness and the desired product purified by crystallization of the residue.

Removal of the amine protecting group is readily accomplished hydrolytically by addition of mineral acid or strong organic acid to about pH 2, and allowing the solution to stir at ambient room temperature until crystallization has begun, then cooling. After crystallization has reached substantial completion, the solid 7-aminoacylamidocephalosporanic acid is removed by filtration, washed, and dried.

For better understanding, the process of the present invention may be illustrated by the following specific examples.

EXAMPLE 1

D- α -Phenylglycine, 10.419 kg., were slurried in 45 liters of benzene. An aqueous 50 percent sodium hydroxide solution prepared from 2760 g. of sodium hydroxide (minimum assay 90 percent) and 2760 g. of water was added and thoroughly mixed with the benzene slurry. The mixture was heated with stirring to $50-60^{\circ}\text{C}$. for one to two hours. Methyl acetoacetate, 8.0 kg., was added (using 3.8 liters of benzene wash) to the hot mixture. The mixture was distilled until free of water, and the resulting benzene slurry of the solid product was cooled to 25°C . and filtered. The resulting salt was washed with benzene and heated to 60°C . for four hours. Yield: 16 kg. (85 percent) of methyl 3-(α -carboxybenzylamino)crotonate as the sodium salt.

A solution containing 150 g. of the above sodium salt was prepared using 1,680 ml. of acetonitrile and 1.2 ml. of dimethylbenzylamine. This solution was cooled to -10°C ., and 72 g. of ethyl chlorocarbonate were added in one portion. Stirring was continued for 20 minutes at -10°C . A solution of 151 g. of 7-aminocephalosporanic acid and 81.6 g. triethylamine in 720 g. of water was added in one portion, and the mixture stirred for one hour at 0°C . The resulting mixture was filtered and the filtrate evaporated *in vacuo* to a volume of about 960 ml. To this solution were added 1800 ml. of methyl isobutyl ketone and 240 ml. of formic acid (98-100 percent). This mixture was allowed to stir at about 0°C . until crystallization was complete. The product was removed by filtration and washed by slurrying successively with 300 ml. of 3:2 methyl isobutyl ketone-water, twice with 150 ml. of water, and twice with 150 ml. of methyl isobutyl ketone. Yield: 50-57 g. (22-25 percent) of 7-D- α -phenylglycylcephalosporanic acid.

EXAMPLE 2

To a solution of 11 g. (0.2 mole) of potassium hydroxide in 200 ml. of methanol were added 30.0 g. (0.2 mole) of D-phenylglycine. With stirring, 400 ml. (0.4 mole) of acetylacetone were added slowly. A thick white precipitate formed immediately. After three hours a lesser amount of precipitate seemed to be present. The mixture was cooled and filtered, and the residue was washed with a small amount of methanol and air-dried. This material (7.0 g.) was identified as D-phenylglycine and was subsequently discarded.

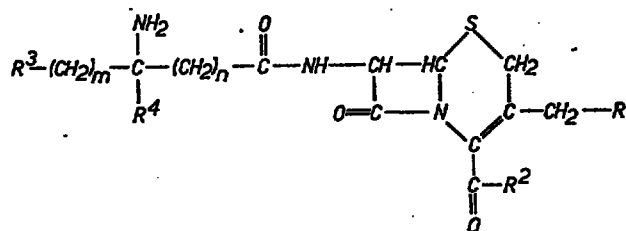
The filtrate was concentrated *in vacuo* to dryness and the resulting residue was dissolved in benzene. Addition of a large amount of petroleum ether (boiling range $60-90^{\circ}\text{C}$.) yielded a gelatinous precipitate which was collected and dried *in vacuo*.

compound

Yield: 28.0 g. of potassium D - N - [2 - (4 - keto - 2 - propenyl)]phenylglycine. A suspension of 3.5 g. of this solid in 50 ml. of tetrahydrofuran was stirred at -10°C . and 1.78 ml. of isobutyl chloroformate were added slowly. The temperature was maintained at -10°C . for one hour. A solution of 3.5 g. of 7-aminocephalosporanic acid in 25.0 ml. of tetrahydrofuran, 25.0 ml. of water, and 1.78 ml. of triethylamine was added slowly. The mixture was stirred at 0° to -10°C . for one hour and at room temperature for one hour, then diluted with 100 ml. of water and extracted with 2×100 ml. of ethyl acetate. The aqueous layer was cooled in an ice bath, overlaid with ethyl acetate, and adjusted to pH 3.0 with 10 percent hydrochloric acid. The layers were separated and the organic layer was dried and concentrated *in vacuo* to dryness. The residue was treated with a mixture of 200 ml. of ether and 60 ml. of petroleum ether (boiling range: $30-60^{\circ}\text{C}$.) to crystallize the 7 - (D - α - N[2 - (4 - keto - 2 - propenyl)]aminophenylacetamido)cephalosporanic acid, which was collected and vacuum-dried. Yield: 1.9 g. (30 percent).

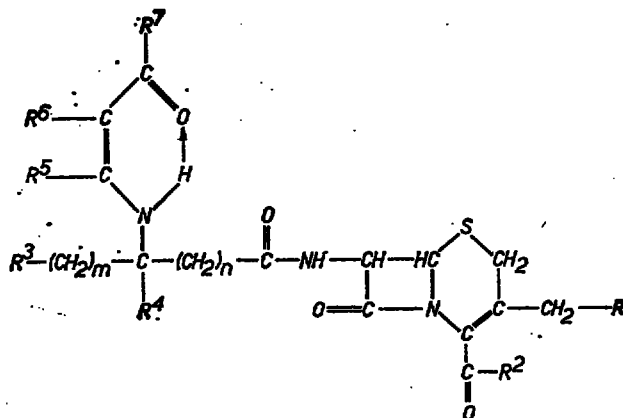
WHAT WE CLAIM IS:—

1. A process for preparing 7-aminoacyl cephalosporin compounds represented by the formula



(I)

in which R^1 is acetoxy or pyridino; R^2 is OH when R^1 is acetoxy; R^2 is O^- when R^1 is pyridino; R^3 is C_1-C_4 alkyl, C_5-C_6 cycloalkyl, phenyl, naphthyl, thienyl, benzothienyl, furyl, benzofuryl, indolyl, or pyridyl; R^4 is hydrogen, methyl, or ethyl; and m and n are 0 or 1; which comprises hydrolyzing at a pH below 5 an N-protected aminoacyl cephalosporin compound represented by the formula:



wherein R^1 , R^2 , R^3 , R^4 , m and n are as defined above; R^5 , taken alone, is hydrogen, C_1-C_4 alkyl, or phenyl; R^6 , taken alone, is hydrogen, C_1-C_4 alkyl, phenyl-substituted C_1-C_4 alkyl, or phenyl; R^7 , taken alone, is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or phenyl; R^6 and R^7 , when taken together with the carbon atoms to which they are attached, complete a carbocyclic ring having the structure of benzene or naphthalene; and R^5 and R^7 , when taken together with the interconnecting carbon atoms, complete a C_6-C_7 cycloaliphatic ring; and wherein R^1 when pyridino and each of R^3 to R^7 when other than hydrogen may optionally be substituted; to thereby remove the amine protecting group, and recovering the desired 7-aminoacylcephalosporin compound.

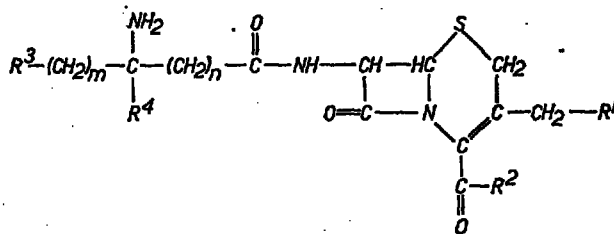
2. A process for preparing N-protected 7-aminoacyl cephalosporin compounds represented by Formula I of claim 1 which comprises reacting an N-protected amino acid of the formula:



Yield: 28.0 g. of potassium D - N - [2 - (4 - keto - 2 - propenyl)]phenylglycine. A suspension of 3.5 g. of this solid in 50 ml. of tetrahydrofuran was stirred at -10°C . and 1.78 ml. of isobutyl chloroformate were added slowly. The temperature was maintained at -10°C . for one hour. A solution of 3.5 g. of 7-aminocephalosporanic acid in 25.0 ml. of tetrahydrofuran, 25.0 ml. of water, and 1.78 ml. of triethylamine was added slowly. The mixture was stirred at 0° to -10°C . for one hour and at room temperature for one hour, then diluted with 100 ml. of water and extracted with 2×100 ml. of ethyl acetate. The aqueous layer was cooled in an ice bath, overlaid with ethyl acetate, and adjusted to pH 3.0 with 10 percent hydrochloric acid. The layers were separated and the organic layer was dried and concentrated *in vacuo* to dryness. The residue was treated with a mixture of 200 ml. of ether and 60 ml. of petroleum ether (boiling range: $30-60^{\circ}\text{C}$.) to crystallize the 7 - (D - α - N[2 - (4 - keto - 2 - propenyl)]aminophenylacetamido)cephalosporanic acid, which was collected and vacuum-dried. Yield: 1.9 g. (30 percent).

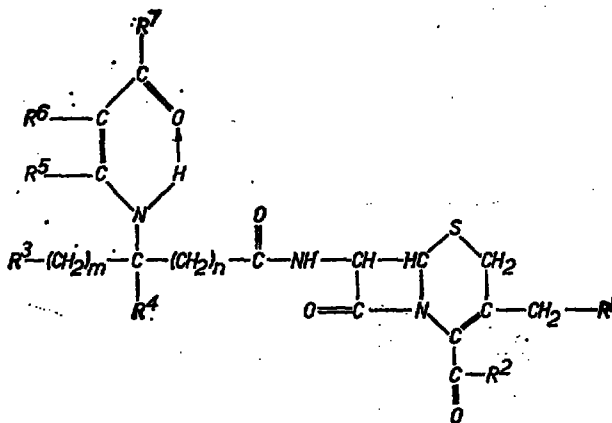
WHAT WE CLAIM IS:—

1. A process for preparing 7-aminoacyl cephalosporin compounds represented by the formula



(I)

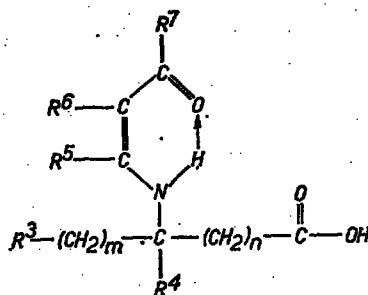
in which R^1 is acetoxy or pyridino; R^2 is OH when R^1 is acetoxy; R^2 is O- when R^1 is pyridino; R^3 is C_1-C_4 alkyl, C_6-C_6 cycloalkyl, phenyl, naphthyl, thienyl, benzothienyl, furyl, benzofuryl, indolyl, or pyridyl; R^4 is hydrogen, methyl, or ethyl; and m and n are 0 or 1; which comprises hydrolyzing at a pH below 5 an N-protected aminoacyl cephalosporin compound represented by the formula:



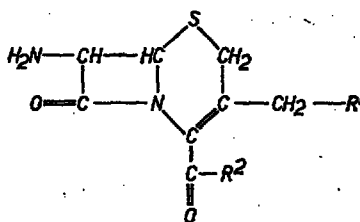
wherein R^1 , R^2 , R^3 , R^4 , m and n are as defined above; R^5 , taken alone, is hydrogen, C_1-C_4 alkyl, or phenyl; R^6 , taken alone, is hydrogen, C_1-C_4 alkyl, phenyl-substituted C_1-C_4 alkyl, or phenyl; R^7 , taken alone, is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or phenyl; R^5 and R^7 , when taken together with the carbon atoms to which they are attached, complete a carbocyclic ring having the structure of benzene or naphthalene; and R^5 and R^7 , when taken together with the interconnecting carbon atoms, complete a C_5-C_7 cycloaliphatic ring; and wherein R^1 when pyridino and each of R^3 to R^7 when other than hydrogen may optionally be substituted; to thereby remove the amine protecting group, and recovering the desired 7-aminoacylcephalosporin compound.

2. A process for preparing N-protected 7-aminoacyl cephalosporin compounds represented by Formula I of claim 1 which comprises reacting an N-protected amino acid of the formula:





wherein R^3 , R^4 , R^5 , R^6 , R^7 , m and n have the same meaning as in claim 1, with a cephalosporin nucleus represented by the formula:



(IV)

5 wherein R^1 and R^2 has the same meaning as in claim 1, to form the said N'-protected aminoacyl cephalosporin compound which is isolated or converted to a salt with a pharmaceutically acceptable cation. 5

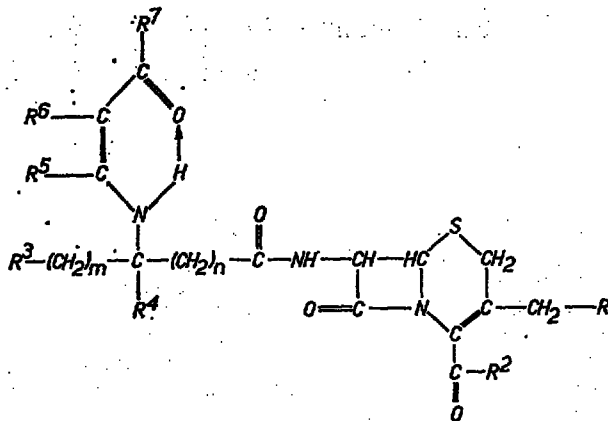
3. The process of claim 1 wherein the N-protected 7-aminoacylcephalosporin compound is prepared by the process of claims 2.

10 4. The process of claim 2 or 3 wherein said N-protected amino acid is reacted with said cephalosporin nucleus in the presence of an equimolar proportion or more of a carbodiimide. 10

5. The process of claim 2 or 3 wherein said N-protected amino acid, in the form of its salt with a cation of the group consisting of tertiary amines and alkali metals in cationic form, is reacted with an alkyl chlorocarbonate, and the resulting mixed anhydride is reacted with said cephalosporin nucleus. 15

6. The process of claim 2 or 3 wherein said N-protected amino acid in the form of its alkali metal salt is reacted with an alkyl chlorocarbonate, in a non-aqueous, nonhydroxylic water-miscible solvent, in the presence of a tertiary amine; and the resulting mixed anhydride is reacted in an aqueous solution with the said cephalosporin nucleus. 20

7. A compound of the formula



(II)

wherein R^1 to R^7 and m and n are as defined in claim 1.



8. A process for preparing the compounds represented by Formula I as defined in claim 1, substantially as herein described with particular reference to any one of the specific Examples.

9. A process for preparing the compounds represented by Formula II as defined in claim 7, substantially as herein described with particular reference to any one of the specific Examples.

10. The products obtained by the processes defined in any of claims 1 to 6, 8 or 9.

11. A pharmaceutical composition comprising a cephalosporin compound whenever prepared by the process claimed in any one of claims 1 to 6 or claim 8, and a pharmaceutical carrier.

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