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PATENT SPECIFICATION

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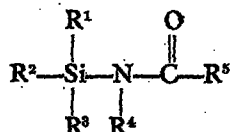
(54) PREPARATION OF CEPHALOSPORIN COMPOUNDS

(71) We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 307 East McCarty 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:—

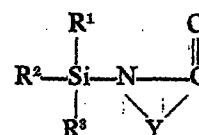
This invention relates to a process which involves reacting a compound having a cephalosporin nucleus with a mono- or bis-silyl-amide, which may be a simple linear or cyclic amide, a urea, or a urethane (carbamate) in a substantially anhydrous aprotic liquid solvent at a temperature of from about -25° to about 50° to form the mono- or di-silylated cephalosporin compounds; the silylated cephalosporin compound are directly acylated with certain acylating groups known to provide the resulting cephalosporin with antibiotic activity. The compounds having a cephalosporin nucleus include 7-aminocephalosporanic acid, commonly abbreviated 7—ACA, and 7-amino-desacetoxy-cephalosporanic acid, commonly abbreviated 7—ADCA.

More particularly, this invention provides a process which comprises (a) reacting 7—ACA or 7—ADCA or a soluble salt form thereof with a silicon compound having one of the formulae:—

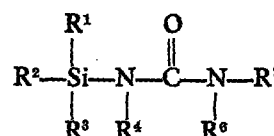
I.



II.



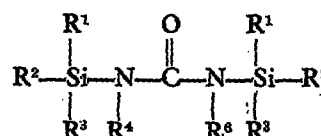
III.



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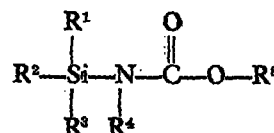
(a)

or

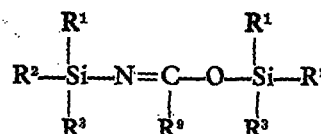


(b)

IV.



V.



wherein each of R^1 , R^2 , and R^3 is hydrogen or 40

a hydrocarbon radical free of aliphatic unsaturation and having from 1 to 8 carbon atoms, with not more than two of any R^1 , R^2 , and R^3 bonded to the same silicon atom being

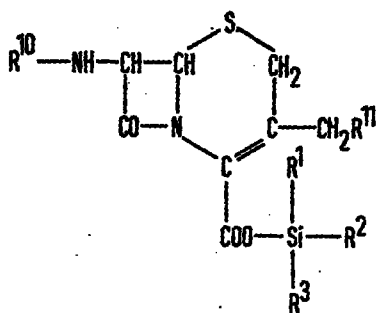
5 R^3 is hydrogen or a hydrocarbon radical which is free of aliphatic unsaturation and contains from 1 to 8 carbon atoms;

10 Y is an alkylene group having from 3 to 18 carbon atoms with a chain of at least 3 but no more than 5 carbon atoms extending between the nitrogen and the carbonyl group to which Y is bonded;

15 each of R^4 , R^6 and R^7 , taken separately, is hydrogen or a hydrocarbon group free of aliphatic unsaturation containing from 1 to 8 carbon atoms, or R^6 and R^7 taken together with the nitrogen to which they are bonded, complete a heterocyclic ring containing from 5 to 6 ring forming atoms, one of which can be oxygen para to the nitrogen, or from 4 to 6 ring forming carbon atoms with the proviso that R^6 and R^7 together contain not more than 18 carbon atoms and that if R^6 is an alkyl with a tertiary carbon bonded to the nitrogen then R^7 is hydrogen, or R^4 and R^6 taken together with the nitrogens to which they are bonded and the carbonyl group complete a heterocyclic ring containing from 5 to 6 ring forming atoms and from 2 to 3 methylene ring forming carbon atoms;

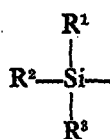
R^8 is a hydrocarbon group free of aliphatic unsaturation and containing from 1 to 8 carbon atoms; and

35 R^9 is either hydrogen or a hydrocarbon group free of aliphatic unsaturation and containing from 1 to 8 carbon atoms, in a substantially anhydrous, aprotic liquid solvent, at a temperature of from about -25°C . to about 40 50°C . to form a compound of the formula



Formula VI

wherein R^1 , R^2 , and R^3 are as defined above and R^{10} is hydrogen or the group



45 wherein R^1 , R^2 , and R^3 are as defined above,

and R^{11} is hydrogen or acetoxy, (b) reacting the product from step (a) with an acylating derivative of thiophene-2-acetic acid or a mixed anhydride of an N-protected phenylglycine, (c) treating the acylated product from step (b) with a C_1 to C_6 alkanol to form cephalosporin, and, (d) recovering the cephalosporin from the reaction mixture of step (c).

Cephalexin or cephaloglycin can be prepared by the above process in the following way:—

in step (a) 7-amino-desacetoxy cephalosporanic acid in the case of cephalexin, or 7-amino-cephalosporanic acid in the case of cephaloglycin, is reacted with a compound of the formula I wherein each of R^1 , R^2 and R^3 is a hydrocarbon radical which is free of aliphatic unsaturation and has from 1 to 8 carbon atoms; R^4 is hydrogen, and R^5 is a hydrocarbon radical which is free of aliphatic unsaturation and has from 1 to 8 carbon atoms, in step (b) the step (a) reaction product is acylated with an activated N-protected phenylglycine, and in step (c) the acylated product from step (b) is treated with methanol to form cephalexin or cephaloglycin.

These silylated cephalosporin intermediates are used for preparing a variety of known cephalosporin antibiotics, such as cephalothin, cephaloridine, cephaloglycin, and cephalexin. For example, these silylated cephalosporin intermediates may be directly acylated with thiophene-2-acetyl chloride and treated with an alcohol to form cephalothin or desacetoxy-cephalothin. Acylation of the above silylated product where R^{11} is acetoxy with an N-protected activated form of phenylglycine, followed by treatment with methanol, and pH adjustment to the isoelectric point yields cephaloglycin.

Silylated cephalosporin intermediates of the above formula where R^{11} is hydrogen are readily prepared by treating 7-ADCA or an internal or external soluble salt thereof with one of the silylating agents I to V set forth above. These compounds are intermediates in the production of cephalosporin antibiotics such as cephalexin, in which process these compounds can be directly acylated with a mixed anhydride of an N-protected form of phenylglycine, treated with alcohol, to remove the silyl groups, treated with acid to lower the pH to remove the N-protecting group and adjusted in pH to one of the isoelectric points of cephalexin to precipitate cephalexin from the solution.

Specific examples of these intermediate compounds include:

Trimethylsilyl 7 - (N - trimethylsilylamino) - 3 - methyl - Δ^3 - cephem - 4 - carboxylate, Trihexylsilyl 7 - (N - trihexylsilylamino) - 3 - methyl - Δ^3 - cephem - 4 - carboxylate, Tricyclohexylsilyl 7 - (N - tricyclohexylsilylamino) - 3 - methyl - Δ^3 - cephem - 4 - carboxylate,

Triphenylsilyl 7 - (N - triphenylsilylamino) - 3 - methyl - Δ^3 - cephem - 4 - carboxylate.

The 7-amino group of the silylated 7—ACA or 7—ADCA intermediates can be reacted with the acylating agent by procedures known to date, for example as described in U.S. Patent 3,382,241. The acylating agent is an acylating derivative of thiophene-2- acetic acid or a mixed anhydride of an N-protected phenylglycine.

Examples of such acylating agents are 2 - (2' - thienyl)acetyl chloride or bromide, and mixed anhydride forms of an N-protected phenylglycine such as the methyl N - (tert - butoxycarbonyloxy)phenylglycine mixed carbonic anhydride, isobutyl N - (benzyloxycarbonyloxy)phenylglycine mixed carbonic anhydride and ethyl N - (2,2,2 - trichloroethoxycarbonyloxy)phenylglycine mixed carbonic anhydride.

The invention provides a process for preparing cephalosporin compounds wherein (a) 7—ACA or 7—ADCA, in zwitterionic or a soluble salt form thereof is reacted with a compound having a formula represented by one of formulas I, II, III, IV, and V above in a substantially anhydrous aprotic solvent at a temperature of from about $-25^{\circ}\text{C}.$ to about $50^{\circ}\text{C}.$ to form a silylated 7—ACA or 7—ADCA ester intermediate, (b) the silylated 7—ACA or 7—ADCA intermediate product from step (a) is reacted with an acylating agent providing the desired 7-acyl group, i.e., an acylating derivative of thiophene-2-acetic acid [e.g., 2-(2'-thienyl)acetyl chloride or bromide] or a mixed anhydride of an N-protected phenylglycine, (c) treating the acylated product from step (b) with a C_1 to C_6 alcohol to obtain the cephalosporin in solution, freed from the silylation groups and (d) recovering the cephalosporin from the solution by known methods. Cephalothin may be recovered as the alkali metal salt, e.g., the sodium or potassium salt by addition of sodium or potassium acetate. When cephaloglycin or cephalixin or similar amino group containing cephalosporin antibiotics are being prepared, the N-protecting group must be removed from the amino-acid moiety of the cephalosporin. For this purpose water, acid, or mixtures thereof are added to the cephalosporin containing mixture simultaneously with or soon after the alcohol addition. The resulting amino-group containing cephalosporin product can be separated from the reaction mixture by adjusting the pH of the mixture to the isoelectric point of the cephalosporin at which pH the cephalosporin separates from the mixture from which it can be recovered by conventional chemical methods.

The organic silicon compounds represented by the formulas I and II are defined in detail in U.S. Patent 2,876,234 issued March 3, 1959. These are monosilylated amides but include both the acyclic and cyclic types. The

silylated urea amide compounds (III) and the silylated urethane or carbamate compounds (IV) can be prepared as described in U.S. Patent 2,876,209. Bis-silyl compounds of formula V are well-known compounds and have been described in publications such as the one found in the *Journal of the American Chemical Society*, Volume 88, page 3390.

Examples of the intermediate compounds which can be produced in the process of this invention and the reactants from which they can be prepared include:

Triethylsilyl 3 - methyl - 7 - (N - triethylsilylamino) - Δ^3 - cephem - 4 - carboxylate from 7—ADCA and N,O - bis (triethylsilyl)-acetamide;

Trihexylsilyl 3 - acetoxymethyl - 7 - (N - trihexylsilylamino) - Δ^3 - cephem - 4 - carboxylate from 7—ACA and 1 - (trihexylsilyl) - 2 - piperidinone;

Triphenylsilyl 3 - methyl - 7 - (N - triphenylsilylamino) - Δ^3 - cephem - 4 - carboxylate from 7—ADCA and 1 - (triphenylsilyl) - 2 - pyrrolidinone;

Tribenzylsilyl 3 - acetoxymethyl - 7 - (N - tribenzylsilylamino) - Δ^3 - cephem - 4 - carboxylate from 7—ACA and N-tribenzylsilyl methyl carbamate;

Dimethyl(phenyl)silyl 3 - methyl - 7 - (N - dimethylphenylsilylamino) - Δ^3 - cephem - 4 - carboxylate from 7—ADCA and dimethyl(phenyl) - silylurea.

Example 1

A 10.0 g. portion of 7-aminocephalosporanic acid, and 17.6 ml. of N, O - bis - trimethylsilylacetamide, and 100 ml. of dry acetonitrile were mixed and stirred at room temperature until trimethylsilyl 7 - (N - trimethylsilylamino) - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylate were formed. In a separate operation 10.0 g. of the N-methyl acetoacetate-blocked phenylglycine, 100 ml. of dry acetonitrile, and 0.04 ml. of dimethylbenzylamine were mixed and cooled to $-10^{\circ}\text{C}.$ while stirring and to this mixture there was added 3.1 ml. of methyl chloroformate (8 percent excess) in one portion, to form a mixed anhydride of the N-protected phenylglycine. The reaction temperature of this second mixture rose to approximately $-3^{\circ}\text{C}.$ Stirring and cooling of the mixture was continued for an additional 3 to 5 minutes during which time the temperature dropped to $-10^{\circ}\text{C}.$ To this a resulting mixed anhydride solution was added the above trimethylsilyl 7 - (N - trimethylsilylamino) - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylate solution which had been previously chilled to about $-10^{\circ}\text{C}.$ at such a rate as to maintain the temperature at $-10^{\circ}\text{C}.$ to about $-5^{\circ}\text{C}.$ Addition generally required from about 4 to 8 minutes. Following the addition, the reaction mixture was stirred, and the cooling vessel was allowed to warm up. After one and one-half hours

the temperature was about 3°C. All of the above operations were conducted with precautions taken to exclude atmospheric moisture. In this example a drying tube containing

5 DRIERITE drying agent was used.

The acylation reaction mixture was then chilled to 0°C, and 50 ml. of methanol was added. Stirring was continued for 10 minutes after which time the mixture was filtered with the aid of a filter aid (HYFLO-SUPER-CEL—the word "Hyflo" is a registered Trade Mark). The volume of the filtrate and the methanol washes which followed was adjusted to 350 ml. and then 50 ml. of deionized water was added. Cephaloglycin as the zwitterion separated after a few minutes stirring at 0°C. Stirring at 0°C. was continued for 2 to 3 hours to insure precipitation of most of the cephaloglycin and then the product was filtered, rinsed with acetonitrile, and vacuum dried at about 40°C. Yield of dry cephaloglycin was 11 to 12 grams (82 to 88 percent of theory).

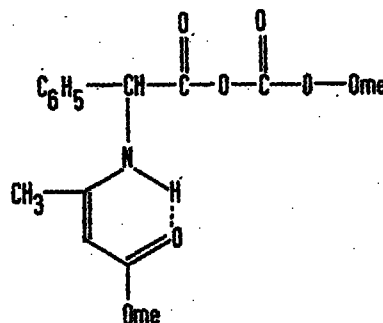
Example 2

25 In an environment protected from atmospheric moisture trimethylsilyl 7 - (N - trimethylsilylamino) - 3 - acetoxyethyl - Δ^3 - cephem - 4 - carboxylate was first prepared by combining 10.0 grams of 7-ACA in 100 ml. of dry acetonitrile with 20 g. (86 millimoles) of N-trimethylsilylacetamide which mixture was stirred at room temperature for 60 minutes to insure solution. The trimethylsilyl 7 - (N - trimethylsilylamino) - 3 - acetoxyethyl - Δ^3 - cephem - 4 - carboxylate solution was cooled to 5°C. and then 5.7 ml. of dry triethylamine was added in one portion. Then while stirring the mixture and continuing the cooling, a solution of 7.45 g. of 2 - (2' - thienyl)acetyl chloride (40.5 millimoles) in 20 ml. of dry acetonitrile was added. The rate of addition was slow enough to keep the temperature below 5°C. The addition required about 25 minutes. When the addition was completed, the mixture was stirred at about 0°C. for one-half hour to insure complete reaction. The acylation reaction mixture was allowed to warm to 35 to 40°C. for about 20 minutes and then the solution was stripped of solvent, and the residue was taken up in methanol and the insoluble material was filtered off. The resulting methanol solution of the crude cephalothin product was stripped and the residue was taken up in water and ethyl acetate mixture. The pH of the mixture was adjusted to about 6.6 with 1 N sodium hydroxide. The aqueous phase of the resulting mixture was separated and the organic phase was discarded. The aqueous phase was layered with fresh ethyl acetate and the pH was adjusted to 2.0 with concentrated hydrochloric acid. After additional washes with ethyl acetate to insure collection of most of the cephalothin product in the organic phase,

the ethyl acetate phases were dried over magnesium sulfate and stripped to obtain about 13 g. of cephalothin as product of the process.

Example 3

In an environment protected from atmospheric moisture, a mixture of 7.2 g. (33.8 millimoles) of 7-amino-desacetoxycephalosporanic acid, (7-ADCA) 17.6 ml. (73.8 millimoles) of N,O-bis(trimethylsilyl)acetamide, and 100 ml. of dry acetonitrile was stirred at room temperature for 2 hours. The resulting trimethylsilylated 7-ADCA was added to the mixed anhydride



resulting from 10 g. of methyl 3 - (alpha-carboxybenzylamino) - crotonate, sodium salt, 3.1 ml. of methyl chloroformate, in 100 ml. acetonitrile, containing 0.04 ml. of N,N-dimethyl-N-benzylamine, cooled to -10°C. The resulting mixture was stirred for 65 minutes and then 50 ml. of methanol was added, and the mixture was stirred for an additional 10 minutes at about -3°C. The mixture was filtered through a filter aid (HYFLO) and rinsed with acetonitrile. The filtrate and the washes were combined and chilled to 0°C. and then 50 ml. of water was added. Concentrated hydrochloric acid was added until the pH of the filtrate and washes was 2.0. Triethylamine was added to raise the pH to pH 4.2. The cephalixin which precipitated was filtered, rinsed with acetonitrile, and vacuum dried at about 40°C. There was obtained 10.0 g. of cephalixin.

Alcohols other than methanol such as ethanol, n-propanol, isopropanol, n-butanol, iso-butanol, tert-butanol mixed amyl alcohols, hexanol can also be used, but methanol or ethanol is preferred.

Example 4

Following the procedure of Example 1, 7-ADCA is reacted with two molar equivalents of N - (triphenylsilyl)ethylcarbamate to form a triphenylsilyl 7-(triphenylsilylamino)-3 - methyl - Δ^3 - cephem - 4 - carboxylate intermediate. This intermediate is reacted with an N-methyl acetoacetate-protected α - amino - 2 - (2 - thienyl) acetyl chloride and

the resulting acylated product is treated with methanol and then with aqueous base to form 3 - methyl - 7 - [(α - amino(2 - thienyl)-acetamido] - Δ^3 - cephem - 4 - carboxylate acid as the zwitterion, a known antibiotic.

Example 5

Following the procedure of Example 3, 7—ADCA is treated with N-(triethylsilyl)urea to form a triethylsilylated 7—ADCA ester. This ester is treated with a mixed anhydride resulting from N - (benzyloxycarbonyl)phenylglycine and methyl chloroformate. The resulting acylated product is treated with methanol and then with aqueous acid to pH 2.0 to remove the protecting groups. Addition of base to the isoelectric point (about pH 4.2) causes cephalixin to precipitate from the reaction mixture.

Example 6

Following the procedure of Example 1, 7—ACA is reacted with an excess molar proportion of the lactam resulting from trimethylsilyl chloride and 2-pyrrolidone to form trimethylsilyl 7 - (trimethylsilylamino) - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylate ester. This ester is treated with (2 - thienyl)-acetyl chloride, and then treated with methanol to form cephalothin, which is removed from the reaction mixture by treatment with sodium acetate to form sodium cephalothin.

Example 7

To a slurry of 3.6 g. (16.9 mmoles) of 7—ADCA in 30 ml. of dry acetonitrile was added 8.8 ml. (33.5 mmoles) of N,O-bis(trimethylsilyl)acetamide (BSA). Upon mixing a slight exotherm was observed and after stirring at room temperature for a period of $\frac{1}{2}$ hour, all of the 7—ADCA had dissolved. Analysis of the resulting solution by nuclear magnetic resonance (NMR) spectroscopy indicated that the product was trimethylsilyl 7 - (trimethylsilylamino) - 3 - methyl - Δ^3 - cephem - 4 - carboxylate in acetonitrile solution. When less BSA was employed under the same conditions, NMR analysis indicated that the reaction product was a mixture of the above bis-silylated cephalosporin together with trimethylsilyl 7-amino - 3 - methyl - Δ^3 - cephem - 4 - carboxylate.

Similar results are obtained using N-trimethylsilylacetamide as silylating agent.

Example 8

5.0 G. of 7—ACA, 8.8 ml. (33.5 millimoles) BSA and 50 ml. dry acetonitrile were mixed and stirred at room temperature for a period of two hours during which time the 7—ACA dissolved. NMR analysis of the resulting solution indicated that the product was trimethylsilyl 7 - trimethylsilylamino -

3 - acetoxymethyl - cephem - (ceph - 3 - em) - 4 - carboxylate mixed with excess BSA.

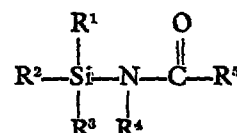
In another experiment run similarly except that 6.0 ml. BSA were employed, NMR analysis indicated that bis-silylation was not complete and the product contained both the above bis-silylated ester and trimethylsilyl - 7 - amino - Δ^3 - cephem - 4 - carboxylate.

WHAT WE CLAIM IS:—

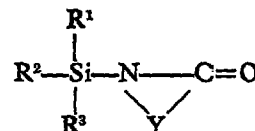
1. A process for preparing a cephalosporin by acylating 7-aminocephalosporanic acid, 7-amino-desacetoxycephalosporanic acid, or a soluble salt form of 7-amino-desacetoxycephalosporanic acid with an acylating derivative of thiophene-2-acetic acid or phenylglycine, which process comprises

(a) reacting 7-aminocephalosporanic acid, 7-aminodesacetoxycephalosporanic acid, or a soluble salt form of 7-aminocephalosporanic acid or 7-amino-desacetoxycephalosporanic acid with a compound having one of the Formulas I, II, III, IV and V as set out and defined below

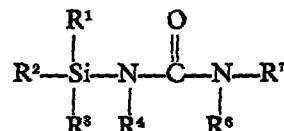
I.



II.

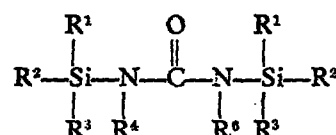


III.



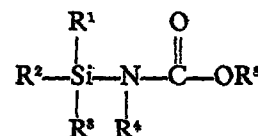
(a)

or



(b)

IV.



the resulting acylated product is treated with methanol and then with aqueous base to form 3 - methyl - 7 - [(α - amino(2 - thienyl)-acetamido] - Δ^3 - cephem - 4 - carboxylate acid as the zwitterion, a known antibiotic.

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Following the procedure of Example 3, 7—ADCA is treated with N-(triethylsilyl)urea to form a triethylsilylated 7—ADCA ester. This ester is treated with a mixed anhydride resulting from N - (benzyloxycarbonyl)phenylglycine and methyl chloroformate. The resulting acylated product is treated with methanol and then with aqueous acid to pH 2.0 to remove the protecting groups. Addition of base to the isoelectric point (about pH 4.2) causes cephalixin to precipitate from the reaction mixture.

Example 6

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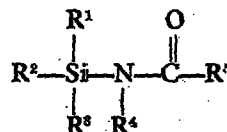
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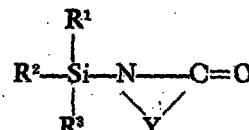
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(a) reacting 7-aminocephalosporanic acid, 7-aminodesacetoxyccephalosporanic acid, or a soluble salt form of 7-aminocephalosporanic acid or 7-amino-desacetoxyccephalosporanic acid with a compound having one of the Formulas I, II, III, IV and V as set out and defined below

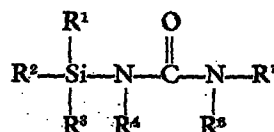
I.



II.

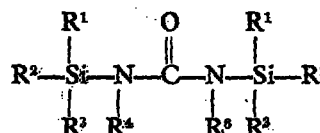


III.



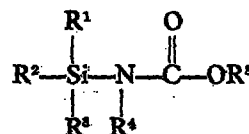
(a)

or

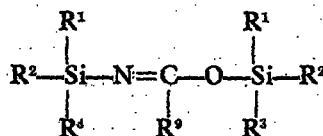


(b)

IV.



V.



wherein each of R¹, R², and R³ is hydrogen or a hydrocarbon radical free of aliphatic unsaturation and having from 1 to 8 carbon atoms, with not more than two of any R¹, R², and R³ bonded to the same silicon atom being hydrogen;

R⁵ is hydrogen or a hydrocarbon radical which is free of aliphatic unsaturation and contains from 1 to 8 carbon atoms;

Y is an alkylene group having from 3 to 18 carbon atoms with a chain of at least 3 but no more than 5 carbon atoms extending between the nitrogen and the carbonyl group to which Y is bonded;

each of R⁴, R⁶ and R⁷, taken separately, is hydrogen or a hydrocarbon group free of aliphatic unsaturation containing from 1 to 8 carbon atoms, or R⁶ and R⁷ taken together with the nitrogen to which they are bonded, complete a heterocyclic ring containing either from 5 to 6 ring forming atoms, one of which can be oxygen para to the nitrogen, or from 4 to 6 ring forming carbon atoms with the proviso that R⁶ and R⁷ together contain not more than 18 carbon atoms, and that if R⁶ is an alkyl with a tertiary carbon bonded to the nitrogen then R⁷ is hydrogen, or R⁴ and R⁶ taken together with a nitrogen to which they are bonded and the carbonyl group complete a heterocyclic ring containing from 5 to 6 ring forming atoms and from 2 to 3 methylene ring forming carbon atoms;

R⁸ is a hydrocarbon group free of aliphatic unsaturation and containing from 1 to 8 carbon atoms; and

R⁹ is either hydrogen or a hydrocarbon group free of aliphatic unsaturation and containing from 1 to 8 carbon atoms in a substantially anhydrous, aprotic liquid solvent, at a temperature of from about -25° to about 50°C.

(b) reacting the product from step (a) with an acylating derivative of thiophene-2-acetic acid or a mixed anhydride of an N-protected phenylglycine,

(c) treating the acylated product from step (b) with a C₁ to C₆ alkanol to form the cephalosporin, and

(d) recovering the cephalosporin from the reaction mixture of step (c).

2. The process of claim 1 wherein the step (a) 7-amino-desacetoxycephalosporanic acid is reacted with a compound of formula I wherein each of R¹, R², and R³ is a hydrocarbon radical which is free of aliphatic unsaturation and has from 1 to 8 carbon atoms; R⁴ is hydrogen, and R⁵ is a hydrocarbon radical which is free of aliphatic unsaturation and has from 1 to 8 carbon atoms,

in step (b) the step (a) reaction product is acylated with an activated N-protected phenylglycine, and

in step (c) the acylated product from step (b) is treated with methanol to form cephalixin.

3. The process of claim 2 wherein in the step (a) 7-aminocephalosporanic acid is used in place of 7-aminodesacetoxycephalosporanic acid so that at the completion of steps (a), (b), and (c) cephaloglycin is formed.

4. The process as claim 1, wherein the reaction product of step (a) is treated in step (b) with 2-(2'-thienyl)acetyl chloride, and the acylated product from step (b) is treated in step (c) with methanol to form cephalothin.

5. A cephalosporin when prepared by the process of claim 1.

6. Cephalixin when prepared by the process of claim 1 or 2.

7. Cephaloglycin when prepared by the process of claim 1 or 3.

8. Cephalothin when prepared by the process of claim 1 or 4.

9. A process for preparing a cephalosporin by acylating 7-aminocephalosporanic acid, 7-amino-desacetoxycephalosporanic acid, or a soluble salt form of 7-aminocephalosporanic acid or 7-amino-desacetoxycephalosporanic acid with an acylating derivative of thiophene-2-acetic acid or phenylglycine substantially as hereinbefore described with particular reference to the examples.

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