

PATENT SPECIFICATION

(11) 1302015

NO DRAWINGS

- (21) Application No. 52755/70 (22) Filed 5 Nov. 1970
 (31) Convention Application No. 876597 (32) Filed 13 Nov. 1969 in
 (33) United States of America (US)
 (44) Complete Specification published 4 Jan. 1973
 (51) International Classification C07D 99/24
 (52) Index at acceptance

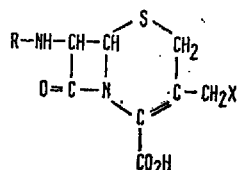
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(54) METHOD OF CLEAVING THE 7-CARBOXAMIDO GROUP OF A CEPHALOSPORIN COMPOUND

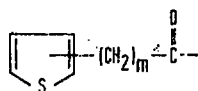
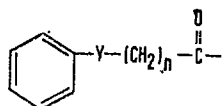
(71) We, ELI LILLY & COMPANY, a Corporation of the State of Indiana, United States of America, of 307 East McCarty Street, City of Indianapolis, State of Indiana, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides, in a method for the cleavage of the 7-carboxamido group of a cephalosporin having the formula

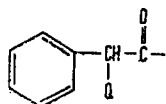


wherein

R is aminoadipoyl,
 C_2-C_8 alkanoyl,



or



X is C_2-C_6 alkanoyloxy,
 C_2-C_6 thioalkanoyloxy,
 C_6-C_{12} thioaroyloxy,
 hydroxy,
 mercapto,
 hydrogen,
 C_1-C_6 alkoxy, or
 C_1-C_6 alkylthio;

Y is oxygen, sulfur, or a carbon to carbon bond;

[Price 25p]

n is an integer of 0 to 3 and is at least 1 when y is oxygen or sulfur;

m is an integer of 1 to 3; and

Q is amino or hydroxy;

- 5 by the steps of blocking the carboxyl, amino, hydroxy and mercapto groups in the molecule, treating the blocked cephalosporin with a halogenating agent to convert the 7-carboxamido group to an imino halide, treating the imino halide with a lower alkanol or benzyl alcohol to form an imino ether, and hydrolyzing the imino ether to form a 7-amino group, the improvement which comprises blocking the carboxyl groups by converting them to a mixed anhydride derived from an acid having the formula

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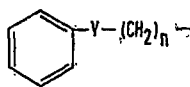


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wherein

R' is C₁—C₈ alkyl, alkenyl, or alkynyl;

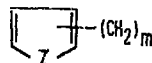
halo C₁—C₈ alkyl, alkenyl, or alkynyl;



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or

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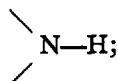


Y is oxygen, sulfur or a carbon to carbon bond;

n is an integer of 0 to 3 and is at least 1 when Y is oxygen or sulfur;

Z is oxygen, sulfur, or

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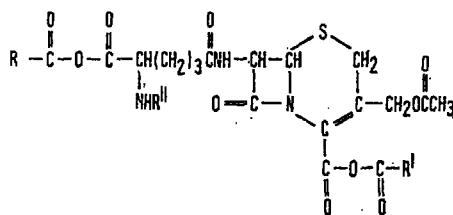
20

and

m is an integer of 1 to 3.

Also, the present invention relates to the intermediate which is a blocked cephalosporin C having the formula

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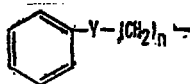


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wherein

R' is C₁—C₈ alkyl, alkenyl, or alkynyl;

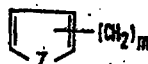
halo C₁—C₈ alkyl, alkenyl, alkynyl;



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or

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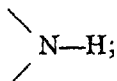


Y is oxygen, sulfur, or a carbon to carbon bond;

n is an integer of 0 to 3 and is at least 1 when

Y is oxygen or sulfur;

Z is oxygen, sulfur, or



m is an integer of 1 to 3; and

R'' is an amino protecting group.

5 The cephalosporins are a well-known family of antibiotics widely used in the treatment of disease. In the chemical modification of members of this family it is often desirable to cleave the 7-carboxamido group to obtain a free amino group in the 7-position. This reaction is of particular importance in the removal of the aminoadipoyl side chain of cephalosporin C to yield 7-aminocephalosporanic acid (7-ACA).

10 One method of cleaving an amido group to obtain the free amine is that described by Lander, *J. Chem. Soc.* 83, 320 (1903). In accordance with Lander's method the amide is treated with a halogenating agent to convert the amido group to an imino halide followed by treating the imino halide with an alcohol to obtain the imino ether which is then hydrolyzed to the free amine. The application of this method to the cleavage of cephalosporin C of 7-ACA is disclosed in Canadian Patent No. 770,125 and British Patents Nos. 1,041,985 and 1,241,655.

15 In order to successfully apply this sequence of reactions to cephalosporins it is necessary first to protect the carboxyl groups in the molecule. It is particularly important to protect the carboxyl group in the 4-position of the cephalosporin nucleus. Heretofore, these carboxyl groups generally have been protected by converting them to esters. With the exception of silyl esters, these esters are generally stable to the reaction conditions and the ester product must be subjected to further treatment in order to obtain the free acid. Such treatment involves a more rigorous acid or base hydrolysis or, in some instances, hydrogenolysis. These added steps result in added processing costs, and in the case of a more rigorous acid hydrolysis there is some hydrolysis of the acetoxy group at the C₃ methyl to desacetyl cephalosporins and in the case of base hydrolysis there is the danger of isomerization of the double bond in the ring.

20 Further, numerous procedures for the preparation of carbon esters leads to isomerization of the double bond in the nucleus so that a Δ^2 product (isocephalosporin) is obtained. Silyl esters are more sensitive to traces of moisture and therefore less stable than carbon esters during the reaction. In fact, in some instances they are too easily removed. Further, the reagents used in the preparation of silyl esters are expensive and not always readily available in commercial quantities.

25 This invention is an improvement in the prior art process for the cleavage of 7-carboxamido groups from cephalosporins. In a method for the cleavage of a 7-carboxamido group of a 7-carboxamidoccephalosporin by blocking the carboxyl and other sensitive groups, treating the blocked cephalosporin with a halogenating agent to convert the amido group to an imino halide, treating the imino halide with an alcohol to obtain an imino ether, and hydrolyzing the imino ether to give a free 7-amino group, this invention is the improvement which comprises blocking the carboxyl groups by converting them to mixed anhydrides. Thus, in this improved process all the steps are the same as in the prior art except for the step of blocking the carboxyl groups.

30 The process can be used with virtually any cephalosporin substituted in the 7-position with a carboxamido group. When R in the above formula is a 5-amino-adipoyl group and X is acetoxy, the cephalosporin is cephalosporin C. R may be such other groups as acetyl, butyryl, heptanoyl, phenylacetyl, phenoxyacetyl, phenylthioacetyl, thienylacetyl, phenylglycyl, or mandelyl.

35 In addition to being acetoxy, X in the above formula can be such as hydrogen, hydroxy, propionyloxy, methoxy, ethoxy, hexoxy, methylthio, propylthio, thioacetyl, thio-butyl, thiobenzoyl or *p*-methylthiobenzoyl.

40 It is to be understood that when the cephalosporin contains an amino, hydroxy or mercapto group such group is blocked prior to the cleavage reaction. Amino, hydroxy, and mercapto blocking groups are well known to those skilled in the art. If the group is in the 7-side chain so that it will be lost in the cleavage reaction, it doesn't matter whether the blocking group is one which can be easily removed or not. The amino protecting group can be such as alkanoyl, aroyl, alkylloxycarbonyl, or arylloxycarbonyl and such groups substituted by halo, nitro, or alkoxy groups. Specific examples of amino protecting groups include acetyl, formyl, chloroacetyl, benzoyl, *p*-nitrobenzoyl, phthaloyl, *p*-tosyl, 2,4-dinitrophenyl, *t*-butyloxycarbonyl and benzyloxycarbonyl. Hydroxyl groups are commonly protected by the formation of esters, and particularly by the formation of formyl esters. Mercapto groups are protected by conversion to

sulfides such as the benzyl, benzhydryl, trityl or t-butyl sulfides, by formation of disulfides, by formation of thioesters, or as the thiocarbamyl or S-acetamido-methyl group. Those skilled in the art will recognize that this list of blocking groups is merely illustrative and that there are many other amino, hydroxy and mercapto protecting groups that can be used.

In accordance with this invention, the carboxyl groups in the cephalosporin molecule are protected by conversion to mixed anhydrides. Specific examples of suitable mixed anhydrides include those derived from acetic acid, chloroacetic acid, propionic acid, valeric acid, crotonic acid, propiolic acid, 3-chloro-2-pentenoic acid, 4-bromo-2-butynoic acid, phenylacetic acid, phenoxyacetic acid, benzoic acid, furylacetic acid, and thienylacetic acid. The acetic and propionic mixed anhydrides are preferred because of their simplicity and ease of preparation. Those skilled in the art will recognize that there are other mixed anhydrides which will perform the same blocking function as those named and which are equivalent in the process.

Methods of preparing mixed anhydrides are well known to those skilled in the art and any method may be chosen. The particular manner in which the anhydride is formed is not important to this process. Particularly good results have been achieved by treating the cephalosporin with an acid halide, particularly acid chlorides, in the presence of a hydrogen halide acceptor such as a tertiary amine. The acetic mixed anhydride has also been prepared by treatment of a cephalosporin with ketene. The preparation of the mixed anhydride will be illustrated in the examples.

This blocked cephalosporin is now treated with a halogenating agent as described in the prior art to convert the 7-amido group to an imino halide. Suitable halogenating agents for use in this step are described in the prior art and include such compounds as phosphorus pentachloride, phosphorus oxychloride, phosphorus trichloride and thionyl chloride. Phosphorus pentachloride is preferred. The reaction is preferably carried out in the presence of a tertiary amine such as quinoline, pyridine, dimethylaniline, or diethylaniline.

In general, low temperatures are preferred for the halogenation reaction. Both times and temperature are dependent upon halogenating agent employed. Ordinarily, temperatures below about 30°C. are used. For example, phosphorus pentachloride reacts very rapidly so that a temperature below about 0°C. is preferred. Phosphorus oxychloride reacts more slowly so that a somewhat higher temperature may be used.

The imino chloride is then converted to an imino ether by reaction with an alcohol or phenol. This reaction too, is preferably conducted at temperatures below about 30°C. in the presence of a tertiary amine to bind the hydrogen halide that is released. Temperatures below about 0°C. are best. The preferred alcohols are the alkanols containing from one to six carbon atoms or benzyl alcohol. Methanol, ethanol, and n-propanol are especially preferred. Phenols may also be used, but are not as satisfactory as the lower alkanols. Sulfhydryl compounds have also been successfully used.

The imino bond of the imino ether is readily split by mild acidic or basic hydrolysis or alcoholysis. If the addition of acid binder is properly controlled in the preceding steps, the reaction mixture will be sufficiently acidic at this point that hydrolysis will occur merely upon the addition of water. The hydrolysis can also be conducted under mildly alkaline conditions as in the presence of an alkali metal salt of a weak acid. The process of hydrolysis or alcoholysis of imino ethers is well known to those skilled in organic chemistry.

The advantage of this improvement of carboxyl protection through mixed anhydride formation is that double bond isomerization is not a problem as with many esters and the carboxyl blocking group will be removed during the imino ether hydrolysis step. Thus the product from the hydrolysis in the improved process is a free 7-amino cephalosporin acid. No additional carboxyl deblocking step is necessary.

The following examples will illustrate the improvement in the cleavage process.

Example 1

To a suspension of 3.6 g. (4.9 mmole, 87.5 percent pure) of the monoquinoline salt of N-chloroacetylcephalosporin C monohydrate in 38 ml. of freshly distilled chloroform were added 2.08 g. (17.1 mmole) of N,N-dimethylaniline, 1.72 g. (22 mmole) of acetyl chloride and 4 drops of dimethylformamide. The mixture was stirred at room temperature for 45 minutes. The starting material was in solution within twenty minutes, and the solution was a deep yellow color. The mixture was cooled in a carbon tetrachloride-dry ice bath for approximately ten minutes and an additional 2.08 g. (17.1 mmole) of N,N-dimethylaniline and 2.4 g. (11.6 mmole) of phosphorus pentachloride were added. The mixture was stirred in the cold for two hours, after which time about 12 ml. of n-propanol was added. The mixture was stirred in the cold another two hours. Water

(20 ml.) was added and the mixture was allowed to warm to room temperature over a period of about 30 minutes. The chloroform and aqueous phases were separated and the chloroform was washed twice with 5 ml. portions of water. The aqueous phase and the washes were combined and washed first with chloroform, then with ethyl acetate. The pH of the aqueous phase was adjusted to 3.6 with concentrated ammonium hydroxide and the mixture was refrigerated overnight. The 7-ACA that had crystallized was collected by filtration and dried for 24 hours *in vacuo*. The yield of 7-ACA was 1.075 g. The filtrate contained additional 7-ACA as observed on thin layer chromatography.

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Example 2

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Example 1 was repeated except that 2.2 g. of quinoline rather than dimethylaniline was added with the phosphorus pentachloride and 25 percent sodium hydroxide solution rather than ammonium hydroxide was used to adjust the pH of the aqueous phase at the completion of the reaction. The yield of 7-ACA was 1.14 g.

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Example 3

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To a suspension of 3.3 g. (4.9 mmole, 94.7 percent pure) of the monoquinoline salt of N-chloroacetyl-cephalosporin C monohydrate in 38 ml. of redistilled chloroform were added 2.55 g. (17.1 mmole) of N,N-diethylaniline, 1.72 g. (22 mmole) of acetyl chloride and 4 drops of dimethylformamide. The mixture was stirred at room temperature for 45 minutes and then cooled in an ice-salt bath at -5° to -10°C . To the cold mixture were added 2.55 g. (17.1 mmole) of diethylaniline and 2.4 g. (11.6 mmole) of phosphorus pentachloride. The mixture was stirred in the cold for 30 minutes, 12 ml. of cold methanol was added and stirring was continued an additional thirty minutes. Cold water (20 ml.) was added, the cooling bath was removed, and vigorous agitation was maintained for ten minutes. The aqueous layer was separated, washed with chloroform and the pH was adjusted to 3.6 in the cold by the addition of saturated ammonium bicarbonate solution. The precipitated 7-ACA was filtered after 30 minutes, washed with cold acetone and then dried in a vacuum dessicator at 50°C . The yield of 7-ACA was 1.12 g.

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Example 4

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The procedure of Example 1 was repeated using 2.04 g. of propionyl chloride in place of the acetyl chloride. The yield of 7-ACA was 1.07 g.

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Example 5

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The procedure of Example 1 was repeated using 2.48 g. of chloroacetyl chloride in place of the acetyl chloride. The yield of 7-ACA was 700 mg.

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Example 6

Example 1 was repeated using methylene chloride as solvent instead of chloroform. The yield of 7-ACA was 1.01 g.

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Example 7

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Example 6 was repeated substituting N,N-dimethylbenzylamine for the dimethylformamide. The yield of 7-ACA was 1.02 g.

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Example 8

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Example 2 was repeated using 2.2 g. of freshly distilled quinoline instead of the N,N-dimethylaniline in the preparation of the acetic mixed anhydride. The yield of 7-ACA was 790 mg.

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Example 9

Example 1 was repeated except that the N,N-dimethylaniline was replaced by dry pyridine in each of the steps. The yield of 7-ACA was 300 mg.

Example 10

Example 1 was repeated using 3.4 g. of phenylacetyl chloride in the place of the acetyl chloride. The yield of 7-ACA was 584 mg.

Example 11

Example 1 was repeated substituting 3.0 g. of phenoxyacetyl chloride for the acetyl chloride. The yield of 7-ACA was 310 mg.

Example 12

Example 1 was repeated using 2.8 g. of thiophene-2-acetyl chloride for the acetyl chloride. The yield of 7-ACA was 210 mg.

Example 13

5 Example 1 was repeated starting with 2.4 g. of N-*p*-toluenesulfonylcephalosporin C instead of N-chloroacetylcephalosporin C monoquinoline salt monohydrate. The yield of 7-ACA was 200 mg. 5

Example 14

10 To a suspension of 3.3 g. (4.9 mmole, 94.7 percent pure) of the monoquinoline salt of N-chloroacetylcephalosporin C monohydrate in 80 ml. of freshly distilled chloroform was added 8 drops of dimethylacetamide. Ketene was passed through the stirred mixture at room temperature for 35 minutes at which time the starting material was completely dissolved. A stream of nitrogen was then passed through the reaction mixture to drive out the excess ketene. The mixture was cooled to -20°C . and 2.07 g. (17.1 mmole) of N,N-dimethylaniline and 2.4 g. (11.5 mmole) of phosphorus pentachloride were added. The mixture was stirred at -20°C . for two hours, then treated with 12 ml. of *n*-propanol and stirred an additional two hours at -20°C . Water (20 ml.) was added, the cooling bath was removed and the mixture was stirred for 15 minutes. The aqueous layer was separated, washed with chloroform and the pH adjusted to 3.6 in the cold. The precipitated 7-ACA was recovered by filtration and dried *in vacuo* at 50°C . The yield of 7-ACA was 1.01 g. 10 15 20

Example 15

25 Example 1 was repeated substituting heptanoyl chloride for the acetyl chloride. The presence of 7-ACA in the aqueous extract was detected by thin layer chromatography. 25

Example 16

Example 1 was repeated substituting pivaloyl chloride for the acetyl chloride. The presence of 7-ACA in the aqueous extract was detected by thin layer chromatography and bioautography.

Example 17

30 To a suspension of 2.4 g. (5 mmole) of the monoacetic acid salt of cephalosporin C in 38 ml. of methylene chloride were added 3.26 g. (27 mmole) of N,N-dimethylaniline, 1.73 g. (22 mmole) of acetyl chloride and six drops of dimethylformamide. The mixture was stirred at room temperature until complete solution occurred (about two hours). The solution was then cooled to -20°C . and treated with 2.07 g. (17.1 mmole) of N,N-dimethylaniline and 2.4 g. (11.5 mmole) of phosphorus pentachloride. The mixture was stirred at -20°C . for two hours and 12 ml. of *n*-propanol was added. Stirring and cooling were continued for another two hours. Water (10 ml.) was added and the mixture was stirred for about 10 minutes. The aqueous layer was separated, washed with chloroform and the pH adjusted to 3.6 with concentrated ammonium hydroxide in the cold. The yield of 7-ACA was 600 mg. 30 35 40

Example 18

45 A suspension of 2.4 g. (5 mmole) of the monoacetic acid salt of cephalosporin C in 40 ml. of redistilled chloroform was treated with a stream of ketene for one hour at room temperature. The excess ketene was removed using a stream of dry nitrogen. The reaction mixture was then cooled to about -20°C . for the addition of 2.07 g. (17.1 mmole) of N,N-dimethylaniline and 2.4 g. (11.5 mole) of phosphorus pentachloride. The mixture was stirred in the cold for two hours, 12 ml. of *n*-propanol was added, and stirring was continued for two hours more. Hydrolysis was effected by the addition of 50 ml. of water and allowing the mixture to warm to room temperature. The aqueous phase was separated, washed with chloroform, and the pH adjusted to 3.6. The crystalline product, 7-ACA, weighed 758 mg. after drying for three hours at 50°C . *in vacuo*. 45 50

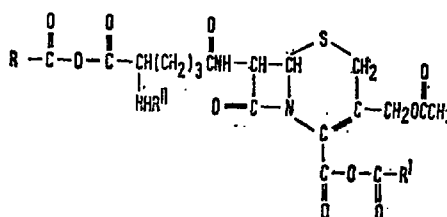
55 Examples 17 and 18 demonstrate the simultaneous blocking of the carboxyl groups and the free amino group. In both examples the carboxyl groups were converted to the mixed acetic anhydrides and the amino group was acetylated at the same time. 55

Example 19

To a suspension of 1.75 g. (5 mmoles) of 7-phenoxyacetamidodesacetoxycephalosporanic acid in 40 ml. of dry benzene were added 10 mmoles of N,N-dimethyl-

aniline, 10 mmoles of acetyl chloride and 10 drops of dimethylformamide. The mixture was stirred until complete solution occurred (approximately 75 minutes). The mixture was placed in a water bath at 45°C. and 7.5 mmoles each of N,N-dimethylaniline and phosphorus pentachloride were added. Stirring was continued at 45°C. for one and one-half hours. The reaction mixture was cooled to room temperature for the addition of 20 ml. of *n*-propanol, and stirring was continued at room temperature for one hour. The solvent was removed *in vacuo* and 40 ml. of chloroform and 20 ml. of water were added. The hydrolysis was completed within 20 minutes. The aqueous phase was separated, washed with chloroform and the pH adjusted to 3.5 in the cold to crystallize 100 mg. of 7-aminodesacetoxycephalosporanic acid. The thin layer chromatogram and ultraviolet and nuclear magnetic resonance spectra of the sample corresponded exactly with those of an authentic sample.

The mixed anhydride blocked cephalosporins obtained as intermediates in this process are compounds not reported heretofore. For example, the mixed anhydride blocked cephalosporin C is one having the formula

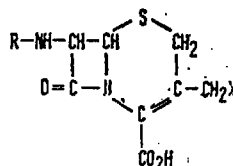


wherein R' has the value assigned above and R'' is an amino protecting group.

Since the preferred mixed anhydrides are the acetic and propionic mixed anhydrides the preferred values of R' are methyl and ethyl. The particular amino protecting group used is not important and is not the novel feature of these compounds. Amino protecting groups are well known to those skilled in the art and are described hereinabove. A preferred amino protecting group is the chloroacetyl group.

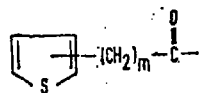
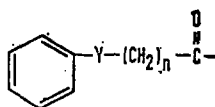
WHAT WE CLAIM IS:—

1. In a method for the cleavage of the 7-carboxamido group of a cephalosporin having the formula

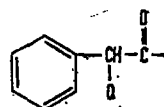


wherein

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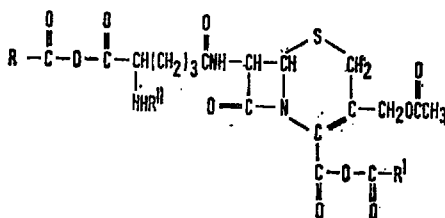
or



X is C₂—C₆ alkanoyloxy,

aniline, 10 mmoles of acetyl chloride and 10 drops of dimethylformamide. The mixture was stirred until complete solution occurred (approximately 75 minutes). The mixture was placed in a water bath at 45°C. and 7.5 mmoles each of N,N-dimethylaniline and phosphorus pentachloride were added. Stirring was continued at 45°C. for one and one-half hours. The reaction mixture was cooled to room temperature for the addition of 20 ml. of *n*-propanol, and stirring was continued at room temperature for one hour. The solvent was removed *in vacuo* and 40 ml. of chloroform and 20 ml. of water were added. The hydrolysis was completed within 20 minutes. The aqueous phase was separated, washed with chloroform and the pH adjusted to 3.5 in the cold to crystallize 100 mg. of 7-aminodesacetoxycephalosporanic acid. The thin layer chromatogram and ultraviolet and nuclear magnetic resonance spectra of the sample corresponded exactly with those of an authentic sample.

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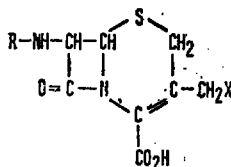


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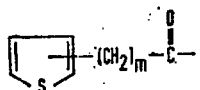
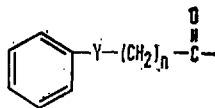
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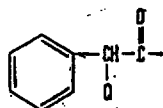


wherein

R is aminoadipoyl,
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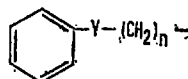
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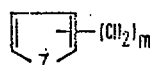
- C_2-C_6 thioalkanoyloxy,
 C_6-C_{12} thioaroyloxy,
 hydroxy,
 mercapto,
 hydrogen,
 C_1-C_6 alkoxy, or
 C_1-C_6 alkylthio;
 Y is oxygen, sulfur, or a carbon to carbon bond;
 n is an integer of 0 to 3 and is at least 1 when y is oxygen or sulfur;
 m is an integer of 1 to 3; and
 Q is amino or hydroxy;
 by the steps of blocking the carboxyl, amino, hydroxy and mercapto groups in the molecule, treating the blocked cephalosporin with a halogenating agent to convert the 7-carboxamido group to an imino halide, treating the imino halide with a C_1-C_6 alkanol or benzyl alcohol to form an imino ether, and hydrolyzing the imino ether to form a 7-amino group, the improvement which comprises blocking the carboxyl groups by converting them to a mixed anhydride derived from an acid having the formula



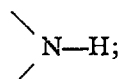
- wherein
 R' is C_1-C_{18} alkyl, alkenyl, or alkynyl;
 halo C_1-C_8 alkyl, alkenyl, or alkynyl;



or



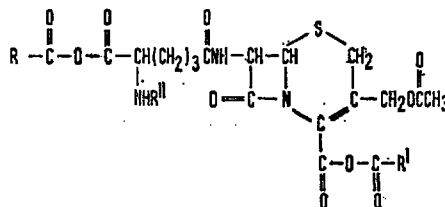
- Y is oxygen, sulfur or a carbon to carbon bond;
 n is an integer of 0 to 3 and is at least 1 when Y is oxygen or sulfur;
 Z is oxygen, sulfur, or



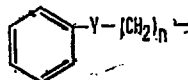
- and
 m is an integer of 1 to 3.
 2. The method of claim 1 characterized in that the halogenating agent is phosphorus pentachloride and the lower alkanol is methanol or n-propanol.

3. The method of claim 1 or 2 characterized in that R' is methyl or ethyl.
 4. The method of claim 1, 2 or 3 characterized in that the cephalosporin is cephalosporin C.

5. A blocked cephalosporin C having the formula

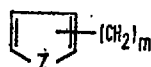


- wherein
 R' is C_1-C_8 alkyl, alkenyl, or alkynyl;
 halo C_1-C_8 alkyl, alkenyl, alkynyl;



or

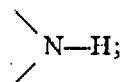




Y is oxygen, sulfur, or a carbon to carbon bond;
n is an integer of 0 to 3 and is at least 1 when

Y is oxygen or sulfur;

Z is oxygen, sulfur, or



m is an integer of 1 to 3; and

R'' is an amino protecting group.

6. The blocked cephalosporin C of claim 5 characterized in that R' is methyl or ethyl.

7. The blocked cephalosporin C of Claim 5 or 6 characterized in that R'' is chloroacetyl.

8. The process of claim 1 substantially as described in any one of Examples 1 to 19.

9. The 7-aminocephalosporanic acid when produced by the method of any one of claims 1 to 4 and 8.

10. A method as claimed in any one of claims 1 to 4 wherein the carboxyl groups are blocked by converting them to mixed acetic or propionicanhydrides.

11. A method as claimed in any one of claims 1 to 4 or 10 wherein the carboxyl groups are blocked by treating the cephalosporin with an acid halide in the presence of a hydrogen halide acceptor.

12. A method as claimed in claim 11 wherein the acid halide is an acid chloride.

13. A method as claimed in any one of claims 1 to 4 or 10 to 12 wherein the blocked cephalosporin is treated with a halogenating agent in the presence of a tertiary amine.

14. A method as claimed in any one of claims 1 to 4 or 10 to 13 wherein the treatment of the cephalosporin with a halogenating agent is conducted at a temperature below 30°C.

15. A method as claimed in any one of claims 1 to 4 or 10 to 14 wherein the halogenating agent is phosphorus pentachloride and the treatment of the cephalosporin with phosphorus pentachloride is conducted at a temperature below 0°C.

16. A method as claimed in any one of claims 1 to 4 or 10 to 15 wherein the imino halide is treated with a C₁—C₆ alkanol or benzyl alcohol at a temperature below 30°C.

17. A method as claimed in any one of claims 1 to 4 or 10 to 16 wherein the imino halide is treated with a lower alkanol or benzyl alcohol at a temperature below 0°C.

18. A method as claimed in any one of claims 1 to 4 or 10 to 17 wherein the imino halide is treated with a lower alkanol or benzyl alcohol in the presence of a tertiary amine.

19. A method as claimed in any one of claims 1 to 4 and 10 to 18 wherein the lower alkanol contains up to six carbon atoms.

20. A method as claimed in any one of claims 1, 3, 4 and 10 to 18 wherein the lower alkanol is methanol, ethanol or n-propanol.

21. A method as claimed in any one of claims 1, 3, 4 and 10 to 18 except in that a phenol or a sulfhydryl compound is used in place of a C₁—C₆ alkanol or benzyl alcohol.

22. A 7-aminocephalosporanic acid whenever prepared by the method of any one of claims 10 to 21.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1973.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

