

PATENT SPECIFICATION

(11) 1 400 697

1 400 697

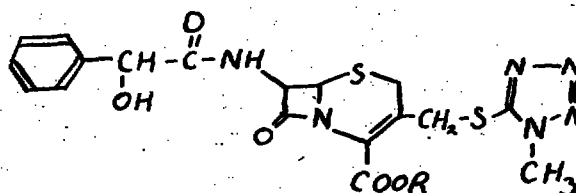
- (21) Application No. 10826/73 (22) Filed 6 March 1973
 (31) Convention Application No. 236 764 (32) Filed 21 March 1972 in (19)
 (33) United States of America (US)
 (44) Complete Specification published 23 July 1975
 (51) INT CL² C07D 501/36//C07D 501/36, 205/08, 257/04, 277/12)
 (52) Index at acceptance
 C2Q 1314 1464 1492 214 215 220 226 22Y 247 250 252 253
 256 25Y 28X 292 29Y 305 30Y 321 32Y 33Y 342
 34Y 351 352 359 360 362 366 367 368 36Y 373 37Y
 386 519 614 628 635 638 650 652 670 761 769 KE
 RP TX



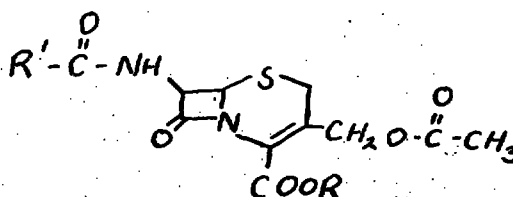
(54) PROCESS FOR PREPARING 7-(α -HYDROXY- α -PHENYL)-ACETAMIDO-3-(1-METHYL-1H-TETRAZOL-5-YLTHIOMETHYL)-3-CEPHEM-4-CARBOXYLIC ACID AND DERIVATIVES THEREOF

(71) We, ELI LILLY AND COMPANY, a Corporation organized and existing under the laws of the State of Indiana, United States of America, of 307 East McCarty Street, 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:—

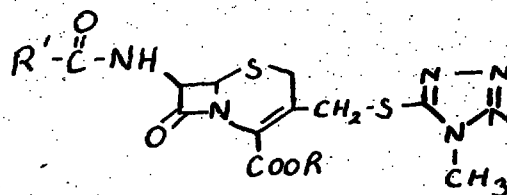
Broadly, this invention relates to a process for preparing a cephalosporin of the formula



wherein R is H or a carboxy-protecting group which comprises (1) reacting a 7 - acyl-amido - 3 - acetoxymethyl compound of the formula



in which R' is hydrogen, C₁ to C₃ alkyl, or 4 - amino - 4 - carboxybutyl, and R is hydrogen or a carboxy protecting group, with 1 - methyl - 1 H - tetrazole - 5 - thiol or a salt thereof with an alkali metal, or alkaline earth metal or ammonium to produce a 7 - acylamido - 3 - (1 - methyl - 1H - tetrazol - 5 - ylthiomethyl) compound having the formula



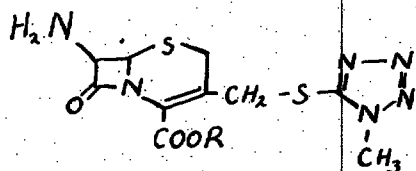
(11)

2

1,400,697

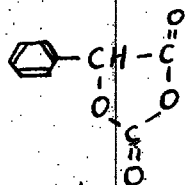
2

(2) cleaving the acylamido group of the 7 - acylamido - 3 - (1 - methyl - 1H-tetrazol - 5 - ylthiomethyl) compound to produce a 7 - amino - 3 - (1 - methyl - 1H-tetrazol - 5 - ylthiomethyl) compound having the formula



5

and (3) N-acylating the resulting 7-amino compound with anhydro-O-carboxymandelic acid having the formula

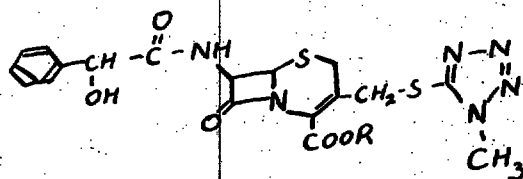
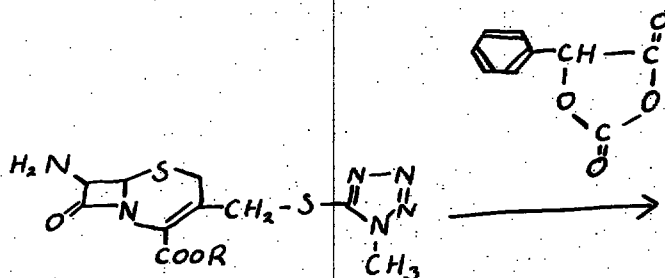
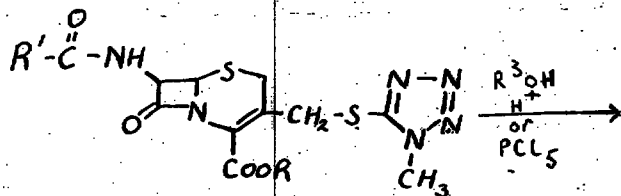
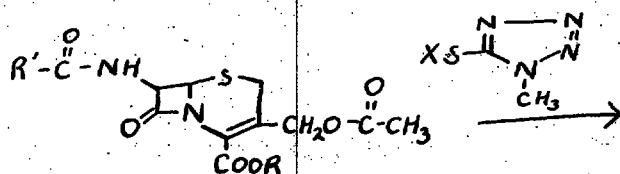


to produce the aforementioned cephalosporin.

The process of this invention can be broadly depicted by the following reaction scheme:

10

10



In the above reaction scheme, R and R¹ are as herein defined. X represents hydrogen, ammonium, or an alkali metal or alkaline earth metal, with appropriate modification as may be dictated by valence considerations. R² represents a C₁—C₄ alkyl group.

One of the starting materials which is employed in the process of this invention is the readily available cephalosporin C. Another is 7 - aminocephalosporanic acid (7-ACA) suitably protected in the 7-position with a formyl or a C₂ to C₄ alkanoyl moiety. Such an N-acylated 7-ACA is readily available by techniques well recognized in the art. One such technique involves the reaction of 7-ACA with an acid which provides the acyl group which is to be substituted in the 7-position. Thus 7-ACA is reacted with a formic acid, acetic acid, propionic acid or butyric acid, to produce the corresponding acylated 7-ACA. Since this reaction is accompanied by the formation of one mole of water per mole of acylated 7-ACA, it is highly preferred to carry out the acylation in the presence of a suitable water acceptor. A highly preferred reagent for this purpose is an acid anhydride, such as for example, acetic anhydride or propionic anhydride. In the instance in which the acyl group is formyl, it is possible to employ as acylating agent a preformed formic-acetic anhydride which can be prepared from the reaction of sodium formate and acetyl chloride.

In accordance with the process of this invention, the N - acyl 7 - aminocephalosporanic acid is reacted with 1 - methyl - 1H - tetrazole - 5 - thiol, or ammonium, alkali metal or alkaline earth metal salt. Typical of the salts of 1 - methyl - 1H - tetrazole - 5 - thiol which can be used therefor are those of sodium, potassium, lithium, ammonium, calcium and magnesium. The displacement of the acetoxy group with the methyltetrazolylthio moiety generally is accomplished in an aqueous medium at a pH which is neutral, slightly acidic or slightly basic and which is within the range of from pH 5.0 to pH 9.5. Preferably, the pH of the initial reaction mixture will be from about 6.5 to about 9.0, and will gradually be lowered during the period of reaction to a pH within the range of from about 5.5 to about 8.5. The N-acyl 7-ACA typically is added to the aqueous medium containing the methyltetrazolylthiol and the desired pH of the mixture is achieved by addition of a suitable buffering agent, such as a phosphate, for example, trisodium phosphate or tripotassium phosphate. Other suitable pH adjusting reagents include moderately weak bases such as ammonium hydroxide, sodium carbonate and sodium bicarbonate. Once the desired pH of the reaction medium has been obtained, the reaction proceeds by heating the mixture to a temperature of from about 50°C. to about 100°C., and preferably to a temperature of about 70°C. The reaction is completed within a period of from about 2 to about 8 hours, and preferably from about 2 to about 4 hours.

During the reaction which displaces the group in the 3-position, the pH of the reaction medium generally drifts moderately downward. The lowering of the pH during the course of the reaction is not harmful to the overall reaction, and therefore, it is not necessary to add reagents which would maintain the reaction mixture at a constant pH.

The next step in the reaction sequence is directed to cleavage of the acyl-amido group at the 7-position to produce the free amino group. If so desired, this can conveniently be accomplished without isolation of the methyltetrazolylthio derivative from the previous step. Preferably, this derivative will not be isolated, and in such an instance, the pH of the reaction mixture is lowered to the range of from about pH 1 to about pH 3 by addition of acid. Preferably, the cleavage of the acyl-amido group is conducted at a pH of about 2.0. Generally, a mineral acid such as hydrochloric acid, sulfuric acid, or phosphoric acid is employed. The acyl-amido group is then cleaved under acid conditions by treatment with alcohol. In general, the alcohol which is employed will be a C₁ to C₄ alkyl alcohol, such as methanol, ethanol or isopropyl alcohol. When the cephalosporin starting material and therefore the ultimate product is the free acid, the 3-substituted 7 - amino - cephalosporin is isolated from the reaction mixture by adjusting the pH of the reaction mixture to the isoelectric point (about 3.9). The resulting product precipitates at this pH and is readily removed from the reaction mixture. In the event that the starting material and therefore the product is an ester of the 3-substituted 7-aminocephalosporin, this product can be isolated from the reaction mixture simply by rendering the reaction medium alkaline by the addition of a suitable base.

Other methods are also available for cleaving the acyl-amido group at the 7-acylated methyltetrazolylthio derivative. For example, the 7-acylated methyltetrazolylthio derivative may be cleaved in the presence of a phosphorus halide, such as phosphorus pentachloride. In the instance of the 3-methyltetrazolylthio derivative of cephalosporin C, the cleavage of the 7-acyl-amido group can be carried out in the presence of a nitrosating agent, for example as described in U.S. Patent Specification No. 3 188 311 such as nitrosyl chloride.

(B)

4

1,400,697

4

The final step of the process of this invention involves the acylation of the 7-amino group of the cephalosporin to produce an α - hydroxy - α - phenylacetamido group in the 7-position. It has been found to be highly advantageous to use anhydro - O - carboxymandelic acid for this purpose. United States Patent No. 3,167,549 mentions the possible use of anhydro - O - carboxymandelic acid for acylating the 7-amino group of a cephalosporin but fails to indicate its exceptional suitability for the N-acylation of 3 - substituted - thio - methyl 7 - aminocephalosporins. It has been discovered in accordance with the process of this invention that increased product yield as well as improved product purity are available by acylating 7 - amino 3 - (1 - methyl - 1H-tetrazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid or its 4 - carboxyl-protected derivative thereof using anhydro-O-carboxymandelic acid as opposed to other recognized acylating agents, such as acid chlorides, mixed anhydrides, and the like. Anhydro - O - carboxymandelic acid is readily available from the reaction of mandelic acid with phosgene.

Should the free acid form of the 3 - substituted 7 - aminocephalosporin be employed as starting material in the acylation step of the process of this invention, the reaction generally is carried out in an aqueous medium and at a neutral or slightly acidic pH. The pH will generally be within the range of from about 5.0 to about 7.0, and preferably within the range from about 6.5 to about 7.0. The pH of the reaction mixture is obtained and maintained using any suitable reagent, such as, for example, a salt of a strong base and a weak acid such as sodium bicarbonate. The pH can also be obtained and maintained by employing a suitable buffering agent, such as any of those mentioned hereinabove or other equivalent known buffering agents. The nature of the buffering agent employed is not a critical feature of this invention. The reaction of the 7-amino cephalosporin with the anhydro - O - carboxymandelic acid is equimolar; however, a slight molar excess of from about 10% to about 50% of the anhydro - O - carboxymandelic acid usually is employed to assure minimal loss and maximum reaction of the more expensive cephalosporin compound. The reaction time, in general, is quite rapid, and the reaction will be completed within about 0.5 to about 2 hours. The time of reaction necessarily is dependent upon the temperature at which the reaction is carried out, the lower the temperature the longer the reaction time. The acylation generally will be conducted at a temperature of from about 20°C. to about 50°C., with ambient room temperature being especially preferred. The resulting product is obtained as its free acid or in the form of a suitable alkali metal or alkaline earth metal salt depending upon the conditions employed to isolate the product. Under moderately strong acid conditions, the free acid will be recovered whereas a salt will be obtained upon addition of an appropriate salt of the desired cation such as, for example, an acetate salt of sodium or potassium.

When the 7 - aminocephalosporin is employed in the form of its ester, it will be isolated as such. In order to obtain an active antibiotic, it will be necessary to cleave the ester group to produce the free acid or acceptable pharmaceutical salt thereof.

As mentioned hereinabove, the initial starting material which is employed in the process of this invention can be a 7-acylamido cephalosporanic acid itself or carboxyl-protected derivative thereof. Protection of the carboxyl function is not essential in carrying out the process of this invention and, preferably, will be avoided. However, the cephalosporin art recognizes many carboxy-protecting groups any of which can be employed in the process of this invention. Preferably, if the cephalosporin starting material, which is employed contains a carboxy protecting group, this will be selected from C₁-C₆ alkyl, 2,2,2 - trihaloethyl, C₆-C₇ *tert*-alkenyl, C₆-C₇ *tert*-alkynyl, benzyl, nitrobenzyl, tetrahydropyranyl, succinimidomethyl, phthalimidomethyl, methoxybenzyl, dimethoxybenzyl, cyanomethyl, nitrophenyl, dinitrophenyl, 2,4,6-trinitrophenyl, bis(*p* - methoxyphenyl)methyl, triphenylmethyl, benzhydryl, benzyloxymethyl, C₂-C₆ alkanoyloxymethyl, C₂-C₆ alkanoyl and phenacyl groups.

The following examples are provided for the purpose of illustrating the process of this invention.

EXAMPLE I:

7-formamido-cephasporanic acid.

In a 2.1, one-neck flask, 800 ml. of 98% formic acid was cooled to -10°C. in an ice-acetone bath. Acetic anhydride (150 ml.) was added over 10 minutes while maintaining the temperature below 0°C. 7 - Aminocephalosporanic acid [100 g., (0.37 ml.)] was added and the mixture was stirred for 10 minutes until solution was nearly complete. The solution was placed under vacuum and its volume reduced to 225 g. of a tan foam. Ethyl acetate (500 ml.) was added, and the mixture was stirred and then filtered to remove a small amount of insoluble material and reduced to

(14)

135 g. of foam. About 500 ml. of ethyl acetate was added, and the mixture was stirred in an ice bath. A solid crystallized. The solid was collected, washed with 200 ml. of ethyl acetate and dried to give 95.8 g. (80%) of 7 - formamidocephalosporanic acid, m.p. 135—37°C.

The following observed values express the nuclear magnetic resonance spectrum, the infrared spectrum, the ultraviolet spectrum, and the elemental analysis for the product:

NMR	δ (DMSO _d ₆)		
		2.00 (s,3,acetyl-CH ₃)	10
		3.54 (s,2,C2 methylene)	
		4.55, 5.12 (m,3,C ₃ methylene, C6 proton)	
		5.63, 5.86 (q,1,C7 proton)	
		8.12 (s,1,formyl proton)	15
		9.78, 10.0 (d,1,amide proton)	

IR (mull) Absorption maxima:

1770 (β -lactam), 1748,
1710, 1655 (ester, carboxyl and amide carbonyl)cm⁻¹.

UV (pH 6 buffer)

ϵ_{250} —9000

Analysis, Calc. for C₁₁H₁₂N₂O₆S: C, 44.00; H, 4.03; N, 9.33; S, 10.68.
Found: C, 43.84; H, 3.76; N, 9.20; S, 10.54.

EXAMPLE II:

7-(5'-amino-5'-carboxy)valeramido-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

To 800 ml. of water was added 27.7 g. (0.2 m. of 1 methyl - 1H - tetrazole - 5-thiol, sodium salt, and the mixture was heated to 70°C. The sodium salt of cephalosporin C [88.0 g. (0.2 m.)] was added, and the mixture maintained at 70°C. for about 2 hours. The mixture was then cooled at 20°C., and the pH was adjusted to about 9 by addition of 50% aqueous sodium hydroxide. About 52 g. (0.4 m.) of propionic anhydride was added to the mixture over a ten minute period during which time the pH was maintained above 8.0 by addition of 50% aqueous sodium hydroxide in order to deactivate the amino group present on the side chain in the 7' position of the cephalosporin C reactant. The mixture was cooled, and one liter of tetrahydrofuran was added. The pH was then adjusted to about 1 by addition of concentrated hydrochloric acid. The mixture was then saturated with sodium chloride, the layers separated, and the organic layer dried over anhydrous magnesium sulfate. The organic solution was evaporated to a foam residue, and the residue was dissolved in methanol. Upon cooling, a solid crystallized. The solid was filtered, washed and dried to give 65 g. (60%) of 7 - (5' - amino - 5' - carboxy) - valeramido - 3 - 1 - methyl - H - tetrazol-5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid.

EXAMPLE III:

7-amino-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

In 200 ml. of tetrahydrofuran was suspended 26.0 g. (0.05 m.) of 7 - (5' - amino-5' - carboxy)valeramido - 3 - (1 - methyl - 1H - tetrazol - 5 - ylthiomethyl) - 3-cephem - 4 - carboxylic acid, and the mixture was cooled to about -10°C. About 2 ml. of quinoline was added, and, with the temperature of the mixture maintained below about 35°C., 41 ml. (0.6 m.) of acetyl chloride was added. (The purpose of the acetyl chloride is to react with the amino group in the side chain so as to inactivate it and to form mixed anhydrides with the carboxyl groups in the 4-position on the nucleus and in the side chain). The mixture was then cooled to -12°C., and 53 ml. (0.33 m.) of diethylalilide was added. The mixture was re-cooled to -12°C., and 20.8 g. (0.1 m.) of phosphorus pentachloride was added. The mixture was stirred at -12°C for about 0.5 hours, and then was cooled to -40°C. About 40 ml. of ethylene glycol was added, and the mixture was maintained at 0°C. to 5°C. for two hours. The mixture was cooled to -12°C., and 30 ml. of water was added. The pH of the mixture was adjusted to 3.9 by addition of ammonium hydroxide, and the mixture was stirred for 0.5 hours during which time solid precipitated and was then collected by filtration.

The solid was washed successively with water and acetone and then dried to yield 7-amino-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

EXAMPLE IV:

7-amino-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

In a 500 ml. of 3-neck flask equipped with a stirrer and thermometer, 21.0 g. (0.07 m.) of 7-formamido-cephalosporanic acid and 9.68 g. (0.07 m.) of 1-methyl-1H-tetrazole-5-thiol, sodium salt were suspended in 200 ml. of water. The pH was adjusted to 6.9 with concentrated ammonium hydroxide, and the mixture was heated for 3½ hours at about 70°C. The final pH of the mixture was 5.9. The solution was cooled and washed with two 100 ml. portions of ethyl acetate. The organic wash was discarded, and the aqueous layer was layered with a mixture of 140 ml. of ethyl acetate and 160 ml. of tetrahydrofuran. The pH was adjusted to 2.0 with concentrated HCl, the layers were separated, and the organic layer was washed with two 40 ml. portions of water and then with 100 ml. of saturated sodium chloride. The organic layer was dried over anhydrous magnesium sulfate and evaporated to 18.0 g. of yellow foam. The foam was dissolved in a mixture of 160 ml. of methanol and 24 ml. of concentrated hydrochloric acid. The solution was stirred for 2½ hours. Water (500 ml.) was added, and the solution was washed with two 300 ml. portions of ethyl acetate. The aqueous layer was placed under vacuum to remove organic solvents and then was cooled. The pH was adjusted to 3.9 by addition of concentrated ammonium hydroxide. Solid separated almost immediately. The mixture was stirred for about one hour in an ice bath, filtered, washed with water, and dried, to give 10.12 g. (44%) of 7-amino-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

NMR

$\delta(D_{2O}/NaHCO_3)$

3.58, 3.71 (d, 2, C2)
4.12 (s, 3, tetrazole CH₃)
4.17, 4.30 (d, 2, C3 methylene)
5.03, 5.12 (d, 1, C6 proton)
5.43, 5.52 (d, 1, C7 proton)

UV

(pH 6 buffer)

$\epsilon_{272} = 10,000$

EXAMPLE V:

Anhydro-O-carboxymandelic acid.

In a 250 ml., 3-neck flask, equipped with a dry ice-acetone condenser, a stirrer, a thermometer and an inlet tube, 15.2 g. (0.1 m.) of D(-)-mandelic acid was dissolved in 150 ml. of dry tetrahydrofuran (THF). Phosgene [14.2 ml., 19.7 g.] (0.02 m.) was collected from a cylinder under a dry ice-acetone condenser. The phosgene was allowed to distill into the reaction flask through the inlet tube opening above the surface of the liquid. The distillation required about 1 hour and the temperature rose from 23°C. to 32°C. The solution was then heated to 45°C. for a period of 7 hours. The reaction mixture was reduced to 175 g. of off-white solid. The solid was dissolved in 70 ml. of hot carbon tetrachloride. Upon cooling, a solid crystallized and was filtered and washed with cold carbon tetrachloride to give 14.8 g. (83%) of anhydro-O-carboxymandelic acid m.p. 74–76°C. dec.

NMR

$\delta(CDCl_3)$

6.00 (s, 1, benzyl proton)
7.50 (m, 5, aromatic)

IR (CHCl₃) Absorption maxima:

1885, 1815 (carbonyl groups),
1235, 1060 (C—O—C)cm⁻¹

Analysis, Calc. for C₈H₆O₄: C, 60.67; H, 3.39.
Found: C, 60.97; H, 3.39.

EXAMPLE VI.

7-(α -hydroxy- α -phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, sodium salt.

In an 800 ml. beaker, 20.9 g. (0.07 m.) of 7-amino-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid was suspended in 320 ml. of water. The pH was adjusted to 6.8 with 5% sodium bicarbonate solution. Anhydro-O-carboxymandelic acid [14.95 g. (0.084 m.), 20% excess] was added over 10 minutes. The pH was maintained for one hour at 6.6-6.8 by addition of 5% sodium bicarbonate solution. To prevent foaming, the mixture was filtered into 300 ml. of ethyl acetate contained in a suction flask. The pH was adjusted to 2.0 with concentrated hydrochloric acid. The layers were separated, and the aqueous layer was washed with 300 ml. of ethyl acetate. The combined organic layers were washed with 200 ml. of water and dried over anhydrous magnesium sulfate. The solution was evaporated to 30 g. of yellow foam which was then dissolved in 400 ml. of ethanol. The sodium salt was precipitated by the addition of 70 ml. of 1M sodium acetate solution in absolute methanol. The thick mixture was stirred in an ice bath for one hour, filtered, washed with 200 ml. of cold ethanol, and dried to give 23.7 g. (70.5%) of 7-(α -hydroxy- α -phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, sodium salt.

NMR

 δ_{D_2O}

3.30, 3.44 (d, 2, C2)
 3.82 (s, 3, tetrazole-CH₃)
 4.00, 4.07 (d, 2, C3 methylene)
 4.86, 4.94 (d, 1, C6 proton)
 5.17 (s, 1, benzyl proton)
 5.47, 5.54 (d, 1, C7 proton)
 7.33 (s, 5, aromatic proton)

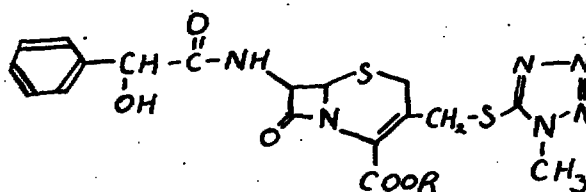
UV (H₂O) ϵ_{289} —10,500

Polarographic assay indicated 90.3% product.

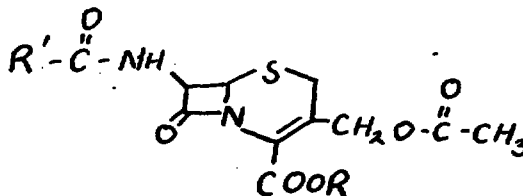
Attention is drawn to the Applicants earlier Specification No. 1,283,811 which could be infringed in the practice of the present invention.

WHAT WE CLAIM IS:—

1. A process for preparing a cephalosporin of the formula



wherein R is H or a carboxy-protecting group, which comprises (1) reacting a 7-acylamido-3-acetoxymethyl compound of the formula



in which R' is hydrogen, C₁ to C₃ alkyl or 4-amino-4-carboxybutyl, and R is hydrogen or a carboxy-protecting group with 1-methyl-1H-tetrazole-5-thiol or a salt thereof with an alkali metal, an alkaline earth metal or ammonium to produce a 7-acyl-amido-3-(1-methyl-1H-tetrazol-5-ylthiomethyl) compound of the formula

EXAMPLE VI.

7-(α -hydroxy- α -phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-
cephem-4-carboxylic acid, sodium salt.

In an 800 ml. beaker, 20.9 g. (0.07 m.) of 7-amino-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-
cephem-4-carboxylic acid was suspended in 320 ml. of water. The pH was adjusted to 6.8 with 5% sodium bicarbonate solution. Anhydro-O-carboxymandelic acid [14.95 g. (0.084 m.), 20% excess] was added over 10 minutes. The pH was maintained for one hour at 6.6-6.8 by addition of 5% sodium bicarbonate solution. To prevent foaming, the mixture was filtered into 300 ml. of ethyl acetate contained in a suction flask. The pH was adjusted to 2.0 with concentrated hydrochloric acid. The layers were separated, and the aqueous layer was washed with 300 ml. of ethyl acetate. The combined organic layers were washed with 200 ml. of water and dried over anhydrous magnesium sulfate. The solution was evaporated to 30 g. of yellow foam which was then dissolved in 400 ml. of ethanol. The sodium salt was precipitated by the addition of 70 ml. of 1M sodium acetate solution in absolute methanol. The thick mixture was stirred in an ice bath for one hour, filtered, washed with 200 ml. of cold ethanol, and dried to give 23.7 g. (70.5%) of 7-(α -hydroxy- α -phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-
cephem-4-carboxylic acid, sodium salt.

NMR

 δ_{D_2O}

3.30, 3.44 (d, 2, C2)
3.82 (s, 3, tetrazole-CH₃)
4.00, 4.07 (d, 2, C3 methylene)
4.86, 4.94 (d, 1, C6 proton)
5.17 (s, 1, benzyl proton)
5.47, 5.54 (d, 1, C7 proton)
7.33 (s, 5, aromatic proton)

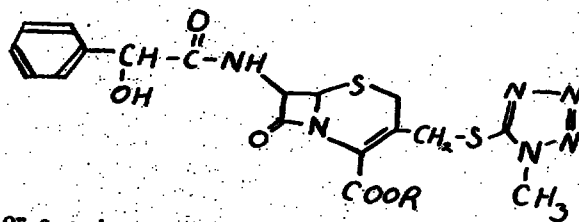
UV (H₂O) ϵ_{269} —10,500

Polarographic assay indicated 90.3% product.

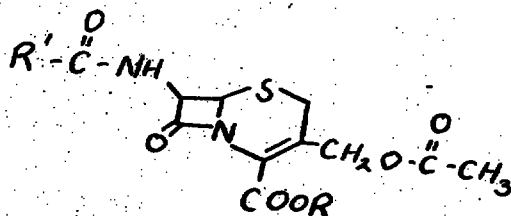
Attention is drawn to the Applicants earlier Specification No. 1,283,811 which could be infringed in the practice of the present invention.

WHAT WE CLAIM IS:—

1. A process for preparing a cephalosporin of the formula

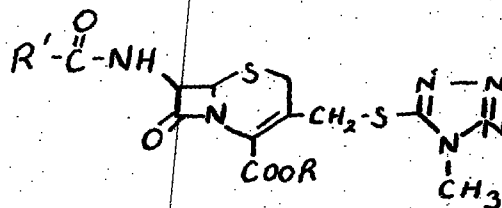


wherein R is H or a carboxy-protecting group, which comprises (1) reacting a 7-acylamido-3-acetoxymethyl compound of the formula

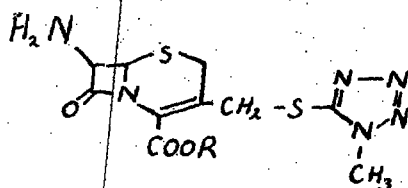


in which R' is hydrogen, C₁ to C₃ alkyl or 4-amino-4-carboxybutyl, and R is hydrogen or a carboxy-protecting group with 1-methyl-1H-tetrazole-5-thiol or a salt thereof with an alkali metal, an alkaline earth metal or ammonium to produce a 7-acyl-amido-3-(1-methyl-1H-tetrazol-5-ylthiomethyl) compound of the formula

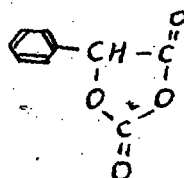




(2) cleaving the 7-acylamido group of the 7 - acylamido - 3 - (1 - methyl - 1H-tetrazol - 5 - ylthiomethyl) compound to produce a 7 - amino - 3 - (1 - methyl - 1H-tetrazol - 5 - ylthiomethyl) compound of the formula



and (3) N-acylating the resulting 7-amino compound with anhydro-O-carboxymandelic acid having the formula



to produce the aforementioned cephalosporin.

2. Process of claim 1, in which R is hydrogen, C₁-C₆ alkyl, 2,2,2 - trihaloethyl, C₅-C₇ tert - alkenyl, C₅-C₇ tert - alkynyl, benzyl, nitrobenzyl, tetrahydropyranyl, succinimidomethyl, phthalimidomethyl, methoxybenzyl, dimethoxybenzyl, cyanomethyl, nitrophenyl, dinitrophenyl, 2,4,6 - trinitrophenyl, bis (p - methoxyphenyl)methyl, triphenylmethyl, benzhydryl, benzyloxymethyl, C₂-C₆ alkanoyloxymethyl, C₂-C₄ alkanoyl, or phenacyl.

3. Process of claim 1, in which the 7 - acyl - amido - 3 - acetoxymethyl compound is reacted with the sodium salt of 1 - methyl - 1H - tetrazole - 5 - thiol.

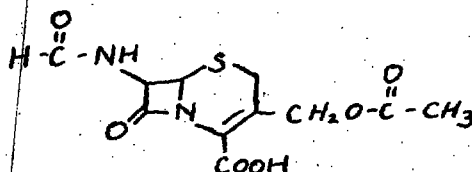
4. Process of claim 3, in which the 7 - acyl - amido - 3 - acetoxymethyl compound is reacted with the methyl - tetrazolethiol sodium salt in an aqueous medium at a pH of from 5.0 to 7.0 and at a temperature of from about 50°C. to about 100°C.

5. Process of claim 1, in which the cleavage of the acyl-amido group of the 7-acylamido - 3 - (1 - methyl - 1H - tetrazol - 5 - ylthiomethyl) compound is carried out by treatment with a C₁ to C₄ alkyl alcohol under acidic conditions.

6. Process of claim 5, in which the alcohol is methanol and the acid is concentrated hydrochloric acid.

7. Process of claim 1, in which the N-acylation of the 7 - amino - 3 - (1 - methyl - 1H - tetrazol - 5 - ylthiomethyl) compound with anhydro - O - carboxymandelic acid is carried out in an aqueous medium at a pH maintained at from about 6.5 to about 7.0 and at ambient room temperature.

8. Process of claim 1, in which a compound of the formula



is reacted in an aqueous medium with the sodium salt of 1 - methyl - 1H - tetrazole - 5 - thiol at an initial pH of 6.9 and at a temperature of about 70°C to produce a 7-



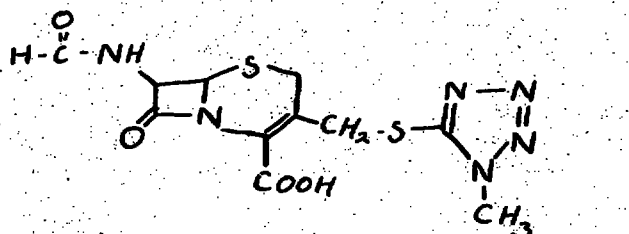


* C L H S *

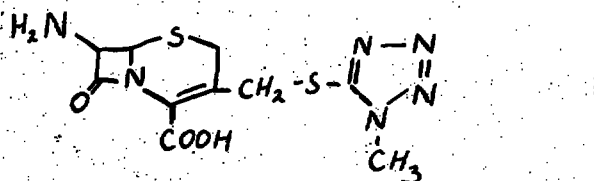
18

1,400,697

formamido - 3 - (1 - methyl - 1H - tetrazol - 5 - ylthiomethyl) compound of the formula

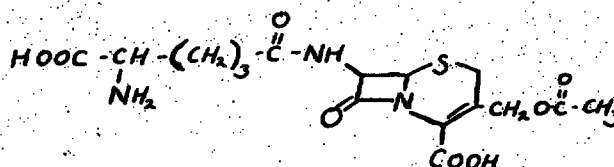


the 7 - formamido - 3 - (1 - methyl - 1H - tetrazol - 5 - ylthiomethyl) compound is treated with methanol and concentrated hydrochloric acid to produce a 7-amino compound of the formula.

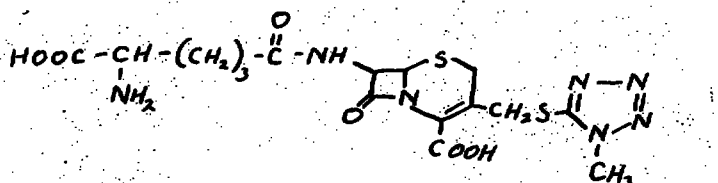


and the 7-amino compound is N-acylated with anhydro - O - carboxymandelic acid in an aqueous medium at a pH maintained at 6.6 - 6.8 and at ambient room temperature.

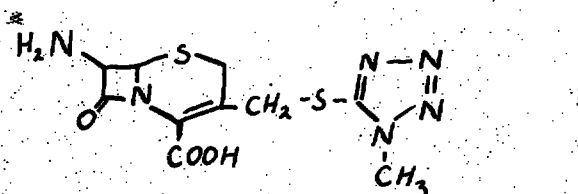
9. Process of claim 1, in which a compound of the formula



is reacted in an aqueous medium with the sodium salt of 1 - methyl - 1H - tetrazole - 5 - thiol at a temperature of about 70°C. to produce a 7 - (5' - amino - 5' - carboxyvaleramido - 3 - (1 - methyl - 1H - tetrazol - 5 - ylthiomethyl) compound of the formula



the 7 - (5' - amino - 5' - carboxy)valeramido - 3 - (1 - methyl - 1H - tetrazol - 5 - ylthiomethyl) compound is cleared in the presence of phosphorus pentachloride to produce a 7-amino compound of the formula



and the 7-amino compound is N-acylated with anhydro - O - carboxymandelic acid in an aqueous medium at a pH maintained at 6.6—6.8 and at ambient room temperature.

(19)

10

1,400,697

10

10. A process substantially as herein described with particular reference to any of Examples II, III, IV and VI.

LANGNER PARRY,
Chartered Patent Agents,
Chichester House,
278—282 High Holborn,
London, W.C.1.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1975.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

