

PATENT SPECIFICATION

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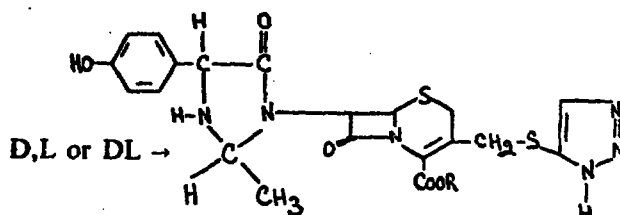


(54) WATER SOLUBLE FORMS OF TRIAZOLYLTHIOMETHYL CEPHEM DERIVATIVES

(71) We, BRISTOL-MYERS COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, having offices at 345 Park Avenue, New York, New York 10022, 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 relates to novel water-soluble pharmaceutically acceptable forms of the antibiotic 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid which (1) upon the addition of water will give true solutions for parenteral administration, (2) have acceptable thermal stability in the solid state, (3) in aqueous solution have a useful life of at least several hours at room temperature and (4) on intravenous or intramuscular injection result in little or no muscle or vein irritation. More particularly, the present invention provides alkali metal salts, especially sodium and potassium salts, of the acetaldehyde reaction product of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

The alkali metal salts of the present invention have the formula



wherein R is an alkali metal, preferably sodium or potassium, and may be prepared by a process which comprises

(1) treating an aqueous suspension of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid or a solvate or hydrate thereof with acetaldehyde and sufficient water-soluble alkali metal base, preferably a sodium or potassium base to raise the pH of the reaction mixture to between about 5.5 and 8 and to form in solution the desired salt of formula I; and

(2) recovering from the solution the desired salt of formula I.

The compounds of formula I have an asymmetric center as indicated by the structural formula. Thus, compounds of formula I may exist in the form of the DL mixture or as the individual D or L isomers.

The starting material cephalosporin used in Step (1) of the above process may

be any form of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamidol-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid including the free acid zwitterion or a hydrate or solvate of said zwitterion. The preferred starting materials for use in the present invention are the methanol and propylene glycol solvates disclosed in U.K. Patent Specification No. 1,483,416 and the sesquihydrate disclosed in our U.K. Patent Specification No. 1,487,658. The most preferred starting material is the methanol solvate because of its lower cost and greater rate of solution relative to the other known forms of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamidol-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid. The concentration of cephalosporin starting material is not critical, and good results have been obtained with concentrations between 25—300 milligrams cephalosporin starting material per milliliter of solvent. The starting material is preferably ground and screened to a finely divided state, most preferably ground to a particle size of less than 200 mesh, so as to increase the surface area and rate of reaction.

The cephalosporin starting material is slurried in water to form an aqueous suspension. An alternative to using an aqueous suspension is Step (1) would be to suspend the cephalosporin starting material in an organic solvent which is (1) a solvent for the alkali metal salt end-product, (2) miscible with acetaldehyde, (3) chemically inert toward the cephalosporin starting material and end-product and (4) easily removable from the end-product as by mild drying. Examples of organic solvents which might be employed are dimethylsulfoxide and dimethylformamide. Because of the difficulty of removing residual organic solvent from the alkali metal salt end-product, however, the starting material is preferably provided as an aqueous suspension.

After obtaining the cephalosporin starting material in suspension, the desired alkali metal salt of formula I is formed in solution by addition of acetaldehyde and an amount of water-soluble alkali metal base, preferably a sodium or potassium base, sufficient to raise the pH of the reaction mixture to between about 5.5 and 8. As the pH is raised to within this range the alkali metal salt of the reaction product of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamidol-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid and acetaldehyde is formed and goes into solution.

The temperature at which Step (1) is carried out is not critical. Most conveniently the reaction is performed at room temperature, but higher or lower temperatures may be used with the expected decrease or increase, respectively, in reaction time.

About 1 mole of acetaldehyde is needed per mol of cephalosporin starting material but the acetaldehyde is preferably added somewhat in excess of the theoretical amount needed so as to ensure complete reaction, i.e. a slight molar excess. The most preferred molar ratio of acetaldehyde to cephalosporin starting material is about 1.3—1.4:1.

The alkali metal base may be any water soluble base capable of (1) providing alkali metal cations, preferably sodium or potassium ions, and (2) raising the pH of the reaction mixture to between about 5.5 and 8, most preferably about 6.7 to 7.2. Preferred bases because of their desirable solubility properties are sodium or potassium hydroxide. The triazole moiety of compound I, while not as unstable at alkaline pH as in the parent cephalosporin, splits off at high pH. For this reason the base is added to the reaction mixture in such a manner that the pH is not allowed to rise above about 8. Preferably the base is used in the form of an aqueous solution and is added slowly to the reaction mixture with stirring until the reaction is shown to be complete by pH measurement and by formation of a solution or near solution. The amount of base used is not critical, but preferably about 1 mole of base is used per mole of cephalosporin starting material.

For best results the solution obtained at the conclusion of Step (1) is filtered to remove solid impurities prior to the recovery Step (2). Before filtration, the solution may optionally be carbon-treated with activated carbon to assist in removal of any colored impurities.

The desired product of formula I is then recovered from aqueous or non-aqueous solution as by precipitation or lyophilization. Precipitation of the alkali metal salt may be effected by addition of an organic solvent in which the desired salt is insoluble, i.e. an antisolvent. Examples of such antisolvents include acetone, isopropanol, n-propanol, ethanol, t-butanol, acetonitrile, ethyl acetate and methyl isobutyl ketone. The solvent to be used in the precipitation step should be one which can be easily removed from the end-product under conditions which will not result in any significant decomposition of the alkali metal salt. The most preferred antisolvent is isopropanol. The antisolvent may be added to the solution

2	3	1,503,030	3
5	5	resulting from Step (1) or, alternatively and preferably, the solution containing the desired alkali metal salt is added with stirring to a large excess of the antisolvent. The alkali metal salt of formula I is then recovered by filtration, washed with a suitable organic solvent, e.g. acetone or isopropanol, and dried by conventional procedures, e.g. vacuum-drying at 50—60°C for 24—48 hours or air drying at 60°C for 48 hours. As an alternative procedure to recovering the end-product by precipitation, the salt of formula I may also be recovered by lyophilization of the solution prepared in Step (1).	5
10	10	An alternative process for preparing the compounds of formula I comprises (1) forming a suspension of 7 - [D - α - amino - α - (p - hydroxyphenyl) - acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid or a solvate or hydrate thereof in a suitable inert organic solvent, said solvent being a solvent for the triethylamine salt of the acetaldehyde reaction product of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid and a non-solvent for the alkali metal salt of formula I;	10
15	15	(2) treating the suspension with acetaldehyde and sufficient triethylamine to form in solution the triethylamine salt of the acetaldehyde reaction product of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid; and	15
20	20	(3) precipitating the desired alkali metal salt of formula I from the solution by adding a solvent-soluble alkali metal base, preferably sodium or potassium base.	20
25	25	The cephalosporin starting material used in the above process may be any of the forms of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid mentioned in connection with the first-described method. The preferred starting materials are the methanol or propylene glycol solvates and the sesquihydrate. The most preferred starting material as in the first-mentioned process is the methanol solvate. The concentration of starting material and particle size are not critical, but the preferred conditions are as described above in connection with the first process.	25
30	30	The starting material is slurried in an inert organic solvent which is a solvent for the triethylamine salt of the acetaldehyde reaction product of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid but which is a non-solvent for the desired alkali metal salt of formula I. The solvent selected for Step (1) should preferably be easily removable from the end-product under conditions which will not result in any appreciable decomposition of the end-product. Appropriate solvents for Step (1) may be determined by simple test. The preferred solvent is methanol as it is readily available, relatively inexpensive and fulfills the solubility requirements mentioned above.	30
35	35	The suspension formed in Step (1) is then treated with acetaldehyde, preferably with a molar excess and most preferably with from about 1.3 to 1.4 moles of acetaldehyde per mole of cephalosporin starting material, and sufficient triethylamine to form in solution the triethylamine salt of the cyclic reaction product of acetaldehyde and 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid. The reaction mixture is preferably stirred for at least about 30 minutes to ensure complete reaction. The amount of triethylamine used is not critical but preferably about 1 mole is used per mole of cephalosporin starting material. The reaction Step (2) is conveniently done at room temperature but temperatures higher or lower than this may be selected with the expected decrease or increase, respectively, in reaction time.	35
40	40	After formation of a solution or near-solution in Step (2), the reaction mixture is preferably carbon-treated and filtered as in the first-mentioned process discussed above.	40
45	45	The desired alkali metal salt of formula I may then be recovered from the solution of Step (2) by addition of a solvent-soluble alkali metal salt, preferably a sodium or potassium salt. The preferred salts are sodium or potassium salts of organic acids having between about 2 and 18 carbon atoms, e.g. solvent-soluble salts of such acids as 2-ethylhexanoic, caproic, oleic, glycolic, propionic and acetic acid. Preferred salts for the methanol solvent system are sodium or potassium 2-ethylhexanoate, most preferably solutions of these salts in a methanol-miscible organic solvent such as acetone or isopropanol. The most preferred alkali metal salts are solutions of sodium or potassium 2-ethylhexanoate in isopropanol. The alkali metal salt is added, preferably slowly and with stirring, in sufficient quantity	45
50	50		50
55	55		55
60	60		60
65	65		65

so as to obtain the maximum amount of precipitate from the solution. After complete precipitation has been effected, the reaction mixture is stirred, preferably for at least about 1 hour, and then filtered. The precipitate is washed with an appropriate organic solvent, e.g. methanol, and dried by conventional procedures, e.g. vacuum-drying at 50—56°C for 24—48 hours or air drying at 60°C for 48 hours.

The second process may also be carried out without use of the triethylamine in Step (2). In this modified procedure the suspension of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid or a solvate or hydrate thereof, preferably the methanol or propylene glycol solvate or sesquihydrate and most preferably the methanol solvate, is suspended in an inert organic solvent which is a non-solvent for the product of formula I, preferably methanol, and the suspension then treated with acetaldehyde, preferably a molar excess, and a solvent-soluble alkali metal base, preferably sodium or potassium base, said base being added in an amount sufficient to raise the pH of the reaction mixture to between about 5.5 and 8. It is preferred to use as bases the sodium or potassium salts mentioned above as being preferred in the second process. In the modified process the cephalosporin starting material goes into solution and the insoluble alkali metal salt then precipitates out almost instantaneously. Since a solution is not obtained upon completion of the reaction, the reaction mixture is preferably stirred and heated to about 45—50°C for a period of time of several hours to ensure maximum yields of end-product. The solid product is removed by filtration, washed and dried to give the desired salt of formula I.

The alkali metal salts of the present invention may be used to provide pharmaceutical formulations of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid which have acceptable thermal stability in the solid state, high solubility in water, satisfactory aqueous stability, little or no muscle or vein irritation upon intravenous or intramuscular injection and excellent *in vivo* and *in vitro* antibacterial activity against a variety of Gram-positive and Gram-negative bacteria.

The salts of formula I may be dissolved in water to form relatively concentrated solutions of at least 250 mg./ml. of activity. Concentrations of 250 mg./ml. of activity (pH 5.7—6.8) of these salts have acceptable aqueous stabilities, i.e. <10% loss in activity, for at least 4 hours at room temperature. Concentrations of 25 mg./ml. of activity (pH 6.9) have acceptable stability for at least 8 hours at room temperature. In solid form the salts of the present invention are stable for at least 2 weeks at 56°C and 1 month at 45°C.

In dilute aqueous solution the compounds of the present invention hydrolyze to the parent cephalosporin, i.e. 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid. Activities of the compounds of formula I are substantially equivalent to those of the parent cephalosporin. Blood levels of the compounds of formula I upon oral administration are somewhat lower than those of the parent cephalosporin but are sufficiently high as shown in Table II below to enable the compounds to be effective antibacterial agents when given orally. Table III indicates that blood levels of the compounds of formula I upon intramuscular administration are generally equal to or somewhat higher than those of the parent compound.

In another aspect the present invention provides a pharmaceutical composition suitable upon reconstitution with water for use as a parenterally-administrable antibiotic formulation, said composition comprising a compound of formula I and a solid pharmaceutically acceptable water soluble organic acid, said organic acid being present in an amount such that the pH of the formulation upon reconstitution with water is between about 5 and 6.

The dry mixture of salt of formula I and organic acid in the above-mentioned composition may be reconstituted with water to provide a high concentration, i.e. up to at least 250 mg./ml., solution suitable for parenteral administration. The composition provided by the present invention may be prepared by admixing a compound of formula I with a sufficient amount of a pharmaceutically acceptable water-soluble solid organic acid such that the pH of the composition upon reconstitution with water is between about 5 and 6. Glycine hydrochloride may also be used in the composition instead of such an acid.

The organic acid used in the composition may be any non-toxic, water-soluble, solid organic acid. Examples of suitable acids include citric, tartaric,

ascorbic, succinic, and the like. The most preferred acid for use in the composition of the present invention is citric acid.

The exact proportions of compound of formula I and solid organic acid or glycine hydrochloride are dependent on the physical and chemical properties of the acid selected, e.g. acidity, solubility, etc. Generally it is found that the desired pH range of 5-6 upon reconstitution with water is achieved when the solid organic acid or glycine hydrochloride is used in an amount of about 4-6% of the weight of the compound of formula I.

The alkali metal salt-organic acid or glycine hydrochloride mixtures provided according to this aspect of the present invention are found to have enhanced aqueous stability relative to the salts *per se*, especially at lower concentrations. Thus, the sodium salt at a concentration of 25 mg./ml. gives a pH 6.9 solution which is stable (<10% loss) for 8 hours at room temperature. A 25 mg./ml. solution of a sodium salt-citric acid mixture (pH 5.7), however, is stable for 24 hours at room temperature.

The compounds of formula I as well as the above-mentioned compositions are potent antibacterial agents useful in the treatment of infectious diseases in poultry and animals, including man, caused by many Gram-positive and Gram-negative bacteria. The compounds and compositions are also of value as nutritional supplements in animal feeds and as agents for the treatment of mastitis in cattle.

The salts and salt-organic acid or glycine hydrochloride mixtures of the present invention may be formulated as pharmaceutical compositions containing in addition to the active ingredient a pharmaceutically acceptable carrier or diluent. The compounds may be administered either orally or parenterally, but because of their high solubility in water, are especially useful for parenteral administration. In the treatment of bacterial infections in man, the compounds and compositions may be administered in an amount of from about 5 to 20 mg./kg./day in divided dosage, e.g. 3 or 4 times a day. They are administered in dosage units containing, e.g. 125, 250 or 500 mg. of active ingredient.

Preparation of Starting Materials.

Preparation of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid methanol solvate.

In a three necked flask equipped with a reflux condenser, overhead stirrer and thermometer, there was placed a well mixed mixture of 8.36 g. (0.05 mole) of D-(-)-p-hydroxyphenylglycine and 3.02 g. (0.075 mole) of magnesium oxide in 120 ml. of 50% aqueous dioxane. The mixture was stirred for 1 hour and then treated with 10.74 g. (0.075 mole) of t-butoxycarbonylazide. The mixture was then stirred and heated at 45-50° for 17 hours under N₂. The solution was diluted with 400 ml. of H₂O and extracted twice with 300 ml. of ethyl acetate. The aqueous phase was acidified with 10% citric acid solution to pH 4 and saturated with NaCl. The aqueous mixture was extracted with 3 x 400 ml. of ethyl acetate. The solution was dried over Na₂SO₄ and the solvent evaporated. The residue was triturated with "Skellysolve B" to yield D- α -t-butoxycarbonylamino- α -(p-hydroxyphenyl)acetic acid as a solid weighing 10.4 g. (78.5%).

To a suspension of 7-amino-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid (6.0 g., 19.0 mmole) in 100 ml. dry methylene chloride there was added 8.5 ml. of 1,1,1,3,3,3-hexamethyldisilazane (40.9 mmole). The mixture was stirred and heated at reflux for 4 hours at which time a clear solution was obtained. The solvent was evaporated and the residual oil was subjected to high-vacuum overnight at room temperature. The foamy residue was dissolved in 85 ml. of dry THF and cooled to about -15° before introduction into the subsequent reaction mixture.

D- α -t-Butoxycarbonylamino- α -(4-hydroxyphenyl)acetic acid, (4.4 g., 16.5 mmole) was dissolved in 145 ml. dry THF. The solution was stirred and cooled to -20°.

N-methylmorpholine (1.6 g., 16 mmoles) and isobutylchloroformate (2.3 g., 16.8 mmole) were added in succession at such rate that the temperature of the mixture did not rise above about -10°. The resulting mixture was then stirred for 20 minutes at -12° to -15°. It was then cooled to -20° and the THF solution of silylated 7-amino-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid was added all at once. The temperature rose to about -12°. External cooling was discontinued until the temperature rose to 0°. At this point an ice-water bath was applied and the mixture stirred for three hours at 2-3°. This was followed by a

period of one hour without external cooling, the temperature rising to 20°. A total of 30 ml. methanol was added and the stirring continued for 15 minutes at room temperature. After evaporating the solvents under reduced pressure, the residue was suspended in 300 ml. ethyl acetate. The suspended solid was filtered off, (11.8 g.). The ethyl acetate solution was extracted three times with NaHCO₃ (5%) solution. The combined sodium bicarbonate extracts were cooled in an ice-bath, layered with ethyl acetate and acidified to a pH of 2.5 with 42.5% H₃PO₄. The phases were shaken and then separated. The ethyl acetate solution was then dried by passing it through sodium sulfate and then evaporated to about 15—20 ml. This solution was then added dropwise to stirred cyclohexane (~400 ml.) contained in an Erlenmeyer flask. After stirring for 1/2 hour the precipitated solid was collected by filtration. The collected, solid 7-[D- α -t-butoxycarbonyl-amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid was air dried. It weighed 1.75 g.

7-[D- α -t-butoxycarbonylamino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, 3.5 g., was dissolved in 80 ml. HCOOH, 98—100%, and stirred for 2 hours at room temperature. The HCOOH was evaporated under reduced pressure (aspirator bath temperature not above 40°) and finally azeotroped 3 times with 30 ml. of toluene. The solid was dried over night under high vacuum over P₂O₅. A total of 3.5 g. of foam was obtained. The foam, 2 g., was stirred with 300 ml. of H₂O:CH₃OH (8:2). The solvent was filtered from some solid (0.3 g.), charcoaled with 700 mg. of "Darco KB" ("Darco" is a registered Trade Mark), filtered through diatomaceous earth ("Celite"—registered Trade Mark) and freeze-dried to yield 0.9 g. of crude 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid. To crystallize the following procedure was used. A suspension of 0.2 g. of the crude material in 6 ml. of 99% methanol was heated in a test tube to boiling. Immediately the heating was discontinued and the melt triturated with seeds. The melt solidified to a crystalline mass. In this manner a total of 0.211 g. of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid was obtained from 0.400 g. of crude material. The material was dried at 56°/0.1 mm over P₂O₅ for 20 hrs., m.p. >200° dec. IR and NMR are consistent with structure. The NMR indicates also the presence of 1/3 mole of CH₃OH.

Anal. Calcd. for C₁₈H₁₈N₆O₅S₂·H₂O·1/3CH₃OH: C, 44.83; H, 4.38; N, 17.10; S, 13.09.
Found: C, 43.97; H, 4.36; N, 15.84; S, 6.18.

A total 6.5 g. (11.55 mmole) of 7-[D- α -t-butoxycarbonylamino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid was dissolved in 175 ml. 98—100% formic acid under anhydrous conditions. The mixture was stirred at room temperature for 2.5 hours. Part of the solution, 125 ml., was evaporated under reduced pressure to an amber oil. The oil was then azeotroped 3 times with 70 ml. of toluene under reduced pressure. The residue was suspended in an 80:20 H₂O—CH₃OH solution (700 ml.) and stirred for 0.5 hour until most of the solid dissolved, then filtered. The filtration was treated with 1.5 g. of ("Darco") charcoal for about 20 minutes. The charcoal was filtered off through a "Celite" pad. The solution was then freeze-dried in 9 separate 100 ml. round bottom flasks. The freeze-dried material weighed 2.415 g. It was recrystallized in batches of 0.200 g. as described above to yield a total of 0.923 g. 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid. NMR was consistent, indicating the presence of a 1/3 mole of CH₃OH.

Anal. Calcd. for C₁₈H₁₈N₆O₅S₂·H₂O·1/3CH₃OH: C, 44.83; H, 4.38; N, 17.10; S, 13.09.
Found: C, 45.77, 44.36; H, 4.44, 4.34; N, 16.61, 16.52; S, 13.01, 13.01.

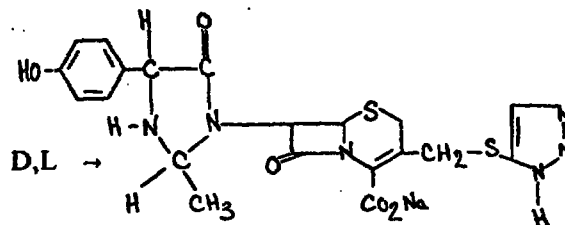
Preparation of Crystalline Methanol Solvate of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.
1. Fifty grams of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid is slurried in 250 ml. of 95% V/V methanol/water (95% methanol) solution, at 22—25°C.

6	7	1,503,030	7
		2. Concentrated hydrochloric acid is added with rapid stirring to a pH of 1.3—1.5. A solution or near solution is obtained.	
		3. Adjust the pH to 1.7 with triethylamine.	
5	5	4. Add 7.5 grams of activated charcoal ("Darco G—60") and slurry for 0.5 hours.	5
		5. The carbon is removed by filtration and washed with 75 ml. of methanol which is added to the filtrate. Steps 2, 3 and 4 should be completed within 5 hours.	
10	10	6. The combined wash and filtrate of Step 5 is rapidly stirred. Triethylamine is added over a 5 minute period to pH 4.5. Crystallization starts in about 1—3 minutes. The mixture is slurried for one hour.	10
		7. The crystals are collected by filtration, washed with 100 ml. of methanol and vacuum dried at 56°C—24 hours. Bio yield 75—90%; bio-assay = 850—900 mcg./mg.; NMR—IR = Consistent for 1 mole of methanol; % H ₂ O, KF = 2—4.0.	
15	15	Preparation of Crystalline 1,2 - Propylene Glycol Solvate of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid.	15
20	20	1. Twenty-five grams of the methanol solvate of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid prepared above is slurried in 150—200 ml. of 75% V/V propylene glycol water solution at 20—25°C.	20
		2. Concentrated hydrochloric acid is added to a pH of 1—1.2 to obtain a solution or near solution.	
25	25	3. Triethylamine (TEA) is slowly added with rapid stirring to obtain a pH of 1.7—1.8.	25
30	30	4. Five grams of "Darco G—60" is added and the mixture is slurried for 0.5 hour. The carbon is removed by filtration (filtration is slow, an 18.5 cm. SS No. 576 paper is suggested). The carbon filter cake is washed with 40 ml. of 75% V/V propylene glycol water solution. The wash is added to the filtrate. Steps 2, 3 and 4 above should be completed within 5 hours.	30
		5. Triethylamine is added to pH 4.5 over a 10 minute period to the rapidly stirring filtrate-wash mixture of Step 4. Crystals form in about 1—3 minutes. The mixture is slurried for one hour.	
35	35	6. The crystals of the propylene glycol solvate of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid are collected by filtration. Filtration is slow (a 12.5—15.0 cm. SS No. 604 paper is suggested). The crystals are washed consecutively with 50 ml. of 75% propylene glycol, 50 ml. of methanol, 50 ml. of acetone and vacuum dried at 56°C for 24 hours. Biological yield: 80—95%.	35
40	40	Properties of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid propylene glycol solvate.	40
		a. Bio-assay = 750—790 mcg./mg.	
45	45	b. IR—NMR = Consistent for a structure containing 1.3—1.5 MOLES of propylene glycol (17—19% propylene glycol). No loss of the 3-triazole side chain evident.	45
		c. % Water, K.F. = 1—3.0.	
		d. Crystal morphology = 100% crystalline microcrystals, triangular shaped.	
50	50	e. M.P. = 182—184°C (D, hot stage).	50
		f. $[\alpha]_D^{25}$ (C = 1%; 1N—HCl) = +53°.	
		g. Water solubility = Approximately 10 mg./ml. in water at 23°C.	
		h. Loss of bioactivity on storage at elevated temperatures: 100°C, 24 hours = <6%; 48 hours = <12%; 56°C, 1 month = <10%.	
55	55	Preparation of Crystalline Methanol Solvate from Crystalline Propylene Glycol Solvate.	55
		The propylene glycol solvate of 7 - [D - α - amino - α - (p - hydroxyphenyl) - acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid (50 g.) as prepared above is slurried in 250 ml. of 95% (volume/volume) methanol-water solution at 22—25°C. Concentrated HCl is added with rapid stirring to a pH of 1.1—1.5 whereupon a solution or near solution is obtained. The pH is adjusted to 1.7 with triethylamine and 7.5 g. of activated charcoal is added with slurring for 0.5 hours. The charcoal is removed by filtration and washed with	60
60	60		60

- 75 ml. of methanol. The wash solution is then added to the filtrate. (The steps from addition of the HCl to this point should be completed within 5 hours). The combined wash and filtrate is rapidly stirred and triethylamine added over a 5 minute period until a pH of 4.5 is reached. Crystallization starts in about 1—3 minutes. The mixture is slurried for 1 hour, and the crystals are removed by filtration, washed with 100 ml. methanol and vacuum dried at 56°C for 24 hours. Bio Yield 75—90%; bio-assay = 850—900 mcg./mg.; NMR—IR = consistent for 1 mole of methanol; % H₂O, K.F. = 2—4.0. 5 5
- Preparation of Crystalline 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid sesquihydrate. 10 10
- 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate (15 g.) was slurried in 60 ml. of water. The pH was raised to 6.5 by addition of 4N NaOH and the mixture was passed through a 200 mesh screen. The reaction mixture was slurried at room temperature for 2 hours, the pH being maintained at 6.5 during this period. The crystals were removed by filtration, washed with 20 ml. of water and air dried at 37°C for 24 hours to give 11.5 g. of title crystalline product. Bio assay = 924 mcg./mg. (average). % H₂O, K.F. = 5.26. NMR and IR were consistent for the proposed structure and indicated that the product contained no methanol but did have a trace of propylene glycol. 15 15
- Preparation of Crystalline 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid sesquihydrate and formation of other crystalline hydrates. 20 20
- 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate (200 mesh; 10.0 g.) substantially free of propylene glycol is slurried in 30—40 ml. of deionized water at ambient room temperature (20—25°C) to give a pH 3—4 aqueous suspension. NaOH (40%) is slowly added with rapid stirring to bring the pH to 6.3—6.7. The mixture is slurried at pH 6.3—6.7 for 2 hours. The crystals are removed by filtration, washed with water and air dried at room temperature for 24 hours to give a 75—80% weight yield of 950—1000 mcg./mg. crystals of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid dihydrate. IR and NMR analyses were consistent for the proposed structure and indicated that the product contained no methanol but did have a trace of propylene glycol. H₂O, K.F. = 6.56. 25 25
- A sample of the crystalline dihydrate was air dried at 37°C for 24 hours giving the crystalline sesquihydrate of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid. H₂O, K.F. = 4.26. 30 30
- A second sample of the dihydrate was air dried at 45°C for 24 hours to give the crystalline sesquihydrate. H₂O, K.F. = 5.5. 35 35
- A sample of the dihydrate was air dried at 56°C for 24 hours to give the crystalline monohydrate of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid. H₂O, K.F. = 4.38 (theoretical % H₂O for monohydrate—3.75). 40 40
- A sample of the dihydrate was vacuum dried over P₂O₅ at room temperature for 24 hours giving the crystalline hemihydrate of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid. H₂O, K.F. = 2.63 (theoretical % H₂O for hemihydrate—1.91). 45 45
- A sample of the dihydrate was vacuum dried at 56°C for 24 hours giving the crystalline hemihydrate. H₂O, K.F. = 1.6—2.0. 50 50
- The following examples are given in illustration of, but not in limitation of, the present invention.

Description of the Preferred Embodiments.

Example 1.



Sodium - 7 - [2 - methyl - 4 - (p - hydroxyphenyl) - 5 - oxo - 1 - imidazolidinyl] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylate.

To a slurry of 3 g. of the methanol solvate of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid in 15 ml. of water was added 0.3 ml. of acetaldehyde. The pH of the slurry was then slowly brought to 7.1 by addition of 40% NaOH whereupon a solution was obtained. The solution was left at room temperature for 20 minutes and the pH fell to 6.8. The solution was added with rapid stirring to 300 ml. of isopropanol. An amorphous precipitate formed. After slurrying the reaction mixture for 10 minutes, the precipitate was removed by filtration, washed with 50 ml. of isopropanol and vacuum-dried at 56°C for 24 hours to give 2.5 g. of the title product.

Bio-assay = 822 mcg./mg.

% H₂O (K.F.) = 1.44

% Na by ash = 1.08

IR and NMR spectra were consistent for the proposed structure.

Elemental analysis results:

% C = 46.5
% H = 4.18
% N = 16.46
% S = 11.94

Example 2.

Preparation of Potassium Salt of Acetaldehyde Reaction Product of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthio - methyl) - 3 - cephem - 4 - carboxylic Acid.

A slurry was prepared of 2 g. of 7 - [D - α - amino - α - (p - hydroxyphenyl) - acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate, 20 ml. methanol and 0.6 ml. acetaldehyde. To this slurry was added 0.5 ml. of triethylamine to give pH of 9.0. A solution was obtained after 1 hour of stirring.

To approximately 1/2 of the above solution was added with rapid stirring 1.2 ml. of a 30% potassium 2-ethylhexanoate (KEH)-isopropanol (IPA) solution. An amorphous precipitate formed. The reaction mixture was slurried for 0.5 hour and then filtered. The precipitate was washed with 10 ml. methanol and vacuum-dried at 56°C for 24 hours to give 1 g. of title product.

Bio-assay = 768 mcg./mg.

% H₂O (K.F.) = 3.47

% K by ash = 2.77

IR and NMR were consistent for the cyclic acetaldehyde reaction product.

Example 3.

Sodium 7 - [2 - methyl - 4 - (p - hydroxyphenyl) - 5 - oxo - 1 - imidazolidinyl] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylate.

Three grams of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate was suspended in 10 ml. of water. To the suspension was added 0.6 ml. of acetaldehyde and then sufficient 40% NaOH to bring the pH of the reaction mixture to 7.0. A pH of 6-6.5 was maintained for 1 hour. The solution which

formed was lyophilized for 18 hours and then vacuum-dried at 56°C for 6 hours to give the title salt.

Bio-assay (average) = 812 mcg./mg.

% H₂O (K.F.) = 2.19

% Na by ash = 2.53

IR and NMR spectra were consistent for the cyclic sodium salt.

Example 4.

Sodium - 7 - [2 - methyl - 4 - (p - hydroxyphenyl) - 5 - oxo - 1 - imidazolidinyl] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylate.

Thirty grams of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate is slurried in 100 ml. of deionized water at 22—24°C. Ice-cold acetaldehyde (4.5 ml.) is added and the mixture is titrated to pH 7.0 with 40% NaOH (The pH is not allowed to rise over 7.5). A solution is obtained at about pH 5.8. The solution is stirred and maintained at a pH of 6.7—7.2 for 0.5 hour. Darco—G60 activated carbon (4.5 g.) is added and the reaction mixture slurried for 0.5 hour. The carbon is removed by filtration, washed with 5 ml. water and the wash water added to the filtrate. The pH is in the range of 6.7—7.3. The solution is sterile filtered and the filtrate added with rapid stirring to 350 ml. of sterile isopropanol under sterile conditions. An amorphous precipitate forms. The reaction mixture is slurried for 10 minutes and the solids are removed by filtration, washed with 70 ml. of sterile acetone, 70 ml. of sterile isopropanol and vacuum dried under sterile conditions at 50—56°C for 24—48 hours to give approximately 30 g. of title product. Bio-assay = 800 mcg./mg.

Example 5.

Potassium 7 - [2 - methyl - 4 - (p - hydroxyphenyl) - 5 - oxo - 1 - imidazolidinyl] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylate.

Ten grams of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate is slurried in 100 ml. of methanol. Two ml. of ice-cold acetaldehyde is added followed by 3 ml. of triethylamine. The mixture is slurried for 0.5 hour at ambient room temperature and a near solution is obtained. The mixture is warmed to 40—45°C and kept within this temperature range for 15 minutes. After cooling to 22—25°C, Darco—G60 (1.5 g.) is added and the mixture slurried for 0.5 hour. The carbon is removed by filtration, washed with 10 ml. methanol and the wash solution then added to the filtrate. The filtrate is sterilized and 22 ml. of a sterile solution of 30% potassium 2-ethylhexanoate in isopropanol is added with very rapid stirring over a 5 minute period. An amorphous precipitate forms. The mixture is vigorously slurried for 1 hour. The precipitate is removed by filtration under sterile conditions, washed with 75 ml. of sterile methanol and vacuum-dried under sterile conditions at 50—55°C for 24—48 hours to yield approximately 9 g. of the title potassium salt. Bio-assay = 750—790 mcg./mg.

Example 6.

Sodium 7 - [2 - methyl - 4 - (p - hydroxyphenyl) - 5 - oxo - 1 - imidazolidinyl] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylate.

Ten grams of 200 mesh 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate is slurried in 100 ml. of sterile methanol under sterile conditions. The sterile reaction vessel should be capable of operation as a closed system under moderate pressure. Fifty ml. of a sterile 30% sodium 2-ethylhexanoate solution (in isopropanol) and 2 ml. of sterile ice-cold acetaldehyde are added with rapid stirring. The reaction vessel is closed or sealed and the mixture is rapidly stirred for 2 hours. The temperature is raised to 45—50°C and the mixture is slurried for 2 hours. The temperature is lowered to 20—25°C and the mixture is slurried for 1 hour. The amorphous solids are removed by sterile filtration, washed with 10 ml. of sterile methanol and vacuum-dried at 50—56°C for 24—48 hours at sterile conditions to give approximately 8 g. of title product.

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	Example 7.	
5	Sodium 7 - [2 - methyl - 4 - (p - hydroxyphenyl) - 5 - oxo - 1 - imidazolidinyl] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl - 3 - cephem - 4 - carboxylate with citric acid for parenteral use. (Label claim is 250 mg./ml. of 7 - [D - α - amino - α - (p - hydroxyphenyl) - acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid activity).	5
10	Formula. Sodium 7 - [2 - methyl - 4 - (p - hydroxyphenyl) - 5 - oxo - 1 - imidazo - lidinyl] - 3 - (1,2,3 - triazol - 5 - ylthio - methyl) - 3 - cephem - 4 - carboxylate, milled 100 mesh, sterile * 0.250 g.	10
15	Sterile anhydrous citric acid, 100 mesh ** 0.050 g.	
15	* Calculate the amount of sodium salt to use as follows: $\frac{0.250 \text{ gram} \times 1000}{\text{Potency of sodium salt in mcg./mg.}} = \text{Grams of sodium salt per single 1 ml. dose}$	15
25	** This is an approximate weight required to obtain the desired pH of 5.5. An acceptable pH range is 5.2—5.9.	
20	Procedure. 1) Double check all weights before using. 2) Use sterile lint free procedures. 3) Spray blender room with peracetic acid before starting. 4) Relative humidity should be 50% or less.	20
25	4) Aseptically mill the sterile monosodium salt through a suitable sterile mill such as a Fitzmill using a sterile mesh screen to obtain appromixately 100 mesh particle size. Note: The sodium salt is amorphous, does not readily pass through a 60 mesh screen and becomes <i>highly</i> charged upon screening and handling.	25
30	6) Pass the sterile milled monosodium salt into a suitable sterile blender (blender may have to be earthed to dissipate charge on the powder). 7) Aseptically add the sterile, anhydrous 100 mesh citric acid.	30
40	8) Blend for at least 5 hours to assure complete mixing. 9) Drop into suitable sterile container for storage.	
35	10) Fill into officially designated sterile flint glass vials, capped with designated stoppers.	35

TABLE I.

Antibiotic Activity In Nutrient Broth.

Organism		MIC (mcg./ml.)		
		Sodium Salt Of Ex. 4	BL—S640±	Cephalothin
<i>D. pneumoniae</i> *	(10 ⁻³)** A9585	0.02	0.02	0.04
<i>Str. pyogenes</i>	(10 ⁻³)** A9604	0.02	0.02	0.04
<i>S. aureus</i> Smith	(10 ⁻⁴) A9537	0.3	0.3	0.08
<i>S. aureus</i> + 50% serum	(10 ⁻⁴) A9537	0.5	1	0.3
<i>S. aureus</i> BX1633	(10 ⁻³) A9606	0.6	0.6	0.16
<i>S. aureus</i> BX1633	(10 ⁻²) A9606	1	1	0.3
<i>S. aureus</i> Meth-Res	(10 ⁻³) A15097	2	4	0.5
<i>Sal. enteritidis</i>	(10 ⁻⁴) A9531	0.3	0.3	0.16
<i>E. coli</i> Juhl	(10 ⁻⁴) A15119	1	1	16
<i>E. coli</i>	(10 ⁻⁴) A9675	2	4	63
<i>K. pneumoniae</i>	(10 ⁻⁴) A9977	0.5	0.5	1
<i>K. pneumoniae</i>	(10 ⁻⁴) A15130	2	2	16
<i>Pr. mirabilis</i>	(10 ⁻⁴) A9900	0.5	0.5	1
<i>Pr. morganii</i>	(10 ⁻⁴) A15153	16	16	>125
<i>Ps. aeruginosa</i>	(10 ⁻⁴) A9843A	>125	>125	>125
<i>Ser. marcescens</i>	(10 ⁻⁴) A20019	>125	>125	>125
<i>Ent. cloacae</i>	(10 ⁻⁴) A9656	>125	>125	>125
<i>Ent. cloacae</i>	(10 ⁻⁴) A9657	0.5	0.5	2
<i>Ent. cloacae</i>	(10 ⁻⁴) A9659	16	32	>125

Footnotes to Table I.

* 45% AAB + 5% serum + 50% broth listed above.

** Dilution of overnight broth culture.

‡ BL—S640 = 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid.

TABLE II.

Mouse Blood Levels After Oral
Administraion Of 100 mg./kg. Body Weight.

Compound	Blood Level (μ g/ml.)			
	0.5 Hrs. After Administration	1	2	3.5
Compound of Ex. 4	19.7	29.1	25.8	15.2
‡ BL—S640	45.0	51.0	25.6	11.0
Cephalexin	40.0	24.5	10.1	<5.6

The compounds were prepared
in Tween—registered Trade
Mark—carboxymethylcellulose
and 8 mice were used for each
compound

‡ BL—S640 — 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid

TABLE III.

Mouse Blood Levels After Intramuscular
Administration Of 10 mg./kg. Body Weight.

Compound	Blood Level (μ g/ml.)			
	15 Minutes After Administration	30	60	90
Compound of Ex. 4	14.0	13.3	8.8	6.8
‡ BL—S640	13.5	13.6	8.4	5.7
Cephalothin	5.1	2.8	<1.7	<1.7

The compounds were prepared
in 0.001% phosphate buffer
and 8 mice were used for each
compound.

‡ BL—S640 = 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid



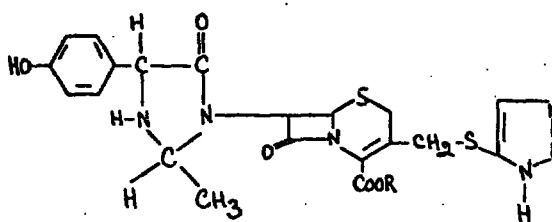
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WHAT WE CLAIM IS:—

1. Compounds of the formula



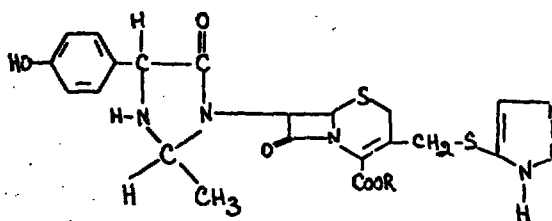
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wherein R is an alkali metal.

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2. A compound of Claim 1 wherein R is sodium.
3. A compound of Claim 1 wherein R is potassium.
4. A process for the preparation of a compound of the formula

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wherein R is an alkali metal; which process comprises

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- (1) treating an aqueous suspension of 7 - [D - α - amino - α - (p - hydroxy - phenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid or a solvate or hydrate thereof with acetaldehyde and sufficient water-soluble alkali metal base to raise the pH of the reaction mixture to between about 5.5 and 8 and to form in solution the desired salt of formula I; and

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- (2) recovering from the solution the desired salt of formula I.

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5. The process according to Claim 4 wherein the 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid starting material is in the form of the methanol or propylene glycol solvate or the sesquihydrate.

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6. The process of any one of the preceding Claims wherein R is sodium or potassium.

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7. The process of Claim 6 wherein the base is sodium or potassium hydroxide.

8. The process of any one of Claims 4 to 7 wherein the desired salt of formula I is recovered from the solution by lyophilization.

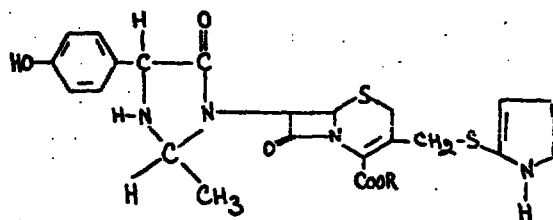
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9. The process of any one of Claims 4 to 8 wherein in Step (2) the desired salt of formula I is precipitated from the solution by addition of an organic solvent in which the salt is insoluble.

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10. The process of Claim 9 wherein the organic solvent is isopropanol.

11. A process for preparing a compound of the formula



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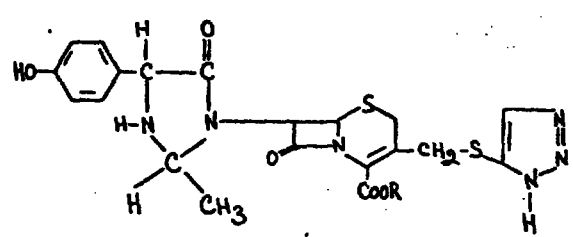
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wherein R is sodium or potassium; which process comprises

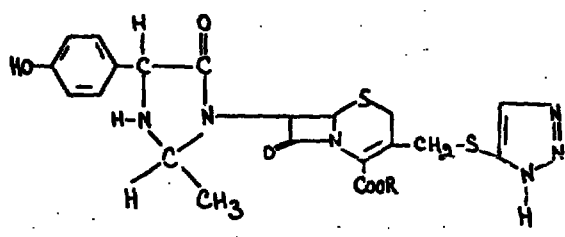
- (1) treating an aqueous suspension of 7 - (D - α - amino - α - (p - hydroxy - phenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate with a slight molar excess of acetaldehyde and sufficient sodium hydroxide or potassium hydroxide to raise the pH of the reaction mixture to between about 5.5 and 8 and to form in solution the desired salt of formula I; and
- (2) precipitating the salt of formula I from the solution by addition of isopropanol.
12. The process of any one of Claims 4 to 11 wherein the pH in Step (1) is raised to between about 6.7 and 7.2.
13. The process of any one of Claims 4 to 12 wherein the solution obtained in Step (1) is filtered prior to precipitation Step (2).
14. The process of any one of Claims 4 to 13 wherein the solution obtained in Step (1) is treated with activated carbon prior to the filtration step.
15. A process for the preparation of a compound of the formula



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wherein R is an alkali metal; which process comprises

- (1) forming a suspension of 7 - (D - α - amino - α - (p - hydroxyphenyl) - acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid or a solvate or hydrate thereof in a suitable inert organic solvent, said solvent being a solvent for the triethylamine salt of the acetaldehyde reaction product of 7 - (D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid and a non-solvent for the alkali metal salt of formula I;
- (2) treating the suspension with acetaldehyde and sufficient triethylamine to form in solution the triethylamine salt of the acetaldehyde reaction product of 7 - (D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid; and
- (3) precipitating the desired alkali metal salt of formula I from the solution by adding a solvent-soluble alkali metal base.
16. The process of Claim 15 wherein the 7 - (D - α - amino - α - (p - hydroxy - phenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid starting material is in the form of the methanol or propylene glycol solvate or the sesquihydrate.
17. The process of Claim 15 or 16 wherein the solvent in Step (1) is methanol.
18. The process of any one of Claims 15 to 17 wherein R in formula I is sodium or potassium.
19. The process of Claim 18 wherein the sodium or potassium salt in Step (3) is sodium 2-ethylhexanoate or potassium 2-ethylhexanoate.
20. A process for preparing a compound of the formula



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wherein R is sodium or potassium; which process comprises

(1) forming a suspension of 7 - [D - α - amino - α - (p - hydroxyphenyl) - acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate in methanol;

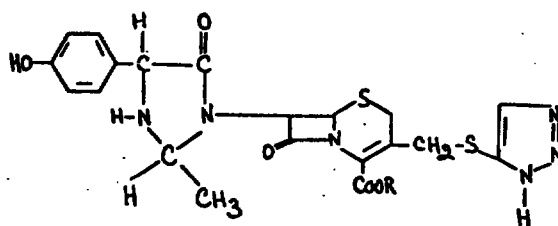
(2) treating the suspension with a molar excess of acetaldehyde and sufficient triethylamine to form in solution the triethylamine salt of the acetaldehyde reaction product of 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid; and

(3) precipitating the desired alkali metal salt of formula I from the solution by adding a solution of sodium or potassium 2-ethylhexanoate in isopropanol.

21. The process of any one of Claims 15 to 20 wherein the solution obtained in Step (2) is filtered prior to precipitation Step (3).

22. The process of any one of Claims 15 to 21 wherein the solution obtained in Step (2) is treated with activated carbon prior to the filtration step.

23. A process for the preparation of a compound of the formula



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wherein R is an alkali metal; which process comprises

(1) forming a suspension of 7 - [D - α - amino - α - (p - hydroxyphenyl) - acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid or a solvate or hydrate thereof in a suitable inert organic solvent, said solvent being a non-solvent for the alkali metal salt of formula I;

(2) treating the suspension with acetaldehyde and a solvent-soluble alkali metal base, said base being used in sufficient amount to raise the pH of the reaction mixture to between about 5.5 and 8; and

(3) recovering the desired product of formula I from the reaction mixture.

24. The process of Claim 23 wherein the 7 - [D - α - amino - α - (p - hydroxyphenyl)acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid starting material is in the form of the methanol or propylene glycol solvate or sesquihydrate.

25. The process of Claim 23 or 24 wherein the inert organic solvent is methanol.

26. The process of any one of Claims 23 to 25 wherein R in formula I is sodium or potassium.

27. The process of Claim 26 wherein the base used in Step (2) is sodium or potassium 2-ethylhexanoate.

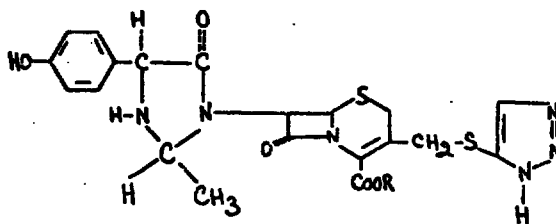
28. A process according to any one of Claims 23 to 27 wherein

(1) a suspension is formed of 7 - [D - α - amino - α - (p - hydroxyphenyl) - acetamido] - 3 - (1,2,3 - triazol - 5 - ylthiomethyl) - 3 - cephem - 4 - carboxylic acid methanol solvate in methanol;

(2) the suspension is treated with a molar excess of acetaldehyde and a sufficient amount of a solution of sodium or potassium 2-ethylhexanoate in isopropanol to raise the pH of the reaction mixture to between about 5.5 and 8; and

(3) the desired product of formula I is recovered by filtration.

29. A pharmaceutical composition suitable upon reconstitution with water for use as a parenterally-administrable antibiotic formulation, said composition comprising a compound of the formula



I



wherein R is an alkali metal and a solid pharmaceutically acceptable water-soluble organic acid or glycine hydrochloride, said organic acid or glycine hydrochloride being present in an amount such that the pH of the formulation upon reconstitution with water is between about 5 and 6.

5 30. A composition of Claim 29 wherein the solid organic acid is present in an amount of about 4—6% of the weight of the compound of formula I.

31. A composition of Claim 26 or 27 wherein the solid organic acid is citric acid.

32. A composition of Claim 29, 30 or 31 wherein R in formula I is sodium or potassium.

33. A pharmaceutical composition according to any one of Claims 29 to 32 further comprising a pharmaceutical diluent or carrier.

34. A pharmaceutical composition comprising a compound of Formula I substantially as hereinbefore described.

15. 35. A pharmaceutical composition comprising a compound of Formula I substantially as hereinbefore described with reference to any one of the Examples.

36. A process for the preparation of a compound of Formula I substantially as hereinbefore described.

20 37. A process for the preparation of a compound of Formula I substantially as hereinbefore described with reference to any one of the Examples.

38. A compound of Formula I whenever prepared by a process according to any one of Claims 4 to 28, Claim 36, or Claim 37.

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