

1283811

PATENT SPECIFICATION

(11)

1283811

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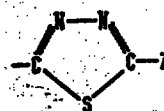


(54) 3-MERCAPTOTHIAZOLE OR MERCAPTOTETRAZOLE
 CEPHALOSPORINS AND PROCESS FOR PREPARING THE
 SAME

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

- 10 The present invention relates to cephalosporins substituted in a 3-position with a mercaptothiazole or mercaptotetrazole and in the 7-position with a phenyl- or thienyl-acetyl group bearing an α -amino or hydroxy group.
- 15 More specifically, the present invention provides a compound having the formula

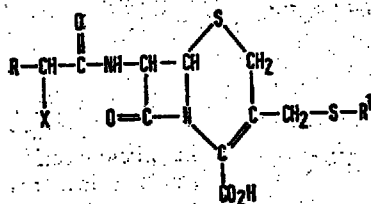
trifluoromethyl, amino, nitro, hydroxy, C_1-C_3 alkyl, or C_1-C_3 alkoxy;
 R^1 is



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Formula I

- 20 wherein R is



or

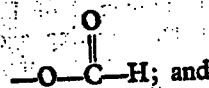


Y is hydrogen, chlorine, bromine, fluorine,

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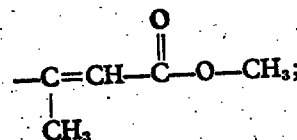
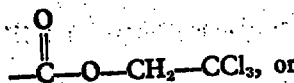
Z is hydrogen or C_1-C_3 alkyl;
 Q is C_1-C_3 alkyl;

X is $-NH_2$, $-NHR^2$, $-OH$, or



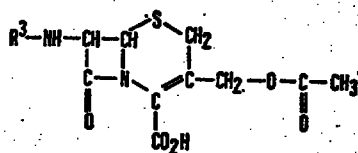
R^2 is $-C(=O)-O-C(CH_3)_3$;

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and the pharmaceutically acceptable salts thereof.

The compounds of the invention may be prepared by reacting a cephalosporin compound of the formula

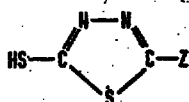


Formula II

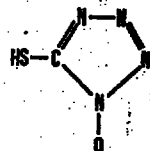
wherein R^3 is hydrogen or



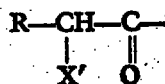
wherein R and X are as defined above, with a thiol of the formula



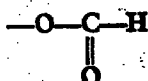
or



wherein Z and Q are as defined above, to displace the acetoxy moiety in the 3-position of said compound of Formula II; and, when R^3 is hydrogen, acylating the amino group in the 7-position of said compound of Formula II by reaction with an acylating agent having at least one constituent radical of the formula



wherein R is as defined above and X' is



or $-NHR^2$ wherein R^2 is as defined above.

The cephalosporin antibiotics of the invention exhibit a high degree of activity yet are unusually stable. These compounds are not only relatively stable toward liver enzymes but are also stable toward the cephalosporinases proliferated by gram negative bacteria.

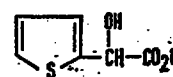
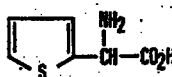
As a consequence, the compounds remain available to supply antimicrobial activity for a longer period.

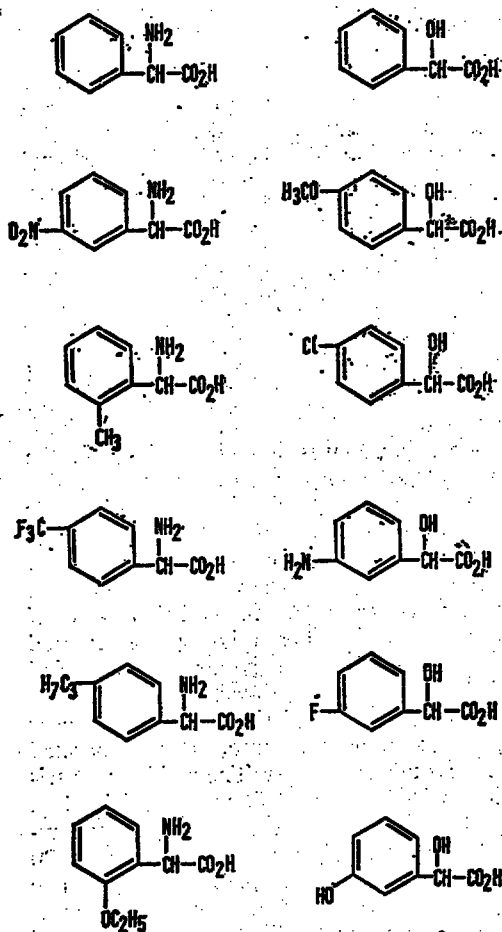
Those cations which form pharmaceutically acceptable salts with acids are well known to those skilled in the art. Among the more commonly used cations for this purpose are the sodium, potassium, and ammonium ions. Too, the amino group in the side chain may be converted to a salt by treatment with such acids as hydrochloric acid, hydrobromic acid, and *p*-toluenesulfonic acid.

These compounds may be prepared by the displacement of the 3-acetoxy group of 7-aminocephalosporanic acid with either 1-alkyl-1,2,3,4-tetrazole-5-thiol or a 1,3,4-thiadiazole-5-thiol followed by acylation of the 7-amino group with the desired hydroxy- or aminoacetic acid. The displacement of an ester group with a thiol group is a well-known reaction and may be accomplished in aqueous solution at a temperature within the range of about 50° to 100°C. in the presence of a mild base such as sodium bicarbonate. An excess of the thiol is preferably employed. The alkyl group in the 1-position of the tetrazole employed may be methyl, ethyl or propyl. The thiadiazole used may have a hydrogen, methyl, ethyl, or propyl group in the 2-position.

The claimed compounds are then obtained by acylation of the 7-amino group of the thio compounds from the displacement reaction with the proper amino- or hydroxyacetic acid. The acylation of the 7-amino group of cephalosporins is a well-known reaction and may be accomplished by means of the acid halide or a mixed anhydride. The particular method of acylation is unimportant to this invention.

Typical acids that can be used in acylating the thio compounds to obtain compounds of this invention are the phenylacetic acids, the substituted phenylacetic acids, and the thienylacetic acids substituted on the α -carbon atom with an amino or hydroxy group. Substituents that may be present on the phenyl ring of the acid include chlorine, bromine, fluorine, trifluoromethyl, amino, nitro, hydroxy, C_1-C_3 alkyl, or C_1-C_3 alkoxy. Examples of suitable acids including the following.

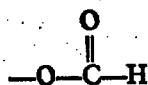




Stereoisomerism occurs around the asymmetric α -carbon atom of these acids. It is well known that it is generally the D-isomer that exhibits biological activity.

It is to be understood that the α -amino and α -hydroxy groups of the acids will be protected during the acylation step. Thus, for example, the hydroxyl group may be converted to the formate ester while the amine group would be protected by such groups as the *t*-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, or the enamine obtained from methyl acetoacetate. These protecting groups can then be removed (e.g. by hydrolysis) at the completion of the acylation step to yield the antibiotically-active compounds.

Thus, in the formula those compounds in which X is $-\text{NHR}''$ or



are merely intermediates in the preparation of the desired antibiotics. Those compounds in which X is amino or hydroxy are the active compounds of the invention, and

pharmaceutical compositions containing these compounds and an excipient are within the scope of the present invention. The preferred compounds of this invention are those in which R is phenyl or 2- or 3- thienyl, X is amino or hydroxy, and Z and Q are methyl.

The preparation of these compounds will be illustrated by the following examples.

EXAMPLE 1

To a stirred mixture of 27.2 g. (0.1 mole) of 7-aminocephalosporanic acid in 200 ml. of water and 100 ml. of acetone was added a saturated solution of sodium bicarbonate to a pH of 7.9. This solution was placed in an 80°C. bath and when the internal temperature had reached 45°C. a solution of 19.6 g. (1.15 mole) of 2-methyl-1,3,4-thiadiazole-5-thiol in 200 ml. of acetone was added. The mixture was heated in the 80°C. bath for three hours and then cooled to 10°C. and the pH was adjusted to 3.9 by the addition of 6 N hydrochloric acid. The cold mixture was stirred for 15 minutes and the solid was collected, washed with acetone, and dried. There was obtained 24 g. (70 percent) of 7-amino-3-(2-methyl-1,3,4-thiadiazole-5-thiomethyl)- Δ^3 -cephem-4-carboxylic acid. The expected structure was confirmed by nuclear magnetic resonance and ultraviolet spectroscopy.

EXAMPLE 2

Example 1 was repeated using 1-methyl-1,2,3,4-tetrazole-5-thiol instead of the thiadiazole. There was obtained 25 g. (76 percent) of 7-amino-3-(1-methyl-1,2,3,4-tetrazole-5-thiomethyl)- Δ^3 -cephem-4-carboxylic acid. Once again the structure was confirmed by nuclear magnetic resonance and ultraviolet spectroscopy.

EXAMPLE 3

D-mandelic acid (15.2 g., 0.1 mole) was stirred into 250 ml. of formic acid and the mixture was allowed to stand at room temperature for two days. The solution was concentrated under vacuum, the residue dissolved in benzene, the benzene solution washed with water, dried over magnesium sulfate, filtered, and concentrated to dryness to yield 13.2 g. of D-mandelic acid formate ester. To a solution of 3.6 g. (0.02 mole) of the D-mandelic acid formate ester and 25 ml. of dry benzene at room temperature were added 5 ml. of oxalyl chloride and 1 drop of dimethylformamide. After stirring two hours at room temperature the solution was concentrated under vacuum to yield the formate ester of D-mandelyl chloride as an oil which was dissolved in 40 ml. of acetone. The acid chloride solution was added to an ice cold solution of 3.44 g. (0.01 mole) of the product from Example 1 and 5 g. of sodium bicarbonate in 100 ml. of water and 100

ml. of acetone. This mixture was stirred in the cold for one hour and then at room temperature for two hours. The acetone was removed under reduced pressure and the resulting aqueous mixture was added to a cold, stirred mixture of 100 ml. of water and 200 ml. of ethyl acetate. The pH was adjusted to 2.0 by the addition of 6 N hydrochloric acid. After filtration through a filter aid the water layer was discarded and the ethyl acetate layer was washed with water, dried over magnesium sulfate, and concentrated under vacuum to an oil. The oil was triturated with ether to cause solidification and the solid was collected and dried, yielding 4 g. of 7-(D-2 - formyloxy - 2 - phenylacetamido) - 3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thio - methyl)- Δ^3 -cephem-4-carboxylic acid. To 2.64 g. (0.54 mole) of the formate protected tetrazole cephalosporanic acid in 30 ml. of water was added 2.5 g. of sodium bicarbonate and the mixture was stirred for three hours at room temperature. The mixture was diluted to 50 ml. with water, overlayer with 50 ml. of ethyl acetate, cooled in an ice bath, and the pH adjusted to 2 by the addition of hydrochloric acid. The layers were separated and the ethyl acetate layer was washed with water, dried over magnesium sulfate, and slurried with ether to precipitate the product which was collected to yield 1.4 g. of crude 7 - D - mandelamido - 3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - Δ^3 - cephem-4-carboxylic acid. To 1.3 g. (0.0026 mole) of the crude acid in 5 ml. of absolute ethanol was added 2.6 ml. of 1 N sodium acetate in methanol. The mixture was stirred and cooled and the solid which precipitated was collected to yield 1.1 g. of the sodium salt of the cephalosporin acid. This sodium salt was recrystallized by dissolving in methanol and adding isopropanol to cause precipitation. This treatment gave sodium 7-D-mandelamido - 3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - Δ^3 - cephem - 4-carboxylate. The structure was confirmed by nuclear magnetic resonance and ultraviolet spectroscopy. The compound had a pKa of 4.9. The free acid was also converted to the dicyclohexylamine salt which was subjected to elemental analysis.

Analysis:

Calculated for $C_{19}H_{18}N_4O_5S_2 \cdot C_{12}H_{23}N$:

C, 56.42; H, 6.26; N, 10.61.

55 Found:

C, 56.45; H, 6.34; N, 10.41.

EXAMPLE 4

The procedure of Example 3 was repeated using as the nucleus the product from Example 2. There was obtained 1.1 g. of sodium 7 - D - mandelamido - 3 - (1 - methyl - 1,2,3,4 - tetrazole - 5 - thiomethyl) - Δ^3 - cephem-4-carboxylate. The structure was confirmed by nuclear magnetic resonance and

ultraviolet spectroscopy. The product had a pKa of 5.2.

EXAMPLE 5

A solution of 2.46 g. (0.01 mole) of D-phenyl-glycine in which the amino group was protected with the *t*-butoxycarbonyl group in 50 ml. of tetrahydrofuran was cooled to -10°C . in an ice-acetone bath. To this cold solution were added 1.4 ml. of triethylamine and 1.3 ml. of isobutyl chloroformate. The solution of the resulting mixed anhydride was stirred in the cold for 20 minutes then added to a cold stirred solution of 3.44 g. (0.01 mole) of the product from Example 1 and 1.4 ml. of triethylamine in 50 ml. of water and 50 ml. of tetrahydrofuran. This reaction mixture was stirred one hour in the cold and two hours at room temperature. The tetrahydrofuran was stripped off under vacuum and the aqueous mixture was poured into a cold, stirred mixture of 50 ml. of water and 100 ml. of ethyl acetate. The pH was adjusted to 2 by the addition of 6 N hydrochloric acid. The mixture was filtered through a filter aid and the aqueous and ethyl acetate layers were separated. The ethyl acetate layer was washed with water, dried over magnesium sulfate, filtered, and evaporated to dryness under vacuum. The residue was triturated with ether and filtered to yield 4 g. of solid product. To remove the *t*-butoxycarbonyl group this solid was stirred in 20 ml. of ice-cold trifluoroacetic acid for five minutes and the mixture was then concentrated under vacuum. Ten milliliters of ethyl acetate was added and the mixture was again evaporated under vacuum. The residue was stirred with 30 ml. of water and 30 ml. of methyl isobutyl ketone and tributylamine was added to a pH of 4.0. The precipitated solid was collected to yield 0.75 g. of crude 3-(2-methyl - 1,2,3 - thiadiazole - 5 - thiomethyl) - 7 - D - phenylglycylamido - Δ^3 - cephem - 4-carboxylic acid. The water layer was washed with methyl isobutyl ketone, evaporated to dryness and the residue slurried with acetonitrile and filtered to give an additional 0.86 g. of solid material. To obtain pure material 0.59 g. of the solid which was precipitated at a pH of 4 was stirred with 3 ml. of formamide, 3 ml. of water, and 1 ml. of methanol, the solution was filtered, and 20 ml. of acetonitrile was added. This mixture was cooled for several hours and the solid which precipitated was collected to give 0.15 g. of pure product. The nuclear magnetic resonance spectrum was consistent with the proposed structure and bioautograph showed one-spot material.

Analysis:

Calculated for $C_{19}H_{18}N_4O_5S_2 \cdot H_2O$:

C, 46.04; H, 4.27; N, 14.13.

Found:

C, 46.10; H, 4.55; N, 14.06.

ct had a 65

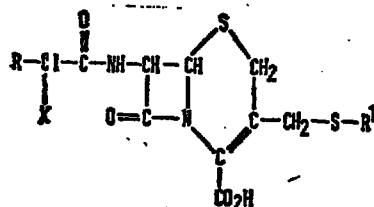
EXAMPLE 6

The procedure of Example 5 was repeated replacing the thiadiazole with 1-methyl-1,2,3,4-tetrazole-5-thiol to yield 3-(1-methyl-1,2,3,4-tetrazole-5-thiomethyl)-7-D-phenylglycylamido- Δ^3 -cephem-4-carboxylic acid. The nuclear magnetic resonance spectrum and the bioautograph of the crude product confirmed that the desired compound had been obtained.

Following the procedures of Examples 3 to 6 the corresponding thienyl and substituted phenyl compounds are prepared by acylation with the appropriate acid. It is also possible to first acylate 7-aminocephalosporanic acid and then conduct the displacement reaction to replace the acetoxy group with the proper thio group. The particular method of preparation chosen is not important.

WHAT WE CLAIM IS:—

1. A compound having the formula



Formula I

wherein R is



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or

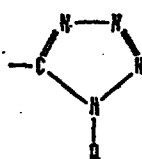


Y is hydrogen, chlorine, bromine, fluorine, trifluoromethyl, amino, nitro, hydroxy, C_1-C_3 alkyl, or C_1-C_3 alkoxy; R^1 is

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or



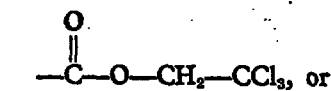
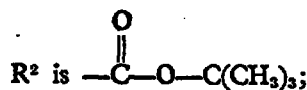
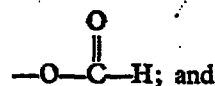
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Z is hydrogen or C_1-C_3 alkyl;

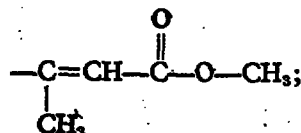
Q is C_1-C_3 alkyl;

X is $-NH_2$, $-NHR^2$, $-OH$, or

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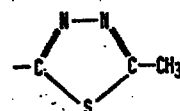


and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein X is $-NH_2$ or $-OH$; and the pharmaceutically acceptable salts thereof.

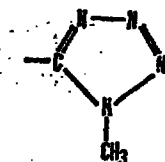
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3. The compound of claim 1 or 2 wherein R is phenyl, X is amino, and R^1 is



4. The compound of claim 1 or 2 wherein R is phenyl, X is amino, and R^1 is

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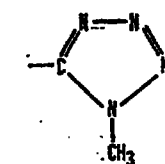


5. The compound of claim 1 or 2 wherein R is phenyl, X is hydroxy, and R^1 is



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6. The compound of claim 1 or 2 wherein R is thienyl, X is hydroxy, and R^1 is





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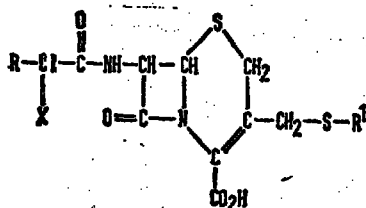
EXAMPLE 6

The procedure of Example 5 was repeated replacing the thiadiazole with 1-methyl-1,2,3,4-tetrazole-5-thiol to yield 3-(1-methyl-1,2,3,4-tetrazole-5-thiomethyl)-7-D-phenylglycylamido- Δ^3 -cephem-4-carboxylic acid. The nuclear magnetic resonance spectrum and the bioautograph of the crude product confirmed that the desired compound had been obtained.

Following the procedures of Examples 3 to 6 the corresponding thienyl and substituted phenyl compounds are prepared by acylation with the appropriate acid. It is also possible to first acylate 7-aminocephalosporanic acid and then conduct the displacement reaction to replace the acetoxy group with the proper thio group. The particular method of preparation chosen is not important.

WHAT WE CLAIM IS:—

1. A compound having the formula



Formula I

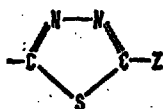
wherein R is



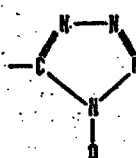
or



Y is hydrogen, chlorine, bromine, fluorine, trifluoromethyl, amino, nitro, hydroxy, C_1-C_3 alkyl, or C_1-C_3 alkoxy;
R¹ is



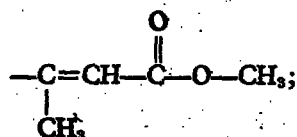
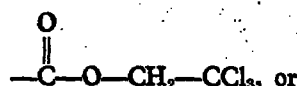
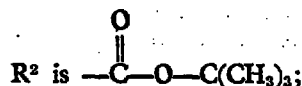
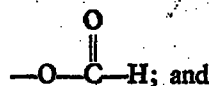
or



Z is hydrogen or C_1-C_3 alkyl;

Q is C_1-C_3 alkyl;

X is $-NH_2$, $-NHR^2$, $-OH$, or



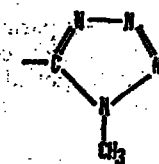
and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein X is $-NH_2$ or $-OH$; and the pharmaceutically acceptable salts thereof.

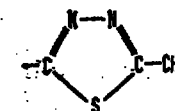
3. The compound of claim 1 or 2 wherein R is phenyl, X is amino, and R¹ is



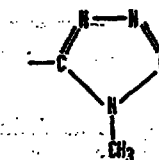
4. The compound of claim 1 or 2 wherein R is phenyl, X is amino, and R¹ is



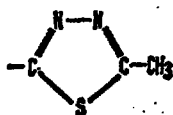
5. The compound of claim 1 or 2 wherein R is phenyl, X is hydroxy, and R¹ is



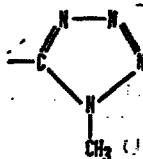
6. The compound of claim 1 or 2 wherein R is thienyl, X is hydroxy, and R¹ is



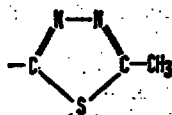
7. The compound of claim 1 or 2 wherein R is thienyl, X is amino, and R¹ is



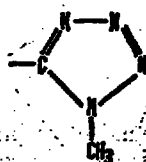
5 8. The compound of claim 1 or 2 wherein R is thienyl, X is amino, and R¹ is



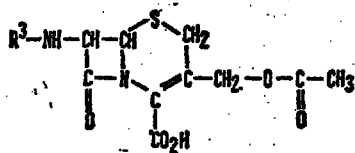
9. The compound of claim 1 or 2 wherein R is thienyl, X is hydroxy, and R¹ is



10 10. The compound of claim 1 or 2 wherein R is thienyl, X is hydroxy, and R¹ is

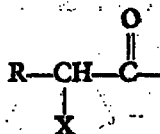


11. A process for preparing a compound according to claim 1 which comprises reacting a cephalosporin compound of the formula

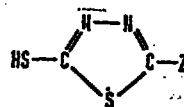


Formula II

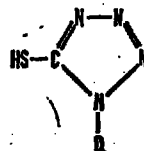
wherein R³ is hydrogen or



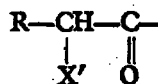
20 wherein R and X are as defined in Claim 1, with a thiol of the formula



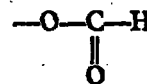
or



wherein Z and Q are as defined in Claim 1, to displace the acetoxy moiety in the 3-position of said compound of Formula II; and, when R³ is hydrogen, acylating the amino group in the 7-position of said compound of formula II by reaction with an acylating agent having at least one constituent radical of the formula

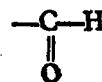


wherein R is as defined above and X' is



or -NHR² wherein R² is as defined in Claim 1.

12. The process of claim 11 which comprises removing the protective moieties



or R² when present in the final product.

13. The process of claim 12 wherein the removal is effected by hydrolysis.

14. The process of claim 11, 12 or 13 wherein the displacement of the acetoxy moiety is effected at a temperature in the range of 50—100°C. in the presence of a mild base.

15. The process of claim 14 wherein the base is sodium bicarbonate.

16. The process of any of claims 11 to 15 for preparing 7 - D - mandelamido - 3 - (1 - methyl - 1,2,3,4 - tetrazole - 5 - thiomethyl) - Δ³ - cephem - 4 - carboxylic acid which comprises displacing the acetoxy moiety in 7-amino-cephalosporanic acid by reaction with 1-methyl - 1,2,3,4 - tetrazole - 5 - thiol, acylating the amino group in the resulting 7-amino-3 - (1 - methyl - 1,2,3,4 - tetrazole - 5 - thiomethyl) - Δ³ - cephem - 4 - carboxylic acid by reaction with the formate ester of



* C L M S *

6

7

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7

D-mandelyl chloride, and removing the formyl protective group from the 7-(D-2-formyloxy - 2 - phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazole - 5 - thiomethyl) - Δ^3 - cephem-4-carboxylic acid thus obtained.

17. The process of any of claims 11 to 15 for preparing 3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - 7 - D - phenylglycylamido - Δ^3 - cephem - 4 - carboxylic acid which comprises displacing the acetoxy moiety in 7 - aminocephalosporanic acid by reaction with 2 - methyl - 1,3,4 - thiadiazole - 5 - thiol, acylating the amino group in the resulting 7 - amino - 3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - Δ^3 -cephem-4-carboxylic acid by reaction with the mixed anhydride of *t*-butyloxycarbonyl-protected D-phenylglycine and isobutyric acid, and removing the *t*-butyloxycarbonyl protective group from the compound thus obtained.

18. The process of any of claims 11 to 15 for preparing 3 - (1 - methyl - 1,2,3,4 - tetrazole - 5 - thiomethyl) - 7 - D - phenylglycylamido - Δ^3 - cephem - 4 - carboxylic acid which comprises displacing the acetoxy moiety in 7-aminocephalosporanic acid by reaction with 1 - methyl - 1,2,3,4 - tetrazole - 5 - thiol, acylating the amino group in the resulting 7 - amino - 3 - (1 - methyl - 1,2,3,4 - tetrazole - 5 - thiomethyl) - Δ^3 - cephem - 4 - carboxylic acid by reaction with the mixed anhydride of isobutyric acid and *t*-butyloxy carbonyl-protected D-phenylglycine, and removing the *t*-butyloxy-carbonyl-protective group from the compound thus obtained.

19. The process of any of claims 11 to 15 for preparing 7 - D - mandelamido - 3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - Δ^3 -cephem-4-carboxylic acid which comprises displacing the acetoxy moiety in 7-aminocephalosporanic acid by reaction with 2-methyl - 1,3,4 - thiadiazole - 5 - thio, acylating the amino group in the resulting 7-amino-3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - Δ^3 - cephem - 4 - carboxylic acid by reaction with the formate ester of D-mandelyl chloride, and removing the formyl protective group from the 7-(D-2-formyloxy - 2 - phenylacetamido) - 3 - (2 -

methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - Δ^3 -cephem-4-carboxylic acid thus obtained.

20. The process of any of claims 11 to 19 which comprises reacting the product thus obtained with a base selected to provide a pharmaceutically acceptable carboxylate salt.

21. The process of any of claims 11 to 19 which comprises reacting the product thus obtained with an acid selected to provide a pharmaceutically acceptable acid addition salt.

22. The process of claim 19 which comprises the step of reacting the 7-D-mandelamido - 3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - Δ^3 - cephem - 4 - carboxylic acid with sodium acetate to provide the corresponding sodium 7-D-mandelamido-3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - Δ^3 - cephem - 4 - carboxylate.

23. A pharmaceutical composition which comprises an excipient and a compound as defined in any of claims 2 to 10.

24. The composition of claim 23 which comprises 7 - D - mandelamido - 3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - Δ^3 -cephem-4-carboxylic acid or a pharmaceutically acceptable salt thereof.

25. The composition of claim 23 which comprises 7 - D - mandelamido - 3 - (1 - methyl - 1,2,3,4 - tetrazole - 5 - thiomethyl) - Δ^3 -cephem-4-carboxylic acid or a pharmaceutically acceptable salt thereof.

26. The composition of claim 23 which comprises 3 - (2 - methyl - 1,3,4 - thiadiazole - 5 - thiomethyl) - 7 - D - phenylglycylamido - Δ^3 - cephem - 4 - carboxylic acid or a pharmaceutically acceptable salt thereof.

27. The composition of claim 23 which comprises 3 - (1 - methyl - 1,2,3,4 - tetrazole - 5 - thiomethyl) - 7 - D - phenylglycylamido - Δ^3 - cephem - 4 - carboxylic acid or a pharmaceutically acceptable salt thereof.

28. A process for preparing a compound according to Claim 1, substantially as hereinbefore described with particular reference to the examples.

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