

**1,174,335**

**Complete Specification Published: 17 Dec., 1969.**



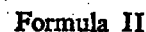
**International Classification:—C 07 d 99/24**

**7-Alpha-Amino-3-Methyl Cephalosporin Analogues,  
Pharmaceutical Compositions comprising the  
same and processes for preparing the same**

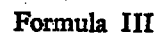
More specifically, the present invention provides an antibiotic compound having the structure



30 The invention also provides a process for preparing an antibiotic compound of Formula I which comprises subjecting to hydrogenolysis a compound of the structure



wherein R' is a hydrogen atom or the radical R—CHNH<sub>2</sub>—C:O— wherein R is as defined above, and, when R' is a hydrogen atom, acylating the 7-amino-3-methyl-Δ<sup>3</sup>-cephem-4-carboxylic acid thus obtained in a conventional manner with an acylating agent comprising said radical R—CHNH<sub>2</sub>—C:O—; or heating under acid conditions a penicillin sulfoxide of the formula:

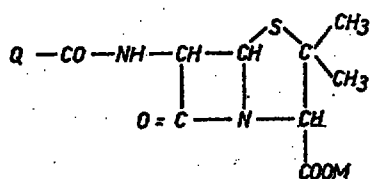


It will be apparent that the product can exist in the form of the inner salt, or as a salt of a pharmaceutically acceptable acid, or as a salt of a pharmaceutically acceptable cation. If desired, the product may be converted to a salt by reacting it with a base in a conventional manner. If this product is reacted with an acid in a conventional manner, the product

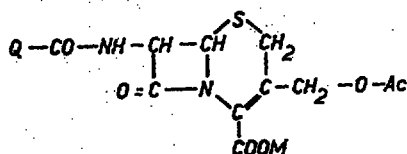
SPECIFICATION AMENDED - SEE ATTACHED SLIP

will be converted to an acid addition salt. Such salt forms are considered to lie within the scope of the invention as claimed. Suitable cations include sodium, potassium, ammonium, or any of a wide variety of substituted ammoniums (e.g., procaine, trimethylammonium). Suitable acids include hydrochloric, hydrobromic, hydriodic, sulfuric, phosphoric, nitric, citric, trichloroacetic and thiocyanic. It will also be apparent that the product can exist in optically active forms, and such forms (as well as racemic or other mixtures thereof) are considered to lie within the scope of the invention as claimed.

The first of the antibiotics to be discovered were the penicillins, which contain the penam nucleus, a thiazolidine ring with a fused  $\beta$ -lactam. A more recent discovery is the cephalosporins, which contain the  $\Delta^3$ -cephem nucleus, a dihydrothiazine ring with a fused  $\beta$ -lactam. These two classes of antibiotics are thus somewhat related in structure, as will be seen from the following general structural formulas:

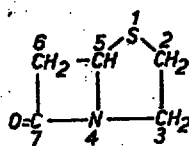


Penicillins

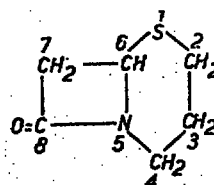


Cephalosporins

wherein Q represents essentially any organic radical, as exemplified by hundreds of examples in the prior art, and M represents a pharmaceutically acceptable cation. The penam nomenclature for the penicillins is described by Sheehan, Henery-Logan, and Johnson in the J. Am. Chem. Soc., 75, 3293, footnote 2 (1953), and has been adapted to the cephalosporins by Morin, Jackson, Flynn, and Roeske in the J. Am. Chem. Soc., 84, 3400 (1962). In accordance with these systems of nomenclature, "penam" and "cepham" refer respectively to the following saturated ring structures:



Penam



Cepham

while "cephem" refers to the cepham ring structure with a double bond, the position of which is indicated by a prefixed " $\Delta$ " with superscript denoting the carbon atom of lowest number to which the double bond is connected.

While both the penicillins and the cephalosporins have been remarkably effective in the treatment of a variety of infections, there is a continuing need for different and improved antibiotics. There has also been a need for a simple and economical method for synthesizing the cephalosporin compounds from available starting materials.

In one aspect, the process for preparing the compounds of the present invention involves subjecting the corresponding 7-( $\alpha$ -amino- $\beta$ -phenylacetamido)-cephalosporanic acid compound (having acetoxymethyl in the 3 position) to hydrogenolysis, suitably by contact with hydrogen at elevated pressure in the presence of a platinum or other noble metal selective hydrogenation catalyst. For this purpose, a palladium-on-barium sulfate catalyst is preferred. The starting material is dissolved in water, ethanol, dimethylformamide, ethylene glycol monomethyl ether, or other inert organic solvent or mixtures thereof with water, the catalyst is added, and the mixture is exposed to hydrogen at ordinary or elevated pressure, preferably 10 psig or higher, at ordinary or elevated temperatures (e.g., around 20 to 100° C.) until the absorption of hydrogen comes to a stop. It will be recognized that the hydrogenation time will vary inversely with the temperature and pressure. This treatment effects hydrogenolysis of the acetoxy group, with hydrogenation of the methylene residue, leaving methyl attached in the 3 position, thus producing the desired substance, which is recovered in a simple manner from the solution. In general, best results are obtained under somewhat basic conditions. (pH 7.5—9), using an excess of catalyst. In acidic solutions, the  $\Delta^3$  double bond tends to hydrogenate, whereas in slightly basic solutions, the uptake of hydrogen ceases after hydrogenolysis has taken place, with the result that the double bond remains unreduced.

In another aspect the process for preparing the compounds of the present invention involves similarly subjecting the so-called "cephalosporin nucleus", 7-aminocephalosporanic acid, to hydrogenolysis to produce 7-amino-3-

methy- $\Delta^3$ -cephem-4-carboxylic acid, which is then converted to the products of the invention by acylation of the 7-amino group in a known manner, employing a carboxyl-activated N-protected phenylglycine of appropriate structure or N-protected phenylglycine acid chloride hydrochloride. Activation of the carboxy group is achieved via a mixed anhydride, dicyclohexyldiimide, Woodward's reagent, or the like. Woodward's reagent is an isoxazolium compound, for example N-ethyl-5-phenylisoxazolium-3'-sulfonate or N-tert-butyl-5-methylisoxazolium perchlorate, and functions as an activator of the carboxyl group of the N-protected phenylglycine through opening of the isoxazolium ring and reaction with the carboxyl group of the phenylglycine to form an ester. The phenylglycine ester so formed then reacts with the 7-amino group of the 7-amino-3-methyl  $\Delta^3$ -cephem-4-carboxylic acid to form the desired 7-acylamino compound. The N-protective group may be carbo-t-butoxy, carbo-t-butylmercapto, carbobenzyloxy, and the like.

In still another aspect the process for preparing the compounds of the present invention involves subjecting a penicillin having the corresponding 6-( $\alpha$ -amino- $\alpha$ -phenylacetamido) substituent group of the desired cephalosporin product to the following series of reactions: (1) The  $\alpha$ -amino group of the penicillin is protected with a suitable group, such as carbo-2, 2,2-trichloroethoxy, carbobenzydryloxy or trityl. (2) The penicillin carboxy group is esterified with a suitable protective group, such as trichloroethyl, benzhydryl, p-methoxybenzyl or p-methoxyphenyl. (3) The protected penicillin is converted into the sulfoxide in a known manner by reaction with an oxidizing agent such as hydrogen peroxide in acetic acid, metaperiodic acid or perbenzoic acid. (4) The protected penicillin sulfoxide is heated to elevated temperature (around 100 to 175° C.) in the presence of a strong mineral acid (sulfuric acid, phosphoric acid or the like), preferably in the presence of an inert organic solvent, for a period of 0.1 to 1 hour or less, as short as possible to minimize side reactions. The penicillin thiazole ring is expanded thereby to the cephalosporin thiazine ring, with methyl attached in the 3 position. (5) The reaction product is treated in a known manner to cleave the protective groups from the  $\alpha$ -amino group and the carboxyl group. (6) The resulting cephalosporin, having the desired structure, is purified by chromatography or in other known manner.

The new compounds provided by the present invention are chemically and metabolically more stable than the corresponding 3-acetoxymethyl analogues. The acids and salts exhibit the ability in greater or lesser degree to destroy or inhibit the growth of many microorganisms, among which are the *Staphylococci*, the *Streptococci*, and the *Enterobacilli*, and

are thus useful in the treatment of a broad range of infections.

The structures of the compounds of the present invention have been proved by way of their infrared, ultraviolet, and nuclear magnetic resonance spectra. They are conveniently analyzed by the method of Ford, *Analytical Chemistry*, 19, 1004 (1946), which is based upon the quantitative determination of the  $\beta$ -lactam moiety of the molecule via reaction with hydroxylamine. Their antibiotic potencies are readily determined against a standard organism such as *Staphylococcus aureus* 209 P by appropriate modifications of the paper disc plate methods of Higgins et al., *Antibiotics & Chemotherapy*, 3, 40-54 (1953) and Loo et al., *Journal of Bacteriology*, 50, 701-709 (1945).

The invention will be more fully understood from the following operating examples:

#### EXAMPLE 1.

A solution of 2 g. of 7-(D- $\alpha$ -amino- $\alpha$ -phenylacetamido)-cephalosporanic acid in 100 ml. of 2 percent sodium bicarbonate solution is shaken with 5 g. of 5 percent palladium-on-barium sulfate in a Parr shaker for 1 hour at room temperature and 50 psig hydrogen pressure. The catalyst is then filtered off, the filtrate is acidified with trifluoroacetic acid, and the solution is filtered. The colorless filtrate is evaporated to dryness. The residue is dissolved in 15 ml. of water and the solution is acidified to pH 1 with trifluoroacetic acid. The solution is extracted three times with methyl isobutyl ketone, and the extracts are combined and evaporated to dryness. The residue is triturated with ether, and the solid is filtered off and dried under vacuum. The product, weighing 1.52 g., is shown by titration, ultraviolet analysis, and Moore-Stein analysis to be 7-(D- $\alpha$ -amino- $\alpha$ -phenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid in the form of the trifluoroacetate salt.

#### EXAMPLE 2.

A solution of 25 g. (0.05 mole) of a 7-(D- $\alpha$ -carbo-t-butoxamido- $\alpha$ -phenylacetamido)cephalosporanic acid sodium salt is prepared by adding 5 g. of sodium bicarbonate to a suspension of the free acid in 750 ml. of water, then diluting with water to one liter. The solution is then treated with hydrogen at 50 psig and room temperature in a large Parr bottle for one hour in the presence of 50 g. of 5 percent palladium-on-barium sulfate. Additional catalyst (25 g.) is then added and the hydrogen treatment is continued for 30 minutes. The catalyst is removed by filtration. The filtrate is overlaid with ethyl acetate, cooled in an ice bath, and acidified with concentrated hydrochloric acid to pH 2.5. The ethyl acetate layer is separated, washed with water, dried with magnesium sulfate, and evaporated to dryness. The residue obtained

thereby weighs 18.7 g. The carbo-t-butoxy protective group is cleaved therefrom by addition of 100 g. of ice-cold trifluoroacetic acid. After 15 minutes, the unreacted trifluoroacetic acid is removed under vacuum. The residue is triturated with ether and dried under vacuum, giving 16.9 g. of the crude trifluoroacetic acid salt of 7-(D- $\alpha$ -amino- $\alpha$ -phenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid.

The crude product thus obtained is readily converted into the free acid (in the form of the inner salt) by dissolving in 150 ml. of water and treating with 150 ml. of a 25 percent solution of secondary amine liquid phase anion exchange resin Amberlite LA-1 (Amberlite is a Trade Mark), acetate form, in methyl isobutyl ketone solution. The treated aqueous phase is diluted with 400 ml. of acetonitrile and refrigerated overnight. The solid thus obtained is collected, washed with 1:1 aqueous acetonitrile, and dried at 45° C. under vacuum. A yield of 8.22 g. of 99 percent pure 7-(D- $\alpha$ -amino- $\alpha$ -phenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid is obtained, as shown by Moore-Stein analysis.

#### EXAMPLE 3.

A solution of D- $\alpha$ -phenylglycine, 22.7 g. (150 mmoles), in 300 ml. of water is commingled with 160 ml. of aqueous 1N sodium hydroxide and 150 ml. of ether and cooled in an ice-alcohol bath. While stirring, simultaneous dropwise additions of 2,2,2-trichloroethyl chloroformate, 42.5 g. (200 mmoles), in 200 ml. of dry dioxane, and 200 ml. of aqueous 1N sodium hydroxide are made over a period of one hour. The mixture is maintained near 0° C. for another hour. It is then washed with a large volume of cold ether, overlaid with cold ethyl acetate, and acidified to pH 2.5. The organic layer is separated, washed with cold water, dried with magnesium sulfate, and evaporated to dryness under vacuum. The crystalline solid residue weighing 45 g. is dissolved in 150 ml. of benzene. The solution is filtered and diluted with 40 ml. of petroleum ether. A precipitate of N-(2,2,2-trichloroethylcarbonyl)-D- $\alpha$ -phenylglycine is obtained thereby weighing 30.2 g. M.p. 142—144° C.

Isobutyl chloroformate, 11.6 g. (85 mmoles), is dissolved in 420 ml. of acetone containing a few drops of dimethylbenzylamine. The solution is cooled in an ice-alcohol bath and to it are added dropwise with stirring N-(2,2,2-trichloroethylcarbonyl)-D- $\alpha$ -phenylglycine, 28.0 g. (85 mmoles) and triethylamine, 8.7 g. (86 mmoles) in 420 ml. of acetone over a period of 30 minutes, after which the mixture is stirred in the cold for 15 additional minutes. To the resulting mixed anhydride solution is added in one portion a solution of 6-aminopenicillanic acid, 18.6 g. (85 mmoles), and triethylamine, 8.7 g. (86

mmoles), in 70 ml. of cold water, after which the mixture is stirred in the cold for 2 hours. The reaction product mixture is concentrated under vacuum to remove the acetone. The residual aqueous solution is diluted 1:1 with water, overlaid with ethyl acetate, cooled, and acidified to pH 2.5 with aqueous 1N hydrochloric acid. The ethyl acetate layer is separated, washed with cold water, and back-titrated into water to pH 6.7 with aqueous 1N sodium hydroxide solution. The aqueous phase is separated, filtered, and evaporated to dryness under vacuum. The residue, after trituration with dry acetone, is a white amorphous powder weighing 24.6 g. and having infrared and nuclear magnetic resonance spectra in conformity with the expected structure, 6-[N-(2,2,2-trichloroethylcarbonyl)-D- $\alpha$ -amino- $\alpha$ -phenylacetamido]penicillanic acid sodium salt.

The product thus obtained, 18 g. (33 mmoles), is dissolved in 300 ml. of water and acidified to pH 5.4 with aqueous 1N hydrochloric acid. To the solution is added sodium metaperiodate, 7.1 g. (33 mmoles), portionwise, and stirring is continued at room temperature for 2 hours. The reaction product mixture is overlaid with ethyl acetate, cooled, and acidified to pH 2.5. The organic layer is separated, washed with cold water, dried with magnesium sulfate, and evaporated to dryness under vacuum. The crude residue, weighing 16 g., is dissolved in 64 ml. of N,N-dimethylacetamide. The solution is diluted with 640 ml. of anhydrous ether, filtered, and slowly further diluted with 40 ml. of petroleum ether. The purified product thus obtained weighs 11.6 g. and melts at 153—155° C. It is shown by analysis to be 6-[N-(2,2,2-trichloroethylcarbonyl)-D- $\alpha$ -amino- $\alpha$ -phenylacetamido]penicillanic acid sulfoxide, solvated with one mole of N,N-dimethylacetamide.

The sulfoxide thus obtained, 7 g. (11.2 mmoles), is dissolved in 85 ml. of dry tetrahydrofuran containing pyridine, 1.77 g. (22.3 mmoles). The solution is cooled in an ice-alcohol bath and stirred while a solution of 2,2,2-trichloroethyl chloroformate, 3.6 g. (16.7 mmoles), in 20 ml. of dry tetrahydrofuran is added. The completed mixture is stirred in the cold for 2 hours, then at room temperature for 3 hours, and is finally heated to gentle reflux for 15 minutes. The solvent is evaporated under vacuum. The residue is taken up in cold ethyl acetate and the solution is washed successively with water, aqueous 5 percent sodium bicarbonate solution, and water. The washed solution is dried with magnesium sulfate and evaporated to dryness under vacuum. The amorphous residue, 5.2 g., is crystallized from 7 ml. of ethanol to give 4.5 g. of purified product melting at 180—182° C. Further recrystallization from aqueous ethanol produces a sample of the product, 6-[N-(2,2,2-trichloroethylcarbonyl)-D- $\alpha$ -amino- $\alpha$ -phenylacetamido]penicillanic acid sulfoxide

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2,2,2-trichloroethyl ester, melting at 185—186° C.

- The sulfoxide ester thus obtained, 3.2 g. (4.5 mmoles), is dissolved in 125 ml. of xylene, and a strong acid such as 0.25 g. of p. toluene-sulfonic acid is added, and the mixture is heated at reflux for one hour. The solvent is evaporated at reduced pressure. The residue is taken up in 150 ml. of 95 percent acetic acid and cooled in ice. Zinc dust, 10 g. (153 mmoles), is added, and the mixture is stirred in the cold for three hours, then filtered. The zinc is washed with acetic acid. The filtrate and washings are combined and concentrated to dryness under vacuum. The residue is taken up in 100 ml. of water, cooled, acidified to pH 1 with trifluoroacetic acid, and extracted with methyl isobutyl ketone. The extract is dried with magnesium sulfate and evaporated to dryness under vacuum. The residue is triturated with anhydrous ether, giving the trifluoroacetic acid salt of 7-(D- $\alpha$ -amino- $\alpha$ -phenylacetamido) - 3 - methyl -  $\Delta^3$  - cephem - 4 - carboxylic acid as a pink, amorphous powder.

- A paper chromatogram of the product, developed with butanol, acetic acid, and water (3:1:1) and bioautographed against a *Bacillus subtilis* seeded agar plate, shows a single biologically active spot corresponding exactly in  $R_f$  value with that of an authentic specimen of the product prepared by another method. Nuclear magnetic resonance showed the characteristic C $\alpha$ -methyl group as a singlet at  $\tau$  7.90.

#### EXAMPLE 4.

- A saturated aqueous solution of sodium 7-aminocephalosporanate (1 mole) is diluted 1:1 with water, alkalized with a saturated aqueous solution of disodium orthophosphate and triethylamine (1:1 molar), and hydrogenated at room temperature and 1000 psig in the presence of 5 percent palladium-on-barium sulfate of the same weight as the starting material. After hydrogen uptake has ceased, the mixture is acidified with sulfuric acid and filtered to remove the catalyst, using a combination of activated carbon, talc, and diatomaceous earth as filter aid. To the filtrate is added aqueous ammonia, thereby precipitating 7-amino-3-methyl - 3 - cephem - 4 - carboxylic acid, which is filtered off and washed with aqueous acetone. The product and an equimolar amount of triethylamine are dissolved in acetonitrile.
- A suspension of sodium methyl 3-(D- $\alpha$ -carboxybenzyl-amino)crotonate in acetonitrile is reacted successively at room temperature with equimolar quantities of dimethylbenzylamine, methyl chloroformate, and the solution (prepared above) of 7-amino-3-methyl-3-cephem-4-carboxylic acid. After completion of the reaction, the reaction product mixture is stratified by adding triethylamine and sodium chloride. The upper layer is separated and acidified with formic acid, whereupon 7-

(D- $\alpha$ -amino- $\alpha$ -phenylacetamido) - 3 - methyl-3-cephem-4-carboxylic acid precipitates. The precipitate is filtered off, washed with acetonitrile, and recrystallized from a mixture of water, formamide, methanol and acetonitrile. The recrystallized material, after being washed with acetonitrile and dried, is obtained in excellent yield.

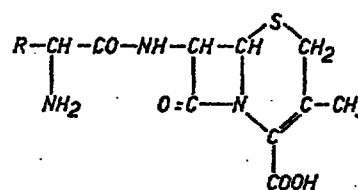
#### EXAMPLES 5—13.

The following additional compounds are also obtained via hydrogenolysis of the 3-acetoxy-methyl analogue generally under the conditions illustrated in Example 1, and all are found to be effective as antibiotics against penicillin-resistant strains of *Staphylococcus aureus*:

- 7-(dl- $\alpha$ -Amino - *m* - chlorophenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid
- 7-(dl- $\alpha$ -Amino - *p* - chlorophenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid
- 7-(dl- $\alpha$ -Amino - *m* - bromophenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid
- 7-(dl- $\alpha$ -Amino - *m* - fluorophenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid
- 7-(dl- $\alpha$ -Amino - *m* - methoxyphenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid
- 7-(D- $\alpha$ -Amino - *m* - hydroxyphenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid

#### WHAT WE CLAIM IS:—

1. An antibiotic compound having the structure



Formula I

wherein

R is phenyl or phenyl substituted with halo, hydroxy, C<sub>1</sub>—C<sub>4</sub> alkyl, nitro, amino, C<sub>1</sub>—C<sub>4</sub> alkanoyl, trifluoromethyl, C<sub>1</sub>—C<sub>4</sub> alkoxy, or C<sub>1</sub>—C<sub>4</sub> alkylmercapto; or a salt thereof with a pharmaceutically acceptable cation or a pharmaceutically acceptable acid.

2. 7-( $\alpha$ -Aminophenylacetamido) - 3 - methyl- $\Delta^3$ -cephem-4-carboxylic acid.
3. 7-( $\alpha$ -Amino - *m* - chlorophenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.
4. 7-( $\alpha$ -Amino - *p* - chlorophenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.
5. 7-( $\alpha$ -Amino - *m* - bromophenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.
6. 7-( $\alpha$ -Amino - *m* - fluorophenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.
7. 7-( $\alpha$ -Amino - *m* - methoxyphenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.
8. 7-( $\alpha$ -Amino - *m* - hydroxyphenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.
9. A process for preparing an antibiotic compound having the structure



2,2,2-trichloroethyl ester, melting at 185—186° C.

- 5 The sulfoxide ester thus obtained, 3.2 g. (4.5 mmoles), is dissolved in 125 ml. of xylene, and a strong acid such as 0.25 g. of p. toluene-sulfonic acid is added, and the mixture is heated at reflux for one hour. The solvent is evaporated at reduced pressure. The residue is taken up in 150 ml. of 95 percent acetic acid and cooled in ice. Zinc dust, 10 g. (153 mmoles), is added, and the mixture is stirred in the cold for three hours, then filtered. The zinc is washed with acetic acid. The filtrate and washings are combined and concentrated to dryness under vacuum. The residue is taken up in 100 ml. of water, cooled, acidified to pH 1 with trifluoroacetic acid, and extracted with methyl isobutyl ketone. The extract is dried with magnesium sulfate and evaporated to dryness under vacuum. The residue is triturated with anhydrous ether, giving the trifluoroacetic acid salt of 7-(D- $\alpha$ -amino- $\alpha$ -phenylacetamido) - 3 - methyl -  $\Delta^3$  - cephem - 4 - carboxylic acid as a pink, amorphous powder.

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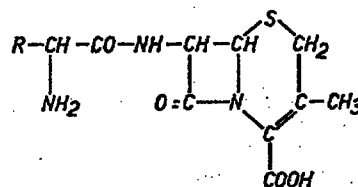
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7-(dl- $\alpha$ -Amino - *p* - chlorophenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid  
7-(dl- $\alpha$ -Amino - *m* - bromophenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid  
7-(dl- $\alpha$ -Amino - *m* - fluorophenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid  
7-(dl- $\alpha$ -Amino - *m* - methoxyphenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid  
7-(D- $\alpha$ -Amino - *m* - hydroxyphenylacetamido)-3-methyl- $\Delta^3$ -cephem-4-carboxylic acid

#### WHAT WE CLAIM IS:—

1. An antibiotic compound having the structure



Formula I

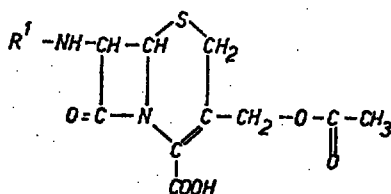
wherein

R is phenyl or phenyl substituted with halo, hydroxy,  $C_1$ — $C_4$  alkyl, nitro, amino,  $C_1$ — $C_4$  alkanoyl, trifluoromethyl,  $C_1$ — $C_4$  alkoxy, or  $C_1$ — $C_4$  alkylmercapto; or a salt thereof with a pharmaceutically acceptable cation or a pharmaceutically acceptable acid.

2. 7-( $\alpha$ -Aminophenylacetamido) - 3-methyl- $\Delta^3$ -cephem-4-carboxylic acid.  
3. 7-( $\alpha$ -Amino - *m* - chlorophenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.  
4. 7-( $\alpha$ -Amino - *p* - chlorophenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.  
5. 7-( $\alpha$ -Amino - *m* - bromophenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.  
6. 7-( $\alpha$ -Amino - *m* - fluorophenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.  
7. 7-( $\alpha$ -Amino - *m* - methoxyphenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.  
8. 7-( $\alpha$ -Amino - *m* - hydroxyphenylacetamido)-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid.  
9. A process for preparing an antibiotic compound having the structure

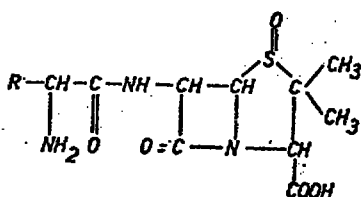


wherein R is phenyl or phenyl substituted with halo, hydroxy, C<sub>1</sub>—C<sub>4</sub> alkyl, nitro, amino, C<sub>1</sub>—C<sub>4</sub> alkanoyl, trifluoromethyl, C<sub>1</sub>—C<sub>3</sub> alkoxy, or C<sub>1</sub>—C<sub>4</sub> alkylmercapto; which comprises subjecting to hydrogenolysis a compound of the structure:



### Formula II

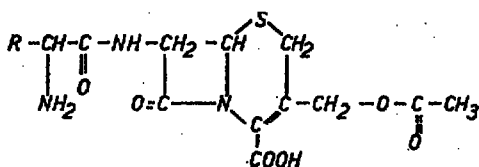
wherein R' is a hydrogen atom or the radical  
10  $R-CHNH_2-C:O$  wherein R is as defined  
above, and, when R' is a hydrogen atom, acy-  
lating the 7-amino-3-methyl- $\Delta^3$ -cephem-4-  
carboxylic acid thus obtained in a conventional  
manner with an acylating agent comprising  
15 said radical  $R-CHNH_2-C:O$ ; or heating  
under acid conditions a penicillin sulfoxide of  
the formula:



### Formula III

20 wherein R is as defined above and wherein the amino group in the 6-position and the carboxylate group in the 3-position are protected in a conventional manner, and thereafter removing the protective groups.

10. The process according to claim 9, which  
25 comprises dissolving a compound of the structure



### Formula IV

wherein R is as defined in claim 1 in an inert solvent and contacting the dissolved compound with hydrogen at an elevated pressure and in the presence of a noble metal selective hydrogenation catalyst.

11. The process according to claim 9 which comprises dissolving 7-aminocephalosporanic acid in an inert solvent, contracting the dissolved compound with hydrogen at an elevated pressure and in the presence of a noble metal selective hydrogenation catalyst and acylating the 7-amino-3-methyl -  $\Delta^3$  - cephem-4-carboxylic acid thus obtained.

12. The process according to claim 9 which comprises heating a protected penicillin sulfoxide of Formula III in the presence of an acid at a temperature in the range of from 100 to 175° C.

13. The process according to claim 10 or 11 wherein the noble metal catalyst is palladium supported on barium sulfate.

14. The process according to any one of claims 10, 11 or 13 wherein the hydrogenolysis is conducted at an elevated temperature.

15. The process according to claim 12 wherein the acid is a strong mineral acid.

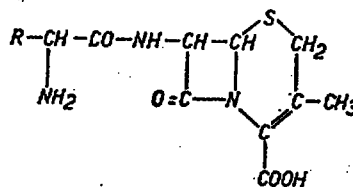
16. The process according to claim 15 wherein the acid is sulfuric or phosphoric acid.

17. The process according to any one of claims 12, 15 or 16 wherein the heating is carried out for a period of time ranging from 0.1 to 1 hour.

18. The process according to any one of claims 9 to 17 wherein the product obtained is converted to a salt by reaction with a base in a conventional manner.

19. The process according to any one of claims 9 to 17 wherein the product thus obtained is converted to an acid addition salt by reaction with an acid in a conventional manner.

20. A process for preparing an antibiotic compound having the structure



### Formula I

wherein R is phenyl or phenyl substituted with halo, hydroxy, C<sub>1</sub>—C<sub>4</sub> alkyl, nitro, amino, C<sub>1</sub>—C<sub>4</sub> alkanoyl, trifluoromethyl, C<sub>1</sub>—C<sub>4</sub> alkoxy, or C<sub>1</sub>—C<sub>4</sub> alkylmercapto; or a salt thereof with pharmaceutically acceptable cation or a pharmaceutically accepted acid; substantially as herein described with particular reference to any one of the Examples.

21. An antibiotic compound as claimed in 80

claim 1 whenever prepared by the process  
claimed in any one of claims 9 to 20.

22. A pharmaceutical composition com-  
prising an excipient and an antibiotic com-  
5 pound according to any one of claims 1 to 8  
and 21.

BOULT, WADE & TENNANT,  
111 & 112, Hatton Garden, London, E.C.1.  
Chartered Patent Agent.  
Agents for the Applicants.

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Reference has been directed, in pursuance of Section 9, subsection (1) of the Patents  
Act, 1949, to Specification No. 957,569.

THE PATENT OFFICE  
8 June 1970

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