

PATENT SPECIFICATION

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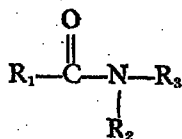


(54) PROCESS FOR CONVERTING A PENICILLIN SULFOXIDE ESTER TO A CEPHALOSPORIN ANTIBIOTIC

(71) We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 740 South Alabama 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:—

This invention relates to a process for improving the yield and quality of desacetoxy cephalosporan produced by heating analogous penicillin sulfoxide esters, using tertiary carboxamides or ureas to direct the conversion of penicillin sulfoxide esters to desacetoxy cephalosporan.

More particularly, the present invention provides a process for converting a penicillin sulfoxide ester to a desacetoxy-cephalosporan by heating the penicillin sulfoxide ester under acid conditions for a time sufficient to effect conversion thereof, which comprises heating the penicillin sulfoxide ester dissolved in a tertiary carboxamide or a tertiary urea or mixtures thereof as a diluent at a temperature of from 80° C. to 175° C., said tertiary carboxamide or urea being represented by the structural formula



wherein:

when taken alone

R₁ is hydrogen, alkyl, phenyl, tolyl, xylyl or —N—R₅; and



R₂, R₃, R₁ and R₅ are alkyl, phenyl, tolyl or xylyl and when taken together

R₂ and R₃ and/or R₁ and R₅ together with the nitrogen atom to which they are bonded form a saturated mono-cyclic ring having from 4—6 carbon atoms, and having optionally an oxygen ring member in a position gamma to the ring nitrogen; and

R₁ and R₂ together with the intervening

amide grouping ($\text{—}\overset{\text{O}}{\parallel}\text{C—N—}$) to which they are bonded form a monocyclic ring having from 4—6 carbon atoms with a carbonyl group adjacent to the nitrogen ring member; and R₂ and R₁ together with the intervening urea grouping

($\text{—N—}\overset{\text{O}}{\parallel}\text{C—N—}$) to which they are bonded form a 5 to 6 membered heterocyclic ring;

with the further limitation that R₁, R₂, R₃, R₄ and R₅ can in no case have a combined total of more than 18 carbon atoms, can have now more than 14 carbon atoms when R₁ is hydrogen, and can have no more than 12 carbon atoms when any two of the substituents R₁—R₅ are taken together with one or more nitrogen atoms to form a nitrogen-containing ring. The diluent of the above invention may be one wherein R₁ is hydrogen and each of R₂ and R₃ is alkyl, phenyl, tolyl or xylyl such that R₂ and R₃ together contain up to about 14 carbon atoms.

United States Patent No. 3,275,626 discloses and claims a method for preparing antibiotic substances by heating a penicillin sulfoxide ester under acid conditions to effect conversion thereof to a variety of products, including desacetoxycephalosporin-type antibiotics. The foregoing patent discloses that the characteristic thiazolidine ring of penicillin can be converted to the characteristic thiazine ring of the cephalosporins by heating a

penicillin sulfoxide ester at a temperature of from 100° C. to 175° C. in the presence of an acid.

The process of the present invention, like the processes to which it is an improvement, is broadly applicable to the conversion of the prior art penicillins, so long as they are not otherwise converted under the employed conditions of acidity and elevated temperature. In all cases, they must be esterified and converted into the corresponding sulfoxide prior to treatment. A wide range of penicillins can be effectively treated in accordance with the invention, including benzyl penicillin, n-heptyl penicillin, phenylmercaptomethyl penicillin. The preferred penicillin is phenoxymethyl penicillin ("penicillin-V"). Penicillin nucleus (6-aminopenicillanic acid, "6-APA") can also be treated successfully, but the 6-amino group should first be protected with an easily removable group, such as carboallyloxy, tert-butoxy-carbonyloxy, or the like. The product obtained by treatment of the N-protected or blocked 6-APA is the corresponding N-protected 7-aminodesacetoxycephalosporanic acid ("7-ADCA") ester, which, after cleavage of the N-protecting group, can be acylated in a known manner to produce the desired desacetoxycephalosporin in the form of the ester.

Examples of tertiary carboxamides of the types described above, which may be used to effect the process of this invention include:

N,N - dimethylformamide (DMF), N,N-diethylformamide, N,N - diisopropylformamide, N,N - dibutylformamide, N,N - dipentylformamide, N - methyl - N - ethylformamide, N - methyl - N - phenylformamide, N - ethyl - N - (m - tolyl)formamide, N-propyl - N - (3,5 - dimethylphenyl)formamide, N,N - diphenylformamide, N,N - bis(4-methyl - phenyl)formamide, N - (3,5 - dimethylphenyl) - N - methylformamide, N,N-bis - (2,4 - dimethylphenyl)formamide, N,N-dimethylacetamide (DMA), N,N - diethylacetamide, N,N - diisopropylacetamide, N,N-dibutylacetamide, N,N - di - tert - butylacetamide, N,N - dimethylpropionamide, N,N-diethylpropionamide, N,N - dipentylpropionamide, N,N - dimethylbutanamide, N,N - diethylbutanamide, N,N - dimethyldecanamide, N,N - dimethylbenzamide, N,N - diethylbenzamide, N,N - diethyl - m - toluamide, N,N - dipropyl - m - toluamide, N,N - dibutyl - p - toluamide, N - phenyl - N-methyl - acetamide, N - (p - tolyl) - N - ethylacetamide, N - (3,5 - dimethylphenyl) - N-methylpropionamide, N,N - dimethyl - 3,5-dimethylbenzamide, N,N - dibutyl - 4 - ethylbenzamide, N,N - diphenylacetamide, N - (3-methyl - phenyl) - N - ethylbenzamide, N,N-bis (6 - methylphenyl)propionamide, N,N-bis(3,5 - dimethylphenyl)propionamide, N-formylpiperidine, N - acetylpyrrolidine, N-propionylmorpholine, N - acetyl - 4,5 - dimethylpyrrolidine, N - butanoylpiperidine, N-

acetyl - 6 - methyl - piperidine, 1 - methyl - 2 - pyrrolidone, 1 - phenyl - 2 - pyrrolidone, 1 - butyl - 2 - piperidone, 1 - pentyl - 2 - piperidone, 1 - (m - tolyl) - 2 - piperidone, 1 - ethyl - 2 - piperidone, 1 - (3,5 - dimethylphenyl) - 2 - piperidone, 1 - methyl - 2 - piperidone, 1 - phenyl - 2 - piperidone, 1-propyl - 2 - piperidone, 1 - isopropyl - 2 - pyrrolidone, 1 - (3 - methyl - phenyl) - 2 - pyrrolidone, N - methyl - 2 - homopiperidone, N - ethyl - 2 - homopiperidone and N,N-diethyl - m - toluamide.

Examples of tertiary urea derivatives of the types described above, which may be used to effect the process of this invention include: tetramethylurea, tetraethylurea, N,N - dimethyl - N', N' - diethylurea, N,N' - dimethylcarbanilide, 6 - (p - tolyl) - N,N',N'-trimethylurea, N,N' - bis (3,5 - dimethylphenyl) - N,N' - diethylurea, 1,3 - dimethyl - 2 - imidazolidone, 1,3 - di - n - propyl - 2 - imidazolidone, 1,3 - diisobutyl - 2 - imidazolidone, 1 - methyl - 3 - phenyl - 2 - imidazolidone, 1,3,4,5 - tetramethyl - 2 - imidazolidone, 1,3 - dimethyl - 4,5 - diethyl - 2 - imidazolidone, 1 - ethyl - 3 - (p - tolyl) - 2 - imidazolidone, 1,3 - dimethyl - 2 - hexahydropyrimidone, 1,3 - bis(hydroxymethyl) - 2 - tetrahydropyrimidone, 1 - isopropyl - 2 - tetrahydropyrimidone, 1,3 - di - tert - butyl - 2 - tetrahydropyrimidone, 1,3 - diisopropyl - 2 - hexahydropyrimidone, 1,1' - carbonyldimorpholine, 1,1' - carbonyldipyrrolidine and 1,1' - carbonyldipiperidine.

In conducting the process of this invention, the penicillin sulfoxide ester is dissolved in a tertiary carboxamide or urea solvent system wherein the amide or urea is employed either as the only solvent, or is mixed with an optimum proportion of another tertiary carboxamide, urea, or an inert organic liquid diluent or both with the aid of heat, if necessary, as defined above, and with the acid substance used to promote the rearrangement. Generally, the tertiary carboxamide or urea constitutes at least 25 percent by volume of the liquid medium in which the reaction is conducted. Preferably, the amide or urea constitutes at least 50 percent by volume of the reaction medium. Use of a single solvent is preferred for highest yields of desacetoxycephalosporin products. For best results, the concentration of penicillin sulfoxide ester in the final solvent system is maintained below about 15 percent by weight, preferably below 10 percent by weight.

The acid substance can be commingled or mixed with the solvent medium before, simultaneously with, or after the penicillin sulfoxide ester starting material is dissolved therein. The acid substance should be a non-oxidizing protic acid or Lewis acid capable of accepting electrons from the oxygen of the thiazolidine sulfoxide bond of the penicillin sulfoxide ester.

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5 Preferred acid substances include the al-
 kanoic acid anhydrides having from 2 to 6
 carbon atoms in each acid moiety, such as
 acetic anhydride, propionic anhydride, n-
 butanoic anhydride, pentanoic anhydride, hex-
 anoic anhydrides, and mixed anhydrides of
 C_2-C_6 alkanic acids; cyclic saturated di-
 basic acid anhydrides such as succinic an-
 hydride, glutaric anhydride; strong Lewis
 acids such as aluminum chloride, boron tri-
 fluoride, hydrogen fluoride, ferric chloride;
 strong non-oxidizing mineral acids such as p-
 toluenesulfonic, benzenesulfonic, methane-sul-
 fonic, naphthalenesulfonic, and other sulfonic
 acids; various phosphorus acids such as ortho
 phosphoric acid and methylphosphonic, hydro-
 chloric acid, as well as other acidic substances
 such as thionyl chloride and cyanogen bromide.
 Acetic anhydride and aluminum chloride are
 especially preferred acid substances.

10 In general, amounts of acid substance rang-
 ing from about 1 percent to about 20 percent
 by volume of total solvent medium can be
 used. With lower amounts of acid, the rate of
 reaction is undesirably slow for practical use.
 Larger amounts of acid may be used but are
 not necessary. For best results it is preferred
 that the acid substance be present in amounts
 at least equimolar to the molar concentration
 of the penicillin sulfoxide esters, and in most
 cases the higher yields are obtained in the
 shortest times when from 2 to 5 molar equi-
 valents of the acid substance per molar equi-
 valent of the penicillin sulfoxide ester are
 used at the optimum temperature.

15 The penicillin sulfoxide ester in the acidified
 tertiary carboxamide or urea solvent is heated
 to from 80° C. to 175° C. to direct the re-
 arrangement of the penicillin sulfoxide ester
 to the corresponding desacetoxycephalosporin
 ester. The preferred reaction temperature is
 between about 90° C. to 150° C.; preferred
 reaction time is from about 1 to 15 hours.
 Lower temperatures require more time, while
 at higher temperatures the reaction mixture
 tends to discolor and produce a more com-
 plex rearrangement product.

20 In preparing the penicillin sulfoxide esters
 for use as starting materials in the process of
 this invention, the penicillin sulfoxide may be
 prepared prior to esterifying the penicillanic
 acid carboxyl group, or alternatively the select-
 ed penicillin may be esterified first and then
 the resulting penicillin ester may be sulfoxyl-
 ated according to conventional methods. Refer-
 ence is made to the Morin and Jackson
 patent, U.S. 3,275,626.

25 By way of example and for completeness,
 the following summarizes the steps that can
 be taken to prepare a desired desacetoxy-
 cephalosporin from a given penicillin sul-
 foxide ester. A typical example involves the
 preparation of a 7 - (D - α - phenylglycyl-
 amido)desacetoxycephalosporanic acid, an
 orally active cephalosporin-type antibiotic,

from the corresponding 6 - (D - α - phenyl-
 glycyamido)penicillanic acid sulfoxide ester.

(a) The penicillin sulfoxide ester is dis-
 solved in a tertiary carboxamide or urea sol-
 vent medium together with acetic anhydride or
 other equivalent acid substance to obtain an
 acidified liquid solution of the penicillin sul-
 foxide ester.

(b) The penicillin sulfoxide ester solution is
 heated between 80° C. to 175° C. and pre-
 ferably from about 90° C. to about 150° C. to
 form the corresponding desacetoxycephalo-
 sporin ester.

(c) The desacetoxycephalosporanic acid is
 recovered from the reaction product obtained
 in step (b), e.g., by treating the product with
 90 percent acetic acid and zinc dust for 1-3
 hours at -5° to 20° C. to obtain the 7-(D- α -
 phenylglycyl - amido) - 3 - cephem - 4 - car-
 boxylic acid [7 - (D - α - phenylglycylamido)-
 desacetoxycephalosporanic acid] which is use-
 ful as an antibiotic in combatting diseases
 caused by penicillin-resistant strains of
Staphylococcus aureus.

The prior art describes literally thousands
 of penicillin compounds, almost all of which
 can be converted to desacetoxycephalosporin
 compounds by the process of this invention.
 The only limitation on the penicillin com-
 pounds which can be employed in the pro-
 cess of this invention is that they must not
 undergo other undesirable conversions under
 the reaction conditions of the process. A few
 typical examples will illustrate, to those fami-
 liar with the art, penicillins which may be
 used as starting materials, and the desacet-
 oxycephalosporins obtained therefrom. The
 desacetoxycephalosporin compounds produced
 by the process of this invention from the cor-
 responding penicillin sulfoxide esters, are use-
 ful, especially after ester group removal, as
 antibiotics in the therapy of diseases caused
 by various Gram-positive and Gram-negative
 microorganisms. 7 - Aminodesacetoxycephalo-
 sporanic acid (7-ADCA), produced from a
 corresponding 6 - amino penicillanate sul-
 foxide ester by this invention, is useful as an
 intermediate to prepare desacetoxycephalo-
 sporin antibiotic substances. It is preferred
 to prepare a pharmaceutical composition com-
 prising the cephalosporin antibiotic and a
 pharmaceutical carrier.

The penicillins listed below yield the in-
 dicated corresponding desacetoxycephalospor-
 ins after heat rearrangement of the penicillin
 sulfoxide esters according to the method of
 this invention and removal of the ester group
 by conventional methods.

6 - [2' - Methoxy - 2' - (2'' - thienyl)
 acetamide] - 2,2 - di - methylpenam - 3-
 carboxylic acid yields 7 - [2' - methoxy 1 2'-
 (2'' - thienyl)acetamide] - 3 - methyl - 3-
 cephem - 4 - carboxylic acid.

6 - (Phenylacetamido) - 2,2 - dimethyl-
 penam - 3 - carboxylic acid yields 7 - (phenyl-

acetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

5 6 - (Thiophene - 2 - acetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (thiophene - 2 - acetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

10 6 - (Phenylmercaptoacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (phenylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

6 - (2' - Furylacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (2' - furylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

15 6 - (2' - protected amino - 2' - phenylacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (2' - protected amino - 2' - phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

20 6 - (Butylmercaptoacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (butylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

25 6 - (Heptylamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (heptylamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

6 - Benzoyl - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - benzoyl - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

30 6 - (2' - phenoxyacetamido) - 2,2 - dimethyl - penam - 3 - carboxylic acid yields 7 - (2' - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

35 The invention is further illustrated by the following detailed examples.

Preparation of Trichloroethyl Penicillin Esters.

40 The preparation of the trichloroethyl esters of the penicillins employed in the present invention is illustrated by the following procedure for the preparation of the trichloroethyl ester of benzyl penicillin.

45 Penicillin G potassium salt [benzyl penicillin, potassium salt] (37.1 g., 0.1 mole) was stirred in one liter of methylene chloride while a slurry of pyridine hydrochloride (12 g., 0.1 mole) in 50 ml. of methylene chloride was added. After a few minutes a solution of 15 g. (0.1 mole) of 2,2,2 - trichloroethanol in 50 ml. of methylene chloride was added followed by a solution of 20.6 g. (0.1 mole) of dicyclohexyl carbodiimide in 100 ml. of methylene chloride. The various additions were made at a temperature below 20° C. The reaction mixture was then stirred at room temperature overnight.

55 The reaction mixture was filtered and the solvent was removed at reduced pressure on the rotary evaporator. The crude trichloroethyl - 6 - (phenylacetamido)penicillanic acid ester residue was dissolved in ethyl acetate, cooled, and washed with dilute HCl and 5 percent NaHCO₃ solution, dried and concentrated. The crystalline residue was dissolved in

300 ml. of ethyl acetate and refrigerated over the weekend. The small amount of solid precipitate was removed by filtration, the filtrate then being concentrated. The evaporation residue was slurried with 200 ml. of ether, cooled, and then filtered. The purified ester solid was washed with ether, then vacuum dried. Yield 30.3 g., m.p. 157—159° C. The nuclear magnetic resonance (NMR) spectrum was consistent with the expected structure for 2,2,2 - trichloroethyl - 6 - (phenylacetamido) penicillanate. The ester was used for sulfoxide preparation without further purification. Although as described above the ester used was 2,2,2 - trichloroethyl, it is understood that the ester group may also be the p - methoxyphenyl or p - methoxybenzyl group.

Preparation of Sulfoxides of Penicillin Esters.

85 The preparation of the sulfoxides of the penicillin esters employed in the present invention is illustrated by the following procedure for the preparation of trichloroethyl - 6 - phenylacetamido - penicillanate sulfoxide.

To a solution of 4.7 g. (0.01 mole) of trichloroethyl - 6 - (phenylacetamido)penicillanate in 50 ml. of chloroform was added a solution of 2.2 g. (0.011 mole) of 85 percent m - chloroperbenzoic acid in 25 ml. of chloroform. An ice bath was used to hold the temperature below 25° C. during the addition. After 2 hours of stirring, the chloroform solution was washed with 5 percent sodium bicarbonate solution, dried with magnesium sulfate, and concentrated. The residue was triturated with ethyl ether and filtered. The white solid, 2,2,2 - trichloroethyl - 6 - (phenylacetamido)penicillanate sulfoxide ester was washed with ether and vacuum dried. A yield of 4.05 g. was obtained, m.p. 167—169° C. Recrystallized from an ether-tetrahydrofuran mixture, the product gave 2.47 g. of a more pure sample, m.p., 174—176° C. Analysis—Calcd. for C₁₈H₁₉Cl₃N₂O₅S: C, 44.88; H, 3.97; N, 5.81; Cl, 22.07.

110 Found: C, 45.04; H, 4.20; N, 5.73; Cl, 21.75. The NMR spectrum was consistent with the proposed structure.

115 It will be understood by those skilled in the art that alternative methods for esterification or oxidation may be employed. It will be further understood that the sequence of steps can be reversed and that the sulfoxide of the penicillin acid can be prepared prior to esterification.

EXAMPLE 1.

120 This example illustrates the advantages of the present process by comparing the effect of various solvents on the rearrangement of penicillin sulfoxide esters to desacetoxycephalsporin products.

125 In this controlled study the rearrangement reaction was run using various liquids as solvents or diluents, by keeping constant, ex-

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cept as indicated, the starting penicillin material, the amount thereof, the acid catalyst, the amount of acid catalyst, the reaction time, and the reaction temperature. The only variation was that after the reaction was completed, some of the test solvents or diluents were removed by distillation (procedure A), some were removed by washing with water (procedure B), and some were not removed at all prior to treatment with zinc dust (procedure C). Parallel runs using dimethylformamide as the solvent confirmed that equivalent results are obtained by either method of solvent removal.
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The test procedures used were as follows:
A. A suitable vessel containing a solution of 1 g. of penicillin V sulfoxide trichloroethyl ester and 1 g. of acetic anhydride in 50 ml. of the test solvent was placed in a stirred bath at 130° C. for a period of either 1 hour or 19 hours. At the end of the selected time, the test solvent was removed from the reaction vessel by distillation at reduced pressure using a rotary evaporator. A sample of the residue was examined by thin layer chromatography (on silica gel using ethyl acetate or a benzene-ethyl acetate mixture as the developing solvent), to establish that the expected product was the main product as seen in a dominant single spot. The residue was then taken up in 25 ml. of 90 percent acetic acid solution and stirred in an ice bath at 5 to 10° C. while 1 g. of zinc dust was added to the solution. After three hours of stirring at 5 to 10° C., the reaction solution was filtered to remove zinc, and evaporated to dryness. The residue was taken up in a mixture of 100

ml. of water and 100 ml. of ethyl acetate and the pH of the resulting mixture adjusted to pH 2 with 1 N hydrochloric acid. The ethyl acetate and water layers were separated. The ethyl acetate layer was washed with water, and then stirred with 25 ml. of water, after which the pH was adjusted to pH 6.5 with 1 N sodium hydroxide. The water layer was separated and diluted to 50 ml.
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Two microliters of this aqueous solution were then used to run a bioautograph. Two microliters of an aqueous solution of the 7-(phenoxymethyl) - 3 - methyl - 3 - cephem-4 - carboxylic acid product obtained by using xylene as solvent was used as a standard. The spot obtained from the standard was considered for this test as representing 100 percent of biological activity (the xylene reaction spot). The area of the spot obtained from the aqueous extracts of the reaction products obtained using the respective test solvents was compared to the area of the xylene reaction spot and the result was expressed as a relative percentage of the xylene reaction spot standard.
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B. The same test procedure as is described in A above was used with the exception that the rearrangement reaction test solvent was not removed by distillation but was washed away from the reaction product with water. This procedure was used only with high boiling (b.p. over 180° C.) test solvents. The results of the test are tabulated below.
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C. The same test procedure as described in A above was used except that solvent was not removed prior to treatment with zinc.

TABLE I

Test Solvent	Reaction Time	Recovery Procedure	Biological Activity ¹ Percent of Standard
Xylene ² (Standard)	1	A	100
Xylene (Standard)	19	A	37.5
Methylisobutyl ketone	1	A	0
Anisole	1	A	0
1-Nitropropane	1	A	0
Tetrachloroethane	1	A	0
Chlorobenzene	1	A	0
Dioxane	1	A	0
Formamide	1	A	0
Dimethylformamide	1	A	250
Dimethylformamide	1	B	250
N-acetylmorpholine	1	B	125
N-methylpyrrolidone	1	B	188
Dimethylformamide ²	1	A	125
Tetramethylurea	1	B	237
Dimethylmethanesulfonamide	1	B	112
Dimethylformamide	1	C	250
N,N-diethyl-m-toluamide	1	C	112
N,N-dimethyldodecanoamide	1	C	112

FOOTNOTES:

¹The biological activity (bioautograph) test is a paper chromatography test procedure, described in *Antibiotics and Chemotherapy*, Vol. IV, No. 7, July 1954, pp. 750—752 using *Bacillus subtilis* as the test organism.

²p-Toluenesulfonic acid was used as the acid substance in a chemically equivalent amount.

EXAMPLE 2.

7 - Phenylacetamido - 3 - methyl - 3 - cephem-
4 - carboxylic acid.

- 5 A solution of 1 g. (2.1 m moles) of 2,2,2-trichloroethyl - 6 - (phenylacetamido)penicillanate sulfide and 1.2 g. of acetic anhydride in 50 ml. of dimethylformamide (DMF) was warmed in a 130° C. oil bath for one
10 hour. The DMF was then removed on a rotary evaporator. The residue of crude re-arrange-

ment product was shown by thin layer chromatography (TLC) to have only one major component. Without further purification, the oil was dissolved in 25 ml. of 90 percent acetic acid and 5 g. of zinc dust were added. The reaction mixture was stirred and cooled in an ice bath for three hours to remove the trichloroethyl ester group and to form the corresponding desacetoxyccephalosporanic acid. The zinc was then filtered off and washed with

acetic acid. The acetic acid solution was concentrated. The 7 - (phenylacetamido)desacetoxycephalosporanic acid residue was stirred with water and ethyl acetate while adding 5 NaHCO_3 to pH 7.5. The NaHCO_3 solution was acidified to pH 2 with concentrated HCl while being overlaid with ethyl acetate. The ethyl acetate layer containing the 7 - (phenylacetamido)desacetoxycephalosporanic acid was shaken several times with water, dried with magnesium sulfate and concentrated. The residue was dissolved in 10 ml. of ethyl acetate to which were added 20 ml. of "Skelly B" petroleum ether (b.p. 60--64° C.). The precipitated acid solid was collected, washed with "Skelly B" and vacuum dried, yielding 196 mg. of a light yellow solid. The NMR spectrum, titration, and UV absorption of this material were consistent with the proposed structure for 7 - (phenylacetamido)-3 - methyl - 3 - cephem - 4 - carboxylic acid. Results of paper and thin layer chromatography of the product were identical to those with an authentic sample prepared by acylation of 7 - amino - 3 - methyl - 3 - cephem - 4 - carboxylic acid with phenylacetic acid.

EXAMPLE 3.

By varying the penicillin sulfoxide ester employed as a starting material, esters of the following cephalosporin acids were prepared by the procedure of Example 2:

7 - (Thiophene - 2 - acetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid from trichloroethyl - 6 - (2' - chloro - 2' - phenylacetamido)penicillanate sulfoxide.

7 - Phenylacetamido - 3 - methyl - 3 - cephem - 4 - carboxylic acid from trichloroethyl - 6 - (2' - chloro - 2' - phenylacetamido)penicillanate sulfoxide ester.

7 - Phenylmercaptoacetamido - 3 - methyl - 3 - cephem - 4 - carboxylic acid from a 2,2,2-trichloroethyl phenylmercaptomethyl penicillin sulfoxide ester.

7 - (α,α - Dimethyl - α - phenoxyacetamido) - 3 - desacetoxycephalosporanic acid from 2,2,2 - trichloroethyl 7 - (α,α - dimethyl - 2 - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylate ester.

7 - (α - Aminophenylacetamido) - 3 - desacetoxycephalosporanic acid from 2,2,2 - trichloroethyl 6 - [N - (2,2,2 - trichloro ethoxycarbonyl) - D - phenylglycylamido] - 2,2-dimethylpenam - 3 - carboxylate sulfoxide ester.

EXAMPLE 4.

A solution of 1 gram of 2,2,2 - trichloroethyl 6 - (phenylacetamido)penicillanate sulfoxide and 1.2 g. of acetic anhydride in 50 ml. of tetraethylurea is warmed to 130° C. in an oil bath for about 5 hours to insure complete reaction. This tetraethylurea solvent is

removed and the crude product which remains as residue is dissolved in 25 ml. of 90 percent acetic acid and then 5 g. of zinc dust is added to the solution. The resulting mixture is stirred and cooled in an ice bath for three hours to remove the trichloroethyl ester group and to form the corresponding 7 - (phenylacetamido)desacetoxycephalosporanic acid [7 - (phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid].

EXAMPLE 5.

A mixture of 1 g. of 2,2,2 - trichloroethyl 6 - (thiophene - 2 - acetamido)penicillanate sulfoxide, 1.2 g. of propionic anhydride and sufficient N,N - dimethylcarbanilide to make 50 ml. of solution upon warming is warmed to 130° C. for effect solution and stirred at that temperature for 5 to 5 hours to insure complete reaction of the penicillin sulfoxide ester. The N,N - dimethylcarbanilide is removed and the crude product which remains as residue is taken up in 25 ml. of 90 percent acetic acid solution and then 5 grams of zinc dust is added. The resulting mixture is stirred at ice bath temperature to remove the ester group and to form the 7 - (thiophene - 2 - acetamido)desacetoxycephalosporanic acid [7 - (thiophene - 2 - acetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid].

EXAMPLE 6.

Phenoxyisopropylpenicillin sulfoxide 2,2,2-trichloroethyl ester was prepared by reacting phenoxyisopropylpenicillin potassium salt with sodium metaperiodate in acidified water; solution to form the sulfoxide, and reacting the resulting phenoxyisopropylpenicillin sulfoxide as the sodium salt with 2,2,2 - trichloroethanol in methylene chloride containing a small amount of pyridine and N,N - dicyclohexylcarbodiimide in an amount equivalent to the penicillin to form the 2,2,2 - trichloroethyl phenoxyisopropyl - penicillin sulfoxide [2,2,2-trichloroethyl 6 - (α,α - dimethyl - α - phenoxyacetamido) - 2,2,2 - dimethylpenam - 3 - carboxylate sulfoxide].

A 3.0 g. (5.7 m moles) portion of the 2,2,2-trichloroethyl phenoxyisopropyl penicillin sulfoxide ester is dissolved in 120 ml. of warmed N,N - dimethyl - N',N' - diethylurea containing 2.9 g. (28.5 mmoles) of acetic anhydride. The mixture is heated in an oil bath for about 5 hours to insure complete reaction. The N,N - dimethyl - N',N' - diethylurea is removed under high vacuum. The crude 2,2,2 - trichloroethyl 7 - (α,α - dimethyl - α - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylate product is dissolved in 90 percent acetic acid and zinc dust as described in Example 4, to obtain the free 7 - (α,α - dimethyl - α - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

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EXAMPLE 7.

7 - (α, α - Dimethyl - α - phenoxyacetamido) - 3 - desacetoxycephalosporanic acid *p* - methoxyphenyl ester; *p* - methoxybenzyl ester, 2,2 - dichloromethyl ester.

The *p* - methoxyphenyl, *p* - methoxybenzyl, and 2,2 - dichloroethyl esters of 7 - (α, α - dimethyl - α - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid, are prepared by dissolving their respective penam sulfoxide esters in tetramethylurea, together with from 2 to 5 molar equivalents of acetic anhydride, relative to the respective penam sulfoxide esters therein and heating the resulting solutions to about 130° to 140° C. for about 1 hour.

EXAMPLE 8.

7 - (α - Amidophenylacetamido) - 3 - desacetoxycephalosporanic acid.

A 3.2 g. (4.5 mmoles) portion of the 2,2,2 - trichloroethyl 6 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - α - phenylglycylamido] - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide ester is dissolved in 120 ml. of tetramethylurea solvent containing acetic anhydride, 2.3 g. (22.5 mmoles), and heated in an oil bath at 135° C. for one hour to effect rearrangement. The solvent and excess acid reagent are removed under high vacuum. The residual oil is taken up in 50 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 to remove the blocking group from the glycyl amino nitrogen. The reaction mixture is filtered. The zinc is washed with two volumes of acetic acid. The wash and filtrate are combined and concentrated to dryness *in vacuo*. The crude desacetoxycephalosporin residue is taken up in 100 ml. water, cooled, and acidified to pH 1 with trifluoroacetic acid, and the desacetoxycephaloglycin trifluoroacetic acid salt is extracted with methyl isobutyl ketone. The organic solvent is dried over magnesium sulfate and evaporated *in vacuo*, and the residue is triturated with anhydrous ethyl ether, giving the trifluoroacetic acid salt of desacetoxycephaloglycin as a pink, amorphous powder. A bioautograph of this product (against a *Bacillus subtilis* seeded agar plate) of a paper chromatogram developed with butanol, acetic acid, water (3:1:1) shows a single biologically-active spot corresponding exactly in *R_f* value with that of desacetoxycephaloglycin [7 - (D - phenylglycyl - amido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid] prepared by an alternate synthesis. The NMR analysis shows the C-3 methyl absorption band characteristic of desacetoxycephalosporins as a singlet at τ 7.90.

EXAMPLE 9.

A 0.55 g. portion of the *p* - methoxybenzyl phenylmercaptomethyl penicillin sulfoxide ester, obtained by reacting phenylmercapto-

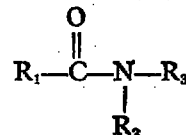
methylpenicillin potassium salt with *p* - methoxybenzyl alcohol to form the ester *p* - methoxybenzyl ester, and then reacting this penicillin ester with sodium metaperiodate to form the *p* - methoxybenzyl phenylmercaptomethylpenicillin sulfoxide ester, is dissolved in 50 ml. of 1,3 - dimethyl - 2 - imidazolidone using acetic anhydride to provide acid conditions, and heated to 110° C. for 1 hour to form the *p* - methoxybenzyl 7 - (phenylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylate. This cephem ester is taken up in 90 percent acetic acid solution and treated with zinc dust, which mixture is stirred on an ice bath for 1 hour to remove the *p* - methoxybenzyl group and to form the 7 - (phenylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid antibiotic.

EXAMPLE 10.

2,2,2 - Trichloroethyl 6 - (2' - chloro - 2' - phenylacetamido)penicillanate sulfoxide was prepared by esterifying 6 - (2' - chloro - 2' - phenylacetamido)penicillanic acid potassium salt with 2,2,2 - trichloroethyl chloroformate and then forming the sulfoxide by reacting the ester with chloroperbenzoic acid in chloroform in an ice bath. A portion of the 2,2,2 - trichloroethyl 6 - (2' - chloro - 2' - phenylacetamido)penicillanate sulfoxide is dissolved in about 50 ml. of warmed 1,1' - carbonyldi-pyrrolidine with *p* - toluenesulfonic acid being added in slight molar excess relative to the penicillin sulfoxide ester to provide acid conditions. The mixture is heated to about 120° C. for about 1 hour to form 2,2,2 - trichloroethyl 7 - (2' - chloro - 2' - phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylate. After removing most of the 1,1 - carbonyldi-pyrrolidine, the crude residue cephem ester product is taken up in 90 percent acetic acid solution, zinc dust is added, and the mixture is stirred for about 2 hours to remove the ester group and to form the 7 - (2' - chloro - 2 - phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid antibiotic.

WHAT WE CLAIM IS:—

1. A process for converting a penicillin sulfoxide ester to a desacetoxycephalosporin antibiotic by heating the penicillin sulfoxide ester under acid conditions for a time sufficient to effect conversion thereof, which comprises heating the penicillin sulfoxide ester dissolved in a tertiary carboxamide or a tertiary urea or mixtures thereof, as a diluent at a temperature of from 80° C. to 175° C., said tertiary carboxamide or urea being represented by the structural formula



EXAMPLE 7.

7 - (α, α - Dimethyl - α - phenoxyacetamido) - 3 - desacetoxycephalosporanic acid p-methoxyphenyl ester, p - methoxybenzyl ester, 2,2 - dichloromethyl ester.

The p - methoxyphenyl, p - methoxybenzyl, and 2,2 - dichloroethyl esters of 7 - (α, α - dimethyl - α - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid, are prepared by dissolving their respective penam sulfoxide esters in tetramethylurea, together with from 2 to 5 molar equivalents of acetic anhydride, relative to the respective penam sulfoxide esters therein and heating the resulting solutions to about 130° to 140° C. for about 1 hour.

EXAMPLE 8.

7 - (α - Amidophenylacetamido) - 3 - desacetoxycephalosporanic acid.

A 3.2 g. (4.5 mmoles) portion of the 2,2,2-trichloroethyl 6 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - α - phenylglycylamido] - 2,2-dimethylpenam - 3 - carboxylate sulfoxide ester is dissolved in 120 ml. of tetramethylurea solvent containing acetic anhydride, 2.3 g. (22.5 mmoles), and heated in an oil bath at 135° C. for one hour to effect rearrangement. The solvent and excess acid reagent are removed under high vacuum. The residual oil is taken up in 50 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 to remove the blocking group from the glycyl amino nitrogen. The reaction mixture is filtered. The zinc is washed with two volumes of acetic acid. The wash and filtrate are combined and concentrated to dryness *in vacuo*. The crude desacetoxycephalosporin residue is taken up in 100 ml. water, cooled, and acidified to pH 1 with trifluoroacetic acid, and the desacetoxycephaloglycin trifluoroacetic acid salt is extracted with methyl isobutyl ketone. The organic solvent is dried over magnesium sulfate and evaporated *in vacuo*, and the residue is triturated with anhydrous ethyl ether, giving the trifluoroacetic acid salt of desacetoxycephaloglycin as a pink, amorphous powder. A bioautograph of this product (against a *Bacillus subtilis* seeded agar plate) of a paper chromatogram developed with butanol, acetic acid, water (3:1:1) shows a single biologically-active spot corresponding exactly in R_f value with that of desacetoxycephaloglycin [7 - (D - phenylglycyl - amido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid] prepared by an alternate synthesis. The NMR analysis shows the C-3 methyl absorption band characteristic of desacetoxycephalosporins as a singlet at τ 7.90.

EXAMPLE 9.

A 0.55 g. portion of the p - methoxybenzyl phenylmercaptomethyl penicillin sulfoxide ester, obtained by reacting phenylmercapto-

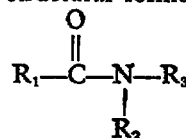
methylpenicillin potassium salt with p - methoxy benzyl alcohol to form the ester p - methoxybenzyl ester, and then reacting this penicillin ester with sodium metaperiodate to form the p - methoxybenzyl phenylmercaptomethylpenicillin sulfoxide ester, is dissolved in 50 ml. of 1,3 - dimethyl - 2 - imidazolidone using acetic anhydride to provide acid conditions, and heated to 110° C. for 1 hour to form the p - methoxybenzyl 7 - (phenylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylate. This cephem ester is taken up in 90 percent acetic acid solution and treated with zinc dust, which mixture is stirred on an ice bath for 1 hour to remove the p - methoxybenzyl group and to form the 7 - (phenylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid antibiotic.

EXAMPLE 10.

2,2,2 - Trichloroethyl 6 - (2' - chloro - 2' - phenylacetamido)penicillanate sulfoxide was prepared by esterifying 6 - (2' - chloro - 2' - phenylacetamido)penicillanic acid potassium salt with 2,2,2 - trichloroethyl chloroformate and then forming the sulfoxide by reacting the ester with chloroperbenzoic acid in chloroform in an ice bath. A portion of the 2,2,2-trichloroethyl 6 - (2' - chloro - 2' - phenylacetamido)penicillanate sulfoxide is dissolved in about 50 ml. of warmed 1,1' - carbonyldipyrrolidine with p - toluenesulfonic acid being added in slight molar excess relative to the penicillin sulfoxide ester to provide acid conditions. The mixture is heated to about 120° C. for about 1 hour to form 2,2,2-trichloroethyl 7 - (2' - chloro - 2' - phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylate. After removing most of the 1,1-carbonyldipyrrolidine, the crude residue cephem ester product is taken up in 90 percent acetic acid solution, zinc dust is added, and the mixture is stirred for about 2 hours to remove the ester group and to form the 7 - (2' - chloro - 2 - phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid antibiotic.

WHAT WE CLAIM IS:—

1. A process for converting a penicillin sulfoxide ester to a desacetoxycephalosporin antibiotic by heating the penicillin sulfoxide ester under acid conditions for a time sufficient to effect conversion thereof, which comprises heating the penicillin sulfoxide ester dissolved in a tertiary carboxamide or a tertiary urea or mixtures thereof, as a diluent at a temperature of from 80° C. to 175° C., said tertiary carboxamide or urea being represented by the structural formula





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wherein:

when taken alone

R₁ is hydrogen, alkyl, phenyl, tolyl, xylyl
or —N—R₅; and

R₄

5 R₂, R₃, R₄ and R₅ are alkyl, phenyl,
tolyl or xylyl

and when taken together

10 R₂ and R₃ and/or R₄ and R₅ together
with the nitrogen atom to which they
are bonded form a saturated mono-
cyclic ring having from 4—6 carbon
atoms, and having optionally an oxygen
ring member in a position gamma to the
ring nitrogen; and

15 R₁ and R₂ together with the intervening

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amide grouping (—C—N—) to which
they are bonded form a mono-cyclic ring
having from 4—6 carbon atoms with a
carbonyl group adjacent to the nitrogen
ring member; and R₂ and R₄ together
with the intervening urea grouping

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(—N—C—N—) to which they are bond-
ed form a 5 to 6 membered heterocyclic
ring;

25 with the further limitation that R₁, R₂, R₃,
R₄ and R₅ can in no case have a combined
total of more than 18 carbon atoms, can have
no more than 14 carbon atoms when R₁ is
hydrogen, and can have no more than 12
carbon atoms when any two of the substitu-
ents R₁—R₅ are taken together with one or
more nitrogen atoms to form a nitrogen-con-
taining ring.

30 2. A process of claim 1 wherein the diluent
is one wherein R₁ is hydrogen, and each of R₂
and R₃ is alkyl, phenyl, tolyl or xylyl such
that R₂ and R₃ together contain up to 14 car-
bon atoms.

35 3. The process of claim 1 or 2 wherein the
diluent is N,N - dimethylformamide.

40 4. The process of claim 1 or 2 wherein the
diluent is N,N - diphenylformamide.

45 5. The process of claim 1 wherein the dilu-
ent is one wherein at least one of R₁, R₂ and
R₃ is alkyl, and not more than two of R₁, R₂,
and R₃ are phenyl, tolyl or xylyl, and R₄,
R₅, and R₆ together contain up to 18 carbon
atoms.

50 6. The process of claim 1 or 5 wherein
the diluent is N,N - diethyl - m - toluamide.

7. The process of claim 1 wherein the dilu-
ent is N,N - dimethylacetamide.

8. The process of claim 1 wherein the dilu-
ent is tetramethylurea.

55 9. The process of claim 1 wherein the dilu-
ent is N,N - dimethylcarbanilide.

10. The process of claim 1 or 8 which
comprises (a) dissolving in tetramethylurea a
6 - [N - (2,2,2 - trichloroethoxycarbonyl)-

D - α - phenylglycylamido] - 2,2 - dimethyl- 60
penam - 3 - carboxylic acid sulfoxide ester,
the ester group being a 2,2,2 - trichloroethyl
group, with acetic anhydride in molar excess
relative to said ester, (b) heating the resulting
solution from step (a) to from 90° C. to 150° C. to form the corresponding 7 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - α - phenyl - glycylamido] - 3 - methyl - 3 - cephem - 4 - carboxylate ester, and (c) recovering 7 - (D - α - phenylglycylamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid from the respective ester obtained in step (b).

11. The process of claim 1, 2, 3 or 7 which
comprises (a) dissolving in dimethylformamide
or dimethylacetamide, or a mixture thereof,
a 6 - [N - (2,2,2 - trichloroethoxycarbonyl)-
D - phenyl - glycylamido] - 2,2 - dimethyl-
penam - 3 - carboxylic acid sulfoxide ester,
said ester group being a 2,2,2 - trichloroethyl
group, and acetic anhydride in molar excess
relative to said ester, (b) heating the resulting
solution from step (a) to from 90° C. to 150°
C. to form the corresponding 7 - [N - (2,2,2-
trichloroethoxycarbonyl) - D - phenylglycyl-
amido] - 3 - methyl - 3 - cephem - 4 - car-
boxylic acid ester, and (c) recovering the cor-
responding 7 - (D - phenylglycylamido) - 3-
methyl - 3 - cephem - 4 - carboxylic acid
from the respective ester obtained in step (b).

12. The process of claim 1, 2, 3 or 7 which
comprises (a) dissolving in dimethylforma-
mide, dimethylacetamide, or a mixture there-
of, a 6 - (2' - phenylacetamido) - 2,2 - di-
methyl - penam - 3 - carboxylic acid sul-
foxide ester, the ester group being a 2,2,2-
trichloroethyl, p - methoxyphenyl, or p - meth-
oxybenzyl group, and acetic anhydride in
molar excess relative to said ester, (b) heat-
ing the resulting solution from step (a) to
from 90° C. to 150° C. to form the corres-
ponding 7 - (2' - phenylacetamido) - 3-
methyl - 3 - cephem - 4 - carboxylic acid
ester, and (c) recovering the corresponding
7 - (2' - phenylacetamido) - 3 - methyl - 3-
cephem - 4 - carboxylic acid from the respec-
tive ester obtained from step (b).

13. The process of claim 1, 2, 3 or 7 which
comprises (a) dissolving in dimethylformamide,
dimethylacetamide, or a mixture thereof, a
6 - (2' - phenoxyacetamido) - 2,2 - dimethyl-
penam - 3 - carboxylic acid sulfoxide ester,
the ester group being a 2,2,2 - trichloroethyl,
p - methoxyphenyl or p - methoxybenzyl group
and acetic anhydride in molar excess relative
to said ester, (b) heating the resulting solution
from step (a) to from 90° C. to 150° C. to
form the corresponding 7 - (2' - phenoxy-
acetamido) - 3 - methyl - 3 - cephem - 4 -
carboxylic acid ester, and (c) recovering the
corresponding 7 - (2' - phenoxyacetamido)-3-
methyl - 3 - cephem - 4 - carboxylic acid
from the respective ester obtained from step
(b).

14. The process of claim 1, 2, 3 or 7 which

- comprises (a) dissolving in dimethylformamide, dimethylacetamide, or a mixture thereof, a 6 - benzoyl - 2,2 - dimethylpenam - 3 - carboxylic acid sulfoxide ester, the ester group being a 2,2,2 - trichloroethyl, p - methoxyphenyl or p - methoxybenzyl group, and acetic anhydride molar excess relative to said ester, (b) heating the solution resulting from step (a) to from 90° C. to 150° C. to form 7 - benzoyl - 3 - methyl - 3 - cephem - 4 - carboxylic acid ester, and (c) recovering the corresponding 7 - benzoyl - 3 - methyl - 3 - cephem - 4 - carboxylic acid from the respective ester obtained in step (b).
- 15 15. The process of claim 1 or 8 which comprises (a) dissolving in tetramethylurea a 6 - (2' - phenylacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid sulfoxide ester, the ester group being a 2,2,2 - trichloroethyl, p - methoxyphenyl or p - methoxybenzyl group, and acetic anhydride in molar excess relative to said ester, (b) heating the resulting solution from step (a) to from 90° C. to 150° C. to form the corresponding 7 - (2' - phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid ester, and (c) recovering the corresponding 7 - (2' - phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid from the respective ester obtained in step (b).
- 30 16. The process of claim 1 or 8 which comprises (a) dissolving in tetramethylurea a 6 - (2' - phenoxyacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid sulfoxide ester, the ester group being a 2,2,2 - trichloroethyl, p - methoxyphenyl or p - methoxybenzyl group, and acetic anhydride in molar excess relative to said ester, (b) heating the resulting solution from step (a) to from 90° C. to 150° C. to form the corresponding 7 - (2' - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 -

carboxylic acid ester, and (c) recovering the corresponding 7 - (2' - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid from the respective ester obtained from step (b).

17. The process of claim 1 or 8 which comprises (a) dissolving in tetramethylurea a 6 - (α,α - dimethyl - α - phenoxyacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid sulfoxide ester, the ester group being a 2,2,2 - trichloroethyl, p - methoxyphenyl or p - methoxybenzyl group, and acetic anhydride in molar excess relative to said ester, (b) heating the solution resulting from step (a) to from 90° C. to 150° C. to form 7 - (α,α - dimethyl - α - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid ester, and (c) recovering the corresponding 7 - (α,α - dimethyl - α - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid from the respective ester obtained in step (b).

18. A process according to claim 1 for converting a penicillin sulfoxide ester to a desacetoxycephalosporin antibiotic by heating the penicillin sulfoxide ester under acid condition for a time sufficient to effect conversion thereof substantially as hereinbefore described with particular reference to the Examples.

19. A desacetoxycephalosporan antibiotic whenever prepared by a process as claimed in any one of claims 1 to 18.

20. A pharmaceutical composition comprising a desacetoxycephalosporan antibiotic as claimed in claim 19 and a pharmaceutical carrier.

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