

PATENT SPECIFICATION

(11) 1204394

NO DRAWINGS

- (21) Application No. 21833/68 (22) Filed 8 May 1968
 (31) Convention Application No. 636629 (32) Filed 8 May 1967 in
 (33) United States of America (US)
 (45) Complete Specification published 9 Sept. 1970
 (51) International Classification C 07 d 99/24
 (52) Index at acceptance
 C2A 1C2C 2C1 2E
 (72) Inventor ROBIN COOPER

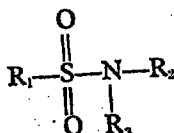


(54) PROCESS FOR CONVERTING A PENICILLIN SULFOXIDE ESTER TO A CEPHALOSPORIN ANTIBIOTIC

(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 desacetoxycephalosporan antibiotics produced by heating analogous penicillin sulfoxide esters using tertiary sulfonamides to direct the conversion of penicillin sulfoxide esters to desacetoxycephalosporan antibiotics.

More particularly, the present invention provides a process for converting a penicillin sulfoxide ester to a desacetoxycephalosporan 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 sulfonamide at a temperature of from about 80°C. to about 175°C., which tertiary sulfonamide is represented by the formula:



wherein

(a) each of R_1 , R_2 , and R_3 is C_1 to C_{10} alkyl, phenyl, tolyl, or xylol, at least one of R_1 , R_2 , and R_3 is C_1 to C_{10} alkyl, and R_1 , R_2 and R_3 together contain not more than 18 carbon atoms;

(b) R_1 is a C_1 to C_{10} alkyl, phenyl, tolyl, or xylol, and R_2 and R_3 are taken together with the nitrogen atom to which they are bonded to complete a monocyclic ring radical bonded to the sulfur atom, which radical contains from 4 to 6 saturated carbon atoms, and which

radical can contain a ring member oxygen atom gamma to the ring nitrogen, such that R_1 , R_2 , and R_3 together contain up to about 12 carbon atoms;

(c) R_1 and R_2 are taken together with the sulfonamide grouping to which they are bonded to form a sulfur oxide and mononitrogen monocyclic ring having from 3 to 5 saturated ring carbon atoms, wherein, and R_3 is alkyl, phenyl, tolyl, or xylol such that R_1 , R_2 , and R_3 together contain up to about 12 carbon atoms, and/or

(d) R_1 is $-\text{NR}_4$, and each R_2 , R_3 , R_4 , and R_5 is alkyl such that the sulfondiamide formed thereby contains up to about 12 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 a penicillin can be converted to the characteristic thiazine ring of the cephalosporins by heating a penicillin sulfoxide ester at a temperature of from about 100°C. to about 175°C. in the presence of an acid.

The process of the present invention is broadly applicable to the conversion of the prior-art penicillins, so long as they are not otherwise converted under the conditions of acidity and elevated temperature employed. In all cases they must be esterified and must be 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, and the like. 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-

butoxycarbonyloxy or the like. The product obtained by the treatment of the N-protected 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.

5 Examples of sulfonamides which may be used in the process of this invention include:

10 (1) N,N - dimethylmethanesulfonamide, N,N - diethylmethanesulfonamide, N,N - di-tert - butylmethanesulfonamide, N,N - dioctylmethanesulfonamide, N,N - dimethylethanesulfonamide, N - phenyl - N - ethylmethanesulfonamide, N,N - bis(4 - methylphenyl)butanesulfonamide, N - (p - tolyl) - N - propylmethanesulfonamide, N - methyl - N - (3,5 - dimethylphenyl)ethanesulfonamide, 15 N - ethyl - N - methylbenzenesulfonamide, N, N - dimethyloctanesulfonamide, N,N - dichyloctanesulfonamide, N,N - dimethyl - 4 - ethylbenzenesulfonamide;

20 (2) N - (methylsulfonyl)pyrrolidine, N - (ethylsulfonyl) - pyrrolidine, N - (phenylsulfonyl)pyrrolidine, N - (propylsulfonyl) - pyrrolidine, N - (hexylsulfonyl)pyrrolidine, N - (propylsulfonyl) - piperidine, N - (methylsulfonyl)morpholine, N - phenylsulfonyl)morpholine, N - heptylsulfonyl)piperidine;

25 (3) 2 - phenylisothiazolidine - 1,1 - dioxide, 2 - methylisothiazolidine - 1,1 - dioxide, 2 - hexylisothiazolidine - 1,1 - dioxide, 2 - phenyltetrahydro - 2H - 1,2 - thiazine - 1,1 - dioxide, 2 - ethyltetrahydro - 2H - 1,2 - thiazine - 1,1 - dioxide; and 30

(4) tetramethylsulfondiamide and N,N' - tetrapropylsulfondiamide.

40 In conducting the process of this invention, the penicillin sulfoxide ester is dissolved in the tertiary sulfonamide solvent system, either as the only solvent, or mixed with an optimum proportion of another tertiary sulfonamide or an inert organic liquid diluent or both 45 with the aid of heat, if necessary as defined above, and with the acid substance used to promote the rearrangement. Use of the tertiary sulfonamide as the only solvent except for the acid substance is preferred for highest yields of desacetoxycephalosporin products. 50 For best results, the penicillin sulfoxide ester concentration in the selected tertiary sulfonamide medium, that is, the total solvent, is maintained below about 15 percent, by weight, preferably below 10 percent by weight. 55

The acid substance can be commingled or mixed with the tertiary sulfonamide medium before, simultaneously with, or after the penicillin sulfoxide ester starting material is dissolved therein. The acid substance should be a nonoxidizing protic acid or Lewis acid capable of accepting electrons from the oxygen 60 of the thiazolidine sulfoxide bond in the ter-

tiary sulfonamide/penicillin sulfoxide ester/ acid medium. Preferred acid substances for use in the improved process of this invention include the alkanolic acid anhydrides having from 2—6 carbon atoms in each acid moiety, such as acetic anhydride, propionic anhydride, n-butanoic anhydride, pentanoic anhydride, hexanoic anhydrides, and mixed anhydrides of C₂—C₆ alkanolic acids, cyclic saturated dibasic acid anhydrides such as succinic anhydride, glutaric anhydride, strong Lewis acids such as aluminum chloride, boron trifluoride, hydrogen fluoride, ferric chloride, and strong nonoxidizing mineral acids such as p-toluenesulfonic, benzenesulfonic, methanesulfonic, naphthalenesulfonic, and other sulfonic acids or various phosphorus acids such as orthophosphoric acid, methylphosphonic, and the like, hydrochloric acid, as well as other acidic substances such as thionyl chloride, cyanogen bromide, and the like. For reasons of availability, cost, and generally better results, acetic anhydride and aluminum chloride are especially preferred acid substances. 70 75 80 85 90

In general, amounts of acid substance ranging 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 practice 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 about 2 to about 5 molar equivalents of the acid substance per molar equivalent of the penicillin sulfoxide ester are used at the optimum temperature. 95 100 105

The penicillin sulfoxide ester in the acidified tertiary sulfonamide solvent is heated to from about 80°C. to about 175°C. to direct the rearrangement of the penicillin sulfoxide ester to the corresponding desacetoxycephalosporin ester. The preferred temperature range is from about 90°C. to about 150°C., and the preferred reaction time is from about 1 to about 15 hours. Lower temperatures require more time, while at higher temperatures the reaction mixture tends to discolor and produce a more complex rearrangement product. 110 115

In preparing the penicillin sulfoxide esters for 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 selected penicillin may be esterified and then the resulting penicillin ester may be sulfoxylated according to conventional methods. Reference is made to the Morin and Jackson patent, U.S. 3,275,626. 120 125

By way of example and for completeness, 130

ester/
s for
ntion
aving
oicty,
iride,
iride
rides
rated
cinic
ewis
tri-
ride,
h as
ane-
ther
cids
nos-
as
nyl
For
ally
um
ab-
ice
20
um
he
c-
ed
is
at
le
e
n
e
e
105
110
115
120
125
130

- the following summarizes the steps that can be taken to prepare a desired desacetoxycephalosporin from a given penicillin sulfoxide 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 - phenylglycylamido)penicillanic acid sulfoxide ester.
- 5 (a) The penicillin sulfoxide ester is dissolved in a tertiary sulfonamide solvent medium together with acetic anhydride or other equivalent acid substance to obtain an acidified liquid solution of the penicillin sulfoxide ester.
 - 10 (b) The penicillin sulfoxide ester solution is heated to between from about 80°C. to 175°C. and preferably 90°C to 150°C to form the corresponding desacetoxycephalosporin ester.
 - 15 (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 to 3 hours at -5°C. to 20°C. to obtain the 7 - (D - α - phenylglycylamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid [7 - (D - α - phenyl - glycylamido)desacetoxycephalosporanic acid] (generic name—cephalexin) which is
 - 20 useful as an antibiotic in combating diseases caused by penicillin-resistant strains of *Staphylococcus aureus*.
 - 25 The prior art describes literally thousands of penicillin compounds almost all of which can be converted to desacetoxycephalosporin compounds by the improved process of this invention. The only limitation on the penicillin compounds which can be employed in the process of this invention is that they must
 - 30 not undergo other undesirable conversions under the reaction conditions of the process. A few typical examples will illustrate, to those familiar with the art, penicillins which may be used as starting materials, and the desacetoxycephalosporins obtained therefrom.
 - 35 The desacetoxycephalosporin compounds produced by the process of this invention from the corresponding penicillin sulfoxide esters are useful, after ester group removal, as bacteriostatic and bactericidal antibiotics in the therapy of diseases caused by various Gram-positive and Gram-negative microorganisms. 7 - Aminodesacetoxycephalosporanic acid, produced from a corresponding
 - 40 6 - amino - penicillanate sulfoxide ester by this invention is useful as an intermediate to prepare desacetoxycephalosporin antibiotic substances. Pharmaceutical compositions are prepared by utilizing the desacetoxycephalosporin antibiotic as prepared by the present invention with a pharmaceutical carrier.
 - 45 The esterified penicillin sulfoxides listed below yield the indicated corresponding desacetoxycephalosporins after heat rearrange-
 - 50
 - 55
 - 60
 - 65

ment 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)-acetamido] - 2,2 - dimethyl - penam - 3 - carboxylic acid yields 7 - [2' - methoxy - 2' - (2'' - thienyl) - acetamido] - 3 - methyl - 3 - cephem - 4 - carboxylic acid. 70

6 - (Phenylacetamido) - 2,2 - dimethyl - penam - 3 - carboxylic acid yields 7 - (phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid. 75

6 - (Thiophene - 2 - acetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (thiophene - 2 - acetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid. 80

6 - (Phenylmercaptoacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (phenylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid. 85

6 - (2' - Furylacetamido) - 2,2 - dimethylpenam-3-carboxylic acid yield 7-(2'-furylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid. 90

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. 95

6 - (Butylmercaptoacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (butylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid. 100

6 - (Heptylamido) - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - (heptylamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid. 105

6 - Benzoyl - 2,2 - dimethylpenam - 3 - carboxylic acid yields 7 - benzoyl - 3 - methyl - 3 - cephem - 4 - carboxylic acid. 105

This invention is further illustrated by the following detailed examples.

EXAMPLE 1

2,2,2 - Trichloroethyl - 6 - (phenylacetamido)penicillanate sulfoxide was prepared by reacting penicillin G potassium salt [benzylpenicillin, potassium salt] with 2,2,2 - trichloroethanol in methylene chloride in the presence of pyridine hydrochloride and dicyclohexylcarbodiimide and then reacting the resulting 2,2,2 - trichloroethyl 6 - (phenylacetamido)penicillanate ester intermediate with 85 percent m - chloroperbenzoic acid in chloroform in an ice bath medium to form the 2,2,2 - trichloroethyl 6 - (phenylacetamido)penicillanate sulfoxide. 110

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 N - (propylsulfonyl)piperidine is warmed to 130°C. in an oil bath for about 5 hours to insure complete reaction. The N - (propylsulfonyl)piperidine solvent is removed and the crude product which remains as 125

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 2

2,2,2 - Trichloroethyl 6 - (thiophene - 1 - acetamido)penicillanate sulfoxide was prepared from 6 - (thiophene - 2 - acetamido) - penicillanic acid potassium salt following the procedure set forth in Example 1.

A mixture of 1 g. of 2,2,2 - trichloroethyl 6 - (thiophene - 2 - acetamido)penicillanate sulfoxide, 1.2 g. of propionic anhydride and sufficient 2 - methylisothiazolidine - 1,1 - dioxide to make 50 ml. of solution upon warming is heated to 130°C. for effect solution and stirred at that temperature for 4 to 5 hours to insure complete reaction of the penicillin sulfoxide esters. The 2 - methylisothiazolidine - 1,1 - dioxide 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 3

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 phenoxyisopropylpenicillin sulfoxide [2,2,2 - trichloroethyl 6 - (α,α - dimethyl - α - phenoxyacetamido) - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide].

A 3.0 g. (5.7 mmoles) portion of the 2,2,2 - trichloroethyl phenoxyisopropyl penicillin sulfoxide ester, described above, is dissolved in 120 ml. of warmed tetramethylsulfondiamide 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 tetramethylsulfondiamide 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 1, to obtain the free 7 - (α,α - dimethyl - α - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid. 65

EXAMPLES 4, 5 and 6.

α,α - Dimethyl - α - phenoxyethylpenicillin sulfoxide p - methoxy - phenyl ester (4)

The p - methoxyphenyl 6 - (α,α - dimethyl - α - phenoxyacetamido) - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide was prepared using p - methoxyphenol in place of 2,2,2 - trichloroethanol, as described in Example 3. Recrystallization of this ester from chloroform-petroleum ether afforded an analytical sample; m.p. 159°C. to 161°C.; IR and NMR analyses were satisfactory for this penicillin sulfoxide aromatic ester; thin-layer chromatography showed single-spot material. 70 75 80

α,α - Dimethyl - α - phenoxyethylpenicillin sulfoxide p - methoxy - benzyl ester (5)

The p - methoxybenzyl 6 - (α,α - dimethyl - α - phenoxyacetamido) - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide was prepared using p - methoxybenzyl alcohol in place of 2,2,2 - trichloroethanol, as described in Example 3. This ester purified from ethyl acetate-petroleum ether has a m.p. of 163—165°C. IR and NMR analyses were consistent with this penicillin sulfoxide aromatic ester; thin-layer chromatography showed single-spot material. 85 90 95

α,α - Dimethyl - α - phenoxyethylpenicillin sulfoxide 2,2 - dichloroethyl ester (6)

The 2,2 - dichloroethyl 6 - (α,α - dimethyl - α - phenoxyacetamido) - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide was prepared as described in Example 3 by using 2,2 - dichloroethanol in place of 2,2,2 - trichloroethanol. This ester, purified from ethyl acetate-petroleum ether, gave a m.p. 113°C. to 115°C., IR and NMR analyses were consistent with this penicillin sulfoxide ester; thin-layer chromatography showed single-spot material. 100 105

7 - (α,α - Dimethyl - α - phenoxyacetamido) - 3 - desacetoxycephalosporanic acid p - methoxyphenyl ester (4), p - methoxybenzyl ester (5), 2,2 - dichloromethyl ester (6) 110

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 the above respective penam sulfoxide esters in N,N - dimethyl - p - tolylsulfonamide, 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°C. to 140°C. for about 1 hour. 115 120

EXAMPLE 7

2,2,2 - Trichloroethyl chloroformate

To a solution of phosgene, 40 g. (400 moles), in 200 ml. of dry benzene there were added dropwise 2,2,2 - trichloroethanol, 15.8 g. (100 moles), and pyridine, 12 g. (152 moles) in a mixture of 200 ml. of dry benzene and 400 ml. of anhydrous ethyl ether with occasional cooling to keep the temperature slightly below 20°C. The addition required two hours. The precipitated pyridine hydrochloride was filtered off. The filtrate was cooled, poured into 1 liter of ice water and shaken in a separatory funnel. The organic layer was separated, dried over $MgSO_4$, and evaporated *in vacuo*. Distillation of the residue from over $CaCO_3$ gave a 15 g. (67 percent) yield of the 2,2,2 - trichloroethyl chloroformate; b.p. 43°C./10.5 mm.; $[n]_D^{20} = 1.4698$; λ max. 5.62 μ ; the NMR analysis was satisfactory.

Anal. Calcd. for $C_2H_3Cl_3O_2$: Cl, 66.94. Found: Cl, 66.74.

N - (2,2,2 - Trichloroethoxy carbonyl) - D - phenylglycine (I)

A solution of D - phenylglycine, 22.7 g. (150 mmoles), in 300 ml. of water, 160 ml. of 1 N NaOH and 150 ml. of ether was cooled in an ice-alcohol bath. While stirring, simultaneous dropwise additions of 2,2,2 - trichloroethyl chloroformate, 42.5 g. (220 mmoles) in 200 ml. of dry dioxane and 200 ml. of 1 N NaOH were made. The additions required about one hour. The reaction mixture was maintained near 0°C. for another hour, washed with a large volume of cold ether, and then acidified to pH 2.5 in the presence of cold ethyl acetate. The organic layer was separated, washed with cold water, dried ($MgSO_4$), and evaporated *in vacuo*. The crystalline solid residue weighed 45 g. and was recrystallized by dissolving in 150 ml. of benzene, filtering, and diluting with 40 ml. of petroleum ether. The yield of pure N - (2,2,2 - trichloroethoxy - carbonyl) - phenylglycine product was 30.2 g. (62 percent); m.p. 142—144°C.; electrometric titration in 66 percent aqueous dimethylformamide showed a $pK'_a = 5.55$ and an apparent molecular weight = 332 (calcd. 327); the NMR analysis was satisfactory.

Anal. Calcd. for $C_{11}H_{10}Cl_3NO_4$: C, 40.45; H, 3.09; N, 4.29. Found: C, 40.60; H, 3.24; N, 4.55.

6 - [N - (2,2,2 - Trichloroethyl carbonyl) - D - phenylglycyl]aminopenicillanic acid (II)

2,2,2 - Trichloroethyl chloroformate, 11.6 g. (85.0 mmoles), was dissolved in 420 ml. of analytical grade acetone containing a few drops of dimethylbenzylamine and cooled in an ice-alcohol bath. While stirring, N - (2,2,2 - trichloroethoxy carbonyl) - D -

phenylglycine, 28.0 g. (85.0 mmoles), and triethylamine, 8.7 g. (86.0 mmoles) in 420 ml. of acetone were added dropwise over a period of thirty minutes to form the N - (2,2,2 - trichloroethoxycarbonyl) - D - phenylglycyl 2,2,2 - trichloroethyl carbonate. The mixture was stirred in the cold an additional fifteen minutes. 6 - Aminopenicillanic acid (6-APA), 18.6 g. (85.0 mmoles), in 70 ml. of cold water containing triethylamine, 8.7 g. (86.0 mmoles), was added in one portion to the reaction. The mixture was stirred in cold for two hours, concentrated *in vacuo* to remove the acetone and diluted with a volume of water. The aqueous solution was layered with ethyl acetate, cooled, and acidified to pH 2.5 with 1 N HCl. The ethyl acetate was separated, washed with cold water, and back-titrated into water to pH 6.7 with 1 N NaOH to form the sodium salt. The aqueous salt-containing layer was separated, filtered and evaporated to dryness *in vacuo*. The residue, after trituration with dry acetone, was a white amorphous powder, weighing 24.6 g. (53 percent yield); electrometric titration in 66 percent aqueous dimethylformamide showed a $pK'_a = 5.25$ and an apparent molecular weight = 539 (calcd. 547); IR and NMR were as expected for the desired product.

6 - [N - (2,2,2 - Trichloroethoxycarbonyl) - D - phenylglycyl]aminopenicillanic acid sulfoxide (III)

An 18 g. portion of 6 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - phenylglycyl]aminopenicillanic acid sodium salt was dissolved in 300 ml. of water. The pH of the solution was adjusted to 5.4 with 1 N HCl. Sodium metaperiodate, 7.1 g. (33 mmoles), was added portionwise and the mixture was stirred at room temperature for two hours, acidified to pH 2.5 in the cold and in the presence of ethyl acetate. The organic layer containing the penicillin sulfoxide was separated, washed with cold water, dried over $MgSO_4$ and evaporated *in vacuo*. The crude penicillin sulfoxide residue weighed 16 g. Crystallization was effected by dissolving the product in 64 ml. of N,N - dimethylacetamide and diluting with 640 ml. of anhydrous ether, filtering, and diluting slowly with 40 ml. of petroleum ether. The yield of pure 6 - { α - [N - (2,2,2 - trichloroethoxycarbonyl)amino] - α - phenylacetamido} - 2,2 - dimethylpenam - 3 - carboxylic acid sulfoxide product was 11.6 g. (56 percent); m.p. 153—155°C. As evidenced by NMR and IR analysis, this product was solvated with one mole of dimethylacetamide.

Anal. Calcd. for $C_{19}H_{20}Cl_3N_3O_7SC_4H_9NO$: C, 43.99; H, 4.65; N, 8.92. Found: C, 44.26; H, 5.02; N, 8.65.

6 - [N - (2,2,2 - Trichloroethoxycarbonyl) -

D - phenylglycylaminopenicillanic acid sulfoxide 2,2,2 - trichloroethyl ester (IV)

A 7 g. (11.2 mmoles)-portion of 6 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - phenylglycylamido] - 2,2 - dimethylpenam - 3 - carboxylic acid sulfoxide was dissolved in 85 ml. of dry tetrahydrofuran (THF) containing pyridine, 1.77 g. 22.3 mmoles). The solution was cooled in an ice-alcohol bath and stirred while adding 2,2,2 - trichloroethyl chloroformate, 3.6 g. 16.7 mmoles), in 20 ml. of THF. The mixture was stirred in the cold for two hours, at room temperature for three hours, and heated to gentle reflux for fifteen minutes. The solvent was removed *in vacuo*. The amine - protected - D - phenylglycylpenicillin sulfoxide ester residue was taken up in cold ethyl acetate for successive washes with water, 5 percent NaHCO_3 solution, and water. The ethyl acetate solution was dried (MgSO_4) and evaporated *in vacuo*, giving 5.2 g. of an amorphous solid. Crystallization from 7 ml. of ethanol gave a 4.5 g. (59 percent) yield of 2,2,2 - trichloroethyl 6 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - phenylglycylamido] - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide ester product; m.p. 180—182°C. A 1-gram sample of this product was recrystallized from ethanol-water for analysis; m.p. 185—186°C.

Anal. Calcd. for $\text{C}_{22}\text{H}_{25}\text{Cl}_3\text{N}_3\text{O}_5\text{S}$: C, 37.51; H, 3.14; N, 6.25. Found: C, 37.96; H, 3.39; N, 6.02.

7 - (α - Aminophenylacetamido) - 3 - desacetoxyccephalosporanic acid (V)

A 3.2 g. (4.5 mmoles) portion of the 2,2,2 - trichloroethyl 6 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - phenylglycylamido] - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide ester is dissolved in 120 ml. of N,N - dimethylmethanesulfonamide 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 was 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 desacetoxyccephalosporin residue is taken up in 100 ml. water, cooled, and acidified to pH 1 with trifluoroacetic acid, and the desacetoxyccephaloglycin trifluoroacetic acid salt is extracted with methylisobutyl ketone. The organic solvent is dried (MgSO_4) and evaporated *in vacuo*, and the residue triturated with anhydrous ethyl ether, giving the trifluoroacetic acid salt of desacetoxyccephaloglycin as a pink, amorphous

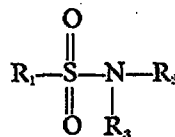
powder. A bioautograph of this product (against a *Bacillus subtilis* seeded agar plate) of a paper chromatogram developed with butanol, acetic acid, water (3:1:1) shows a single biologically-active spot corresponding exactly in R_f value with that of resacetoxyccephaloglycin [7 - (D - phenylglycylamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid] prepared by an alternate synthesis. The NMR analysis showed the C - 3 - methyl absorption band characteristic of desacetoxyccephalosporins as a singlet at τ 7.90.

EXAMPLE 8

A 1-gram portion of 2,2,2 - trichloroethylheptylmercaptomethylpenicillin sulfoxide ester, obtained by reacting heptylmercaptomethylpenicillin potassium salt with 2,2,2 - trichloroethanol in methylene dichloride, and then treating the resulting ester with sodium metaperiodate at ice bath temperatures to form the 2,2,2 - trichloroethyl heptylmercaptomethylpenicillin sulfoxide, is dissolved in 50 ml. of warmed N,N - diethylbenzenesulfonamide with 1.5 grams of aluminum chloride. The resulting mixture is warmed to 95°C. for 1 hour to form the 2,2,2 - trichloroethyl 7 - (heptylmercaptoacetamido) - trichloroethyl 7-(heptylmercaptoacetamido)-3-methyl 3-cephem-4-carboxylate ester. Most of the N,N - diethylbenzene - sulfonamide is removed under vacuum and the crude cephem ester product is taken up in 90 percent acetic acid and treated with zinc dust at 0°C. to 20°C. to remove the ester group and to form the 7 - (heptylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid antibiotic.

WHAT WE CLAIM IS:—

1. A process for converting a penicillin sulfoxide ester to a desacetoxyccephalosporan 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 sulfonamide at a temperature of from about 80°C. to about 175°C., which tertiary sulfonamide is represented by the formula:



(a) each of R₁, R₂, and R₃ is C₁ to C₁₀ alkyl, phenyl, tolyl, or xylyl, at least one of R₁, R₂, and R₃ is C₁ to C₁₀ alkyl, and R₁, R₂, and R₃ together contain not more than 18 carbon atoms;

(b) R₁ is a C₁ to C₁₀ alkyl, phenyl, tolyl, or xylyl, and R₂ and R₃ are taken together with the nitrogen atom to which they are bonded to complete a monocyclic ring radical bonded



* C L M S *

D - phenylglycyl]aminopenicillanic acid sulfoxide 2,2,2 - trichloroethyl ester (IV)
 A 7 g. (11.2 mmoles)-portion of 6 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - phenylglycylamido] - 2,2 - dimethylpenam - 3 - carboxylic acid sulfoxide was dissolved in 85 ml. of dry tetrahydrofuran (THF) containing pyridine, 1.77 g. 22.3 mmoles). The solution was cooled in an ice-alcohol bath and stirred while adding 2,2,2 - trichloroethyl chloroformate, 3.6 g. 16.7 mmoles), in 20 ml. of THF. The mixture was stirred in the cold for two hours, at room temperature for three hours, and heated to gentle reflux for fifteen minutes. The solvent was removed *in vacuo*. The amine - protected - D - phenylglycylpenicillin sulfoxide ester residue was taken up in cold ethyl acetate for successive washes with water, 5 percent NaHCO_3 solution, and water. The ethyl acetate solution was dried (MgSO_4) and evaporated *in vacuo*, giving 5.2 g. of an amorphous solid. Crystallization from 7 ml. of ethanol gave a 4.5 g. (59 percent) yield of 2,2,2 - trichloroethyl 6 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - phenylglycylamido] - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide ester product; m.p. 180—182°C. A 1-gram sample of this product was recrystallized from ethanol-water for analysis; m.p. 185—186°C.

Anal. Calcd. for $\text{C}_{27}\text{H}_{31}\text{Cl}_3\text{N}_3\text{O}_5\text{S}$: C, 37.51; H, 3.14; N, 6.25. Found: C, 37.96; H, 3.39; N, 6.02.

7 - (α - Aminophenylacetamido) - 3 - desacetoxycephalosporanic acid (V)

A 3.2 g. (4.5 mmoles) portion of the 2,2,2 - trichloroethyl 6 - [N - (2,2,2 - trichloroethoxycarbonyl) - D - phenylglycylamido] - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide ester is dissolved in 120 ml. of N,N - dimethylmethanesulfonamide 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 was 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 methylisobutyl ketone. The organic solvent is dried (MgSO_4) and evaporated *in vacuo*, and the residue triturated with anhydrous ethyl ether, giving the trifluoroacetic acid salt of desacetoxycephaloglycin as a pink, amorphous

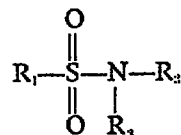
powder. A bioautograph of this product (against a *Bacillus subtilis* seeded agar plate) of a paper chromatogram developed with butanol, acetic acid, water (3:1:1) shows a single biologically-active spot corresponding exactly in R_f value with that of resacetoxycephaloglycin [7 - (D - phenylglycylamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid] prepared by an alternate synthesis. The NMR analysis showed the C - 3 - methyl absorption band characteristic of desacetoxycephalosporins as a singlet at τ 7.90.

EXAMPLE 8

A 1-gram portion of 2,2,2 - trichloroethylheptylmercaptomethylpenicillin sulfoxide ester, obtained by reacting heptylmercaptomethylpenicillin potassium salt with 2,2,2 - trichloroethanol in methylene dichloride, and then treating the resulting ester with sodium metaperiodate at ice bath temperatures to form the 2,2,2 - trichloroethyl heptylmercaptomethylpenicillin sulfoxide, is dissolved in 50 ml. of warmed N,N - diethylbenzenesulfonamide with 1.5 grams of aluminum chloride. The resulting mixture is warmed to 95°C. for 1 hour to form the 2,2,2 - trichloroethyl 7 - (heptylmercaptoacetamido) - trichloroethyl 7-(heptylmercaptoacetamido)-3-methyl 3-cephem-4-carboxylate ester. Most of the N,N - diethylbenzene - sulfonamide is removed under vacuum and the crude cephem ester product is taken up in 90 percent acetic acid and treated with zinc dust at 0°C. to 20°C. to remove the ester group and to form the 7 - (heptylmercaptoacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid antibiotic.

WHAT WE CLAIM IS:—

1. 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 sulfonamide at a temperature of from about 80°C. to about 175°C., which tertiary sulfonamide is represented by the formula:



(a) each of R_1 , R_2 , and R_3 is C_1 to C_{10} alkyl, phenyl, tolyl, or xylyl, at least one of R_1 , R_2 , and R_3 is C_1 to C_{10} alkyl, and R_1 , R_2 , and R_3 together contain not more than 18 carbon atoms;

(b) R_1 is a C_1 to C_{10} alkyl, phenyl, tolyl, or xylyl, and R_2 and R_3 are taken together with the nitrogen atom to which they are bonded to complete a monocyclic ring radical bonded

product 65
(ar plate)
ed with
shows a
sponding
sacetyl- 70
amide
[lic acid]
is. The
methyl
acetoxyl- 75

richloro-
sulfoxide
mercapto- 80
2,2,2 -
ide, and
sodium
ures to
mercapto- 85
d in 50
zenesul-
uminum
warmed
2,2,2 - 90
mido) -
nido)-3-
Most
amide is 95
cephem
it acetic
0°C. to
to form
- 3 -
lic acid 100

enicillin
osporan
r under 105
o effect
heating
d in a
of from
tertiary 110
rmula:

, alkyl,
R₁, R₂,
and R₃ 115
carbon

yl, or
r with
bonded 120
bonded

to the sulfur atom, which radical contains from 4 to 6 saturated carbon atoms, and which radical can contain a ring member oxygen atom gamma to the ring nitrogen, such that R₁, R₂, and R₃ together contain up to about 12 carbon atoms;

(c) R₁ and R₂ are taken together with the sulfonamide grouping to which they are bonded to form a sulfur oxide and mononitrogen monocyclic ring having from 3 to 5 saturated ring carbon atoms therein, and R₃ is alkyl, phenyl, tolyl, or xylyl such that R₁, R₂, and R₃ together contain up to about 12 carbon atoms, and/or

(d) R₁ is —NR₄R₅ and each R₂, R₃, R₄, and R₅ is alkyl such that the sulfondiamide formed thereby contains up to about 12 carbon atoms.

2. The process of claim 1 wherein the tertiary sulfonamide is one in which each of R₁, R₂, and R₃ is C₁ to C₁₀ alkyl, phenyl, tolyl, or xylyl, at least one of R₁, R₂ and R₃ is C₁ to C₁₀ alkyl and R₁, R₂ and R₃ together contain not more than 18 carbon atoms.

3. The process of claim 2 wherein the tertiary sulfonamide is N,N - dimethylmethanesulfonamide.

4. The process of claim 1 which comprises (a) dissolving in tetramethylsulfondiamide a 6 - (α,α - dimethyl - α - phenoxyacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid sulfoxide ester, the ester group being a 2,2,2 - trichloroethyl, with acetic anhydride in molar excess relative to said ester,

(b) heating the resulting solution from step (a) to from about 90°C. to about 150°C. to form the corresponding 7 - (α,α - dimethyl - α - phenoxyacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylate ester, and

(c) recovering 7 - (α,α - dimethyl - α - phenoxy acetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid from the respective ester obtained in step (b).

5. The process of claim 1 which comprises (a) dissolving 2,2,2 - trichloroethyl 6 - (phenylacetamido) penicillanate sulfoxide in N - (propylsulfonyl)piperidine with acetic

anhydride in molar excess relative to said sulfoxide,

(b) heating the resulting solution from step (a) to from about 90°C. to about 150°C. to form the 7 - (phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylate ester, and

(c) recovering 7 - (phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid from the ester obtained in step (b).

6. The process of claim 1 which comprises (a) dissolving in N,N - dimethylmethanesulfonamide a 2,2,2 - trichloroethyl 6 - [N - (protected amino) - D - α - phenylglycylamido] - 2,2 - dimethylpenam - 3 - carboxylate sulfoxide ester, and acetic anhydride in molar excess relative to said ester,

(b) heating the solution resulting from step (a) to from about 90°C. to about 150°C. to form 2,2,2 - trichloroethyl 7 - [N - (protected amino) - D - α - phenylglycylamido] - 3 - methyl - 3 - cephem - 4 - carboxylate ester, and

(c) recovering 7 - (D - α - phenylglycylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid from the ester obtained in step (b).

7. A process according to claim 1 for converting a penicillin sulfoxide ester to a desacetoxyl - cephealosporan by heating the penicillin sulfoxide ester under acid conditions for a time sufficient to effect conversion thereof substantially as hereinbefore described with particular reference to the examples.

8. A desacetoxyl - cephealosporan antibiotic whenever prepared by a process as claimed in any one of claims 1 to 7.

9. A pharmaceutical composition comprising a desacetoxyl - cephalosporan antibiotic as claimed in claim 8 and a pharmaceutical carrier.

BOULT, WADE & TENNANT,
111 & 112, Hatton Garden,
London, E.C.1.
Chartered Patent Agents,
Agents for the Applicant(s).

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1970.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.



* C L M S *