

PATENT SPECIFICATION

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(54) CONVERSION OF A PENICILLIN SULFOXIDE ESTER TO A DESACETYLCEPHALOSPORIN ESTER

(71) We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 307, East McCarty Street, 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 the improvement in yields of desacetoxycephalosporin esters obtained by heating a penicillin sulfoxide ester dissolved in a non-aqueous solvent containing a tertiary carboxamide in an amount to provide at least 10% by volume of the reaction mixture under acid conditions in a temperature range of from about 80°C. to about 150°C., characterized by using a sulfonic acid or a substance which forms a sulfonic acid in the mixture in an amount effective to provide the acid conditions while providing a means for removing or inactivating water in the reaction mixture during the heating operation.

The acid substance is a sulfonic acid, or a substance which is converted to a sulfonic acid upon heating with aqueous media, such as a sulfonic acid anhydride, a sulfonic acid ester, or a sultone which is converted to a sulfonic acid by water in the reaction mixture. Examples of preferred sulfonic acids are the C₁ to C₁₂-hydrocarbonsulfonic acids such as the C₁ to C₁₂-alkanesulfonic acids such as methanesulfonic, ethanesulfonic, hexanesulfonic, nonanesulfonic, dodecanesulfonic acids, as well as the C₄ to C₇-cycloalkanesulfonic acids such as cyclobutanesulfonic, cyclopentanesulfonic, cyclohexanesulfonic, and cycloheptanesulfonic acids, the C₆ to C₁₂-aromatic aryl and alkaryl hydrocarbonsulfonic acids such as benzenesulfonic, dodecylbenzenesulfonic, alpha- and beta-naphthalenesulfonic, biphenylsulfonic, p-toluenesulfonic, xylenesul-

fonic acids, disulfonic acids such as methane-disulfonic acid, benzenedisulfonic acid, C₆ to C₁₂-aryl aminodisulfonic acids such as 2-amino-1,4-benzenedisulfonic acid, and 2-amino-1,6-naphthalenedisulfonic acid, benzenetri-sulfonic acid and mixtures of sulfonic acids, and such sulfonic acids substituted with groups that do not interfere with the penicillin sulfoxide ester rearrangement reaction, such as chlorine, bromine, nitro and cyano, exemplified by p-chlorobenzenesulfonic, 3,5-dibromobenzenesulfonic, 4-nitro-alpha-naphthalenesulfonic, and 4-cyanobenzenesulfonic acids, as well as terpene-type sulfonic acids such as cymenesulfonic, methanesulfonic, lemonenesulfonic, pinenesulfonic, camphorsulfonic acid, and bornylsulfonic acids. For economic reasons, the preferred sulfonic acids are C₁ to C₈-alkanesulfonic acids such as methanesulfonic acid, ethanesulfonic acid, and the simple C₆ to C₈ aromatic aryl and alkaryl hydrocarbon sulfonic acids such as benzenesulfonic acid and p-toluenesulfonic acid. Sulfonic acid precursors such as sulfonic acid anhydrides which may be used are exemplified by methanesulfonic anhydride, and p-toluenesulfonic anhydride. Other sulfonic acid precursors such as sulfonic acid ester and sultones which may be used are exemplified by the C₁ to C₈-lower alkyl and benzyl esters of C₁ to C₈-alkanesulfonic acids and the C₆ to C₈-aryl and alkaryl sulfonic acids such as the methyl, ethyl, or propyl esters of methanesulfonic, benzenesulfonic, and p-toluenesulfonic acids, and propanesultone, butanesultone and 2,5-pentanesultone. The concentration of the acid substance will vary depending upon the nature of the acid substance, the concentration of the penicillin sulfoxide ester, the tertiary carboxamide used and the desired time of reaction. In general, the molar ratio of the penicillin sulfoxide ester to the acid substance can range from 1:1 to about 50:1. Preferably a molar ratio of peni-

cillin sulfoxide ester to acid ranges from about 5:1 to about 15:1. The concentration of the penicillin sulfoxide ester in the total solvent system can vary extensively but preferably constitutes from about 1 to about 20 percent by weight of the reaction mixture.

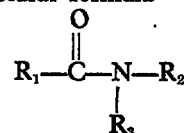
The penicillin sulfoxide ester in the acidified tertiary carboxamide solvent system, including means for removing water, is heated to from about 80°C. to about 150°C. to direct the rearrangement of the penicillin sulfoxide ester to the desacetoxycephalosporin ester. In the preferred tertiary carboxamide solvents, the preferred heating temperature is from about 90°C. to about 130°C. for from about 2 to about 24 hours. Lower temperatures require more time, while at higher temperatures the reaction mixture tends to produce a more complex rearrangement product.

The means for removing or inactivating water in the reaction mixture during the heating operation can be provided by chemical or physical procedures known in the art, or by combinations of both chemical and physical means, for example, by adding to the reaction mixture a drying substance which does not interfere with the desired penicillin sulfoxide ester conversion, e.g., C₂ to C₆-alkanoic acid anhydride in molar excess relative to the water present or produced in the reaction. Preferably, however, the best yields of desacetoxycephalosporin esters have been obtained when the reaction mixture includes a liquid or mixture of liquids which forms an azeotrope with water, which water-containing azeotrope is distilled out of the reaction mixture during the heating operation. Numerous types of chemicals are known to form binary or ternary water-containing azeotropes having boiling points sufficient for distillation during the heating operation. Such chemicals include hydrocarbons especially C₆ to C₈-alkanes and C₆ to C₈-aromatic hydrocarbons, halogenated hydrocarbons, particularly those containing from 1 to 6 carbon atoms, and from 1 to 4 chlorine or bromine atoms, ethers, esters, organic acids, ketones and aldehydes, as set forth in various chemistry handbooks; e.g., *Handbook of Chemistry*, Edited by N. A. Lange, Ninth Edition (1965), Published by Handbook Publishers, Inc., Sandusky, Ohio, pp. 1484 to 1486, and 1493, and in the Chemical Rubber Co., *Handbook of Chemistry and Physics*, 45th Edition, pp. D-1 to D-18, (1964-65). We prefer that the liquid that is used to form a water-containing azeotrope in the reaction mixture be a readily available, economical, inert organic liquid. Examples of suitable water-azeotrope forming liquids that are heavier than water, which may be used include 1,2-dichloroethane, chloroform, methylene chloride, and carbon tetrachloride. Examples of suitable water-azeotrope forming liquids that are lighter than water which may be used include methyl ethyl ketone, methyl

isobutyl ketone, benzene, toluene, xylene, pentane, hexane, heptane, ethyl acetate and isopropyl acetate. In some cases the azeotropic liquid can readily form part of the tertiary carboxamide-containing solvent system used to dissolve the penicillin sulfoxide ester. The tertiary carboxamide should constitute at least about 10 percent by volume of the reaction mixture. The water-azeotrope forming substances can form the remainder of the solvent system. However, it is not necessary that the azeotrope forming liquid form a large part of the solvent system. The water-containing azeotrope vapors can be condensed and collected in known types of chemical equipment, and the azeotrope-forming substances can be returned to the reaction mixture, preferably after being totally dried by some physical or chemical means, for additional water azeotrope formation, or additional dry azeotrope-forming liquid can be added to replace the water-containing azeotrope which is removed by distillation. Regardless of whether a water-inactivating chemical is added to the reaction mixture, use of the azeotropic distillation procedure appears to enhance the yield of the desacetoxycephalosporin ester product. It is contemplated that chemical and physical drying means can be used in combination to hasten water removal from the reaction mixture.

The water-containing azeotrope liquids can be collected and condensed in known types of chemical equipment including the usual Dean-Stark trap, and Barrett types of water traps and dried, if desired, for recycle of the top layer (azeotropic liquid) or other types of equipment such as is disclosed in ANALYTICAL CHEMISTRY, 29, p. 100 (1957), and in INDUSTRIAL AND ENGINEERING CHEMISTRY, Analytical Edition, 8, p. 314 (1936), for recycle of the lower layer, that is, when the water-azeotrope forming liquid has a density greater than water, water forms a top layer as it separates, and the heavier azeotropic liquid returns to the reaction vessel to be recycled. Commercial scale equipment operating on similar water removal principles can be used. It should also be noted that water can be removed by filtering the distillate through a column packed with a suitable drying agent such as anhydrous sodium sulfate, magnesium sulfate, calcium carbide, calcium chloride and molecular sieves, particularly types 3A and 4A. The dried azeotrope-forming liquid can then be returned to the reaction mixture.

The general types of tertiary carboxamides which can be used can be one or more which have the structural formula



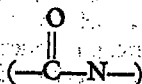
wherein

(1) R_1 is hydrogen, and each of R_2 and R_3 is alkyl, phenyl, tolyl, or xylyl such that and R_2 together contain up to 14 carbon atoms;

or (2) at least one of R_1 , R_2 , and R_3 is alkyl, and not more than two of R_1 , R_2 , and R_3 are phenyl, tolyl, xylyl, and R_1 , R_2 , and R_3 together contain up to 18 carbon atoms;

or (3) R_1 is hydrogen or alkyl, R_2 and R_3 are taken together with the nitrogen to which they are bonded to form a saturated monocyclic ring which contains from 4 to 6 carbon atoms in the ring, which ring can also contain an oxygen ring member, gamma to the ring nitrogen, and R_1 , R_2 , and R_3 together contain not more than 12 carbon atoms; or

(4) R_1 and R_2 are taken together with the amide grouping



to which they are bonded to form a saturated carbonyl-containing monocyclic ring having from 4 to 6 ring carbon atoms, R_3 is alkyl, phenyl, tolyl, or xylyl, and R_1 , R_2 , and R_3 together contain not more than 14 carbon atoms.

Examples of tertiary carboxamides of the types described above, which may be used in the process include:

(1) 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 - methylphenyl)formamide, N - (3,5 - dimethyl) - N - methylformamide, and N,N - bis(2,4 - dimethylphenyl)formamide;

(2) 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 - dimethylbutanoamide, N,N - diethylbutanoamide, N,N - dimethyldecanoamide, N,N - dimethylbenzamide, N,N - diethylbenzamide, N,N - dipropyl - m - toluamide, N,N - dibutyl - p - toluamide, N - phenyl - N - methylacetamide, N - (p - tolyl) - N - ethylacetamide, N - (3,5 - dimethylphenyl) - N - methylpropionamide, N,N - dimethyl - 3,5 - dimethylbenzoamide, N,N - dibutyl - 4 - ethylbenzoamide, N,N - diphenylacetamide, N - (3 - methylphenyl) - N - ethylbenzoamide, N,N - bis(6 - methylphenyl)propionamide, and N,N - bis(3,5 - dimethylphenyl)propionamide;

(3) N - formylpiperidine, N - acetylpyrroli-

dine, N - propionylmorpholine, N - acetyl - 4,5 - dimethylpyrrolidine, N - butanoylpiperidine, and N - acetyl - 6 - methylpiperidine; and

(4) 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 - methylphenyl) - 2 - pyrrolidone, N - methyl - 2 - homopiperidone and N - ethyl - 2 - homopiperidone. However, we especially prefer to use dimethylacetamide, dimethylformamide, or N - methyl - 2 - pyrrolidone in this heating process.

The process of the present invention, like the processes as to which it is an improvement, is broadly applicable to the conversion of sulfoxide esters of the prior-art penicillins to desacetoxycephalosporin esters, so long as they are not otherwise converted under the conditions of acidity and elevated temperature employed. In all cases, the penicillins must be esterified and must be converted into the corresponding sulfoxide prior to treatment, after which a wide range of penicillins can be effectively treated in accordance with the invention, including benzyl penicillin, n-heptyl penicillin and phenylmercaptomethyl penicillin. The preferred penicillins are phenoxy-methyl penicillin ("penicillin-V"), phenyl-acetyl penicillin (penicillin G), and p-methoxyphenoxy-methyl penicillin. The 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, or tert-butoxycarbonyloxy. The product obtained by treatment of the N-protected or blocked 6-APA sulfoxide 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. The ester group can be cleaved before or after acylation, as desired. For example, the 2,2,2-trichloroethyl 7-aminodesacetoxycephalosporanate ester (7-ADCA ester) prepared by the heat conversion of 2,2,2-trichloroethyl 6-aminopenicillanate sulfoxide ester (6-APA sulfoxide ester) by the improved method of this invention, can be acylated with 2 - (2 - thiophene)acetyl chloride to form the 2,2,2 - trichloroethyl 7 - (2 - thiopheneacetamido)desacetoxycephalosporanate ester, which ester can be treated with acetic acid and zinc dust by known methods to remove the 2,2,2-trichloroethyl ester group and to form 7 - (2 - thiopheneacetamido)desacetoxycephalosporanic acid, a known antibiotic.

However, it is preferred to apply the process of this invention to the direct conversion of a penicillin sulfoxide ester (a 6-acylated penam sulfoxide ester) to the desired corresponding desacetoxycephalosporin ester. To prepare the starting material, a penicillin which has an acylamido group in the 6 position of the penicillin nucleus, is treated with an oxidizing agent to convert the penicillin thiazolidine sulfur to the sulfoxide oxidation state, and with an esterifying agent to esterify the penicillin carboxyl group with an easily cleaved ester group. Examples of easily cleaved ester groups which can be used in the penicillin sulfoxide ester starting materials include 2,2,2-trichloroethyl, 2,2-dichloroethyl, p-methoxybenzyl, p-nitrobenzyl, 3,5-dimethoxybenzhydryl, 4,4 - dimethoxybenzhydryl, benzhydryl, phthalimidomethyl, succinidomethyl, C₄ to C₆ - tert - alkyl such as tert-butyl, tert-pentyl, and tert-hexyl, C₆ to C₇ - tert-alkenyl and C₆ to C₇ - tert-alkynyl such as 1,1 - dimethyl - 2 - propenyl, 1,1 - dimethyl - 2 - butenyl, 1,1 - dimethyl - 2 - pentenyl, 1,1 - dimethyl - 2 - propynyl, 1,1 - dimethyl - 2 - butynyl and 1,1 - dimethyl - 2 - pentynyl.

The penicillin sulfoxide ester is dissolved, with the aid of heat if necessary, in the solvent containing at least about 10 percent by volume of the selected tertiary carboxamide. If desired, the penicillin sulfoxide ester can be added to a refluxing mixture of solvent, such as dimethylacetamide, methanesulfonic acid, and benzene or other azeotrope-forming liquid over a period of time. The process can be conducted on a batch or continuous basis.

Examples of substances which can be included in the solvent system for chemically reacting with, or physically absorbing the water introduced in the reaction system with the solvent and diluting reagents, and with the water produced during the heat rearrangement reaction, include the alkanolic acid anhydrides having from 2 to 6 carbon atoms in each acid moiety such as acetic anhydride, propionic anhydride, n-butyric anhydride, pentanoic anhydride, hexanoic anhydride, and mixed anhydrides of C₂ to C₆-alkanoic acids, cyclic saturated dibasic acid anhydrides such as succinic anhydride, glutaric anhydride, as well as economical aromatic dibasic acid anhydrides such as phthalic acid anhydride. For reasons of availability, cost, and generally better results, acetic anhydride and phthalic anhydride are preferred if this is the means selected for inactivating the water in the reaction mixture. Other water-removing chemicals include acetylenedicarboxylic acid esters such as dimethyl acetylenedicarboxylate, diethyl acetylenedicarboxylate and 2,2-dimethoxypropane. Volatile substances generated by water-uptake by some of these chemicals such as acetic acid (from acetic anhydride), and methanol and acetone (from 2,2-dimethoxy-

propane) can also be removed by azeotropic distillation during the heating operation.

The esterified penicillin sulfoxides listed below yield the indicated corresponding desacetoxycephalosporins 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)-acetamido] - 2,2 - dimethylpenam - 3 - carboxylic acid to obtain 7 - [2'methoxy - 2' - (2'' - thienyl) - acetamido] - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

6 - (Phenylacetamido) - 2,2 - dimethylpenam - 3 - carboxylic acid to obtain 7 - (phenylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylic acid.

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

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

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

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

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

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

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

The invention is further illustrated by the following detailed examples.

Example 1

This example compares and illustrates the effects and advantages of the combined use of a sulfonic acid and anhydride versus the separate use of the anhydride or the sulfonic acid in this ring expansion process.

A solution of 15 g. (0.03 mole) of p-nitrobenzyl penicillin V sulfoxide ester in 150 ml. of dry, N,N - dimethylacetamide was divided into three equal portions, labeled A, B, and C and placed in 250 ml. round-bottomed flasks.

Portion A was treated with 1.2 ml. (0.012 mole) of acetic anhydride. This quantity of acetic anhydride is believed to be about

the optimum for the best yields of the des-acetoxycephalosporin ester product using this reagent alone.

5 Portion B was treated with 0.13 g. of methanesulfonic acid. This proportion of acid is also believed to be the optimum amount to use for best yields of product using this acid alone.

10 Portion C was treated with 1.2 ml. of acetic anhydride plus 0.13 g. of methanesulfonic acid.

Each of the three flasks A, B, and C, so treated, was fitted with a condenser and

drying tube, and the three flasks were im- 15
mersed side by side in an oil bath at 100°C.
for 12 hours. Each solution — A, B, and C —
was then processed by vacuum distillation of
the solvent to a residue weight of 8.5 g. and
the p - nitrobenzyl 7 - phenoxyacetamido -
3 - methyl - Δ^3 - cephem - 4 - carboxylate 20
ester product was crystallized from the residue
by treatment thereof with 50 ml. of a 1:1 v/v
isopropanol/ethyl ether mixture and washed
and vacuum dried at 50°C. The yields of pro-
duct from the three runs were as follows: 25

Portion	Wt. (gm.)/percent yield	Melting Point, °C.
A	0.75, 16 percent	177—185
B	1.81, 37 percent	187—189
C	3.00, 62 percent	186.5—188

Each product was identified with aid of
thin layer chromatography and infrared (IR)
and nuclear magnetic resonance (NMR)
30 spectra. The melting point for the pure pro-
duct is said to be 189—191°C.

Example 2

A solution containing 5.0 g. (0.010 M) of
p-nitrobenzyl penicillin V sulfoxide ester,
35 0.05 ml. of methanesulfonic acid, 1.2 ml. of
2,2-dimethoxypropane, and 50 ml. of dry
N,N-dimethylacetamide was added to a 200
ml. round bottomed flask equipped with an
air condenser and "Drierite" drying tube.
40 The solution was immersed in an oil bath at
100°C. for 12 hours. The red solution was
concentrated under vacuum at 60—65°C. to
a residue weight of 10.0 g. Crystallization
from 50 ml. of 1/1 isopropanol/ether gave
45 2.51 g. (52.2 percent yield) of p-nitrobenzyl
7 - (α - phenoxyacetamido) - 3 - methyl - 3 -
cephem - 4 - carboxylate, m.p. 186—188°C.

Example 3

A 300 ml. round-bottomed, three-necked
50 flask was equipped with a mechanical stirrer,
heating mantle, thermometer, and Dean-Stark
water trap. The latter was connected to a
condenser to which was attached a "Drierite"
drying tube. The flask was charged with
55 10.0 g. (0.02 M) of p-nitrobenzyl penicillin V
sulfoxide ester, 80 ml. of dry benzene, 60 ml.
of dry N,N-dimethylacetamide, and 0.12 ml.
of methanesulfonic acid. The Dean-Stark trap
was filled with dry benzene. The resulting
60 mixture was refluxed 12 hours. Approximately
0.4 ml. of water collected in the trap. Thin
layer chromatography (silica gel/isoamyl
acetate) showed only one major component.
The red solution was concentrated under
65 vacuum at 60—65°C. to a residue weight of

17.5 g. Crystallization from 100 ml. of 1/1
isopropanol/ether gave 7.08 g. (73.3 percent
yield) of p - nitrobenzyl 7 - (α - phenoxyacet-
amido) - 3 - methyl - 3 - cephem - 4 -
carboxylate as a very light cream colored 70
solid, m.p. 188—190°C. The infrared and
nuclear magnetic resonance spectra were iden-
tical with a known sample of the pure ester.

Example 4

The procedure of Example 3 was repeated 75
except that 2.0 g. (0.016 mole) of 1,3-propane-
sultone was used instead of methanesulfonic
acid. Approximately 0.4 ml. of water was
collected in the water trap. The yield of p-
nitrobenzyl 7 - (α - phenoxyacetamido) - 3 -
80 methyl - 3 - cephem - 4 - carboxylate was
6.83 g. (70.8 percent), m.p. 183—187°C.

Example 5

The procedure of Example 3 was repeated 85
except that 0.2 g. of methanesulfonic an-
hydride was used in place of the methane-
sulfonic acid. Approximately 0.4 ml. of water
was collected in the trap. The yield of p-nitro-
benzyl 7 - (α - phenoxyacetamido) - 3 -
methyl - 3 - cephem - 4 - carboxylate was 90
6.83 g. (70.8 percent), m.p. 186—188°C.

Example 6

A 300 ml., round-bottomed, three-necked
flask was equipped with a mechanical stirrer,
heating mantle, thermometer, and a Soxhlet 95
extractor. The extractor contained a coarse
disc rather than the usual siphon tube so that
solvent could run directly back into the re-
action flask. The flask was charged with 5.0 g.
(0.01 M) of p-nitrobenzyl penicillin V sulf-
oxide ester, 0.07 ml. of methanesulfonic acid,
75 ml. of 1,2-dichloroethane, and 25 ml. of
dry N,N-dimethylacetamide. Anhydrous 100

sodium sulfate, 15 g., was placed in the Soxhlet extractor. The solution was refluxed 16 hours while drying the distillate and returning the 1,2-dichloroethane to the reaction flask. The mixture was then concentrated under vacuum at 60–65°C. to a residue weight of 8.6 g. Crystallization from 50 ml. of 1/1 isopropanol/ether gave 2.44 g. (50.5 percent yield) of *p*-nitrobenzyl 7-(α -phenoxyacetamido)-3-methyl-3-cephem-4-carboxylate as a very light pink solid, m.p. 185.5–188°C.

Example 7

In a run substantially similar to Example 6, but involving the use of a moisture trap for solvent heavier than water and the above solvent system, the yield of *p*-nitrobenzyl 7-(α -phenoxyacetamido)-3-methyl-3-cephem-4-carboxylate was 64.4 percent.

Example 8

The procedure of Example 6 was substantially duplicated except that benzene was used as the azeotrope forming liquid and 20 g. of anhydrous calcium chloride was used instead of anhydrous sodium sulfate to dry the benzene-water azeotrope. The yield of *p*-nitrobenzyl 7-(α -phenoxyacetamido)-3-methyl-3-cephem-4-carboxylate was 3.74 g. (77.7 per cent) m.p. 184–186.5°C.

Example 9

A 300 ml., round-bottomed, three-necked flask equipped with a mechanical stirrer, thermometer, and condenser to which was added a "Drierite" brand of anhydrous calcium sulfate filled drying tube was charged with 5.0 g. (0.010 M) of *p*-nitrobenzyl penicillin V sulfoxide ester, 0.05 ml. of methanesulfonic acid, 25 ml. of dry *N,N*-dimethylacetamide, 50 ml. of 1,2-dichloroethane, and 1.2 ml. (ca. 0.012 M) of acetic anhydride. The solution was refluxed 12 hours and then concentrated under vacuum. Crystallization of the residue from methanol gave 2.37 g. (49.0 percent yield) of *p*-nitrobenzyl 7-(α -phenoxyacetamido)-3-methyl-3-cephem-4-carboxylate as a cream colored solid, m.p. 188–189.5°C.

Example 70

Combination of rearrangement and side-chain cleavage without isolation of the intermediate desacetoxycephalosporin ester.

The rearrangement of 10.0 g. (0.02 M) of 2,2,2-trichloroethyl penicillin V sulfoxide ester was conducted substantially as described in Example 3 for the *p*-nitrobenzyl ester. The red colored reaction mixture was cooled to room temperature, 50 ml. of benzene was added, and the solution was washed with three 50 ml. portions of cold 1 *N* hydrochloric acid, two 50 ml. portions of 2.5 percent sodium bicarbonate solution, and 50 ml. of 2 percent sodium chloride solution, and then dried over anhydrous magnesium sulfate. The solution was filtered from drying agent, diluted to 150 ml. with dry benzene, and added to a 500 ml., round-bottomed, three-necked flask equipped with a mechanical stirrer, heating mantle, air condenser with "Drierite" drying tube, and a thermometer. To the stirred solution was added 4.61 g. of phosphorous pentachloride followed by 1.61 ml. of dry pyridine. The mixture was heated at 55–57°C. for one hour. Vacuum was carefully applied through the air condenser to lower the temperature to 0°C. and 200 ml. of cold, absolute methanol was added. The deep red solution was allowed to stand 16 hours at room temperature and vacuum was again applied to lower the temperature to 5°C. Water, 150 ml., was added and most of the organic solvents were evaporated under vacuum at 5–15°C. The resulting mixture was treated with 100 ml. of ethyl acetate and the pH of the aqueous phase was adjusted to 6.80 by addition of 1 *N* sodium hydroxide solution. The two layers were separated and the aqueous layer was extracted with an additional 50 ml. of ethyl acetate. The combined organic layers were washed with two 50 ml. portions of cold water and then dried briefly over anhydrous magnesium sulfate. Addition of 4.0 g. of *p*-toluenesulfonic acid, monohydrate resulted in crystallization of 5.16 g. (49.8 percent yield) of 2,2,2-trichloroethyl 7-amino-3-methyl-3-cephem-4-carboxylate, *p*-toluenesulfonic acid salt as a very light yellow solid, m.p. 181–183°C. with decomposition. The infrared, ultraviolet, and nuclear magnetic resonance spectra were identical with a known sample of the same compound.

This cephalosporin ester salt is useful directly in the process for making cephalixin and similar cephalosporin antibiotics.

In summary, the yield improvements of this invention are demonstrated by the following table:

Example	Solvent	Acid	Method of Removing Water	Percent Yield
1B	DMAC	CH ₃ SO ₃ H	None	37.0
1A	"	Ac ₂ O	None except reagent itself	16.0
1C	"	CH ₃ SO ₃ H	Addition of acetic anhydride	64.7
2	"	"	Addition of 2,2-dimethoxypropane	52.2
3	DMAC Benzene	"	Azeotropic distillation with benzene	73.3
6	DMAC — 1,2- di-chloroethane	"	Azeotropic distillation with 1,2-dichloroethane	64.4
8	DMAC Benzene	"	Azeotropic distillation with benzene and drying of the returning azeotroping solvent with anhydrous calcium chloride	77.7

Examples 1B and 1A represent the method of Morin-Jackson as improved by Cooper while Examples 2, 3, 6, and 8 show that the yield of desacetoxycephalosporin ester product is improved substantially by the combined use of acid with chemical and/or physical water removal methods.

Although the invention has been illustrated in the detailed examples using penicillin V (phenoxymethyl penicillin) sulfoxide esters, the invention is not limited thereto. This one penicillin was selected so that the percentage yield figures would be comparable. Improved yields of desacetoxycephalosporin esters can also be demonstrated with other commonly available penicillin starting materials, after conversion thereof to the corresponding penicillin sulfoxide esters.

WHAT WE CLAIM IS:—

1. A process for converting a penicillin sulfoxide ester to a desacetoxycephalosporin ester by heating the penicillin sulfoxide ester dissolved in a non-aqueous solvent containing a tertiary carboxamide in an amount to provide at least 10% by volume of the reaction mixture under acid conditions in a temperature range of from about 80°C. to about 150°C., characterized by using a sulfonic acid or a substance which forms a sulfonic acid in the mixture in an amount effective to provide the acid conditions while providing a means for removing or inactivating water in the reaction mixture during the heating operation.

2. A process as claimed in claim 1 wherein there is present in the reaction mixture a sulfonic acid, or a substance which forms a sulfonic acid in an amount to provide the acid in a molar ratio of penicillin sulfoxide ester to acid in the range of from 1:1 to about 50:1.

3. A process as claimed in claim 1 or 2 wherein the means for removing or inactivating water is provided by incorporating into the reaction mixture an inert liquid which forms an azeotrope with water during the heating operation, and distilling the water-containing azeotrope from the reaction mixture.

4. The process of claim 1, 2 or 3, wherein the acid is a C₁ to C₆-alkanesulfonic acid.

5. The process of claim 4 wherein the acid is methanesulfonic acid and the azeotrope is that with a C₆—C₈-aromatic hydrocarbon.

6. The process of claim 4 wherein the acid is methanesulfonic acid and the azeotrope is that with a halogenated hydrocarbon having from 1 to 6 carbon atoms and from 1 to 4 chlorine or bromine atoms.

7. The process of claim 1, wherein the acid is a C₁ to C₃-alkanesulfonic acid and the water is inactivated in the reaction mixture by the addition thereto of an acid anhydride of a C₂ to C₆-alkanoic acid, in molar excess relative to the amount of water present or produced therein.

8. The process of claim 5, wherein a phenoxymethyl-penicillin sulfoxide ester is converted to a phenoxymethyl desacetoxycephalosporin ester in a N,N-dimethylacetamide-containing solvent and the aromatic hydrocarbon is benzene.

9. The process of claim 3, wherein the inert liquid which forms an azeotrope with water is a C₅ to C₈ hydrocarbon.

10. The process of claim 9 wherein the C₅ to C₈ hydrocarbon is benzene.

11. The process of claim 3, wherein the inert liquid which forms an azeotrope with water is a haloalkane having from 1 to 6 carbon atoms and from 1 to 4 chlorine or bromine atoms.



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Examples 1B and 1A represent the method of Morin-Jackson as improved by Cooper while Examples 2, 3, 6, and 8 show that the yield of desacetoxycephalosporin ester product is improved substantially by the combined use of acid with chemical and/or physical water removal methods.

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2. A process as claimed in claim 1 wherein there is present in the reaction mixture a sulfonic acid, or a substance which forms a sulfonic acid in an amount to provide the acid in a molar ratio of penicillin sulfoxide ester to acid in the range of from 1:1 to about 50:1.

3. A process as claimed in claim 1 or 2 wherein the means for removing or inactivating water is provided by incorporating into the reaction mixture an inert liquid which forms an azeotrope with water during the heating operation, and distilling the water-containing azeotrope from the reaction mixture.

4. The process of claim 1, 2 or 3, wherein the acid is a C₁ to C₆-alkanesulfonic acid.

5. The process of claim 4 wherein the acid is methanesulfonic acid and the azeotrope is that with a C₆—C₈-aromatic hydrocarbon.

6. The process of claim 4 wherein the acid is methanesulfonic acid and the azeotrope is that with a halogenated hydrocarbon having from 1 to 6 carbon atoms and from 1 to 4 chlorine or bromine atoms.

7. The process of claim 1, wherein the acid is a C₁ to C₃-alkanesulfonic acid and the water is inactivated in the reaction mixture by the addition thereto of an acid anhydride of a C₂ to C₆-alkanoic acid, in molar excess relative to the amount of water present or produced therein.

8. The process of claim 5, wherein a phenoxymethyl-penicillin sulfoxide ester is converted to a phenoxymethyl desacetoxycephalosporin ester in a N,N-dimethylacetamide-containing solvent and the aromatic hydrocarbon is benzene.

9. The process of claim 3, wherein the inert liquid which forms an azeotrope with water is a C₅ to C₈ hydrocarbon.

10. The process of claim 9 wherein the C₅ to C₈ hydrocarbon is benzene.

11. The process of claim 3, wherein the inert liquid which forms an azeotrope with water is a haloalkane having from 1 to 6 carbon atoms and from 1 to 4 chlorine or bromine atoms.



12. The process of claim 3, wherein the water-containing azeotrope is contacted with a drying agent before returning the azeotrope forming liquid to the reaction mixture.
- 5 13. A process according to claim 1 substantially as hereinbefore described with particular reference to the examples 2 to 10.
- 10 14. The process of any one of claims 1 to 7, wherein a phenylmethyl penicillin sulf-oxide ester is converted to a phenylmethyl desacetoxycephalosporin ester.
15. A desacetoxycephalosporin ester whenever prepared by a method as claimed in any one of the preceding claims.

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