

PATENT SPECIFICATION

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(54) 3-HALOMETHYL- Δ^3 -CEPHALOSPORIN ESTERS AND SULFOXIDES THEREOF USEFUL IN THE PRODUCTION OF ANTIBIOTICS, AND PROCESS FOR PREPARING THE INTERMEDIATES AND ANTIBIOTICS

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

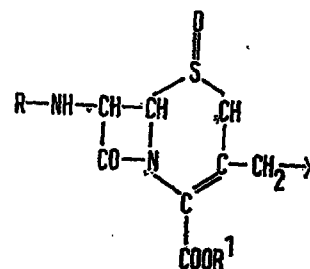
This invention concerns 3 - halomethyl - Δ^3 - cephalosporin (sulfide) esters and sulfoxides thereof, and their preparation, which are useful as intermediates in the production of known and new antibiotics.

These compounds useful as intermediates are 3 - halomethyl - Δ^3 - cephalosporin esters wherein the sulfur atom in the 1-position of the dihydrothiazine ring moiety of the cephalosporin can be in bivalent sulfide ($-S-$) state or in the sulfoxide [$-S(O)-$] state, and they are prepared by reacting a phosphorus halide with a 3 - hydroxy - methyl - Δ^3 - cephalosporin sulfoxide ester.

It is an object of the invention to provide 3 - halomethyl - Δ^3 - cephalosporin esters and sulfoxides thereof, which are especially useful as intermediates in production of new and known 3 - halomethyl - Δ^3 - cephalosporins which have antibiotic activity and new and known nitrogen and sulfur containing 3 - (nucleophile - methyl) - Δ^3 - cephalosporin antibiotics, and processes for preparing said intermediates and antibiotics.

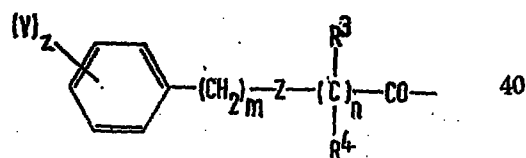
More particularly, the present invention provides a compound having the formula

[Price 25p]



II

wherein X is chlorine, bromine or iodine;
 R has the formula



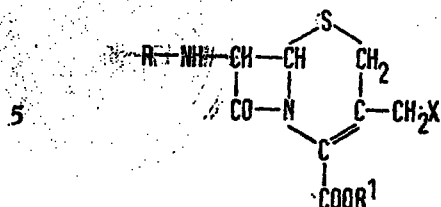
wherein m is an integer of from 0 to 4, n is an integer of from 1 to 4, Z is oxygen or sulfur or a chemical bond, R^3 and R^4 are, separately, hydrogen or methyl, and Y is hydrogen or a substituent on the phenyl ring carbon atoms such as fluorine, chlorine, bromine, iodine, C_1 to C_2 -alkyl, C_1 to C_2 -alkyloxy, N - protected - α - amino - C_1 to C_6 -alkyl, butoxycarbonyl, nitro, cyano or trifluoromethyl and z is 1 or 2;

and R^1 is 2,2,2-trichloroethyl, C_4 to C_6 - tert - alkyl, C_5 to C_7 - tert - alkenyl, C_6 to C_7 - tert - alkynyl, benzyl, methoxybenzyl,

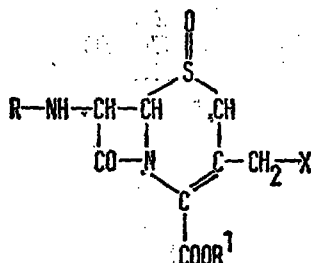
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nitrobenzyl, phenacyl, phthalimido - methyl, benzhydryl or succinimidomethyl.

This invention further provides a process for preparing a compound having the formula

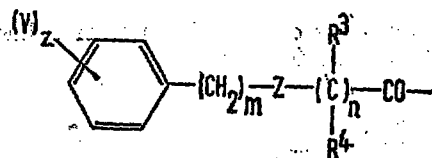


or



wherein X in each of formulas I and II is chlorine, bromine or iodine;

10 R has the formula



wherein m is an integer of from 0 to 4, n is an integer of from 1 to 4, Z is oxygen or sulfur or a chemical bond, R^3 and R^4 are, separately, hydrogen or methyl, and Y is hydrogen or a substituent on the phenyl ring carbon atoms such as fluorine, chlorine, bromine, iodine, C_1 to C_2 -alkyl, C_1 to C_2 -alkyloxy, N -protected- α -amino- C_1 to C_3 -alkyl, butoxycarbonyl, nitro, cyano or trifluoromethyl and z is 1 or 2;

20 and R^1 is 2,2,2-trichloroethyl, C_4 to C_6 -tert-alkyl, C_6 to C_7 -tert-alkenyl, C_5 to C_7 -tert-alkynyl, benzyl, methoxybenzyl, nitrobenzyl, phenacyl, phthalimidomethyl, benzhydryl or succinimidomethyl, which comprises reacting a phosphorus compound of the groups

(1) phosphorus trichloride or phosphorus tribromide, or

30 (2) phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride, or phosphorus oxybromide

with a 3 - hydroxymethyl - Δ^3 - cephalosporin sulfoxide ester in the presence of a tertiary amine in a substantially anhydrous aprotic liquid organic diluent at a temperature of from about -75°C . to about 50°C . to form as product the corresponding compound

(1) (a) 3-chloro or bromomethyl - Δ^3 - cephalosporin ester when at least an equimolar amount of phosphorus trichloride or phosphorus tribromide and temperatures above about -25°C . are used, or

(1) (b) 3 - chloro or bromomethyl - Δ^3 - cephalosporin sulfoxide ester from an approximately equimolar amount of phosphorus trichloride or phosphorus tribromide and temperatures below about -25°C . are used, or

(2) 3-chloro or bromomethyl - Δ^3 - cephalosporin sulfoxide ester when phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride or phosphorus oxybromide are used,

and, optionally, treating the product with an alkali metal iodide to form the corresponding 3 - iodomethyl - Δ^3 - cephalosporin ester or 3 - iodomethyl - Δ^3 - cephalosporin sulfoxide ester.

The 3 - halomethyl - Δ^3 - cephalosporin (sulfoxide) esters and sulfoxides thereof of the present invention are useful as intermediates in preparing 3 - halomethyl - Δ^3 - cephalosporins which have antibiotic activity and which can be used to form 3 - (nucleophile - methyl) - Δ^3 - cephalosporins.

The amino-protecting group represented by R in above formulas I and II is one known to protect the nitrogen to which it is bonded from attack by the phosphorus compounds. Many acyl groups suitable for use as the group R are already known in the penicillin and cephalosporin antibiotic literature. Specific examples of some such acyl groups include:

phenylacetyl
phenoxyacetyl
phenylmercaptoacetyl
benzyloxyacetyl
benzylmercaptopropionyl
phenylpropionyl
phenylethylmercaptopropionyl
phenylbutoxybutyryl
3-fluorophenoxyacetyl
4-bromophenylacetyl
2-chlorobenzoyloxypropionyl
3-methylphenylbutyryl
4-nitrophenylmercaptoacetyl
N - protected - 4 - aminomethylphenylacetyl
3-cyanophenylpropionyl
and 4-trifluoromethylphenoxyacetyl.

Numerous other acyl groups which can be used as the R group are known in the prior

art; e.g., those disclosed in the U.S. Patents 2,479,295 to 2,479,297 and 2,562,407 to 2,562,411 and 2,623,876.

The R^1 symbol in the above formulas I and II represents a group that is easily removable by the use of trifluoroacetic or formic acids or a non-oxidizing mineral acid such as hydrochloric acid, or sulfuric acid, or by the use of zinc in an alkanoic acid such as formic acid, acetic acid, trifluoroacetic acid, or a mixture containing such acids, or by hydrogenation in the presence of a suitable hydrogenation catalyst such as palladium or rhodium on carbon, barium sulfate, alumina or other suitable carrier, or by the suspension of a palladium or rhodium compound in the hydrogenation reaction mixture. Thus R^1 can be 2,2,2-trichloroethyl, C_4 to C_6 - tert. - alkyl, C_6 to C_7 - tert. - alkenyl, C_6 to C_7 - tert. - alkynyl, (such as tert-butyl, tert-pentyl, 1,1-dimethyl - 2 - propenyl, 1,1 - dimethyl - 2 - butynyl, and 1,1 - dimethyl - 2 - pentynyl), benzyl, methoxybenzyl, nitrobenzyl, phenyl, benzhydryl, phthalimidomethyl, and succinimidomethyl.

The 3 - halomethyl - Δ^3 - cephalosporin esters can be prepared by reacting at least an equimolar amount of phosphorus trichloride or tribromide with 3 - hydroxymethyl - Δ^3 - cephalosporin sulfoxide ester in the presence of a tertiary amine in a substantially anhydrous aprotic organic liquid diluent at a temperature of from just above -25°C . to about 50°C . When a phosphorus trihalide is used at such temperatures, the product is a 3 - halomethyl - Δ^3 - cephalosporin ester in which the sulfur in the 1-position is in the sulfide or bivalent state. This means that no separate reduction step is needed when phosphorus trichloride or phosphorus tribromide is thus used. When temperatures below about -25°C . are used with equimolar ratios of phosphorus trichloride or tribromide, the 3 - chloro or bromomethyl - Δ^3 - cephem sulfoxide product can be obtained. When a phosphorus pentahalide or a phosphorus oxyhalide is used, the product of the resulting reaction is a 3 - halomethyl - Δ^3 - cephalosporin sulfoxide ester, which can be used as such as an intermediate for replacing the halogen with an appropriate nucleophilic group. These products are especially useful as intermediates for halogen displacement by basic nucleophiles, which produce a basic pH condition which might otherwise cause the Δ^3 - double bond to isomerize to the Δ^2 - position. The sulfoxide protects or keeps the Δ^3 - double bond in the 3-position.

The 3 - chloromethyl and 3 - bromomethyl - Δ^3 - cephalosporin ester products are converted to the corresponding 3 - iodomethyl - Δ^3 - cephalosporin compounds by reacting the 3 - chloromethyl- or 3 - bromomethyl - Δ^3 - cephalosporin ester product of the first step with an alkali metal iodide

in an appropriate anhydrous organic liquid solvent system.

The phosphorus halide used in the first step of the process can be any trivalent or pentavalent phosphorus compound having at least one chlorine or bromine atom bonded directly to the phosphorus atom. Preferred phosphorus halides are phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride ($\text{O}=\text{PCl}_3$), and phosphorus oxybromide ($\text{O}=\text{PBr}_3$). When phosphorus pentabromide is used, temperatures in the lower part of the range must be used.

When the 3 - iodomethyl - Δ^3 - cephalosporin compounds are being prepared, an iodide ion is mixed with the 3 - chloromethyl- or 3 - bromomethyl - Δ^3 - cephalosporin ester in an organic solvent. The iodine ion is preferably added as an alkali metal iodide salt, e.g., the sodium, potassium, lithium, rubidium or cesium salt, but as a practical, economic matter, only the sodium and potassium salts are of interest. Alkaline earth metals including magnesium, iodide salts, and other reactive metal iodide salts can also be used but are not preferred.

The 3 - hydroxymethyl - Δ^3 - cephalosporin sulfoxide ester starting material can be prepared by treating a corresponding 3 - halomethyl - Δ^2 - cephalosporin ester with a mixture of an organic solvent and water in an organic aprotic diluent such as benzene to form the 3 - hydroxymethyl - Δ^2 - cephalosporin ester, and then oxidizing the 3 - hydroxymethyl - Δ^2 - cephalosporin ester by known methods which results in the formation of the desired 3 - hydroxymethyl - Δ^3 - cephalosporin sulfoxide ester. The organic solvent can be dimethylsulfoxide, or diethylsulfoxide. The dialkylsulfoxide/water mixture should contain at least about 25 percent by volume of the dialkylsulfoxide. However, the water content of the mixture should be at least equivalent to the halide content of the 3 - halomethyl - Δ^2 - cephalosporin ester. For example, p-methoxybenzyl 3 - hydroxymethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide can be prepared by reacting p-methoxybenzyl 3 - bromomethyl - 7 - phenoxyacetamido - Δ^2 - cephem - 4 - carboxylate with 10 molar equivalents of water (relative to the 3-bromomethyl compound) in 1:1 v/v mixture of benzene and dimethylsulfoxide followed by treatment with 85 percent m-chloroperbenzoic acid in a mixture of isopropyl alcohol and methylene chloride. The 2,2,2 - trichloroethyl 3 - hydroxymethyl - Δ^3 - cephem - 4 - carboxylate esters can be prepared by oxidizing with a peracid such as m-chloroperbenzoic acid the 2,2,2-trichloroethyl 3 - hydroxymethyl - Δ^2 - cephem - 4 - carboxylate compounds disclosed, e.g., in

South African Patent 66/5105 in an organic solvent system such as methylene chloride/20% v/v isopropanol.

The phosphorus halide and the 3-hydroxymethyl - Δ^3 - cephalosporin sulfoxide ester reactants are combined in a substantially anhydrous aprotic liquid organic solvent such as benzene, toluene, xylene, heptane, hexane, methylene dichloride, chloroform, carbon tetrachloride, dioxane, tetrahydrofuran, lower alkyl alkanooates such as ethyl acetate, and amyl acetate, lower alkanonitriles such as acetonitrile, and propionitrile, or nitroalkanes such as nitromethane, and nitropropane. A tertiary amine is added to moderate the effect of the phosphorus halide and to neutralize the by-product hydrogen halide. When temperatures below about -25°C . are used, substantially any tertiary amine can be used. However, when only moderately low temperatures are used (-25°C . to $+15^\circ\text{C}$.), the selected tertiary amine preferably has a pKa with the range of about 4.5 to about 5.8. Examples of preferred tertiary amines are N,N-dimethylaniline, pyridine, and quinoline. The mixture is preferably maintained at relatively low temperatures, e.g., -75°C . to $+50^\circ\text{C}$. to control the speed of the reaction which ensues spontaneously in most cases. The 3-halomethyl - Δ^3 - cephalosporin esters are formed when at least an equimolar amount of phosphorus trihalide and reaction temperatures above about -25°C . are used. The 3-halomethyl - Δ^3 - cephalosporin sulfoxide esters are formed when an appropriately equimolar amount of a phosphorus trihalide and temperatures below about -25°C . are used. The 3-halomethyl - Δ^3 - cephalosporin sulfoxide esters are formed when the phosphorus pentahalide or phosphorus oxyhalide reactants are used. Stoichiometric equivalents of the reactants may be used, particularly when sulfoxide products are desired, but it is preferred to use at least a slight excess of the phosphorus halide relative to the 3-hydroxymethyl - Δ^3 - cephalosporin sulfoxide ester to insure complete reaction thereof. From 1 to 10 moles of the phosphorus halide may be used per mole of the sulfoxide ester reactant, particularly when trivalent phosphorus trihalides are used to form the reduced cephalosporin ester products. Generally from 30 per cent to 100 percent excess of phosphorus halide will be sufficient to insure substantially complete reaction.

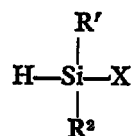
When the reaction is completed, the 3-halomethyl - Δ^3 - cephalosporin ester product may be separated from the reaction mixture by conventional methods. For example, the mixture may be washed with aqueous sodium chloride, sodium bicarbonate, hydrochloric acid solutions and then with water to separate soluble impurities. The organic layer containing the product may then be separated and

evaporated to dryness to give the substantially pure 3-halomethyl - Δ^3 - cephalosporin ester product.

The 3-halomethyl - Δ^3 - cephalosporin ester products of formula I are useful as intermediates in the direct preparation of antibiotic cephalosporin compounds by removing the ester group therefrom by a variety of known methods. The 3-halomethyl - Δ^3 - cephalosporin sulfoxide ester products of formula II may be reduced to compounds of formula I, and then de-esterified by known methods to prepare the free 3-halomethyl - Δ^3 - cephalosporin acid derivatives which are antibiotically active. Alternatively, in some cases, the sulfoxide ester can be de-esterified first and then reduced.

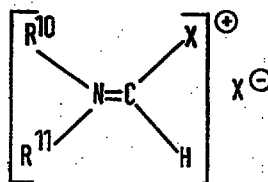
Examples of reduction methods which may be used include the treatment of the 3-halomethyl - Δ^3 - cephalosporin sulfoxide acid or ester with a reducing agent selected from:

- (1) hydrogen in the presence of a hydrogenation catalyst;
- (2) stannous, ferrous, cuprous, or manganoous cations;
- (3) Dithionite, iodide, or ferrocyanide anions;
- (4) Trivalent phosphorus compounds having a molecular weight below about 500;
- (5) halosilane compounds of the formula;



wherein X is chlorine, bromine, or iodine, and each of R' and R² is hydrogen, chlorine, bromine, iodine, or a hydrocarbon radical free from aliphatic unsaturation and having from 1 to 8 carbon atoms; and

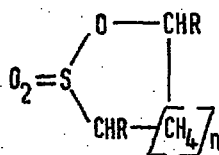
- (6) a halomethylene iminium halide of the formula



where X is chlorine or bromine, and wherein each of R¹⁰ and R¹¹, taken separately, denotes a C₁ to C₈-alkyl or, taken together with the nitrogen to which they are bonded, complete a monocyclic, heterocyclic ring having from

5 to 6 ring-forming atoms and a total of from 4 to 8 carbon atoms;

- together with an activating agent which is either (a) an acyl halide of an acid of carbon, sulfur, or phosphorus, which acid halide is inert to reduction by the reducing agent, and which acid halide has a second order hydrolysis constant equal to or greater than that of benzoyl chloride, or (b) a cyclic sultone of the formula



- where n is 0 or 1, and each R is defined separately as hydrogen or C₁ to C₈-alkyl with not more than one such R being C₁ to C₃-alkyl, in a substantially anhydrous liquid medium at a temperature of from about -20°C. to about 100°C. to form the 3-halomethyl - Δ³ - cephalosporin acid or ester.

- The compounds of both formulas I and II are primarily of interest in the preparation of known and new antibiotically active 3-nucleophile methyl cephalosporin compounds, by replacing the chlorine, bromine, or iodine atom on the 3-halomethyl carbon atom with the desired nucleophilic group. For example, p-nitrobenzyl 3-chloromethyl-7-phenoxyacetamido - Δ³ - cephem - 4-carboxylate can be treated with sodium or potassium acetate in an organic medium to form p-nitrobenzyl 3-acetoxymethyl-7-phenoxyacetamido - Δ³ - cephem - 4-carboxylate, and then the ester group can be removed by hydrogenation by known methods to obtain a known cephalosporin antibiotic, 3-acetoxymethyl-7-phenoxyacetamido - Δ³ - cephem - 4-carboxylic acid. If more active antibiotics are desired, the 7-acylamido group can be cleaved by known methods, e.g., as described in U.S. Patent 3,188,311, and then the resulting cephem nucleus can be acylated with 2'-thiopene-2-acetic acid, acid chloride, or mixed anhydride to form the corresponding 3-halomethyl-7-(2'-thienylacetamido) - Δ³ - cephalosporin ester which can then be de-esterified to the acid antibiotic, or treated with a nucleophilic reagent to displace the chlorine or bromine and then be de-esterified to form the more active antibiotic. By this procedure, cephalothin, a known antibiotic, available commercially as the sodium cephalothin salt, can be obtained from the products and by the process of this invention. Also, the 3-halomethyl - Δ³ - cephalosporin ester product of this invention can be treated with

a sulfur-containing nucleophile such as methyl mercaptan to form the 3-methylthio-methyl - Δ³ - cephalosporin ester. This 3-methylthiomethyl - Δ³ - cephalosporin ester can be treated as described above to remove the 7-acyl group and replacing it with a desired different acyl group such as an N-blocked, D-phenylglycine by known acylation procedures. The N-blocking group and the ester group can then be removed to form 3-methylthiomethyl-7-D-α-phenyl-α-aminoacetamido - Δ³ - cephem-4-carboxylic acid as the zwitterion, hydrate, or salt with a pharmaceutically acceptable cation such as sodium or potassium or anion such as the hydrochloride, nitrate, sulfate or phosphate. These 3-methylthiomethyl - Δ³ - cephalosporin compounds are effective as antibiotics, administered either parenterally or orally. For this purpose, these compounds can be administered, e.g., orally in doses of from about 250 mg. to about 500 mg., in pulvules or tablets, four to six times a day to patients of about 70 kg. body weight.

Specific cephalosporin starting materials, intermediates, and products of the process of this invention are named, for convenience, by use of the "cephem" nomenclature system, well-known to the art.

We have also found that 3-hydroxy-methyl - Δ² - cephalosporin esters will also react with phosphorus trihalides such as phosphorus tribromide or trichloride to form the corresponding 3-bromomethyl or 3-chloromethyl - Δ² - cephalosporin derivative. For example, tert-butyl 7-phenoxyacetamido-3-hydroxymethyl - Δ² - cephem-4-carboxylate can be reacted with phosphorus tribromide to form tert-butyl 7-phenoxyacetamido-3-bromomethyl - Δ² - cephem-4-carboxylate. However, that process is of no particular value to the process route we currently contemplate for an overall method of obtaining 7-acylamido-3-nucleophile-methyl - Δ³ - cephem-4-carboxylic acid cephalosporin antibiotics.

The invention is further exemplified by the following detailed examples, which are not intended to limit the scope of the invention.

Example 1

Preparation of t-butyl 7-(phenoxyacetamido)-3-bromomethyl - Δ³ - cephem-4-carboxylate

To a stirred, cooled (-10°C.) solution of 0.440 g. (1 mmole) of 4-t-butyl 7-(phenoxyacetamido)-3-hydroxymethyl - Δ³ - cephem-4-carboxylate-1-oxide and 0.4 ml. of N,N-dimethylaniline in 15 ml. of methylene chloride was added 0.2 ml. (2 mmoles) of phosphorus tribromide in 10 ml. of methylene chloride dropwise over a 10 minute period. The reaction was stirred an additional 20 minutes at -10°C upon completing the addition. The reaction mixture

was poured into a separator funnel and washed successively with 10 percent sodium chloride in water, 5 percent sodium bicarbonate in water, 5 percent hydrochloric acid solution, and water. The organic solution was evaporated to dryness to give 0.33 g. of the tert-butyl 3 - bromomethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate. A thin layer chromatogram showed pure product and the structure was confirmed by nuclear magnetic resonance (NMR) spectrum.

Example 2

Preparation of t - butyl 7 - (phenoxyacetamido) - 3 - chloromethyl - Δ^3 - cephem - 4 - carboxylate - 1 - oxide

A solution of 0.110 g. (0.25 mmoles) of tert-butyl 3 - hydroxymethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide and 1 drop of pyridine in 10 ml. of anhydrous tetrahydrofuran was treated with 0.060 g. of phosphorus pentachloride. The reaction mixture was stirred at 25°C for 30 minutes. The reaction mixture was then poured into ice water and extracted with methylene chloride. The methylene chloride solution was washed with 5 percent sodium bicarbonate in water, dried over sodium sulfate and evaporated to dryness. The mixture (0.106 g.) was separated by preparative thin layer chromatography to give 0.035 g. of product. An NMR spectrum verified the structure of the tert-butyl 3 - chloromethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide.

Example 3

Preparation of 7 - phenoxyacetamido - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid

A solution of 0.290 g. of t - butyl 7 - (phenoxyacetamido) - 3 - bromomethyl - Δ^3 - cephem - 4 - carboxylate in 10 ml. of acetone was stirred for 24 hours with 0.250 g. of tetramethylammonium acetate. A thin layer chromatogram revealed the presence of two compounds. The solvent was evaporated to dryness and the residue was washed with ethyl acetate. The ethyl acetate solution was washed with 3 percent hydrochloric acid and 5 percent sodium bicarbonate, dried over sodium sulfate, and evaporated to dryness to give 0.19 g. product. The product was dissolved in 5 ml. of formic acid and stirred at 25°C for one hour. The acidic solution was poured into water and extracted with ethyl acetate. The ethyl acetate solution was washed with 5 percent aqueous sodium bicarbonate and the basic solution was acidified. Extraction of the new acid solution with ethyl acetate and evaporation of the ethyl acetate gave 0.072 g. of acidic material. A thin layer chromatogram and a bioautograph of a paper chromatogram of the acidic material showed

it to be 3 - acetoxymethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylic acid, a known antibiotic.

Example 4

p - Methoxybenzyl 3 - chloromethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate

To a solution of 150 mg. of p - methoxybenzyl 3 - hydroxymethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide was added 12 drops of dry pyridine and then 12 drops of phosphorus trichloride. After stirring two hours at room temperature, the reaction mixture was evaporated to dryness, diluted with ethyl acetate, and washed with cold 5 percent HCl, bicarbonate solution 2 times with sodium chloride solution, dried over $MgSO_4$, filtered and evaporated to give 140 mg. of an orange oil.

This oil was applied to two commercial preparative thin layer chromatographic plates (2 mm.) and eluted with a 1:1 benzene-ethyl acetate mixture. There was obtained 56 mg. of the p - methoxybenzyl 3 - chloromethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate, which structure was confirmed by nuclear magnetic resonance (NMR) spectroscopy.

The following additional exemplary compounds are prepared according to the process of this invention by the procedures of the above examples.

1,1 - Dimethyl - 2 - propenyl 3 - chloromethyl - 7 - (p - nitrophenylacetamido) - Δ^3 - cephem - 4 - carboxylate from phosphorus trichloride and 1,1 - dimethyl - 2 - propenyl 3 - hydroxymethyl - 7 - (p - nitrophenylacetamido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide.

Phthalimidomethyl 3 - bromomethyl - 7 - phenylmercaptomethyl - Δ^3 - cephem - 4 - carboxylate from phosphorus tribromide and phthalimidomethyl 3 - hydroxymethyl - 7 - phenylmercaptomethyl - Δ^3 - cephem - 4 - carboxylate - 1 - oxide.

1,1 - Dimethyl - 2 - propynyl 3 - chloromethyl - 7 - (3' - chlorophenylacetamido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide from phosphorus pentachloride and 1,1 - dimethyl - 2 - propynyl 3 - hydroxymethyl - 7 - (3' - chlorophenylacetamido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide.

Example 5

tert-Butyl 7 - phenoxyacetamido - 3 - iodomethyl - Δ^3 - cephem - 4 - carboxylate

A solution of 0.380 g. of crude tert-butyl 7 - phenoxyacetamido - 3 - bromomethyl - Δ^3 - cephem - 4 - carboxylate - 1 - oxide, prepared as described in Example 1, was dissolved in 10 ml. of acetone and stirred at 25°C. for one hour with 0.5 g. of potassium iodide. The resulting reaction mixture was

centrifuged and the supernatant was evaporated in vacuo to give 0.40 g. of crude product, tert - butyl 7 - phenoxyacetamido - 3 - iodomethyl - Δ^3 - cephem - 4 - carboxylate. The NMR spectrum of this product was similar to, but not superimposable on, the spectrum of the 3 - bromomethyl derivative starting material which indicated the complete conversion to the 3 - iodomethyl derivative.

Example 6

To a solution of 2 - methyl - 3 - butynyl 7 - phenoxy - acetamido - 3 - hydroxymethyl - Δ^3 - cephem - 4 - carboxylate - 1 - oxide in 40 ml. of methylene chloride containing 0.4 ml. of N,N - dimethylaniline, cooled at -10°C ., there was added dropwise 0.4 ml. of phosphorus tribromide in 30 ml. of methylene chloride over a 45 minute period. When the addition was completed, the reaction mixture was stirred for an additional 30 minutes at -10°C . to insure complete reaction. The solvent was removed under vacuum and the residue was dissolved in an ethyl acetate/water mixture. The organic solution was separated from the aqueous phase and subsequently washed with 10 percent sodium chloride aqueous solution, 3 percent hydrochloric acid solution, and then with a 5 percent sodium bicarbonate aqueous solution. The washed organic solution was dried over sodium sulfate and evaporated to dryness to give 0.78 g. of the 2 - methyl - 3 - butynyl 7 - phenoxyacetamido - 3 - bromomethyl - Δ^3 - cephem - 4 - carboxylate as product. A thin layer chromatogram showed the presence of one component whose Rf was different from that of the starting material.

The following additional compounds are prepared by procedures described above:

p - Methoxybenzyl 3 - bromomethyl - 7 - (p - tolylacetaido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide from phosphorus pentabromide and p - methoxybenzyl 3 - hydroxymethyl - 7 - (p - tolylacetaido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide;
p - Nitrobenzyl 3 - bromomethyl - 7 - (4' - trifluoromethylphenoxyacetamido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide from phosphorus oxybromide and p - nitrobenzyl 3 - hydroxymethyl - 7 - (4' - trifluoromethylphenoxyacetamido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide;

1,1 - Dimethyl - 2 - pentynyl 3 - chloromethyl - 7 - (3' - methoxyphenylacetamido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide from phosphorus oxychloride and 1,1 - dimethyl - 2 - pentynyl 3 - hydroxymethyl - 7 - (3' - methoxyphenylacetamido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide;

Succinimidomethyl 3 - chloromethyl - 7 -

(4' - cyanophenylacetamido) - Δ^3 - cephem - 4 - carboxylate from phenylphosphonous dichloride and succinimidomethyl 3 - hydroxymethyl - 7 - (4' - cyanophenylacetamido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide; tert - Butyl 3 - bromomethyl - 7 - [(4' - aminomethyl) - phenylacetamido] - Δ^3 - cephem - 4 - carboxylate - 1 - oxide from phosphorus oxybromide and tert - butyl 3 - hydroxymethyl - 7 - [4' - (aminomethyl) phenylacetamido] - Δ^3 - cephem - 4 - carboxylate - 1 - oxide;

2,2,2 - Trichloroethyl 3 - chloromethyl - 7 - (3',4' - dichlorophenoxyacetamido) - Δ^3 - cephem - 4 - carboxylate from phosphorus trichloride and 2,2,2 - trichloro 3 - hydroxymethyl - 7 - (3', 4' - dichlorophenoxyacetamido) - Δ^3 - cephem - 4 - carboxylate - 1 - oxide, and

Benzhydryl 3 - bromomethyl - 7 - phenylacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide from phosphorus pentabromide and benzhydryl 3 - hydroxymethyl - 7 - phenylacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide.

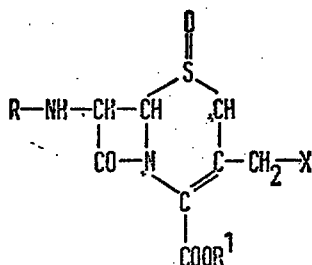
Example 7

Preparation of tert - butyl 7 - (phenoxyacetamido) - 3 - bromomethyl - 3 - cephem - 4 - carboxylate - 1 - oxide

To a stirred solution of 0.208 g. (0.5 millimole) of tert - butyl 7 - phenoxy - acetamido - 3 - hydroxymethyl - 3 - cephem - 4 - carboxylate - 1 - oxide in 40 ml. of methylene chloride at -35°C . containing 0.060 g. (0.50 millimole) of N,N - dimethyl - aniline, was added dropwise a solution of 10 ml. of methylene chloride containing 0.135 g. (0.50 millimole) of phosphorus tribromide. After the addition was completed the reaction mixture was stirred at -35°C . for 1 hour. Then the solvents were evaporated in vacuo and the residue was suspended in ethyl acetate. The ethyl acetate solution was washed three times with 50 ml. portions of 3 percent hydrochloric acid solution, once with saturated sodium bicarbonate solution, once with water, and then dried over sodium sulfate and evaporated to dryness to give 0.160 g. of crude tert - butyl 3 - bromomethyl - 7 - phenoxyacetamido - 3 - cephem - 4 - carboxylate - 1 - oxide as product. The crude product mixture was separated on two 20 cm. by 20 cm. silica gel preparative thin layer chromatography plates. The compound of intermediate polarity was isolated as 0.065 g. of a white foam. A nuclear magnetic resonance spectrum proved the identity of the compound to be tert - butyl 3 - bromomethyl - 7 - phenoxyacetamido - 3 - cephem - 4 - carboxylate - 1 - oxide.

WHAT WE CLAIM IS:—

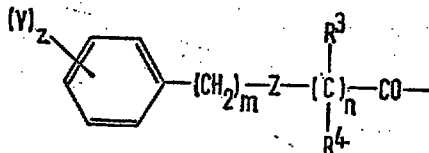
1. A compound having the formula



II

wherein X is chlorine, bromine or iodine;

5 R has the formula



wherein m is an integer of from 0 to 4, n is an integer of from 1 to 4, Z is oxygen or sulfur or a chemical bond, R^3 and R^4 are, separately, hydrogen or methyl, and Y is hydrogen or a substituent on the phenyl ring carbon atoms such as fluorine, chlorine, bromine, iodine, C_1 to C_2 -alkyl, C_1 to C_2 -alkyloxy, N -protected- α -amino- C_1 to C_3 -alkyl, butoxycarbonyl, nitro, cyano or trifluoromethyl and z is 1 or 2;

and R^1 is 2,2,2-trichloroethyl, C_4 to C_6 -tert-alkyl, C_5 to C_7 -tert-alkenyl, C_5 to C_7 -tert-alkynyl, benzyl, methoxybenzyl, nitrobenzyl, phenacyl, phthalimidomethyl, benzhydryl or succinimidomethyl.

2. A compound according to claim 1, wherein R^1 is other than 2,2,2-trichloroethyl.

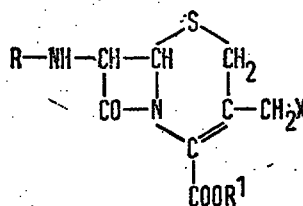
3. A compound as defined in claim 1 or 2, wherein X is chlorine, R is phenoxyacetyl, and R^1 is C_4 to C_6 -tert-alkyl.

4. A compound as defined in claim 1 or 2, wherein X is chlorine, R is phenoxyacetyl, and R^1 is methoxybenzyl.

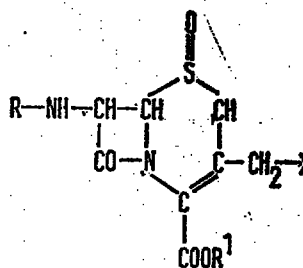
5. A compound as defined in claim 1, wherein X is bromine, R is phenoxyacetyl, and R^1 is C_4 to C_6 -tert-alkyl.

6. A compound as defined in claim 1 or 5, wherein the compound is tert-butyl 3-bromomethyl-7-phenoxyacetamido-3-cephem-4-carboxylate-1-oxide.

7. A process for preparing a compound having the formula



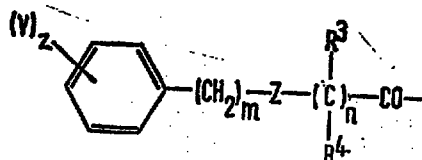
or



II

wherein X in each of formulas I and II is chlorine, bromine or iodine;

R has the formula



wherein m is an integer of from 0 to 4, n is an integer of from 1 to 4, Z is oxygen or sulfur or a chemical bond, R^3 and R^4 are, separately, hydrogen or methyl, and Y is hydrogen or a substituent on the phenyl ring carbon atoms such as fluorine, chlorine, bromine, iodine, C_1 to C_2 -alkyl, C_1 to C_2 -alkyloxy, N -protected- α -amino- C_1 to C_3 -alkyl, butoxycarbonyl, nitro, cyano or trifluoromethyl and z is 1 or 2;

and R^1 is 2,2,2-trichloroethyl, C_4 to C_6 -tert-alkyl, C_5 to C_7 -tert-alkenyl, C_5 to C_7 -tert-alkynyl, benzyl, methoxybenzyl, nitrobenzyl, phenacyl, phthalimidomethyl, benzhydryl or succinimidomethyl, which comprises reacting a phosphorus compound of the groups

(1) phosphorus trichloride or phosphorus tribromide, or

(2) phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride, or



- phosphorus oxybromide with a 3 - hydroxymethyl - Δ^3 - cephalosporin sulfoxide ester in the presence of a tertiary amine in a substantially anhydrous aprotic liquid organic diluent at a temperature of from about -75°C. to about 50°C. to form as product the corresponding compound
- 5 (1) (a) 3 - chloro or bromomethyl - Δ^3 - cephalosporin ester when at least an equimolar amount of phosphorus trichloride or phosphorus tribromide and temperatures above about -250°C. are used, or
- 10 (1) (b) 3 - chloro or bromomethyl - Δ^3 - cephalosporin sulfoxide ester from an approximately equimolar amount of phosphorus trichloride or phosphorus tribromide and temperatures below about -25°C. are used, or
- 15 (2) 3 - chloro or bromomethyl - Δ^3 - cephalosporin sulfoxide ester when phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride or phosphorus oxybromide are used,
- 20 and, optionally, treating the product with an alkali metal iodide to form the corresponding 3 - iodomethyl - Δ^3 - cephalosporin ester or 3 - iodomethyl - Δ^3 - cephalosporin sulfoxide ester.
- 25 8. The process of claim 7, for preparing a compound of formula I or II in which R^1 is other than 2,2,2 - trichloroethyl, and wherein reaction (1) (a) or (2) is carried out at a temperature of from about -25°C. to about 50°C.
- 30 9. The process of claim 7, wherein the reaction (1) (b) is conducted at a temperature of from -75°C. to -25°C.
- 35 10. The process of any of claims 7 to 9, wherein the phosphorus compound employed is phosphorus tribromide.
- 40 11. The process of claim 7 or 8, wherein the phosphorus compound is phosphorus pentachloride.
- 45 12. The process of claim 7 or 8, wherein phosphorus tribromide is reacted with tert-butyl 3 - hydroxymethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide to form tert-butyl 3 - bromomethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate.
- 50 13. The process of claim 7 or 8, wherein phosphorus pentachloride is reacted with tertiary-butyl 3 - hydroxymethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide to form tertiary butyl 3 - chloromethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide.
- 55 14. The process of claim 7, wherein phosphorus tribromide is reacted with tert - butyl 3 - hydroxymethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide to form tert - butyl 3 - bromomethyl - 7 - phenoxyacetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide.
- 60 15. The process of making cephalosporin ester and sulfoxide compounds having the formula (I) or (II) defined in claim 7, substantially as herein described with particular reference to any one of the specific Examples.
- 65 16. The compounds having the formula (I) or (II) as defined in claim 7 obtained by the process of any of claims 7 to 15.
- 70

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