

1315379

PATENT SPECIFICATION

(11) 1315379

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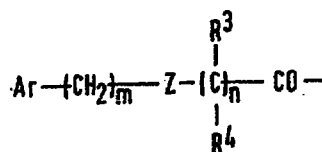
(54) 3-HALOMETHYL-Δ³-CEPHALOSPORIN ESTER COMPOUNDS

(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:—

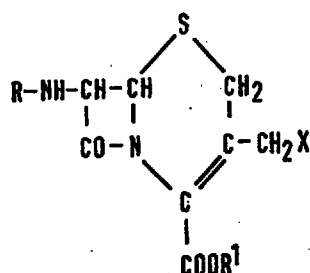
This invention is a patent of addition application to our parent application No. 1,295,908 (14835/70) filed March 26, 1970.

This invention relates to a process for preparing 3 - halomethyl - Δ³ - cephalosporin ester compounds characterized by the formula:

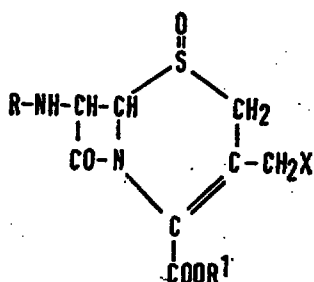
wherein R is C₁ to C₆ alkanoyl, C₂ to C₆ - chloroalkanoyl, or an acyl group of the formula



where Ar is 2 - thienyl, 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, R³ and R⁴ are, separately, hydrogen or methyl, or when R³ is hydrogen, R⁴ can also be an N - protected amino selected from the group consisting of N - tertbutoxycarbonylamino, N - (benzyloxycarbonylamino, N - (allyloxycarbonylamino, N - (cyclopentyloxycarbonylamino, and N - (2 - methoxycarbonyl - 1 - methylvinyl)amino and n is 1; or when R⁴ is N - protected amino as defined above, Ar can also be



or



(II)

wherein Y is hydrogen or a substituent on the phenyl ring carbon atoms, such as fluorine, chlorine, bromine, iodine, C₁ to C₂ - alkyl, C₁ to C₂ - alkyloxy, N - protected alpha-amino - C₁ to C₂ - alkyl, butoxycarbonyl, nitro, cyano or trifluoromethyl, and w is an integer of from 1 to 2; X is chloro, bromo or iodo; and R¹ is 2,2,2 - trichloroethyl, C₄ to C₆ - tert - alkyl, C₆ to C₇ - tert - alkenyl, C₅ to C₇ - tert - alkynyl, benzyl, methoxybenzyl, nitrobenzyl, phenacyl, phthalimidomethyl, or succinimidomethyl.

[Price 25p]

Price 75p

The process for producing these compounds is characterized by reacting a phosphorous compound of the group

- (1) phosphorus trichloride or phosphorus tribromide, or
 (2) phosphorus pentachloride, 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 liquid diluent at a temperature of from -75°C. to 50°C. to form as product the corresponding

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

- (2) 3 - halomethyl - Δ^3 - cephalosporin sulfoxide ester from an approximately equimolar amount of phosphorus tribromide or phosphorus trichloride when temperatures below -25°C. are used, or

- (3) 3 - halomethyl - Δ^3 - cephalosporin sulfoxide ester from phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride or phosphorus oxybromide.

This invention also relates to a compound of the formula II as defined above.

One of the unique advantages of Δ^3 - desacetoxymethyl - cephalosporin compounds is that they can be prepared from penicillin sulfoxide esters by the Morin-Jackson process of U.S. patent 3,275,626.

The 3 - halomethyl - Δ^3 - cephalosporin esters of the present invention are useful as intermediates in production of new and known nitrogen and sulfur containing 3 - (nucleophile - methyl) - Δ^3 - cephalosporin antibiotics and which can be used to form 3 - (nucleophilemethyl) - Δ^3 - cephalosporins, which do not need to be subjected to oxidation and reduction conditions.

The process of this invention circumvents or avoids the problems that can result in some cases following the conversion of a 3 - bromomethyl - Δ^3 - cephalosporin ester to a 3 - (nucleophile - methyl) - Δ^2 - cephalosporin ester where the nucleophile has an oxidizable nitrogen or sulfur atom therein.

The details of the process are the same as those described in our parent application.

If 7 - aminocephalosporanic acid (7-ACA) is to be used as the starting material, the preferred 7 - amino - protecting group will be one which is not only easy to put on the 7 - amino nitrogen, but one which can be removed easily after the desired series of reactions on the 3 - position methyl group are completed. In such event, the preferred

7 - amino - protecting group can be a simple C_1 to C_6 - alkanoyl group such as formyl, acetyl, propionyl, butanoyl, hexanoyl, a C_2 to C_6 - chloroalkenyl, particularly the α - chloroalkenyl groups, such as 2 - chloroacetyl which groups are put on by reacting 7-ACA with the respective acid chloride. If the selected overall process route to the cephalosporin antibiotic calls for acylating 7-ACA, an ester of 7-ACA, 7-ACA sulfoxide, or a 7-ACA sulfoxide ester with the final acyl group; one can acylate with, for example, an activated form of N - protected phenylglycine. Such activated form might be the mixed anhydride formed by reacting isobutyl chloroformate and 2 - [N - (tert - butoxycarbonyl)amino] - 2 - phenylacetic acid.

The R^1 symbol in the above formulas I and II represents an ester group as described in the parent application.

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 as was previously described in our parent application.

The compounds of both formulas I and II are primarily of interest in the preparation of known and new antibiotically active cephalosporin compounds as has been previously discussed in our parent application.

The invention is further exemplified by the following detailed examples, which are not intended to limit the scope of starting materials or products by merely to indicate the operation of the process and typical preparations of new compounds.

EXAMPLE 1

7 - Acetamido - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid is prepared by reacting 7 - aminocephalosporanic acid (7-ACA) with acetyl chloride. The 7 - acetamido - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid is treated with oxalyl chloride in the presence of a small amount of N,N - dimethylformamide to form the corresponding acid chloride. This acid chloride of 7 - acetamido - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid is dissolved in methylene chloride and the solution is treated with tert - butanol and triethylamine to form the tert - butyl 7 - acetamido - 3 - acetoxymethyl - Δ^2 - cephem - 4 - carboxylate ester.

The tert - butyl 7 - acetamido - 3 - acetoxymethyl - Δ^2 - cephem - 4 - carboxylate is oxidized with a peracid such as meta - chloroperoxybenzoic acid in isopropanol/methylene chloride mixture to form the tert - butyl 7 - acetamido - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylate - 1 - oxide.

The tert - butyl 7 - acetamido - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxyl-

ate - 1 - oxide is treated with citrus acetyl-
esterase by known procedures to obtain the
tert - butyl 7 - acetamido - 3 - hydroxy-
methyl - Δ^3 - cephem - 4 - carboxylate - 1 -
oxide.

The tert - butyl 7 - acetamido - 3 -
hydroxymethyl - Δ^3 - cephem - 4 - carboxyl-
ate - 1 - oxide is treated with phosphorus
tribromide, following the procedure described
in Example 7 of our parent application to
obtain as product the tert - butyl 7 - acet-
amido - 3 - bromomethyl - Δ^3 - cephem - 4 -
carboxylate - 1 - oxide.

This product can be used as an inter-
mediate to prepare a wide variety of known
and new cephalosporin antibiotics. For
example, this product can be treated with
methanol to form the 3 - methoxymethyl
analog, or with methyl mercaptan to form
the 3 - methylthiomethyl analog. Such com-
pounds can then be reduced to the sulfide
state, treated by the known



procedures to cleave the 7 - acetyl group,
re-acylated with any acyl group known to
contribute to good activity in the resulting
 Δ^3 - cephalosporin acid. For example, the
tert - butyl 7 - amino - 3 - methylthio-
methyl - Δ^3 - cephem - 4 - carboxylate ester
"nucleus" compound can be acylated with an
alkyl mixed anhydride of an N - D - (tert -
butoxycarbonylamido)phenylglycine, and then
the tert - butoxycarbonyl protecting group
and the tert - butyl esters are removed by
known methods to form the 3 - methylthio-
methyl - 7 - [D - 2' - amino - 2' - phenyl-
acetamido] - Δ^3 - cephem - 4 - carboxylic
acid zwitterion (inner salt), a known anti-
biotic.

EXAMPLE 2

The amino group of 7 - aminocephalo-
sporic acid (7-ACA) is protected with a
formyl group by reacting 7-ACA with the
mixed anhydride formed by adding formic
acid to acetic anhydride to form the 7 -
formamido - 3 - acetoxymethyl - Δ^3 -
cephem - 4 - carboxylic acid. This N - pro-
tected 7-ACA is esterified in the manner
described in Example 1 to form the tert -
butyl 7 - formamido - 3 - acetoxymethyl -
 Δ^3 - cephem - 4 - carboxylate ester. This
 Δ^3 - cephalosporin ester is oxidized as de-
scribed in Example 1 to form the tert - butyl
7 - formamido - 3 - acetoxymethyl - Δ^3 -
cephem - 4 - carboxylate - 1 - oxide. This
 Δ^3 - cephalosporin sulfoxide ester is hydro-
lyzed with citrus acetyl esterase to form the
tert - butyl 7 - formamido - 3 - hydroxy-
methyl - Δ^3 - cephem - 4 - carboxylate - 1 -
oxide, which is the starting material for the
process of this invention.

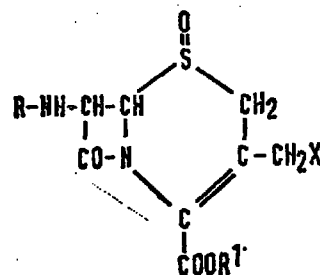
Following the procedure of Example 7, or

our parent application, phosphorus tribromide
is reacted with tert - butyl 7 - formamido -
3 - hydroxymethyl - Δ^3 - cephem - 4 -
carboxylate - 1 - oxide to form tert - butyl
7 - formamido - 3 - bromomethyl - Δ^3 -
cephem - 4 - carboxylate of this invention.

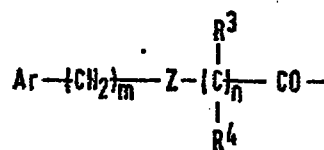
This compound is useful as an intermediate
in the production of known and new cephalo-
sporin antibiotics. For example, this com-
pound can be treated with methanol to form
the tert - butyl 7 - formamido - 3 - methoxy-
methyl - Δ^3 - cephem - 4 - carboxylate - 1 -
oxide, the sulfoxide ester can be reduced with
potassium iodide/acetyl chloride to form the
tert - butyl 7 - formamido - 3 - methoxy-
methyl - Δ^3 - cephem - 4 - carboxylate, the
formyl group can be cleaved with mineral
acid at -15° to 100°C . to form the 7 -
amino - 3 - methoxymethyl - Δ^3 - cephem -
4 - carboxylate ester "nucleus". This nucleus
ester can be acylated with any acyl group
known to contribute to the formation of a
cephalosporin compound having significant
antibiotic activity. For example, the nucleus
ester can be acylated with an activated, N -
protected form of D - phenylglycine to form
the tert - butyl 7 - [D - 2 - (N - protected
amino) - 2' - phenyl - acetamido] - 3 -
methoxymethyl - Δ^3 - cephem - 4 - car-
boxylate ester. The N - protecting group and
the ester group can be removed by known
procedures to form the 7 - [D - 2' - amino -
2' - phenylacetamido] - 3 - methoxymethyl -
 Δ^3 - cephem - 4 - carboxylic acid, and a
known antibiotic.

WHAT WE CLAIM IS:—

1. A 3 - halomethyl - Δ^3 - cephalosporin
ester of the formula:



wherein R is C_1 to C_6 - alkanoyl, C_2 - C_6 -
chloroalkanoyl, or an acyl group of the
formula



where Ar is 2 - thienyl, 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

ate - 1 - oxide is treated with citrus acetyl-
esterase by known procedures to obtain the
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methyl - Δ^3 - cephem - 4 - carboxylate - 1 -
oxide.

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the 3 - methylthiomethyl analog. Such com-
pounds can then be reduced to the sulfide
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acid zwitterion (inner salt), a known anti-
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described in Example 1 to form the tert -
butyl 7 - formamido - 3 - acetoxymethyl -
 Δ^1 - cephem - 4 - carboxylate ester. This
 Δ^2 - cephalosporin ester is oxidized as des-
cribed in Example 1 to form the tert - butyl
7 - formamido - 3 - acetoxymethyl - Δ^3 -
cephem - 4 - carboxylate - 1 - oxide. This
 Δ^3 - cephalosporin sulfoxide ester is hydro-
lyzed with citrus acetyl esterase to form the
tert - butyl 7 - formamido - 3 - hydroxy-
methyl - Δ^3 - cephem - 4 - carboxylate - 1 -
oxide, which is the starting material for the
process of this invention.

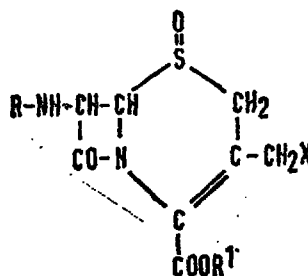
Following the procedure of Example 7, or

our parent application, phosphorus tribromide
is reacted with tert - butyl 7 - formamido -
3 - hydroxymethyl - Δ^3 - cephem - 4 -
carboxylate - 1 - oxide to form tert - butyl
7 - formamido - 3 - bromomethyl - Δ^3 -
cephem - 4 - carboxylate of this invention.

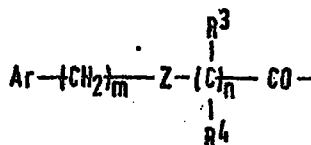
This compound is useful as an intermediate
in the production of known and new cephalo-
sporin antibiotics. For example, this com-
pound can be treated with methanol to form
the tert - butyl 7 - formamido - 3 - methoxy-
methyl - Δ^3 - cephem - 4 - carboxylate - 1 -
oxide, the sulfoxide ester can be reduced with
potassium iodide/acetyl chloride to form the
tert - butyl 7 - formamido - 3 - methoxy-
methyl - Δ^3 - cephem - 4 - carboxylate, the
formyl group can be cleaved with mineral
acid at -15° to 100°C . to form the 7 -
amino - 3 - methoxymethyl - Δ^3 - cephem -
4 - carboxylate ester "nucleus". This nucleus
ester can be acylated with any acyl group
known to contribute to the formation of a
cephalosporin compound having significant
antibiotic activity. For example, the nucleus
ester can be acylated with an activated, N -
protected form of D - phenylglycine to form
the tert - butyl 7 - [D - 2 - (N - protected
amino) - 2' - phenyl - acetamido] - 3 -
methoxymethyl - Δ^3 - cephem - 4 - car-
boxylate ester. The N - protecting group and
the ester group can be removed by known
procedures to form the 7 - [D - 2' - amino -
2' - phenylacetamido] - 3 - methoxymethyl -
 Δ^3 - cephem - 4 - carboxylic acid, and a
known antibiotic.

WHAT WE CLAIM IS:—

1. A 3 - halomethyl - Δ^3 - cephalosporin
ester of the formula:

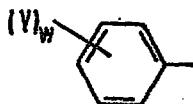


wherein R is C_1 to C_6 - alkanoyl, C_2 - C_6 -
chloroalkanoyl, or an acyl group of the
formula



where Ar is 2 - thienyl, 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, or when R^3 is hydrogen, R^4 can also be an N - protected amino selected from the group consisting of N - tert - butoxycarbonylamino, N - (benzyloxycarbonyl)amino, N - (allyloxycarbonyl)amino, N - (cyclopentylloxycarbonyl)amino, and N - (2 - methoxycarbonyl - 1 - methylvinyl)amino and n is 1; or when R^4 is N - protected amino as defined above, Ar can also be



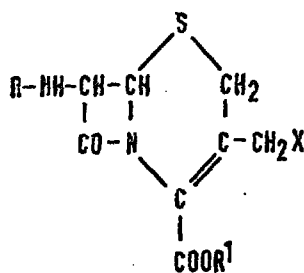
wherein Y is hydrogen or a substituent on the phenyl ring carbon atoms, such as fluorine, chlorine, bromine, iodine, C_1 - C_2 - alkyl, C_1 to C_2 - alkyloxy, N - protected - alpha - amino - C_1 to C_3 alkyl, butoxycarbonyl, nitro, cyano or trifluoromethyl, and w is an integer of from 1 to 2; X is chloro, bromo or iodo; 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, or succinimidomethyl.

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

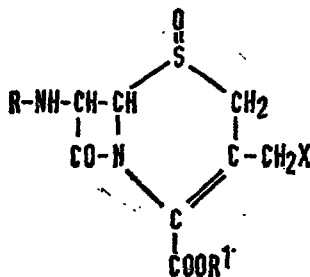
3. A compound as defined in claim 1 wherein X is bromine, R is formyl, and R^1 is C_4 to C_6 - tert - alkyl.

4. The compound of claim 2 or 3 wherein R^1 is tert - butyl.

5. A process for preparing a compound of the formula



35 or



wherein R, R^1 and X are defined in claim 1, characterized by reacting a phosphorus compound of the group

(1) phosphorus trichloride or phosphorus tribromide, or

(2) phosphorus pentachloride, 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 liquid diluent at a temperature of from -75°C . to 50°C . to form as product the corresponding

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

(2) 3 - halomethyl - Δ^3 - cephalosporin sulfoxide ester from an approximately equimolar amount of phosphorus tribromide or phosphorus trichloride when temperatures below -25°C . are used, or

(3) 3 - halomethyl - Δ^3 - cephalosporin sulfoxide ester from phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride or phosphorus oxybromide.

6. The process of claim 5 characterized in that the phosphorus compound is phosphorus tribromide.

7. The process of claim 5 characterized in that the phosphorus compound is phosphorus tribromide and the 3 - hydroxymethyl - Δ^3 - cephalosporin sulfoxide ester is tert - butyl 3 - hydroxymethyl - 7 - acetamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide to form tert - butyl 3 - bromomethyl - 7 - acetamido - Δ^3 - cephem - 4 - carboxylate.

8. The process of claim 5 characterized in that the phosphorus compound is phosphorus tribromide and the 3 - hydroxymethyl - Δ^3 - cephalosporin sulfoxide ester is tertiary - butyl 3 - hydroxymethyl - 7 - formamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide to form tertiary butyl 3 - chloromethyl - 7 - formamido - Δ^3 - cephem - 4 - carboxylate - 1 - oxide.

9. A process as claimed in claim 5 substantially as herein described with particular reference to any one of the specific examples.

10. A compound having the formula I or II as defined in claim 5 that has been prepared by a process as claimed in any one of claims 5 to 9.

11. A process which comprises converting a compound as defined in claim 1 into a 3 - halomethyl - Δ^3 - cephalosporin compound having antibiotic activity.



12. A 3 - halomethyl - Δ^3 - cephalosporin compound having antibiotic activity that has been prepared by the process of claim 11.

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