

# PATENT SPECIFICATION

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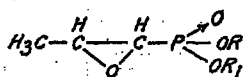
## (54) PHOSPHONIC ACID DERIVATIVES

(71) We, MERCK & Co. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, 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:—

Although many valuable antibiotics are known for the treatment of various diseases, such antibiotics are in general active against a limited number of pathogens, and certain strains of these pathogens develop resistance to a particular antibiotic so that the antibiotic is no longer active against such resistant strains. These shortcomings of the known antibiotics have stimulated further research to discover new antibacterial agents which are active against a wide range of pathogens and against strains of pathogens resistant to previously described antibiotics.

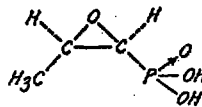
The present invention is concerned with (±) (cis - 1,2 - epoxypropyl)phosphonic acid compounds, mixtures of the (+) and (−) enantiomers, and with their salts and esters, and with the preparation of such substances by the epoxidation of *cis*-propenylphosphonic acid compounds. Compounds in accordance with the present invention have a significant degree of antibacterial activity.

The novel (±) (cis - 1,2 - epoxypropyl) - phosphonic acid compounds of this invention may be represented structurally by the formula below:

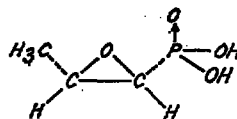


In this formula, each of R and R<sub>1</sub> represents hydrogen or a substituted or unsubstituted hydrocarbyl, acyl or heterocyclic radical or R and R<sub>1</sub> together for a cyclic ester group. The radicals R and R<sub>1</sub> may be the same or different in a specific compound. Also included within the invention, and forming an important and preferred aspect of it, are the organic and inorganic salts of those compounds of Formula I in which at least one of the symbols R and R<sub>1</sub> represent hydrogen.

The structural formulae of the novel compounds of this invention are for convenience shown in the planar formula above because the configuration is adequately defined by the name (±) (cis - 1,2 - epoxypropyl) - phosphonic acid. However, for the sake of completeness, the spatial configuration may be represented structurally as



and



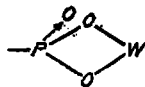
When R and/or R<sub>1</sub> in Formula I represents a substituted or unsubstituted hydrocarbyl radical, such radical may be aliphatic, cycloaliphatic, araliphatic or aromatic. When R and/or R<sub>1</sub> is a substituted or unsubstituted aliphatic radical it may be substituted or

unsubstituted alkyl, alkenyl or alkynyl, representative examples of which are methyl, propyl, isopropyl, t-butyl, hexyl, octyl, decyl, dodecyl, haloalkyl such as chloroethyl, fluoro-  
 5 propyl, bromoethyl or dichloroethyl, acyloxy-alkyl such as acetoxymethyl, propionoxyethyl, or benzoyloxyethyl, hydroxypropyl, amino-methyl, aminoethyl, alkylaminoalkyl such as dimethylaminomethyl, diethylaminoethyl, or  
 10 diethylaminopropyl, *p*-nitrobenzoylamino-methyl, carboalkoxymethyl, cyanoethyl, sulfon-amidoethyl, phthalimidomethyl, pyridylethyl, furylmethyl, thienylpropyl, methoxymethyl, allyl, methallyl, vinyl, propenyl, hexenyl,  
 15 octadienyl, propargyl, ethynyl or chloroethynyl; or cycloalkyl such as cyclohexyl, cyclohexenyl or cyclopropyl. When R is aliphatic, it preferably has from 1—6 carbon atoms, i.e. is substituted or unsubstituted C<sub>1-6</sub> alkyl, C<sub>2-6</sub>  
 20 alkenyl or C<sub>2-6</sub> alkynyl.

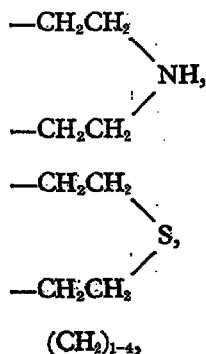
Examples of R and/or R<sub>1</sub> representing a substituted or unsubstituted araliphatic radical are substituted or unsubstituted aralkyl such as benzyl, phenethyl, phenylpropyl, *p*-halo-  
 25 benzyl, *o*-, *m*- or *p*-alkoxybenzyl, nitrobenzyl and aminophenethyl.

R and/or R<sub>1</sub> may also represent an aryl radical such as phenyl, naphthyl or substituted phenyl or naphthyl, e.g. *p*-chlorophenyl, *o*-nitrophenyl, *o,p*-dihalophenyl, cyanophenyl, methoxyphenyl, aminophenyl and tolyl. The  
 30 aryl radical is preferably a mononuclear aromatic residue. When R and/or R<sub>1</sub> are heterocyclic, they may be heteroaromatic such as pyridyl, furyl, thienyl, thiazolyl or pyrazinyl, or alternatively may represent a hydrogenated hetero ring, examples of which are tetrahydro-  
 35 furyl and piperazinyl.

When R and R<sub>1</sub> together form a cyclic ester group, the resulting (±) (*cis* - 1,2 - epoxy-  
 40 propyl)phosphonic acid compounds contain a group of the formula:



where W is derived from a compound having  
 45 two hydroxyl groups. Examples of W are



and



This compounds of Formula I which are acidic, i.e. the free acids and the mono-  
 55 esters, may form salts, and such salts constitute an especially preferred aspect of the invention. Salts in accordance with the invention are useful when the (±) (*cis* - 1,2 - epoxypropyl)phosphonic acid compounds are employed as antibacterial agents since they  
 60 are more stable than the free phosphonic acid, and (except in particular instances) more active than the esters.

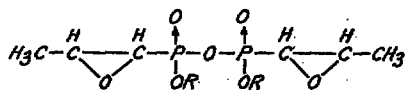
The free phosphonic acid compounds will form both organic and inorganic salts, and both are contemplated by this invention. Ex-  
 65 amples of such salts are inorganic metallic salts such as the sodium, aluminium, potassium, ammonium, calcium, magnesium, silver and iron salts. Organic salts that may be mentioned as representative include the salts  
 70 with primary, secondary or tertiary amines such as monoalkylamines, dialkylamines, trialkylamines and nitrogen-containing heterocyclic amines. Representative examples are salts with amines such as  $\alpha$ -phenethylamine (the (+) $\alpha$ -phenethylamine is preferred), di-  
 75 ethylamine, diethylene triamine, quinine, brucine, lysine, protamine, arginine, procaine, ethanolamine, morphine, benzylamine, ethylenediamine, N,N'-dibenzylethylenediamine, diethanolamine, piperazine, N-aminoethyl-  
 80 piperazine, dimethylaminoethanol, 2-amino-2-methyl-1-propanol, theophylline, esters of amino acids, and N-methylglucamine. Both mono- and di-basic salts may be prepared when the cation is monovalent. If desired, the basic residue of the salt may be bio-  
 85 logically active amine such as erythromycin, oleandomycin or novobiocin.

Those salts which are pharmaceutically ac-  
 90 ceptable and substantially non-toxic may be employed when using the (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid as an anti-bacterial agent. Other salts which are not nor-  
 95 mally employed in pharmaceutical applications are useful as intermediates in forming the free acid and for making other salts by metathesis. In addition, the salts with opti-  
 100 cally active amines may be employed as intermediates in resolving the racemic (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid into its optically active stereoisomers.

In addition to the salts, preferred (±) (*cis* - 1,2-epoxypropyl)-phosphonic acid compounds are those esters which are readily hydrolysed  
 105 chemically or are converted biologically to the free acid or a salt. Such esters may be referred to as labile or biologically labile esters. They include compounds where the radicals R and/

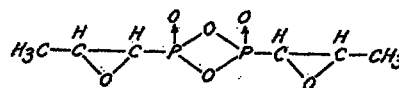
or  $R_1$  (in Formula I above) represents  $C_{2-6}$  alkenyl such as allyl or methallyl; acyl—examples of which are phenylacetyl, phenylpropionyl, *p*-chlorophenylacetyl, benzoyl and  $C_{2-6}$  alkanoyl; substituted alkyl such as pyrrolylmethyl,  $\beta$  - dimethylaminoethyl,  $\beta$  - diethylaminoethyl,  $\beta$ -cyanoethyl,  $\beta$ -methoxymethyl, hydroxypropyl, acetoxymethyl, pivaloxymethyl and propionoxymethyl; or phenyl substituted with one or more electron-withdrawing substituents such as nitro, alkylsulfonyl and aminosulfonyl, and the ester with catechol.

Also embraced by this invention are the pyrophosphonates, anhydrides and isohypophosphates represented by the formulae

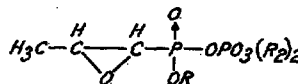


II

or



III

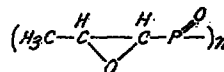
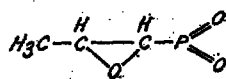


IV

where  $R$  is a hydrogen atom or a  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, cycloalkyl, aryl, aralkyl or heteroaryl radical and  $R_2$  is a  $C_{1-6}$  alkyl or alkali metal radical. Salts of these compounds where  $R$  is hydrogen are especially preferred. Representative examples of compounds of Formula II are

dipiperazinium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-pyrophosphonate, disodium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-pyrophosphonate, dibenzyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-pyrophosphonate, and allyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-pyrophosphonate;

the compound of Formula III is ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonic acid cyclic di-anhydride; examples of the compounds of Formula IV are sodium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - isohypophosphoric acid disodium salt and potassium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - isohypophosphoric acid dibenzyl ester. Although the di-anhydrides are conveniently represented by Formula III above, they may also exist in the forms



where  $n$  is a positive integer. These substances, and particularly those wherein  $R$  is a cation (i.e. salts) or an easily removable ester have antibacterial activity.

Specific representative examples of the compounds of Formula I above, and salts thereof, which may be prepared by the processes described hereinafter are:

( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonic acid, methyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)phosphonate, dimethyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, di-*t*-butyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)phosphonate, diallyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)phosphonate, dimethallyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)phosphonate, dibenzyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)phosphonate, benzyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, decyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, phenyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, *p*-nitrophenyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, *m*-nitrophenyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, cyclohexyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, pentyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, *p*-aminophenyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, tolyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate, tetrahydrofuryl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,

- disodium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 sodium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 potassium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 calcium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 5 aluminium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 benzylammonium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 magnesium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 $\alpha$ -phenethylammonium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 silver ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 10 lysine ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 quinine ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 procain ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 dibenzylammonium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 ethylenediammonium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 15 diethylenediammonium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 disodium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-pyrophosphonate,  
 N,N'-dibenzylethylenediammonium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 mono- and dipiperazinium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 cyclic ester of ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonic acid with catechol,  
 20 cyclic ester of ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonic acid with ethylene glycol,  
 cyclic ester of ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonic acid with bis-hydroxyethylamine,  
 bis-acetoxymethyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 bis- $\beta$ -ethoxyethyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 bis(phenylacetyl) ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 25 pyridylmethyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 methylsulfonylphenyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 $\beta$ -dimethylaminomethyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate,  
 and  $\beta$ -hydroxyethyl ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate.

The ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonic acid described herein and salts and biologically labile esters thereof, have significant antibacterial activity against a large number of pathogens. They are useful antimicrobial agents, which are active in inhibiting the growth of both gram-positive and gram-negative pathogenic bacteria. They are active against species of *Bacillus*, *Escherichia*, *Staphylococci*, *Salmonella* and *Proteus* pathogens, and antibiotic-resistant strains thereof. Illustrative of such pathogens are *Bacillus subtilis*, *Escherichia coli*, *Salmonella schottmuelleri*, *Salmonella gallinarum*, *Salmonella pullorum*, *Proteus vulgaris*, *Proteus mirabilis*, *Proteus morganii*, *Staphylococcus aureus* and *Staphylococcus pyogenes*. Thus, ( $\pm$ ) (*cis* - 1, 2 - epoxypropyl) - phosphonic acid and salts thereof can be used as antiseptic agents to remove susceptible organisms from pharmaceutical, dental and medical equipment and other areas subject to infection by such organisms, and to inhibit harmful bacterial growth in industrial paints. Similarly, they can be used to separate certain microorganisms from mixtures of microorganisms. They are useful in the treatment of diseases caused by bacterial infections in man and animals and are particularly valuable in this respect, since they are active against many strains of pathogens resistant to previously available antibiotics.

Salts of ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)-phosphonic acids are useful as preservatives in industrial applications since they effectively inhibit undesirable bacterial growth in the white

water used in paper mills and in paints. Thus paints containing as preservatives a compound of the invention also form part of the invention e.g. in polyvinyl acetate latex paint. Pharmaceutically acceptable salts in accordance with the invention may be used in antibacterial compositions in admixture with a pharmaceutically acceptable carrier vehicle. Antiseptic compositions containing a compound in accordance with the invention and a diluent or carrier also form part of the invention as do pharmaceutical antibacterial compositions containing a compound of the invention and a non-toxic pharmaceutical diluent, carrier or coating.

When ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonic acid or a salt or labile ester thereof is used for combating bacteria in man or lower animals, it may be administered orally in a dosage form such as a capsule, pill or tablet, or in a liquid solution or suspension. These formulations may be prepared using diluents, granulating agents, preservatives, binders, flavoring agents and coating agents known to those skilled in this particular art. Alternatively, it may be administered parenterally by injection in a sterile vehicle, and for this it is normal to use a salt that is soluble in the liquid vehicle. Representative examples of formulations are given below, it being understood that other salts and other pharmaceutical vehicles could be substituted for those illustrated.

#### A. Capsules

Either 330 mg of anhydrous disodium ( $\pm$ )

equivalent, the actual weight being dependent on the particular salt or ester employed. When the higher dose levels are used, the salt or ester is chosen so that the cation is not unduly toxic at such levels. It will, of course, be understood that the optimum dose in any given instance will depend upon the type and severity of infection to be treated, and that smaller doses will be employed for pediatric use, all of such adjustments being within the skill of the practitioner in the field.

Mixtures of (+) and (-) enantiomers of the (*cis* - 1,2 - epoxypropyl)phosphonic acid compounds of this invention may be administered alone or in combination with other biologically active ingredients and especially with other antibacterial agents such as erythromycin, lincomycin, a penicillin, streptomycin, nontobacin, tylosin, gentamycin, neomycin, colistin, kanamycin, oleandomycin, triacetyl oleandomycin and spiramycin.

## Per Tablet

|    |                                                                               |           |
|----|-------------------------------------------------------------------------------|-----------|
| 15 | Calcium ( $\pm$ ) ( <i>cis</i> - 1,2 - epoxypropyl) - phosphonate monohydrate | 352.5 mg. |
|    | Dicalcium phosphate                                                           | 180       |
|    | Lactose U.S.P.                                                                | 179.5     |
| 20 | cornstarch                                                                    | 80 mg.    |
|    | Magnesium stearate                                                            | 8 mg.     |

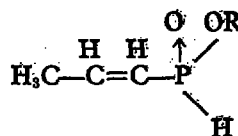
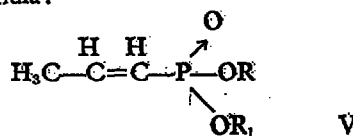
The antibacterially active ( $\pm$ ) - (cis - 1,2 - epoxypropyl) - phosphonic acid, and its salts, may be resolved, if desired, into the (+) and (-) enantiomers, thereof, as by formation of a salt with an optically active amine, separation of the diastereoisomers of such salt, and regeneration of the (+) and (-) enantiomers of (cis - 1,2 - epoxypropyl) - phosphonic acid. The antibiotic activity resides in (-) (cis - 1,2 - epoxypropyl)phosphonic acid so that this acid and its salts possess essentially twice the antibacterial activity (on a weight basis) of the ( $\pm$ ) (cis - 1,2 - epoxypropyl) - phosphonic acid compounds of the present invention.

## Per 1000 MI.

|    |                                                         |            |
|----|---------------------------------------------------------|------------|
|    | Disodium (±) (cis - 1,2 -<br>epoxypropyl) - phosphonate | 132.00 gm. |
| 40 | Sucrose                                                 | 600.0 gm.  |
|    | Glucose                                                 | 250 gm.    |
|    | Citric Acid                                             | 13.0 gm.   |
|    | Sodium benzoate                                         | 1.0 gm.    |
|    | Concentrated Orange Oil                                 | 0.2 ml.    |
| 45 | Purified water U.S.P. to make                           | 1000.0 ml. |

In accordance with the process aspect of this invention, the  $(\pm)$  (*cis* - 1,2 - epoxypromyl) - phosphonic acid compounds of Formula I hereinabove are prepared by the epoxidation of a *cis*-propenylphosphonate compound of the formula:

with a chemical oxidizing agent, where each of R and R<sub>1</sub> is a hydrogen atom or a substituted or unsubstituted hydrocarbyl, acyl or heterocyclic radical (as previously defined) or a cation or R and R<sub>1</sub> together form a cyclic ester group. When R and/or R<sub>1</sub> are cations, the compound is a mono- or di-salt. It is preferred, and is important for best results in this reaction, that at least one of R and R<sub>1</sub> in Formula V be other than hydrogen. According to a preferred embodiment of this process, a compound of the formula:



where R is as defined above, or a salt of the compound in which R is a hydrogen atom, is reacted with an oxidising agent to produce a compound of the invention, in which R<sub>1</sub> is a hydrogen atom, in the form of a mixture of enantiomers. The choice of oxidising agent is not unduly critical although it should be one capable of epoxidising the *cis*-propenylphosphonate compound without undue destruction of the remainder of the molecule. It is preferred to carry out the epoxidation on a salt or ester derivative of the free phosphonic acid since the acid itself tends to be unstable under the reaction conditions. In addition, it is further preferred to use as the oxidising agent a peroxy compound, such as hydrogen peroxide, an inorganic peracid, a perorganic acid, an organic hydroperoxide or peroxy imidate as discussed hereafter. However, other oxidizing agents may also be used if desired, and examples of these are also discussed hereinbelow.

One of the better methods of peroxidising the ethylenic double bond of the olefin Compound VI is by treating said compound with hydrogen peroxide. Although hydrogen peroxide alone may be used, it is preferred to conduct the reaction in the presence of a suitable inorganic peracid since much better results are thereby obtained. In describing this invention the inorganic peracid is sometimes referred to as a catalyst, although the exact role of such peracid is not unequivocally established as a catalyst in the classical sense, and it may participate as an epoxidising agent. Although the peracid itself may be added to the reaction medium, it is generally preferred that the inorganic acid be added to the reaction mixture and the peracid formed *in situ* by reaction with the hydrogen peroxide. Stated another way, acids of metal oxides which react with hydrogen peroxide to form peracids may be employed. Particularly useful catalysts are the peracids of tungsten, vanadium and molybdenum, either as the simple acids or polyacids, including the heteropolyacid forms. The inorganic acids are generally used in the form of neutral salts, such as an alkali metal, e.g. sodium or potassium tungstate, ammonium tungstate, alkaline-earth metal salts such as calcium or barium tungstate or vanadate, a heavy metal salt, examples of which are zinc vanadate, zinc tungstate, tin tungstate, tin molybdate, aluminium tungstate and aluminium molybdate. Alternatively, the neutral salt can be formed *in situ* by adding a free acid, such as tungstic or vanadic acid, and adding sufficient base to form the desired salt.

In addition to the simple peracids, there may be used heteropolyacids, examples of which are the heteropolytungstic acids of arsenic, antimony and bismuth. In the same way heteropolymolybdic and heteropolychromic acids of sulfur, selenium or tellurium may

also be used as catalyst. In general, the heteropolyacids of the acid-forming elements of group VI of the Periodic Table of Elements are satisfactory. More than two different hetero-acid forming elements of group VI may be present in the catalyst, examples being thiotelluro-tungstic acid and selenomolybdotungstic acid. As previously stated, these are preferably converted *in situ* to the corresponding peracid. Other catalysts which are suitable, although not as effective as those mentioned above, are alkali metal carbonates, bicarbonates and phosphates, e.g. sodium carbonate, potassium bicarbonate, sodium phosphate and disodium hydrogen phosphate. At least about 0.1% of catalyst (by weight of *cis*-propenylphosphonic acid compound) is used for best results. Higher amounts are not harmful and up to about 30% by weight may be employed if desired. It is preferred to use from 0.25—5% of inorganic peracid (by weight of propenylphosphonate). When these catalysts are used in the *cis*-propenylphosphonic acid compound of Formula I above is contacted with hydrogen peroxide (or an equivalent peroxide such as sodium or barium peroxide) in the presence of the catalyst and in a suitable liquid reaction medium. The reaction is conveniently brought about at temperatures of from 0° to 90° C., and preferably from room temperature to 80° C. and at a pH of from 3.0 to 11.0, and preferably from 4.0 to 6.0. At a pH below 4.0, reaction temperatures below 15° C. are desirable in order to avoid or minimize decomposition of the desired epoxypentenylphosphonic acid compound. At the higher pH levels, (i.e. above 8.0) the hydrogen peroxide decomposes at an appreciable rate and must be replaced during the reaction.

Good results are obtained by dissolving or suspending the *cis*-propenylphosphonic acid compound in the solvent, adjusting to the desired pH, adding the catalyst and finally the hydrogen peroxide. The rate and temperature of the reaction may be readily controlled by rate of peroxide addition. For best results, at least one mole of peroxide per mole of *cis*-propenylphosphonic acid compound is used, and it is preferable to use at least 3 moles of peroxide per mole of phosphonate. Larger excesses are not deleterious.

Water and/or alcohols compatible with hydrogen peroxide are preferably used as solvent media, suitable alcohols being C<sub>1-6</sub> alkanols such as methanol, ethanol, propanol or butanol. If desired, chelating agents such as ethylene diamine tetraacetic acid, ethylenediamine diacetic acid, glycine or  $\beta$ -alanine may be present during the epoxidation reaction in order to sequester any heavy metals such as iron, nickel or copper which tend to catalyze the decomposition of hydrogen peroxide.

Upon completion of the epoxidation reaction, any excess of hydrogen peroxide is de-

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composed. The ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonic acid compound may be recovered by separation from inorganic compounds and subsequent crystallization or evaporation of the reaction mixture to dryness.

The ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonates of this invention may also be obtained by reaction of the *cis*-propenylphosphonate (V) with an organic peracid such as peracetic perbenzoic, substituted perbenzoic, monoperoxphthalic, performic or peroxytrifluoroacetic acid, preferably at temperatures of from  $-10^{\circ}$  C. to  $150^{\circ}$  C. Peroxyanhydrides may also be used as a source of the peroxy acids if so desired. This peroxidation is preferably carried out in inert hydrocarbon solvents such as chloroform, methylene dichloride, benzene, toluene, pyridine or ethyl acetate. The reaction time is not critical and it is, of course, preferable to continue the peroxidation until the maximum amount of epoxide has been produced. Generally, a molar excess of organic peracid is used for best results. It is preferred that the reaction mixture be buffered when using those peracids which will decompose during the reaction to strong acids, e.g. peroxytrifluoroacetic acid. Disodium hydrogen phosphate is an example of a suitable buffering agent. It should be pointed out at this juncture that use of an optically active organic peracid as the peroxidizing agent, such as percamphoric acid, will afford a reaction mixture containing predominantly only one of the optical isomers of the (*cis* - 1,2 - epoxypropyl) - phosphonic acid compound. Thus, for example, use of (+) percamphoric acid as epoxidizing agent will produce predominantly the (-) (*cis* - 1,2 - epoxypropyl) - phosphonic acid compound. The desired products may be recovered by methods known to those skilled in this art, for instance by decomposition of excess perorganic acid and removal of the solvent or solvents.

Additionally, the *cis*-propenylphosphonic acid compounds of Formula V may be epoxidized to the 1,2-epoxypropyl compounds of Formula I by reaction with an organic hydroperoxide in a suitable solvent medium. Any organic hydroperoxide may be used although the more readily available ones such as *t*-butyl hydroperoxide cumene hydroperoxide and amylene hydroperoxide are preferred. The reaction is conveniently carried out in inert hydrocarbon or halogenated hydrocarbon solvent (similar to those used in the perorganic acid process discussed above) at a temperature of from  $-10^{\circ}$  C. to  $100^{\circ}$  C., preferably from  $60$ — $90^{\circ}$  C. As catalyst, there is preferably used from 0.01% to 5% (by weight of propenyl compound) of an oxide of a metal of group Vb or VIb of the Periodic Table, such as molybdenum, tungsten or vanadium, or a complex or ligand of these metals, as for example molybdenum hexacarbonyl. An alkali metal hydroxide or an organic base such

as Triton B ("Triton" is a registered Trade Mark) may also be used as catalyst although the metal oxides are more satisfactory.

Further, formation of the epoxides of this invention can be brought about by treating the *cis*-propenylphosphonic acid compound of Formula V above with hydrogen peroxide and a nitrile which serves as a source of peroxyimide acid, suitable nitriles being acetonitrile, propionitrile and benzonitrile. At least 1 mole of peroxide and nitrile is used per mole of olefin, although larger quantities of oxidants may be employed if desired. The peroxidizing agent is the peroxyimide acid formed *in situ* from the nitrile and hydrogen peroxide, which is decomposed during reaction to an amide. The reaction is generally conducted in an aqueous or  $C_{1-6}$  alkanolic solvent medium (the alcohol being one that is compatible with hydrogen peroxide), and at a pH of 7—9. The pH may be maintained with an alkali metal bicarbonate buffer or by other means such as the continuous addition of an alkali metal hydroxide, e.g. sodium hydroxide. Time and temperature are not critical factors. Upon completion of the reaction, any excess hydrogen peroxide is decomposed by known methods and the desired product separated from the organic amide by-product by techniques known to those skilled in this art. It is convenient to use a nitrile and solvent such that the resulting amide is insoluble and the epoxide is soluble in the reaction mixture.

A still further method for obtaining the ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonic acid compounds of the invention is by reacting the *cis*-propenylphosphonate compounds with oxygen (or air) in the presence of a suitable catalyst and a basic buffer. Examples of satisfactory catalysts are alkali metal tungstates or vanadates, the naphthenates of cobalt, iron, manganese or vanadium, or *t*-butyl hydroperoxide. It is desirable to carry out the oxidation at temperatures of  $75^{\circ}$  C. to  $125^{\circ}$  C. since the epoxidation proceeds only slowly at lower temperatures. Although a reaction solvent is not absolutely necessary, it is preferable to use an inert liquid solvent, suitable examples of which are ( $C_{1-6}$  alkyl) amides such as dimethylformamide and dimethylacetamide, or a  $C_{1-6}$  alkyl benzoate, e.g. ethyl benzoate. The reaction time is not critical, and periods of from 15—25 hours are normally used in order to obtain maximum yields of epoxyphosphonate. Upon completion of the reaction, the desired product is recovered by known techniques from the solvent after separation of the insoluble catalyst.

Still another procedure for peroxidizing the olefinic *cis*-propenylphosphonate compound is by reacting it with an oxidizing metal salt such as chromium trioxide or an alkali metal permanganate in a basic solvent, examples of which are pyridine,  $\alpha$ -picoline, piperidine and dimethylformamide. The reaction time and

temperature are not unduly critical. It is preferred to peroxidize at about room temperature, although temperatures of from 0° C. to 100° C. may be used. The reaction, in which an excess of oxidizing agent is generally used, is allowed to proceed until the maximum amount of (±) (*cis* - 1,2 - epoxypropyl) - phosphonate is formed, which may then be recovered by known methods. Trialkylamine N-oxides and dimethyl sulfoxides may also be used as oxidizing agents.

An alkali metal hypohalite may also be used as the oxidant in the process of this invention, and for this purpose sodium or potassium hypochlorite or hypobromite are the most suitable. The epoxidation is conveniently brought about in an aqueous medium, or in an organic base such as pyridine or dimethylformamide, at temperatures of from 0° C. to 100° C. and at a pH above about 8.0. If desired, an epoxidizing agent capable of generating hypochlorite *in situ* may be used, an example of such a compound being 5,5-dimethyl 1,3-dichlorohydantoin. The desired product is then recovered by known techniques, one suitable method being removal of cations by adsorption on a cation exchange resin on the hydrogen cycle, and recovery of the (±) (*cis* - 1,2 - epoxypropyl) - phosphonate compound from the resin eluate. It is convenient to recover a salt by collecting the resin eluate in the presence of a base.

In addition, the epoxidation may be carried out by reacting a *cis*-propenylphosphonate of Formula V in a suitable inert solvent with ozone in the presence of either a donor olefin or a compound that form as 1:1 adduct with ozone that decomposes to release oxygen in a very active form. This process is conducted in the cold, i.e. at temperatures of from -30° C. to -50° C., suitable donor olefins being compounds such as stilbene and cyclohexene. The reaction solvent is, of course, one that is inert under the reaction conditions and liquid at the reaction temperatures, suitable solvents being methylene chloride, pentane or hexane. After the reactants are brought together in the cold, the mixture is allowed to warm slowly to ambient temperature in order to complete the reaction. The desired product is recovered by removal of the solvent and purification by known techniques. In this particular embodiment of the invention, best results are obtained where the particular salt or ester of the *cis*-propenylphosphonic acid compound is soluble in the reaction solvent. A dialkyl trioxide may also be the oxidant.

Still another method for preparing the (±) (*cis* - 1,2 - epoxypropyl) - phosphonate compounds of the invention is by epoxidation of the *cis*-propenylphosphonate with an alkyl perborate or alkyl perphosphate. The reaction is conveniently carried out at room temperature, although temperatures of up to

about 80° C. are satisfactory, using a slight excess of epoxidizing agent. A solvent is not necessary, although, if one is used, the *cis*-propenylphosphonate should be soluble in it. The alkyl perborate, such as cyclohexyl perborate, is conveniently prepared by known methods from an alkyl borate and hydrogen peroxide; the alkyl perphosphate reagent may be obtained by reaction of a dialkyl phosphorochloridate



with a C<sub>1-6</sub> alkyl hydroperoxide in the presence of an alkali metal hydroxide.

In accordance with an additional aspect of the invention, the (±) (*cis* - 1,2 - epoxypropyl)-phosphonates of Formula I above are prepared directly by reaction of *cis*-propenylphosphonous acid salts and esters with an oxidizing agent described above, and preferably with a peroxy oxidizing agent. Thus, the oxidation state of the phosphorus atom is changed from P<sup>III</sup> to P<sup>V</sup>, and the olefinic double bond epoxidized in the one reaction.

The (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid, and salts and biologically labile esters thereof obtained in accordance with the above-described process may be used directly as antibiotic agents since they possess substantial antibacterial activity. In addition, the racemic mixture obtained on oxidation of the *cis*-propenylphosphonate may be resolved by formation of a salt with an optically active amine, such as α-phenethylamine, separation of the two diastereomers by fractional crystallization, and recovery of the salt of (-) (*cis* - 1,2 - epoxypropyl) - phosphonic acid. This latter material and salts thereof possess a high degree of antibacterial activity.

The esters of (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid may be converted to the free acid or to mono or di-salts of (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid by a number of methods such as by hydrolysis, or reductive removal of the ester group. The hydrolysis may be with base or acid, by enzymatic, light-catalysed or via a trimethylsilyl derivative. The reduction removal of the ester group may be by hydrogenolysis or chemical, as with sodium-tertiary amine. The preferred method in any given instance depends upon the particular ester involved and representative examples appear in the experimental portion hereof. It should be noted that in some cases the reaction conditions employed to effect the epoxidation of this invention will also lead to at least partial hydrolysis of certain esters. This may occur when the pH during the epoxidation is above about pH 6 because certain of the epoxide diesters described herein are hydrolysed with base to monoesters at higher pH's. Similarly, as will

be appreciated by those skilled in this art, the conversion of esters of  $(\pm)$  (*cis* - 1,2 - epoxypropyl)phosphonic acid to the acid or salts may be brought about without recovering the ester from the epoxidation mixture. Thus, for instance, dibenzyl *cis*-propenylphosphonate may be epoxidized at about pH 4.5 with hydrogen peroxide and sodium pertungstate to dibenzyl  $(\pm)$  (*cis* - 1,2 - epoxypropyl) - phosphonate, and this latter product converted by hydrogenolysis without isolation to disodium  $(\pm)$  (*cis* - 1,2 - epoxypropyl) - phosphonate. The epoxidation process of this invention may also be applied to preparing  $(\pm)$  (*cis* - 1,2 - epoxypropyl) - phosphonic acid or a salt thereof directly from a *cis* - propenylphosphonic acid ester that is easily oxidized, such as the 3-crotonyl, *p*-benzoquinoyl and *p*-naphthoquinoyl esters. These are epoxidized as discussed above but employing a large excess of oxidizing agent. The reaction product thus obtained is the salt of  $(\pm)$  (*cis* - 1,2 - epoxypropyl) - phosphonic acid corresponding to the cation present in the reaction mixture.

The resolution of the racemic phosphonic acid compounds, and the conversion of the esters and derivatives of Formula I above to the parent phosphonic acid and salts thereof are not a part of the invention of this patent application but are inventions claimed in our co-pending applications Numbers 50638/68 and 23137/68 respectively, Serial No's 1239989 and 1236955).

#### EXAMPLE 1

*Cis*-propenylphosphonic acid (2.2 g., .018 mole) is dissolved in 10 ml. of water. The pH of the aqueous solution is adjusted to 5.5-6 by the addition of sodium bicarbonate (1.51 g., 0.017 mole) to produce sodium *cis*-propenylphosphonate. Sodium tungstate dihydrate (0.55 g., 0.0017 mole) is added, and the nearly neutral solution is placed in a water bath and heated to 55° C. The water bath is then removed, and 2 ml. of 30% by weight hydrogen peroxide are added to the reaction mixture during 10 minutes. The reaction is exothermic, and the temperature rises to 65° C. during addition of the peroxide. An additional 1.6 ml. of hydrogen peroxide is added. Oxygen evolves from the solution during the addition, and the temperature remains at 55-57° C. without external heating. After standing 20 minutes, the temperature falls to 53° C. The reaction mixture is then heated in a water bath at 55° C. for an additional 20 minutes, filtered and the solution is freeze-dried to yield the mono-sodium salt of  $(\pm)$  (*cis* - 1,2 - epoxypropyl) - phosphonic acid as a white powder, which is characterized by NMR spectra. This product as well as the other salts and the other compounds of this invention represented by Formulas I-IV above, may also be identified as *dl*(*cis*-1,2-epoxypropyl)-phosphonic acid compounds, but

the  $(\pm)$  nomenclature is used because it is preferred over the *dl* nomenclature by those expert in this field of chemistry. In this system of nomenclature, the  $(-)$  isomer is the same as the *l* isomer.

When the above reaction is carried out using 0.018 moles of dipotassium *cis*-propenylphosphonate, calcium *cis*-propenylphosphonate or magnesium *cis*-propenylphosphonate as starting material, there is obtained dipotassium  $(\pm)$  (*cis* - 1,2 - epoxypropyl) - phosphonate, calcium  $(\pm)$  (*cis* - 1,2 - epoxypropyl)-phosphonate, and magnesium  $(\pm)$  (*cis* - 1,2 - epoxypropyl) ° phosphonate, respectively.

#### EXAMPLE 2

*Cis*-propenylphosphonic acid (.50 g., .041 mole) is dissolved in 0.5 ml. of water, and the solution neutralized to pH 5.5 by careful addition of ammonium hydroxide. Sodium tungstate (10 mg., .00034 mole) is added, and the mixture is heated to 55° C. on a water bath. Hydrogen peroxide (0.5 cc.) is added, and the heating continued for 1½ hours. The reaction mixture is then cooled to room temperature, and the solvent removed by freeze-drying. The residue is dissolved in 50 ml. of methanol, and the insoluble inorganic material filtered off. Upon concentration of the solution, crystalline ammonium salt of  $(\pm)$  (*cis* - 1,2 - epoxypropyl) - phosphonic acid is obtained. The product is characterized by its infrared and NMR spectra.

When this procedure is repeated, and the aqueous solution neutralized with dimethylamine, triethylamine or pyridine, there is obtained dimethylammonium, triethylammonium and pyridinium  $(\pm)$  (*cis* - 1,2 - epoxypropyl) - phosphonate, respectively.

The same result is obtained when the foregoing procedure is repeated using an equimolar amount of potassium vanadate or of aluminium molybdate as catalyst instead of sodium tungstate.

#### EXAMPLE 3

In a two liter, 3-necked flask equipped with a stirrer, thermometer, pH electrode and addition funnel is placed 150 g. (0.655 mole) of monobenzylammonium *cis* - propenylphosphonate and 1.12 liters of water. Sodium tungstate dihydrate (6.0 g., 0.018 mole) is slowly added. After 10 minutes at 50° C., the pH is adjusted to 5.0-5.5 with 2.5 N sodium hydroxide. 150 ml. of 30% by weight hydrogen peroxide is added over 15 minutes at 55-60° C. maintaining a pH of 4.8 to 5.2 by addition of sodium hydroxide as required. After stirring for 1 hour at 55° C., the mixture is cooled to room temperature while 10% by weight aqueous sodium bisulfite is added to obtain a negative starch iodide test. The solids are removed by filtration, and the filtrate is concentrated to dryness *in vacuo* and further dried by washing with 3 × 10 ml.

of benzene. Methanol (630 ml.) and acetone (1250 ml.) are added. After stirring at reflux for 5 minutes, the insolubles are removed by filtration and washed with hot acetone-methanol. The filtrate is concentrated to dryness *in vacuo* and the solids slurried with 625 ml. of acetonitrile at reflux for 20 minutes, and the slurry cooled to 25° C. The yellow product is collected by filtration and washed with acetonitrile at 25° C. The product is dried *in vacuo* at 60° C. to afford (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid as the monobenzylammonium salt. It is purified by recrystallization from 10 volumes of ethanol, m.p. 155—157° C.

Repeating this procedure with 0.655 moles of α-picolinium *cis*-propenylphosphonate and aluminium *cis*-propenylphosphonate yields the α-picoline and aluminium salts of (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid.

#### EXAMPLE 4

In a 250 ml. round-bottom flask equipped with a stirrer and an addition funnel is placed 13.4 g. (0.11 mole) of *cis*-propenylphosphonic acid. 125 ml. of *n*-propanol is added with stirring. The resulting solution is treated dropwise with 12.0 ml. (11.89 g., 0.11 mole) of benzylamine and heated to reflux. After refluxing for 10 minutes the hot solution is filtered to clarify it. The filtrate containing benzylammonium *cis*-propenylphosphonate is charged to a 500 ml. round bottom flask equipped with a stirrer, thermometer and an addition funnel. The solution is heated to 55° C. in an oil bath, and 0.50 g of sodium tungstate dihydrate added. The pH of this mixture is 5.3 (0.1 ml. of solution in 1.9 ml. of water). 35 ml. of hydrogen peroxide (30% by weight) is added dropwise over a 15-minute period while maintaining the temperature between 55—60° C. The reaction is kept at 55—60° C. for an additional hour during which the pH of the solution is maintained at 4.6—5.2 with aqueous sodium hydroxide as necessary.

The heat source is then removed and a 20% aqueous sodium sulfite solution is added dropwise to decompose excess hydrogen peroxide, maintaining the temperature below 55° C. The mixture is then concentrated *in vacuo* to a volume of 62 ml. 62 ml. of *n*-propanol is added and the mixture again concentrated *in vacuo* to a volume of 62 ml. Addition of *n*-propanol (62 ml.) and concentration to 62 ml. is repeated once more. The mixture thus obtained is diluted with 150 ml. of absolute methanol and stirred at room temperature for 1 hour. At the end of this period, the insoluble solids are removed by filtration. The filtered solids are washed with 50 ml. of methanol and the combined filtrates concentrated under vacuum to a volume of 62 ml. 62 ml. of *n*-propanol is added and the resulting solution concentrated again to a volume of 62 ml.

The solution obtained is stirred and cooled in an ice-bath. After cooling for 1 hour the stirring is stopped and the flask kept at 0° C. for an additional 16 hours. The crystalline product is then removed by filtration, washed with two 100 ml. portions of cold *n*-propanol and dried *in vacuo* at 60° C. to afford substantially pure benzylammonium (±) (*cis*-1,2 - epoxypropyl) - phosphonate, m.p. 148—150° C. Recrystallization from *n*-propanol raises the melting point to 155—157° C.

When the above procedure is repeated using 0.11 mole of ethylenediammonium and piperazinium *cis*-propenylphosphonate, there are obtained the ethylenediammonium and piperazinium (*cis* - 1,2 - epoxypropyl) - phosphonates. The salt containing 1 molecule of ethylenediamine melts at 120—130° C. (monohydrate) after recrystallization from 70% (by volume) ethanol; the anhydrous salt melts at 169—171° C. after precipitation from methanol by addition of ethanol. The salt containing 1 molecule of piperazine melts at 195° C. on recrystallization from 85% (by volume) isopropanol.

#### EXAMPLE 5

In a 250 ml. flask equipped with stirrer and addition funnel there is placed 13.4 g. of *cis*-propenylphosphonic acid and 125 ml. of *n*-propanol. (+) α - phenylethylamine is added to the propanol solution dropwise to a pH of 5.7—5.8 (about 14 g. is required). The resulting solution is warmed to 55° C. and to it there is added a solution of 0.5 g. of sodium tungstate and 0.1 g. of disodium ethylenediaminetetraacetic acid in 6 ml. of water. 17.5 ml. of 30% by weight hydrogen peroxide is then added slowly over a 15-minute period at a rate to maintain the temperature between 55 and 60° C. When the hydrogen peroxide addition is complete, the solution is stirred at 55—60° C. for one hour. It is then cooled to -5° C. and stirred at this temperature for 2 hours. The resulting solid is recovered by filtration and washed with 60 ml. of cold *n*-propanol. This product is predominantly (+) α-phenethylammonium (-) (*cis* - 1,2 - epoxypropyl) - phosphonate, m.p. 133—135° C. It is further purified by heating in a mixture of 40 ml. of isopropanol and 10 ml. of water at 75° C. and then cooling the solution slowly to about 0° C. The solid product is recovered by filtration, washed with cold isopropanol to afford substantially pure (+) α-phenethylammonium (-) (*cis*-1,2 - epoxypropyl) - phosphonate, m.p. 135—136° C.

#### EXAMPLE 6

In a 100 ml. round-bottom 3-necked flask fitted with a stirrer, thermometer and addition funnel is placed 3.2 g. (0.01 mole) dibenzyl *cis*-propenylphosphonate in 50 ml. of *n*-propanol. Sodium tungstate dihydrate (0.06 g.)

is added and the mixture is heated to 55° C. Hydrogen peroxide 30% by weight (3 ml.) (0.03 moles) is added dropwise over 15 minutes while the temperature is maintained at 55—60° C. The mixture is aged at 55—60° for 1 hour. Additional hydrogen peroxide is added as needed to give positive reaction with starch iodide test paper. The reaction is then quenched by the addition of a saturated solution of sodium sulfite to destroy excess hydrogen peroxide. The mixture is concentrated to 1/2 volume, more propanol added and the operation repeated. Methanol (50 ml.) is added and the inorganic salt removed by filtration. The solvent is removed *in vacuo* and the dibenzyl ester of (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid isolated as an oil.

When the above process is repeated using 4.32 g. of di (*l*) menthyl *cis*-propenylphosphonate as starting material, there is obtained predominantly di (*l*) menthyl (—) (*cis* - 1,2 - epoxypropyl) - phosphonate together with a lesser amount of di (*l*) menthyl (+) (*cis* - 1,2 - epoxypropyl) - phosphonate.

When 0.01 mole of di - (*p* - chlorobenzyl) or di - (*p* - nitrobenzyl) *cis* - propenylphosphonate is used as starting material, there are obtained the di - (*p* - chlorobenzyl) and di-(*p*-nitrobenzyl) esters of (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid. The cyclic esters of (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid with catechol and with propylene glycol are obtained when the above procedure is used with 0.01 mole of the cyclic esters of *cis*-propenylphosphonic acid with catechol and propylene glycol.

#### EXAMPLE 7

In a 50 ml. round-bottom 3-necked flask fitted with a stirrer, thermometer and addition funnel is placed 1.5 g. (0.01 mole) of monomethyl *cis* - propenylphosphonate in 30 ml. of methanol. The pH is adjusted to 4.5 with 2.5 N sodium hydroxide. Sodium tungstate dihydrate (0.06 g.) is added and the mixture heated to 55° C. Hydrogen peroxide 30% by weight (3 ml.) is added dropwise over 15 minutes at 55—60° C. The mixture is aged for one hour at 55—60° C. Hydrogen peroxide is added as needed to maintain a positive starch-iodide test. The mixture is quenched by adding saturated sodium sulfite solution to a negative starch iodide test. The inorganic solids are removed by filtration, the solution evaporated to one-half volume and chilled. The solid sodium methyl (±) (*cis* - 1,2 - epoxypropyl) - phosphonate thus obtained is separated by filtration, washed with ethanol and dried. The same result is obtained when zinc vanadate or sodium selenomolybdate is used as catalyst in place of sodium tungstate.

When an equimolar amount of *n*-butyl *cis*-propenylphosphonate, ethyl *cis*-propenylphosphonate or phenyl *cis*-propenylphosphonate is

treated with hydrogen peroxide as described above, there is obtained the sodium salt of *n*-butyl (±) (*cis* - 1,2 - epoxypropyl) - phosphonate, ethyl (±) (*cis* - 1,2 - epoxypropyl) - phosphonate and phenyl (±) (*cis* - 1,2 - epoxypropyl) - phosphonate, respectively.

#### EXAMPLE 8

1.53 mole of di-allyl *cis*-propenylphosphonate is added to 1000 ml. of *n*-propanol in a reaction flask, and 0.018 mole of ammonium vanadate added slowly. The mixture is heated to 50° C. and the pH adjusted to 5.3 with ammonium hydroxide. 200 ml. of 30% hydrogen peroxide is then added over a 30 minute period, holding the temperature at 50—60° C. and the pH at 5.0—5.3 by addition of base as necessary. The mixture is stirred for an additional 45 minutes at 60° C., then cooled to room temperature and sodium sulfite added to a negative starch iodide test. The mixture is filtered, and the filtrate concentrated to dryness. The residue is extracted with 1800 ml. of 2:1 acetone-methanol. The extract is then concentrated to dryness *in vacuo* to afford an oil of diallyl (±) (*cis* - 1,2 - epoxypropyl) - phosphonate.

The di-methallyl, diphenyl and ditolyl esters of (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid are prepared in the same manner from the corresponding esters of *cis*-propenylphosphonic acid.

#### EXAMPLE 9

2.2 g. (0.018 mole) of *cis*-propenylphosphonic acid is dissolved in 10 ml. of water. 0.15 g. of sodium tungstate dihydrate is added and the mixture chilled to 5—10° C. 3 ml. of 30% hydrogen peroxide are added over a 15-minute period, maintaining the temperature below 10° C. by external cooling. The mixture is then allowed to stand at 10° C. for 120 minutes. Excess of hydrogen peroxide is decomposed by the addition of a dilute aqueous solution of sodium bisulfite (to a negative starch-iodide test). The reaction mixture is concentrated to a volume of about 3 ml., filtered to remove insoluble material and then freeze-dried to afford a residue of (±) (*cis* - 1,2 - epoxypropyl) - phosphonic acid. This latter product may be converted to the mono-sodium salt by dissolving in a minimum quantity of water and adding sodium bicarbonate to a pH of 5.5. The solution is then freeze-dried to afford the mono-sodium salt.

#### EXAMPLE 10

When the procedure of Example 6 is repeated using 0.01 moles of di-hexyl *cis*-propenylphosphonate, di(*p*-carbethoxyphenyl) *cis*-propenylphosphonate, pivaloxymethyl *cis*-propenylphosphonate or bis-acetoxymethyl *cis*-propenylphosphonate instead of the starting material of Example 6, and 0.8 g. of aluminium tungstate as catalyst, there is obtained

the di-hexyl, di(*p*-carbethoxyphenyl), pivaloxymethyl or bis-acetoxymethyl ester of ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonic acid.

#### EXAMPLE 11

5 In a 50 ml. round-bottom flask fitted with a stirrer and addition funnel is placed 1.22 g. (0.01 mole) of *cis*-propenylphosphonic acid and 20 ml. of water. 2 ml. (0.01 mole) sodium hydroxide solution (20% by weight) is added to form the mono-sodium salt of *cis*-propenylphosphonic acid. The mixture is treated with 3 ml. of 30% by weight hydrogen peroxide. The mixture is stirred at room temperature for 3 weeks. The excess of hydrogen peroxide is quenched with sodium sulfite and the solution is concentrated to a small volume. The solution is then passed over the ion-exchange resin Dowex 50 on the hydrogen cycle at 0° C. and the eluate collected in the presence of 0.01 mole of benzylamine. (Dowex 50 is a polysulfonated polystyrene ion exchange resin; "Dowex" is a registered Trade Mark). The eluate is concentrated to dryness *in vacuo* and the solid recrystallized three times from *n*-propanol to give the benzylamine salt of ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonic acid. The disodium salt of *cis*-propenylphosphonic acid is epoxidized in similar fashion using 0.02 moles of sodium hydroxide; the epoxidized product is separated from the remaining olefin salt by repeated recrystallizations from ethanol or *n*-propanol.

Disodium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate is likewise obtained when 1.6 g. of sodium peroxide and 0.01 of sodium tungstate are used in the above experiment in place of the hydrogen peroxide, and the mixture filtered to remove solids prior to the ion-exchange resin treatment.

#### EXAMPLE 12

40 In a 100 ml. round-bottom flask is placed 5 g. (0.022 mole) of benzylammonium *cis* - 1 - propenylphosphonate and 30 ml. of chloroform. To this is added 3.04 g. (0.022 mole) of perbenzoic acid in 20 ml. of chloroform. The solution is heated at 60° C. for 12 hours. The mixture is then cooled and filtered. The solid product, monobenzylammonium ( $\pm$ ) (*cis*-1,2-epoxypropyl)-phosphonate is purified by recrystallization from 10 parts of 95% by volume ethanol. The pure material melts at 155—157° C.

A similar result is obtained when 0.022 mole of peracetic acid or performic acid is used in place of perbenzoic acid.

When 0.022 mole of the procaine or the diethanolamine salt of *cis*-propenylphosphonic acid is used in the above experiment, there is produced the procaine or diethanolamine salt of ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonic acid. The salt containing 1 molecule of procaine melts at 127—130° C. on re-

crystallization from 80% by volume isopropanol.

#### EXAMPLE 13

Peroxytrifluoroacetic acid is prepared by the method of Emmons (J. Am. Chem. Soc. 75 4623 (1953)). A solution of 2.8 g. of peroxytrifluoroacetic acid in 20 ml. of chloroform is then added to 5 g. (0.022 mole) of benzylammonium *cis*-propenylphosphonate and 7 g. of solid disodium hydrogen phosphate in 30 ml. of chloroform. The mixture is allowed to stand for 16 hours at 0° C. The solids are then separated by filtration. The solids are slurried in about 10 ml. of methanol; the slurry is filtered and the methanol filtrate evaporated to dryness *in vacuo* to give a solid residue of benzylammonium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate. The product is purified by recrystallization from 10 parts of 95% by volume ethanol.

With 0.22 mole of disodium *cis*-propenylphosphonate or diethylammonium *cis* - propenylphosphonate as starting material, the corresponding salts of ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate are produced.

#### EXAMPLE 14

In a 100 ml. round-bottom 3-necked flask equipped with a stirrer, thermometer and an addition funnel is placed 6.4 g. (0.02 mole) dibenzyl *cis*-propenylphosphonate and 30 ml. of methylene dichloride. A solution of monoperphthalic acid (3.6 g., 0.02 mole) in 20 ml. of ethyl acetate is added slowly and the mixture heated to 40° C. The course of the reaction is followed by gas liquid chromatography of the dibenzyl ester or by titration of the peracid. The reaction is essentially complete in 24 hours. At the end of this time, the mixture is cooled to room temperature, the phthalic acid removed by filtration and the dibenzyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate recovered by removing the solvent *in vacuo*. It is purified by recrystallization from 95% by volume ethanol.

When this experiment is carried out using 0.02 mole of di-pyridylmethyl *cis*-propenylphosphonate as starting material, and 4.6 g. (0.02 mole) of permethoxyacetic acid as epoxidizing agent, there is obtained predominantly di-pyridylmethyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate.

#### EXAMPLE 15

When the procedure of Example 13 is repeated using 0.02 mole of dimethyl *cis*-propenylphosphonate, diphenyl *cis*-propenylphosphonate or  $\beta$ -cyanoethyl *cis*-propenylphosphonate, there is obtained dimethyl ( $\pm$ ) (*cis*-1,2 - epoxypropyl) - phosphonate, diphenyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate and  $\beta$ -cyanoethyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate, respectively.

## EXAMPLE 16

4.3 g. (0.02 mole) or (+) percamphoric acid in 20 ml. of ethyl acetate is added slowly to 6.4 g. (0.02 mole) of dibenzyl *cis*-propenylphosphonate in 30 ml. of chloroform. The mixture is heated for 22 hours at 60° C. and then cooled to room temperature and filtered to separate any solid materials. The filtrate is extracted with 3×40 ml. of 2.5 N sodium hydroxide, the organic layer washed with water, dried over sodium sulfate and concentrated to dryness *in vacuo* to afford a residue consisting predominantly of dibenzyl (-) (*cis*-1,2-epoxypropyl)phosphonate.

The di-*n*-propyl and di-decyl esters of (-) (*cis*-1,2-epoxypropyl)-phosphonic acid are prepared according to the above procedure from 0.02 mole of the corresponding esters of *cis*-propenylphosphonic acid.

## EXAMPLE 17

To 0.022 mole of di-*n*-butyl *cis*-propenylphosphonate in 40 ml of benzene in a suitable reaction flask is added 0.04 mole of performic acid solution. The mixture is allowed to stand at room temperature for 16 hours. It is then cooled to 10° C. and any excess per acid decomposed with sodium bisulfite. Any insoluble materials are separated by filtration, and the filtrate concentrated to dryness *in vacuo* at about 35° C. to afford a residue of di-*n*-butyl (±) (*cis*-1,2-epoxypropyl)-phosphonate. The bis-(β-hydroxyethyl) ester of (±) (*cis*-1,2-epoxypropyl)-phosphonic acid is prepared by this procedure from bis-(β-hydroxyethyl) *cis*-propenylphosphonate.

## EXAMPLE 18

In a 100 ml. round-bottom 3-necked flask fitted with a pH electrode, stirrer and addition funnel is placed 11.4 g. (0.05 mole) benzylammonium *cis*-propenylphosphonate and 4.5 g. (0.05 mole) of *t*-butylhydroperoxide in 50 ml. methanol. The mixture is adjusted to pH 8.0 with concentrated sodium hydroxide and stirred at 35–40° C. for 5½ hours, adding sodium hydroxide as necessary to maintain pH 8.0. At the end of this time, the mixture is concentrated *in vacuo* to a small volume, the pH adjusted to 4.6 with sulfuric acid and *n*-propanol added. The solids are removed by filtration, the remaining methanol removed by concentration *in vacuo* and the volume of the propanol mixture adjusted to 25 ml. The mixture is aged at 0° C. for 16 hours. The solid benzylammonium (±) (*cis*-1,2-epoxypropyl)-phosphonate is collected by filtration and dried *in vacuo*.

Similar results are obtained using the diethylene triamine, calcium, magnesium, 1,6-hexamethylenediamine or ethylamine salts in place of the benzylammonium *cis*-propenylphosphonate. The corresponding salt of (±) (*cis*-1,2-epoxypropyl)-phosphonic acid is obtained. The salt containing 1 molecule

of diethylenetriamine melts at 182–183° C. on recrystallization from isopropanol; the salt containing 1 molecule of 1,6-hexamethylenediamine melts at 194° C. on recrystallisation from 1:3:3 by volume water:methanol:isopropanol.

## EXAMPLE 19

A solution of 0.01 g. of molybdenum hexacarbonyl, 4.8 g. (0.05 mole) of *t*-butyl hydroperoxide and 13.0 g. (0.05 mole) of bis(β-ethoxyethyl) *cis*-propenylphosphonate in 100 ml. of benzene is placed in a 200-ml. round-bottom flask fitted with a thermometer, a reflux condenser and a stirrer. The temperature is raised gradually to 80° C. and held at 80° C. for one hour. The reaction mixture is then cooled to room temperature, filtered, and the *t*-butanol and benzene removed by concentration *in vacuo*. The residual product thus obtained is bis(β-ethoxyethyl) (±) (*cis*-1,2-epoxypropyl)-phosphonate.

When 0.5 mole of bis(methylsulfonylphenyl) *cis*-propenylphosphonate or di-(*p*-nitrophenyl) *cis*-propenylphosphonate is employed in the above experiment, the bis(methylsulfonylphenyl) or di-(*p*-nitrophenyl) ester, respectively, of (±) (*cis*-1,2-epoxypropyl)-phosphonate is obtained.

## EXAMPLE 20

In a 200 ml. round-bottom 3-necked flask fitted with a stirrer, reflux condenser and addition funnel is placed 0.01 g. molybdenum hexacarbonyl, 7.5 g. (0.05 mole) of cumene hydroperoxide, 5.0 g. (0.05 moles) of triethylamine, 6.8 g. (0.05 mole) of monomethyl *cis*-propenylphosphonate and 100 ml. of benzene. The reaction mixture is heated slowly to 80° C. and held at 75–80° C. with stirring for 1½ hours. At the end of this time, it is cooled to 20° C., filtered, and the filtrate concentrated to dryness under reduced pressure. The remaining solid is triethylammonium methyl (±) (*cis*-1,2-epoxypropyl)-phosphonate.

## EXAMPLE 21

In a 500-ml. round-bottom 3-necked flask fitted with a stirrer and addition funnel is placed 300 ml. of methanol, 61 g. (0.5 moles) of *cis*-propenylphosphonic acid and 40 grams of sodium hydroxide. Benzonitrile 52 grams (0.5 moles) is added and the mixture cooled to room temperature. 34 g. of hydrogen peroxide (50% by weight) is added slowly from the addition funnel. When the addition is complete, the mixture is stirred at room temperature for 40 hours. The excess peroxide is then decomposed with a saturated solution of sodium sulfite (to a negative starch iodide test). The solution is evaporated to dryness and the residue extracted with 10 volumes of methanol. The methanol solution is filtered and evaporated to dryness. The residue is extracted with 2×20 ml. of water

to extract the disodium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate from benzamide. The aqueous extracts are combined and passed over a column of Dowex 50 resin on the acid cycle at 0 °C. The eluate containing the free phosphoric acid is collected in the presence of 0.5 mole of benzylamine. The monobenylammonium salt of ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonic acid is recovered by evaporating the eluate to dryness *in vacuo*. It is purified by recrystallization from 10 volumes of 95% by volume ethanol.

#### EXAMPLE 22

A solution of 100 ml. of methanol, 15.6 g. (0.05 mole) of dibenzyl *cis*-propenylphosphonate, 1.0 g. of potassium bicarbonate and 2.05 g. of acetonitrile are stirred at room temperature 3.4 g. (0.05 mole) of 50% by weight hydrogen peroxide is added slowly and the mixture is stirred until a negative starch iodide test is obtained. The methanol is then removed by concentration *in vacuo*, the solids dissolved in water and extracted with chloroform. The chloroform extracts are washed well with water to remove the acetamide, dried with magnesium sulfate, and concentrated to an oil *in vacuo* to afford dibenzyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)-phosphonate.

When the above procedure is repeated using 0.05 mole of di-phenethyl *cis*-propenylphosphonate as starting material, there is obtained di-phenethyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate.

#### EXAMPLE 23

In a 200 ml. flask fitted with stirrer is placed 8.3 g. (0.05 mole) of disodium *cis*-propenylphosphonate and 100 ml. of water. 75 ml. of aqueous sodium hypochlorite solution (5% by weight) (0.05 mole) is added slowly and the mixture stirred at room temperature overnight. The aqueous solution is concentrated *in vacuo* to one-half its volume and then freeze-dried to afford disodium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate.

#### EXAMPLE 24

A solution of 2 millimoles of cyclohexene in 5 ml. of methylene chloride is cooled to -40° C. and treated with ozone until saturated. A previously cooled solution of 3.1 g. (10 millimoles) of dibenzyl *cis*-propenylphosphonate in 10 ml. of methylene chloride is added and the mixture allowed to warm slowly to room temperature. The solvent is then removed by evaporation *in vacuo* to afford dibenzyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate.

The above reaction is repeated using equivalent molar amounts of stilbene in place of cyclohexene, and monomethyl *cis*-propenylphosphonate in place of the dibenzyl ester. On completion of the reaction, the solution is extracted with aqueous sodium hydroxide. The sodium salt of methyl ( $\pm$ ) (*cis* - 1,2 -

epoxypropyl) - phosphonate is recovered from the aqueous extract.

#### EXAMPLE 25

In a round-bottom 3-necked flask fitted with a stirrer, thermometer and gas inlet tube and vent is placed 12.2 g. (0.1 mole) of *cis*-propenylphosphonic acid, 100 ml. of dimethylformamide and 8 g. of sodium hydroxide pellets. 0.1 g. of cobalt naphthenate and 0.1 g. of *t*-butyl hydroperoxide are added and the mixture heated to 100° C. Air is bubbled through the mixture at 100° for 21 hours. The mixture is then concentrated to half its volume and diluted with an equal volume of water. The mixture is repeatedly extracted with chloroform to remove dimethylformamide and the aqueous solution of disodium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate is then passed over a column of Dowex 50 on the hydrogen cycle at 0° C. into an aqueous solution of benzylamine (0.1 moles of benzylamine). The resulting benzylammonium salt of ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonic acid is purified by recrystallization from 10 volumes of 95% by volume ethanol.

#### EXAMPLE 26

A mixture of 14.9 g. (0.1 mole) of dimethyl *cis*-propenylphosphonate and 31.8 (0.1 mole) of cyclohexylperborate are stirred at room temperature under a nitrogen atmosphere for 30 minutes. The temperature is then raised to 80° C. for 1 hour. The mixture is cooled to room temperature and quenched by the addition of 30 ml. of water. The organic phase is separated and the water layer extracted with 3×10 ml. of chloroform. The chloroform extracts are combined with the organic phase and the whole is evaporated to dryness *in vacuo* to afford a residue of dimethyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate. The product is purified by distillation, b.p. 70—72° C./0.5 mm mercury.

#### EXAMPLE 27

In a round-bottom flask there is placed 30.0 g. of diphenyl *cis*-propenylphosphonate in 300 ml of chloroform. Dibutyl mono-*t*-butyl perphosphate (28.2 g., 0.1 mole) (made from dibutyl phosphonochloridate and 1 mole of sodium *t*-butyl hydroperoxide) in 150 ml. of chloroform is added at room temperature. The mixture is heated at the reflux temperature for 15 hours. The solvent is then removed by concentration *in vacuo*. The product, diphenyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate is obtained as an oil.

#### EXAMPLE 28

A. Methyl acetylene is passed into a refluxing ethereal solution of ethyl magnesium bromide (from 109 g. of ethyl bromide and 24 g. magnesium) until two layers are formed. The ether is then evaporated by heating in a

stream of nitrogen until only the lower thick solution remains. This is then dissolved in 500 ml. of tetrahydrofuran and 200 ml. of benzene, and cooled with stirring in a dry ice-acetone bath. To this slurry of 1-propynyl magnesium bromide is added a solution of 217 g. of dibutylchlorophosphite in 200 ml. of ether over a period of one hour while maintaining the temperature below  $-40^{\circ}\text{C}$ . The mixture is then allowed to come to room temperature and stirred for 4 hours. 180 ml. of pyridine is added dropwise with stirring and the precipitated pyridine-magnesium bromide complex removed by filtration. The filtrate is concentrated to a thick solution and 600 ml. of petroleum ether added. The petroleum ether extract is decanted from a thick gum and evaporated to a syrup which is distilled under reduced pressure. After a small forerun there is obtained dibutyl 1-propynylphosphonite, b.p.  $80-84^{\circ}\text{C}/0.4\text{ mm}$ .

B. 96 g. of dibutyl - 1 - propynylphosphonite is heated under reflux with 100 ml. of water and 50 ml. of Dowex 50 resin ( $\text{H}^{+}$  cycle) for two hours. The mixture is then evaporated *in vacuo* to remove butanol and the slurry diluted with water and filtered. The resin is washed with 200 ml. of water which is added to the filtrate. The combined aqueous solutions are then evaporated to a thick oil which is allowed to stand at  $0^{\circ}\text{C}$ . for eighteen hours. The resulting oily crystalline mass is broken up by the addition of 20 ml. of ethyl acetate and filtered. The resulting crystals are washed with ether containing a little ethyl acetate to afford 1-propynylphosphonous acid, m.p.  $64-66^{\circ}\text{C}$ .

C. A solution of 4 g. of 1-propynylphosphonous acid in 50 ml. of water is neutralized to pH 7 with sodium bicarbonate and hydrogenated at an initial pressure of 40 p.s.i. in the presence of 1 g. of Raney nickel catalyst. The hydrogenation is stopped when one equivalent of hydrogen is taken up. The solution is filtered from catalyst and evaporated to give the sodium salt of *cis*-1-propenylphosphonous acid.

D. 0.5 g. of the end product of Part C is dissolved in 8 ml. of water. Sodium tungstate (0.13 g.) is added and the pH brought to 6.5 with sulfuric acid. 30% by weight Hydrogen peroxide (0.8 cc.) is added and the mixture heated at  $55^{\circ}\text{C}$ . for four hours, while maintaining the pH at 5.5-5.6 by the addition of 0.1 *N* sodium hydroxide solution. The solution is then evaporated and the residual solid extracted with 50 ml. of methanol and filtered from inorganic salts. The methanolic solution is evaporated to dryness leaving a residue of sodium ( $\pm$ ) (*cis*-1,2-epoxypropyl) - phosphonate.

#### EXAMPLE 29

A. Di - 2' - (methyl - 2' - butenoate) - *cis* - propenylphosphonate is prepared by reacting

together equimolar amounts of methyl - 3 - keto - butenoate, sodium hydride and diethyl ether, and treating the resulting product with *cis*-propenylphosphonic dichloride.

To a solution of 31.8 g. (0.1 m) of di - 2' - (methyl - 2' - butenoate) - *cis* - propenylphosphonate in 300 ml. of *n*-propanol is added 0.6 g. of sodium tungstate dihydrate and the mixture heated to  $55^{\circ}\text{C}$ . 90 ml. of 30% by weight hydrogen peroxide (0.9 m.) is then added over a 45-minute period, maintaining the temperature at  $55-60^{\circ}\text{C}$ . The mixture is stirred at this temperature for 3 hours with hydrogen peroxide being added as needed to maintain a positive starch-iodide test, and sodium hydroxide added as needed to maintain a pH of 4.5-5.5. As the end of this time excess peroxide is destroyed with saturated aqueous sodium sulfite and the reaction mixture concentrated *in vacuo* to 1/2 its volume. It is then diluted to its original volume with water to afford a solution containing sodium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate. The product is purified by passing the aqueous solution over Dowex 50 resin on the hydrogen cycle and collecting the eluate in the presence of one molar equivalent of benzylamine. The resulting benzylammonium phosphonate salt is recrystallized from 95% by volume ethanol to give substantially pure material, m.p.  $155-157^{\circ}\text{C}$ .

B. The bis - *p* - benzoquinone ester of *cis*-propenylphosphonic acid is prepared by reacting together 0.1 m. of *cis*-propenylphosphonic dichloride and 0.2 m. of monocarbobenzoxy hydroquinone in the presence of triethylamine and subsequent removal of the carbobenzoxy group by hydrogenation.

When the procedure of Example 13 is repeated using 3 g. of di - (*p* - benzoquinonyl - *cis* - propenylphosphonate and 3.8 g. of peroxytrifluoroacetic acid, there is obtained sodium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate.

#### EXAMPLE 30

To a stirred suspension of 0.35 ml. (0.0125 mole) of 90% by weight hydrogen peroxide in 2.5 ml. of methylene chloride cooled in an ice-bath there is added dropwise over a ten-minute period of 2.1 ml. (0.015 mole) of trifluoroacetic anhydride. The solution of peroxytrifluoroacetic acid so obtained is stirred in the cold for an additional 15 minutes, and then is added over a period of 15-20 minutes, with vigorous stirring, to a mixture of 0.0005 mole of dibenzyl *cis*-propenylphosphonate, 10 ml. of methylene chloride, 3.8 g. (0.045 mole) of dry sodium bicarbonate, and 5 g. of anhydrous magnesium sulfate. After the addition is complete, the mixture is heated under reflux with continued stirring for 30 minutes. The reaction mixture is then stirred with 25 ml. of water until the inorganic salts are dissolved. The aqueous phase is separated and

extracted once with 5 ml. of methylene chloride. The organic layers are combined, dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give dibenzyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonate.

#### EXAMPLE 31

When the procedure of Example 13 is repeated using as starting material 0.022 mole of dibenzylammonium or diethylenediammonium *cis* - propenylpyrophosphonate, there is obtained dibenzylammonium or diethylenediammonium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)pyrophosphonate, respectively.

The disodium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)pyrophosphonate is obtained from disodium *cis*-propenylpyrophosphate using the procedure of Example 1.

#### EXAMPLE 32

When 0.02 mole of *cis*-propenylphosphonic acid cyclic di-anhydride is reacted with perphthalic acid by the procedure described in Example 14, there is obtained ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonic acid cyclic dianhydride. The product is purified by crystallization from anhydrous ethanol.

#### EXAMPLE 33

The disodium and diammonium salts of sodium and ammonium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)isohypophosphoric acid are produced from the corresponding salts of *cis*-propenyl isohypophosphoric acid by treating the olefin compounds with hydrogen peroxide and sodium tungstate by the procedure of Example 1 (for the sodium salt) and Example 2 (for the ammonium salt).

The *cis*-propenylphosphonic acid compounds employed as starting materials for the present invention are prepared as follows. *Cis*-propenylphosphonic acid itself is made from di-*t*-butyl phosphorochloridite by the procedure:

Phosphorus trichloride (68.7 grams, 0.5 mole) and 750 ml. of anhydrous benzene are placed in a 2-liter, 3-necked flask equipped with mechanical stirrer, thermometer, dropping funnel and a drying tube. The solution is cooled to 5° C. and triethylamine (50.6 grams, 0.5 mole) is added at 5°—10° C. during 20 minutes. The benzene solution is then stirred for 20 minutes. A solution of triethylamine (50.6 grams, 0.5 mole) and *t*-butanol (37.06 grams, 0.5 mole) is added with stirring during 20 minutes at 5°—10° C., and the mixture is stirred for 20 minutes. A second portion of *t*-butanol (37.06 grams, 0.5 mole) is then added at 5°—10° C. over a 20 minute period, and the reaction mixture containing di-*t*-butyl phosphorochloridite is stirred for 90 minutes at 5°—10° C.

Triethylamine, (50.6 grams, 0.5 mole) and propargyl alcohol (28.03 grams, 0.5 mole) are dissolved in 40 ml. of anhydrous benzene, and

the solution is added to the reaction mixture containing di-*t*-butylphosphorochloridite with stirring during 25 minutes, maintaining the reaction temperature between 5°—10° C. by external cooling. The resulting mixture containing di - *t* - butyl - 2 - propynylphosphite is stirred at 5°—10° C for one hour.

The reaction mixture containing di-*t*-butyl-2-propynylphosphite is then heated to reflux, and the refluxing is continued for one hour. The solution is then cooled to room temperature with a water bath, and 185 ml. of water is added in portions. The triethylamine hydrochloride dissolves in the aqueous layer, and the organic layer is separated from the aqueous layer. The benzene solution is heated at atmospheric pressure, and the water is removed by azeotropic distillation. The residual benzene solution contains di-*t*-butylpropadienylphosphonate.

Where desired, the crude ester can be obtained by removing the solvent and distilling the ester under high vacuum; the pure ester is characterized by IR and NMR spectra.

The dried benzene solution of di-*t*-butylpropadienylphosphonate is hydrogenated at 20°—25° C. with 5% by weight palladium-on-carbon catalyst (5.0 grams) until hydrogen absorption ceases. The catalyst is removed by filtration and is washed with 2×50 ml of benzene. Upon removal of the solvent *in vacuo*, di - *t* - butyl - *cis* - propenylphosphonate is obtained and is characterized by NMR and IR spectra. The crude ester can be purified by high vacuum distillation.

Di - *t* - butyl - *cis* - propenylphosphonate (1.0 mole) and *para*-toluene sulfonic acid (0.005 mole) are dissolved in 235 ml. of benzene, and the solution is heated at reflux until the calculated amount of isobutene is formed. A gas metering device is employed to detect the isobutene. The reaction mixture is then cooled to room temperature, the solvent is removed *in vacuo* and *cis*-propenylphosphonic acid is obtained as the residue.

Salts of *cis*-propenylphosphonic acid are made by treating the free acid in ethanol with a base. The metal salts are obtained by employing a metal oxide or hydroxide as the base, and amine salts by employing the appropriate amine. In order to obtain a mono-salt, the pH is adjusted with the base to 4.8 for metal salts and 4.2 for amine salts; for di-salts the pH is adjusted to 8.8 for metal salts and 8.2 for amine salts. In order to recover the salt, the ethanol is removed by evaporation *in vacuo*. Thus, for example, 2 g. of *cis*-propenylphosphonic acid in 50 ml. of ethanol is adjusted to a pH of 4.8 with aqueous sodium hydroxide. The mixture is concentrated to dryness *in vacuo* to afford mono-sodium *cis*-propenylphosphonate. When aqueous sodium hydroxide is added to the above solution to a pH of 8.8, and the mixture concentrated to dryness, di-sodium *cis*-propenylphosphonate

is obtained. The mono- and di-benzylamine salts are obtained in the same fashion by adding benzylamine to the ethanolic solution of *cis*-propenylphosphonic acid to a pH of 4.2 or 8.2. Any of the other salts discussed hereinabove are obtained in the same manner using the appropriate base.

The diesters of *cis*-propenylphosphonic acid are obtained by first converting the free acid to *cis*-propenylphosphonic dichloride, and then reacting this dichloride with 2 molar equivalents of an alcohol represented by the formula R—OH, where R represents the alcohol residue of the resulting ester. The mono-esters are prepared from the di-esters by removal of one of the ester radicals with base. A mono-salt mono-ester may then be prepared by reacting the mono-ester with one equivalent of base. Representative examples for the foregoing reactions are given herein, and it is to be understood that other esters and salts are obtained in the same manner from the appropriate starting materials.

(a) Into a 250 ml. three-necked round-bottomed flask there is added 6.1 g. of *cis*-propenylphosphonic acid, 60 ml. of dry benzene and 9.0 ml of pyridine. The mixture is heated to 50° C., the heat removed and 13.2 g. of thionyl chloride added dropwise at such a rate as to keep the reaction mixture at 50° C. The mixture is then cooled to room temperature and stirred for 2 hours at room temperature. The mixture is filtered and the filtrate concentrated in vacuum at 35° C. to yield 4.5 g. of a turbid oil. It is distilled to afford *cis*-propenylphosphonic dichloride, b.p. 67—69° C./9—10 mm.;  $n_D^{20}$ : 1.4885.

b. A stirred mixture of 0.1 mole of *cis*-propenylphosphonic dichloride and 0.2 mole of triethylamine in 100 ml. of benzene is cooled to 5° C. To the mixture there is added 0.2 mole of methyl alcohol at such a rate as to maintain the temperature at 5—10° C. When the addition is complete, the mixture is stirred at room temperature for 1 hour. The precipitated triethylamine hydrochloride salt is then filtered off and the solvent is removed at reduced pressure to leave dimethyl *cis*-propenylphosphonate. Other di-OR-esters of *cis*-propenylphosphonic acid where R is alkyl, alkenyl, alkynyl, aralkyl or aryl, substituted alkyl, aryl, or alkenyl are prepared in the same manner using 0.2 mole of the alcohol R—OH.

(c) A stirred mixture of *cis*-propenylphosphonic dichloride, 0.1 mole) and triethylamine (0.2 mole) in 100 ml. of benzene is cooled to 5° C. To the mixture there is added benzyl alcohol (0.1 mole) at such a rate as to maintain the temperature at 5—10° C. When the addition is complete, the mixture is stirred at room temperature for 1 hour. Then the precipitated triethylamine hydrochloride salts are filtered off and the solvent is removed at reduced pressure to leave the monochloro-

monobenzyl ester. Aqueous 1 N sodium hydroxide is added and the mixture stirred, during which time a clear solution forms. The solution *in vacuo*. Thus, for example, 2g. of *cis*-butanol. Removal of the solvent leaves monobenzyl *cis*-propenylphosphonate.

Other mono-esters are obtained in the same fashion using the appropriate alcohol.

An alternate method for making esters is represented by the following:

(d) 10 millimoles of *cis*-propenylphosphonic acid in 20 ml. of water is treated with 2.3 g. of silver oxide. The solution is then concentrated under reduced pressure to dryness and the residue of silver salt is washed with a small amount of dimethoxyethane and suspended in 10 ml. of this solvent. One gram of potassium carbonate and 2.55 g. of bromomethyl acetate is added and the mixture stirred for 18 hours at 25° C. The reaction mixture is then filtered and the filtrate concentrated to dryness to give a residue of *bis*-(acetoxymethyl) *cis*-propenylphosphonate.

Esters may also be obtained in the following manner:

(e) 0.2 moles of *cis*-propenylphosphonic dichloride and 200 ml. of ether is cooled to -13° C. and to this solution with stirring is added dropwise a mixture of 0.4 moles of pyridine and 0.4 mole of  $\beta$ -hydroxypropionitrile with good stirring and maintenance of temperature below -10° C. The mixture is poured onto 1 liter of water and 500 grams of ice. The aqueous layer is then separated from the ether and extracted three more times with 100 milliliter portions of ether. The combined ether extracts are washed with water, diluted with hydrochloric acid and finally with water. After drying the ether solution over anhydrous sodium sulfate, it is filtered and concentrated *in vacuo* to give *bis*-(2-cyanoethyl) *cis*-propenylphosphonate.

An alternate method of making alkenyl esters is the following.

(f) A stirred mixture of 0.4 moles of *cis*-propenylphosphonic acid, 2.4 mole of vinyl acetate and 1.6 g. of mercuric acetate and 0.2 ml. of sulfuric acid is refluxed under nitrogen for 3 hours. Sodium acetate (0.83 g.) is added and the low boiling excess vinyl acetate is removed *in vacuo*. The product is obtained by vacuum distillation.

A method of preparing mixed esters is the following.

(g) A stirred solution of *cis*-1-propenylphosphonic dichloride (0.1 mole) in 200 ml. of ether is cooled to 0° C. and then treated dropwise with a solution of absolute ethanol (0.1 mole) and triethylene amine (0.1 mole) in 50 ml. of anhydrous ether. The addition rate is controlled so as to maintain the reaction temperature between 0—5° C. When the addition is complete, the reaction mixture is stirred in the cold for 1 hour more. The precipitate of triethylamine hydrochloride is

then removed by filtration and the filtrate concentrated under reduced pressure to yield O-ethyl *cis* - propenylphosphonochloridate.

- 0.1 mole of O-ethyl-*cis*-propenylphosphonochloridate in 150 ml. of ether is cooled to 10° C. and added dropwise with a mixture of 0.1 mole of benzyl alcohol and 0.1 mole of triethylamine in 40 ml. of ether. The temperature is maintained below about 10° C.
- The reaction mixture is stirred for one hour, filtered and the filtrate concentrated to dryness to afford O - ethyl - O - benzyl - *cis* - propenylphosphonate.

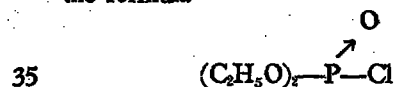
- Bis - (*cis* - propenyl)pyrophosphonic acid: 12.2 g. of *cis*-propenylphosphoric acid is heated gradually to 200° C. under a nitrogen atmosphere at 200 mm. Hg. pressure, and maintained at this temperature for 48 hours. The heating is discontinued. The resulting product is bis (*cis* - propenyl)pyrophosphonic acid.

*Cis* - propenylphosphonic acid cyclic dianhydride:

- One mole of water is added slowly with vigorous stirring to one mole of *cis*-propenylphosphonic dichloride, keeping the temperature below 10° C. by external cooling. When the evolution of heat stops, the mixture is heated to 120° C. under 50 mm. pressure until no more gas is evolved to afford *cis*-propenylphosphonic acid cyclic dianhydride.

*Cis* - propenyl - isohypophosphoric acid:

0.11 mole of diethyl chlorophosphonate of the formula



- (prepared by reaction of ethanol with phosphorus oxychloride) is mixed with 0.1 m. of ethyl *cis*-propenylphosphonate in 150 ml. of ethanol. The mixture is stirred at room temperature for 5 hours and then brought to pH 9 with sodium hydroxide and heated at 80° C. for 6 hours. The solvent is removed *in vacuo* to afford sodium *cis* - propenylisohypophosphoric acid disodium salt.

- When the epoxidation process of the invention leads to an ester of (*cis* - 1,2 - epoxypropyl)phosphonic acid, such ester may be converted to the free acid, or preferably to a salt, by one of several methods, the method of choice depending upon the nature of the hydrocarbyl radical to be removed.

- When R and/or R<sub>1</sub> in Formula I above are alkenyl, alkynyl or aralkyl residues, the preferred method for removing them by hydrolysis, e.g. by the following procedure:

- A solution of 3.2 g. of dibenzyl (*cis* - 1,2 - epoxypropyl)phosphonate in 250 ml. of methanol is hydrogenated at 40 psi at room temperature for 15 minutes in the presence of 800 mg. of 10% by weight palladium on charcoal catalyst and 2 g. of potassium bicarbonate.

The solution is then filtered from the cata-

lyst and evaporated to dryness *in vacuo* at room temperature to give potassium *cis* - 1,2 - epoxypropylphosphonate.

When R and/or R<sub>1</sub> in Formula I is C<sub>1-6</sub> alkyl or aryl, the preferred methods for removing these groups is by ultraviolet light irradiation in the presence of base, by alkaline hydrolysis, or by enzymolysis as exemplified below:

- (1) 4 g. of diphenyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonate in 100 ml. of an aqueous 2% by weight solution of trimethylammonium carbonate is irradiated in a quartz flask at 25—30° C. for 4 hours with an ultraviolet light source. The solution is then evaporated to dryness and the residue extracted into anhydrous methanol. The solution is passed over a sulfonic acid resin column (IR 120 previously dehydrated with methanol) on the hydrogen cycle at 0—5° C. The effluent is collected and rapidly adjusted with cyclohexylamine to pH 5. Concentration of the solution to dryness affords ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonic acid monocyclohexylamine salt.

- (2) 7 g. of diethyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonate is added to 75 ml. of 2% by weight trimethylammonium carbonate solution, in a quartz flask. The solution is irradiated with an ultraviolet light source for 2 hours at 25—30° C. Five ml. of trimethylamine are added and the solution evaporated to dryness *in vacuo*. The resulting product is crystallized from alcohol to afford bis-trimethylammonium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonate.

- (3) 40 ml. of a medium consisting of 0.8% nutrient broth, 0.2% yeast extract, 3% cereose and 0.3% malt extract (by weight), adjusted to pH 7.0, is autoclaved for 15 minutes in a 250 ml. Erlenmeyer flask at 121° C. and 15 psi. The medium is then inoculated with a loopful of inoculum from an agar slant of *Aspergillus niger*, and the flask incubated on a mechanical shaker (220 r.p.m.) at 28° C. until the cultures are well grown (2—4 days). 10 ml. of the fermentation broth is then aseptically transferred to a centrifuge tube and the cells pelleted at 25,000×g. The supernatant is discarded and the cells re-suspended in 4 ml. of distilled water. 2 ml. of this cell suspension are aseptically transferred to a sterile 20×200 mm test tube containing 2γ of sodium methyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonate in 2 ml. of water. The tube is incubated for 20 hours at 28° C. on a mechanical shaker (220 r.p.m.). The cells are then removed by centrifugation (25,000×g.). The supernatant is evaporated to dryness *in vacuo* to afford sodium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonate.

Substituted alkyl and aryl esters are conveniently hydrolyzed with base such as an alkali or alkaline earth metal hydroxide or oxide. Representative conditions are:

0.1 Mole of *bis* - (acetoxymethyl) ( $\pm$ ) (*cis*-1,2 - epoxypropyl)phosphonate is dissolved in 50 ml. of water and then 0.1 mole of calcium oxide is added. The solution is heated with stirring at 60–80° C. for 2 hours. It is then concentrated to dryness *in vacuo* to give a residue of calcium ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonate.

A solution of 50 millimoles of diphenyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonate in 10 ml. of 30% ethanol-water is refluxed with a two-fold excess of barium hydroxide in a nitrogen atmosphere for 1½ hours. The reaction is cooled, adjusted to pH 8 with 4 N sulfuric acid and extracted 3 times with ethyl acetate. The remaining aqueous slurry is stirred overnight at room temperature with 30 g. of sodium sulfate. The solids are removed by filtration and the filtrate evaporated to dryness to give ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonic acid, disodium salt.

Where R and/or R<sub>1</sub> represent aryl or substituted aryl, the conversion to salts is conveniently effected by treatment with sodium in a tertiary amine, i.e.:

5 g. of diphenyl ( $\pm$ ) (*cis* - 1,2 - epoxypropyl) - phosphonate in 5 ml. of methanol is added to 100 ml. of trimethylamine. Small pieces of sodium are added gradually to a total of 2.0 gm. The solvents are removed by concentration, and the product is extracted into methanol. The methanol solution is then passed over a column of IR 120 resin on the hydrogen cycle which has been precooled to 5° C. The effluent is basified to pH 8.2 with phenethylamine and concentrated to give ( $\pm$ ) (*cis* - 1,2 - epoxypropyl)phosphonic acid as the bis-phenethylamine salt.

The (–) (*cis* - 1,2 - epoxypropyl)phosphonic acid referred to herein rotates plane-polarized light in a counterclockwise direction (to the left as viewed by the observer) when the rotation of its disodium salt is measured in water (5% by weight concentration) at 405 mμ.

The designation *cis* used in describing the 1,2 - epoxypropylphosphonic acid compounds means that each of the hydrogen atoms attached to carbon atoms 1 and 2 of the propylphosphonic acid are on the same side of the oxide ring.

A solution of 49.1 g. of the monobenzylammonium salt of racemic (*cis* - 1,2 - epoxypropyl)phosphonic acid in 490 ml. of water is cooled to 0–5° C. and passed through a column containing 330 ml. of a sulfonic acid cation exchange resin of the polystyrene type (Dowex 50) on the acidic cycle, which has been previously cooled to 0–2° C. The phosphonic acid salt is passed over the resin at a rate of 20–40 ml. per minute. The column is then washed with 660 ml. of 0–5° C. water at the same rate. The combined effluents are collected in an agitated mixture of 24.2 g. of (+) - α - phenethylamine in 100

ml. of water. The pH on the resulting solution is then adjusted to 4.8 by the dropwise addition of an aqueous solution of + - α - phenethylamine. The resulting solution is evaporated *in vacuo* to 95–100 ml. and sufficient isopropanol (about 320 ml.), preheated to 70° C., is added so that the resulting solution contains about 20% by weight water. The resulting solution is heated with agitation to 75–79° C. and then quickly cooled to 60° C. and seeded with a small amount of mono - (+) - phenethylammonium (–) (*cis* - 1,2 - epoxypropyl)phosphonate. This solution is then cooled to 0–3° C. and stirred slowly for 16–24 hours, whereupon the crystalline diastereomer precipitates and is collected by filtration. The filter cake is washed with 40 ml. of cold isopropanol-water (9:1) and finally with 40 ml. of cold isopropanol. The crystalline product is then dried at 40° C. to constant weight *in vacuo*. The mono - (+) - phenethylammonium (–) (*cis* - 1,2 - epoxypropyl)phosphonate so obtained melts at 129–132° C. when the sample is inserted at 125° C. and heated at 2° C. per minute. The product has a rotation  $[\alpha]_{405}^{28}$  (C=5%, H<sub>2</sub>O)=2.6°. Recrystallization from aqueous isopropanol affords crystalline product melting at 133–136° C. and having the same rotation.

When the procedure of Example 28 D is repeated using as starting material an optically active *cis*-propenylphosphonite, which has been obtained by resolution of a mixture of enantiomers of an optically active *cis*-propenylphosphonite, there is obtained a mixture of enantiomers of (*cis* - 1,2 - epoxypropyl)phosphonate containing a predominance of one of the enantiomers.

Procedures such as those described in Examples 1, 2 and 4, i.e. those epoxidations using a transition metal catalyst, may also be carried out using as catalyst an optically active salt, complex, ester or mixed anhydride of hexavalent tungsten cation, of tungstic acid or of similar cations and acids of other transition metals such as molybdenum and vanadium. In addition, complexes of such cations with polyamino compounds of the type ethylene diamine, 1,3-diaminopropane or diethylenetriamine, either in a stirred reactor or in a fixed bed, may be utilized as the catalyst. When catalysts of this type are employed the resulting (*cis* - 1,2 - epoxypropyl)phosphonate is obtained as a mixture of enantiomers in which one of the enantiomers is predominant.

#### EXAMPLE 34

To a solution of 5.25 g. of diphenyl *cis* - propenylphosphonate in 250 ml. of methylene chloride is added 119 g. of disodium hydrogen phosphate and the resulting suspension stirred and then heated to reflux. To the re-

fluxing solution is added 100 ml. of 2.5 molar peroxytrifluoroacetic acid in small quantities over a period of 45 hours. The resulting reaction mixture is then cooled and filtered to remove insoluble inorganic salts. The salts are washed with a small volume of methylene chloride and the washes added to the filtrate. The resulting filtrate (ca. 250 ml.) is washed successively with 2×50 ml. of aqueous 20% by weight sodium bisulfite solution, 2×50 ml. of 2.5 N aqueous sodium hydroxide, 2×50 ml. of water, and finally 1×50 ml. of saturated sodium chloride solution. The washed solution is dried over anhydrous sodium sulfate and then evaporated *in vacuo* to an oil which crystallizes on standing. The product, diphenyl (±) (*cis* - 1,2 - epoxypropyl)phosphonate, is found to melt at 46—48° C.

The diphenyl *cis*-propenylphosphonate used above is prepared as follows.

To 30.0 g. of *cis*-propenylphosphonic dichloride in 150 ml. of ethyl ether is added dropwise a solution of 33.87 g. of phenol and 28.8 ml. of pyridine in 200 ml. of ethyl ether while maintaining the reaction mixture at a temperature of 5—10° C. After the addition is complete, the reaction mixture is allowed to stir for 3 hours and then cooled to 5° C. The cooled solution is filtered to remove the precipitated pyridine hydrochloride which is washed with a small amount of ethyl ether. The filtrate is concentrated to a small volume *in vacuo*, filtered to remove solids, and the filtrate concentrated and finally fractionally distilled at under vacuum. The fraction distilling at 138—141° C at 0.20—0.15 mm mercury and amounting to 21.6 g. is recrystallized from hexane to afford diphenyl *cis*-propenylphosphonate melting at 44—46° C.

#### EXAMPLE 35

To a solution of 16.6 g. of disodium *cis*-propenylphosphonate in 50 ml. of water there is added a solution of 23 g. of 85% by weight *m*-chloroperbenzoic acid in 75 ml. of methanol. The reaction mixture is stirred for 4 hours at 25—40° C, maintaining the pH between 5 and 6.5 with 50% by weight aqueous sodium hydroxide solution. At the end of the reaction period the mixture is concentrated at 50—55° C *in vacuo* to about half its volume in order to remove methanol. 75 ml. of water is added and the mixture again concentrated to about half its volume. The mixture is filtered and to the filtrate is added 26 g. of calcium acetate in 75 ml. of water. The mixture is aged at room temperature for 30 minutes and the solid product separated by filtration and dried *in vacuo*. 8 g. of calcium acetate in 25 ml. of water is added to the filtrate and the resulting solution chilled overnight and filtered, and the solid is dried *in vacuo*. The two solid products are combined to afford 32.8 g. of material containing the calcium

salt of (±) (*cis* - 1,2 - epoxypropyl)phosphonic acid in a yield corresponding to 23.7% of the theoretical.

#### EXAMPLE 36

40 ml. of peroxy succinic acid is added at 25° C. to a solution of 8.4 g. of disodium *cis*-propenylphosphonate in 20 ml. of water. The resulting mixture is stirred for 3½ hours at ambient temperature, maintaining the pH between 4.6 and 5.1 with base. The solution is then cooled to room temperature and brought to pH 9 with 50% by weight aqueous sodium hydroxide. 25.9 g. of calcium acetate in 70 ml. of water is added and the resulting thick mixture filtered. The solid is washed with water and dried *in vacuo* at 50° C. to afford a product containing calcium (±) (*cis* - 1,2-epoxypropyl)phosphonate in 12% yield.

#### EXAMPLE 37

To a mixture of 8.3 g. of disodium *cis*-propenylphosphonate in 35 ml. of glacial acetic acid there is added 10 ml. of 40% by weight peroxyacetic acid containing 800 mg. of sodium acetate trihydrate. The resulting mixture is stirred at room temperature for 24 hours and then 200 mg. of 5% palladium on carbon added to decompose any remaining peracid. The mixture is stirred for 2 hours at room temperature and then filtered. The filtrate is freeze dried to afford a product containing calcium (±) (*cis* - 1,2 - epoxypropyl)phosphonate in 24% yield.

#### EXAMPLE 38

To a solution of 15.0 g. of dimethyl *cis*-propenylphosphonate in 80 ml. of benzene is added 1 g. of vanadyl acetylacetonate. To the resulting solution is added 9.9 g. of freshly distilled *t*-butyl hydroperoxide. The reaction mixture is heated to 60° C under nitrogen for 8 hours. At the end of this time the mixture is cooled to room temperature and concentrated to dryness *in vacuo* to remove benzene and excess oxidizing agent. The residue contains predominantly (±) (*cis* - 1,2 - epoxypropyl)phosphonate.

When the above process is carried out on the diethyl ester of *cis* - propenylphosphonic acid in the presence of 1 ml. of glacial acetic acid, and the reaction mixture heated at 60° C for 4 hours, there is obtained diethyl (±) (*cis* - 1,2 - epoxypropyl)phosphonate. Similar results are obtained when other C<sub>2-6</sub> aliphatic acids such as propionic acid are used in place of acetic acid.

#### EXAMPLE 39

To a solution of 6.1 g. of *cis* - 1 - propenylphosphonic acid in 60 ml. of ethyl acetate is added portionwise 6.06 g. of (+)-phenethylamine. The resulting salt (mono - (+) - phenethylammonium - *cis* - 1 - propenylphosphonate) partially precipitates out. The slurry is cooled to room temperature and 9.4 g. of

*m*-chloroperbenzoic acid in 30 ml. of ethylacetate is added over a period of 10 minutes. The mixture is aged for three hours. During this period the salt dissolves. To the clear solution a solvent mixture of 3 ml water and 3 ml. propanol is added. The solution is cooled to 0° C. to -5° C. Crystalline (+) - phenethylammonium - (-) - *cis* - 1,2 - epoxypropylphosphonate monohydrate precipitates and is collected on a funnel, and the cake is washed with cold *n*-propanol.

The crude product is recrystallized from 90% by weight *n*-propanol, to give substantially pure material, m.p. 135-137° C.

- 15 The above procedure may be carried out using solvents such as chloroform, methylene chloride, dichloroethane, acetic acid, ether, or acetone in place of the ethyl acetate, and organic peracids such as peracetic acid, pertrifluoroacetic, perbenzoic, perfuroic, monopersuccinic, and monoperphthalic acids in place of the chloroperbenzoic acid.

#### EXAMPLE 40

- 25 In a 250 ml. three-necked flask equipped with dry ice cooled reflux condenser and gas inlet tube are placed 100 ml. of acetone, 12.2 g. of *cis* - 1 - propenylphosphonic acid, 12.1 g. of (+)-phenethylamine and 40 g. of benzaldehyde. Dry oxygen is introduced through the gas inlet tube with simultaneous irradiation with a 100 W mercury lamp. The temperature of the reaction mixture is maintained between 25° to 35° C. by external cooling. After six hours reaction time 4 ml. of water is added and the mixture cooled to -20° C. The crystalline solid is filtered and recrystallized from 80% by volume isopropanol to give (+) - phenethylammonium - (-) - *cis* - 1,2 - epoxypropylphosphonate.

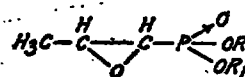
- 40 The above procedure may be carried out using carbon tetrachloride, methylethyl ketone, ether, or tetrachloroethane as solvent instead of acetone.

#### EXAMPLE 41

- 45 To a solution of 6.1 g. of *cis* - 1 - propenylphosphonic acid in 70 ml. of water are added 5.0 mg. of ethylene diamine tetraacetic acid-disodium salt, 250 mg. of sodium tungstate dihydrate and stirred until all dissolves. To the clear solution 8.9 g. of sodium perborate tetrahydrate is added portionwise over a period of five minutes. The solution is warmed up to 50° C and aged with agitation between 50-55° C for one hour. The slight excess of sodium perborate is decomposed by adding a few ml. of 10% by weight sodium bisulfite solution. The reaction mixture (free from perborate) is freeze dried to give a solid residue containing the sodium - (±) - *cis* - 1,2 - epoxypropylphosphonate.

WHAT WE CLAIM IS:—

1. (±) (*cis* - 1,2 - epoxypropyl)phosphonic acid compounds of the formula:—



where each of R and R<sub>1</sub> is a hydrogen atom or a substituted or unsubstituted hydrocarbyl, acyl or heterocyclic radical or R and R<sub>1</sub> together form a cyclic ester group.

2. A compound as claimed in claim 1, in which R and/or R<sub>1</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, cycloalkyl, aryl, aralkyl or heteroaryl radical.

3. (±) (*Cis* - 1,2 - epoxypropyl)phosphonic acid.

4. A salt of a compound as claimed in claim 1.

5. A pharmaceutically acceptable salt of a compound as claimed in claim 1.

6. An alkali metal salt of a compound as claimed in claim 1.

7. A sodium salt of a compound as claimed in claim 1.

8. Disodium (±) (*cis* - 1,2 - epoxypropyl)phosphonate.

9. A monosodium salt of a compound as claimed in claim 1.

10. An alkaline-earth metal salt of a compound as claimed in claim 1.

11. A calcium salt of a compound as claimed in claim 1.

12. An amine salt of a compound as claimed in claim 1.

13. A salt of a compound as claimed in claim 1 and an optically active amine.

14. A phenethylamine salt of a compound as claimed in claim 1.

15. A α-phenethylamine salt of a compound as claimed in claim 1.

16. A (+) α-phenethylamine salt of a compound as claimed in claim 1.

17. A benzylammonium salt of a compound as claimed in claim 1.

18. An ethylenediammonium salt of a compound as claimed in claim 1.

19. A compound as claimed in claim 1 in which R and R<sub>1</sub> are biologically labile hydrocarbyl radicals.

20. A compound as claimed in claim 1, in which at least one of R and R<sub>1</sub> is an acyloxy C<sub>1-6</sub> alkyl radical.

21. A compound as claimed in claim 1, in which R and R<sub>1</sub> are both acetoxymethyl groups.

22. A compound as claimed in claim 1, in which R and R<sub>1</sub> are both diethylamino-ethyl groups.

23. A compound as claimed in claim 1, in which at least one of R and R<sub>1</sub> is a C<sub>1-6</sub> alkyl group.

24. A compound as claimed in claim 1, in which at least one of R and R<sub>1</sub> is an aralkyl group.

25. A compound as claimed in claim 1, in which R and R<sub>1</sub> are both benzyl groups.

26. A compound as claimed in claim 1, in



*m*-chloroperbenzoic acid in 30 ml. of ethylacetate is added over a period of 10 minutes. The mixture is aged for three hours. During this period the salt dissolves. To the clear solution a solvent mixture of 3 ml water and 3 ml. propanol is added. The solution is cooled to 0° C. to -5° C. Crystalline (+) - phenethylammonium - (-) - *cis* - 1,2 - epoxypropylphosphonate monohydrate precipitates and is collected on a funnel, and the cake is washed with cold *n*-propanol.

The crude product is recrystallized from 90% by weight *n*-propanol, to give substantially pure material, m.p. 135-137° C.

The above procedure may be carried out using solvents such as chloroform, methylene chloride, dichloroethane, acetic acid, ether, or acetone in place of the ethyl acetate, and organic peracids such as peracetic acid, pertrifluoroacetic, perbenzoic, perfuroic, monopersuccinic, and monoperephthalic acids in place of the chloroperbenzoic acid.

#### EXAMPLE 40

In a 250 ml. three-necked flask equipped with dry ice cooled reflux condenser and gas inlet tube are placed 100 ml. of acetone, 12.2 g. of *cis* - 1 - propenylphosphonic acid, 12.1 g. of (+)-phenethylamine and 40 g. of benzaldehyde. Dry oxygen is introduced through the gas inlet tube with simultaneous irradiation with a 100 W mercury lamp. The temperature of the reaction mixture is maintained between 25° to 35° C. by external cooling. After six hours reaction time 4 ml. of water is added and the mixture cooled to -20° C. The crystalline solid is filtered and recrystallized from 80% by volume isopropanol to give (+) - phenethylammonium - (-) - *cis* - 1,2 - epoxypropylphosphonate.

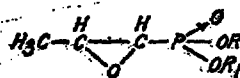
The above procedure may be carried out using carbon tetrachloride, methylethyl ketone, ether, or tetrachloroethane as solvent instead of acetone.

#### EXAMPLE 41

To a solution of 6.1 g. of *cis* - 1 - propenylphosphonic acid in 70 ml. of water are added 50 mg. of ethylene diamine tetraacetic acid-disodium salt, 250 mg. of sodium tungstate dihydrate and stirred until all dissolves. To the clear solution 8.9 g. of sodium perborate tetrahydrate is added portionwise over a period of five minutes. The solution is warmed up to 50° C and aged with agitation between 50-55° C for one hour. The slight excess of sodium perborate is decomposed by adding a few ml. of 10% by weight sodium bisulfite solution. The reaction mixture (free from perborate) is freeze dried to give a solid residue containing the sodium - (+) - *cis* - 1,2 - epoxypropylphosphonate.

#### WHAT WE CLAIM IS:—

1. (+) (*cis* - 1,2 - epoxypropyl)phosphonic acid compounds of the formula:—



where each of R and R<sub>1</sub> is a hydrogen atom or a substituted or unsubstituted hydrocarbyl, acyl or heterocyclic radical or R and R<sub>1</sub> together form a cyclic ester group.

2. A compound as claimed in claim 1, in which R and/or R<sub>1</sub> is a C<sub>1-8</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, cycloalkyl, aryl, aralkyl or heteroaryl radical.

3. (+) (*cis* - 1,2 - epoxypropyl)phosphonic acid.

4. A salt of a compound as claimed in claim 1.

5. A pharmaceutically acceptable salt of a compound as claimed in claim 1.

6. An alkali metal salt of a compound as claimed in claim 1.

7. A sodium salt of a compound as claimed in claim 1.

8. Disodium (+) (*cis* - 1,2 - epoxypropyl)phosphonate.

9. A monosodium salt of a compound as claimed in claim 1.

10. An alkaline-earth metal salt of a compound as claimed in claim 1.

11. A calcium salt of a compound as claimed in claim 1.

12. An amine salt of a compound as claimed in claim 1.

13. A salt of a compound as claimed in claim 1 and an optically active amine.

14. A phenethylamine salt of a compound as claimed in claim 1.

15. A  $\alpha$ -phenethylamine salt of a compound as claimed in claim 1.

16. A (+)  $\alpha$ -phenethylamine salt of a compound as claimed in claim 1.

17. A benzylammonium salt of a compound as claimed in claim 1.

18. An ethylenediammonium salt of a compound as claimed in claim 1.

19. A compound as claimed in claim 1 in which R and R<sub>1</sub> are biologically labile hydrocarbyl radicals.

20. A compound as claimed in claim 1, in which at least one of R and R<sub>1</sub> is an acyloxy C<sub>1-8</sub> alkyl radical.

21. A compound as claimed in claim 1, in which R and R<sub>1</sub> are both acetoxymethyl groups.

22. A compound as claimed in claim 1, in which R and R<sub>1</sub> are both diethylamino-ethyl groups.

23. A compound as claimed in claim 1, in which at least one of R and R<sub>1</sub> is a C<sub>1-8</sub> alkyl group.

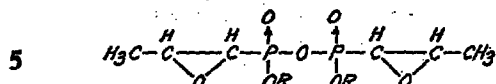
24. A compound as claimed in claim 1, in which at least one of R and R<sub>1</sub> is an aralkyl group.

25. A compound as claimed in claim 1, in which R and R<sub>1</sub> are both benzyl groups.

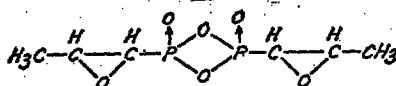
26. A compound as claimed in claim 1, in

which at least one of R and R<sub>1</sub> is a mono-cyclic aryl group.

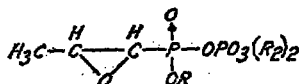
27 (±) (*cis* - 1,2 - epoxypropyl)phosphonic acid compounds of the formula:—



or



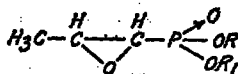
or



10 where R is hydrogen or a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, cycloalkyl, aryl, aralkyl or heteroaryl radical, R<sub>2</sub> is a C<sub>1-6</sub> alkyl or alkali metal radical, and salts thereof in which R is a hydrogen atom.

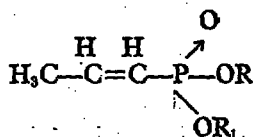
15 28. An antibacterial composition comprising a compound as claimed in claim 5 intimately admixed with a pharmaceutically acceptable carrier vehicle.

20 29. A mixture of the (+) and (−) enantiomers of a compound of the formula:



where R and R<sub>1</sub> are as defined in claim 1, or a salt of such a compound in which at least one of R and R<sub>1</sub> is a hydrogen atom.

25 30. The process that comprises reacting a compound of the formula:



where R and R<sub>1</sub> are as defined in claim 1 or a salt of such a compound in which at least one of R and R<sub>1</sub> is a hydrogen atom, with an oxidising agent to produce a compound as claimed in claim 1 or a salt of a compound as claimed in claim 1 in which at least one of R and R<sub>1</sub> is a hydrogen atom.

30 31. A process as claimed in claim 30, in which the starting material and product are salts.

35 32. A process as claimed in claim 30, in which the starting material and product are esters.

40 33. A process as claimed in claim 31, in which the salts are alkali metal salts.

34. A process as claimed in claim 31, in which the salts are amine salts.

45 35. A process as claimed in claim 31, in which the salts are benzylamine salts.

36. A process as claimed in claim 31, in which the salts are phenethylamine salts.

37. A process as claimed in any one of claims 30 to 36, in which the oxidising agent is a peroxy compound.

38. A process as claimed in any one of Claims 30 to 36 in which the oxidising agent is hydrogen peroxide in the presence of an inorganic peracid.

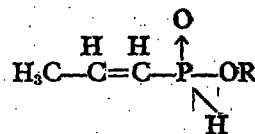
39. A process as claimed in any one of claims 30 to 36, in which the oxidising agent is a perorganic acid.

40. A process as claimed in any one of claims 30 to 36, in which the oxidising agent is a C<sub>1-6</sub> alkyl hydroperoxide.

41. A process as claimed in claim 38, in which benzylammonium *cis*-propenylphosphonate is reacted with hydrogen peroxide in the presence of sodium pertungstate to produce benzylammonium ±(*cis* - 1,2 - epoxypropyl)phosphonate.

42. A process as claimed in claim 38, in which α-phenethylammonium *cis*-propenylphosphonate is reacted with hydrogen peroxide in the presence of sodium pertungstate to produce α-phenethylammonium ±(*cis* - 1,2 - epoxypropyl)-phosphonate.

43. The process that comprises reacting a compound of the formula:



where R is as defined in claim 1, or a salt of the compound in which R is a hydrogen atom with an oxidising agent to produce a compound as claimed in claim 1 in which R<sub>1</sub> is a hydrogen atom in the form of a mixture of enantiomers.

44. A process as claimed in claim 43, in which the starting material is a salt and the oxidising agent is a peroxy compound.

45. A process as claimed in claim 30 substantially as herein before described in any one of Examples 1 to 27, 29, 30, 31, 32 and 34 to 41.

46. A process as claimed in claim 43 substantially as hereinbefore described in Example 28 or 33.

47. (*cis* - 1,2 - epoxypropyl)phosphonic acid compounds when prepared by a process as claimed in any one of claims 30 to 46.

48. An antiseptic composition containing a compound as claimed in any one of claims 1 to 27, 29 and 47 and a diluent or carrier.

49. A pharmaceutical antibacterial composition containing a compound as claimed in any one of claims 1 to 27, 29 and 47 and a non-toxic pharmaceutical diluent, carrier or coating.

50. A composition as claimed in claim 49, in the form of a tablet, capsule or pill.



51. A composition as claimed in claim 49, in parenterally injectable form.

52. A composition as claimed in claim 49, in the form of a solution or suspension.

5 53. A paint containing as preservative a compound as claimed in any one of claims 1 to 27, 29 and 47.

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