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(54) PROCESS FOR PREPARING PENICILLIN AND PENICILLIN SULFOXIDE ESTERS

(71) We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 740 South Alabama Street, City of Indianapolis, State of Indiana, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns a new process for preparing esters of a penicillin or a penicillin sulfoxide.

Esters of penicillin and penicillin sulfoxides have become of commercial importance as intermediates in the heat rearrangement of penicillin sulfoxide esters to corresponding desacetoxycephalosporin esters. These desacetoxyphalosporin esters can be de-esterified or converted to new and know desacetoxyhalosporin antibiotices, e.g. cephalexin.

The object of this invention is to provide a simplified, economical process for preparing these important penicillin and penicillin sulfoxide ester intermediates.

More particularly, the present invention provides a process for preparing an ester of a penicillin or penicillin sulfoxide which comprises commingling a substance selected from phosgene, carbonyl bromide, thiophosgene and carbonyl fluoride with a liquid mixture of (a) the penicillin or penicillin sulfoxide in the acid form or an alkali metal salt thereof, (b) an alcohol or phenol corresponding to the desired penicillin or penicillin sulfoxide ester, and (c) a hydrogen halide acceptor, in (d) an inert organic liquid diluent at a temperature not above 40°C and preferably from −20°C. to 40°C. to form the corresponding penicillin or penicillin sulfoxide ester.

Briefly, according to the process of this invention, phosgene is commingled with a liquid mixture of the selected penicillin or penicillin sulfoxide acid, the selected alcohol or phenol, and a tertiary amine, or an equivalent hydrogen halide acceptor in an inert organic diluent at temperatures low enough to control the exothermic reaction which takes place, thus avoiding any substantial degradation of penicillin ester products, or reactants.

More specifically, it has been found according to this invention that the desired penicillin or penicillin sulfoxide ester is formed in good yield in easily recoverable form by commingling phosgene (carbonyl chloride) with a solution of the corresponding penicillin acid and alcohol or phenol reactants, mixed with an appropriate hydrogen halide acceptor, in an inert organic liquid diluent, at a temperature not above 40°C.

The phosgene may be added to a mixture containing the penicillin acid or penicillin sulfoxide acid and an organic solvent such as acetone, or the phosgene and the penicillin acid or penicillin sulfoxide acid mixture may be concurrently mixed in suitable plant scale equipment, for either batch or continuous operation. The penicillin acid or penicillin sulfoxide and alcohol or phenol and hydrogen halide acceptor should not be added to the phosgene in undiluted form. In the practice of this invention it is unnecessary to separately prepare haloformate reactants. The process of this invention involves an in situ formation of either carbonic acid anhydride or a penicillin acid chloride, either of which is suitable for penicillin ester formation. Ex-phosgene is readily neutralized by the excess halide acceptor present in the mixture, or destroyed by the water which is added after the phosgene addition is completed.

In place of phosgene, carbonyl bromide, thiophosgene or carbonyl fluoride may be used, but for economic reasons, phosgene is preferred.

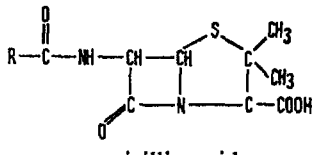
The esterification reaction is conducted in the presence of a hydrogen halide absorber or acid acceptor substance, preferably a tertiary amine which is soluble in the organic liquid diluent. Alkali metal bicarbonates such as lithium, sodium, and potassium bicarbonates, can also be used. Examples of suitable

tertiary halide absorbers include the trialkylamines, such as the C_1 to C_8 trialkylamines, e.g., trimethylamine, tributylamine, dimethylbutylamine, and the heterocyclic amines such as pyridine, guinoline, the picolines, lutidines, and the like, the N, N - di - lower alkylanilines such as N, N - dimethylaniline, N, N - diethylaniline, and the like.

Inert organic liquid diluents which may be used include the common aromatic solvents such as benzene, toluene, and the xylenes; the halogenated C_1—C_4 aliphatic hydrocarbons such as methylene chloride, chloroform and carbon tetrachloride; C_1—C_4 alkanones, such as acetone and methyl ethyl ketone; C_1—C_4 acyl nitriles, such as acetonitrile and propionitrile; C_1—C_4 dialkylsulfoxides, such as dimethylsulfoxide and diethylsulfoxide; dialkylacylamides, such as dimethylformamide and diethylformamide; ethers, such as dioxane, tetrahydrofuran and diethyl ether of diethylene glycol; C_1—C_4 nitro-hydrocarbons, such as nitromethane and nitropropane; and alkyl acylates having up to 7 carbon atoms, e.g., ethyl acetate and propyl acetate; and organic liquid diluent mixtures, such as dioxane-acetone and dimethylsulfoxide-benzene.

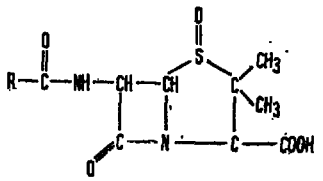
The diluent is preferably water miscible so that the reaction mixture mixes nicely with the water which is added after phosgene addition is completed. A substantially anhydrous liquid medium is preferred, but a small amount of water in the system can be tolerated without serious interference. However, it is desirable to keep the water content in the reaction system below about 5 percent, preferably below about 2.5 percent.

The preferred penicillin and penicillin sulfoxide acid starting materials are those which have one of the following general formulas:



penicillin acid

(I)



Penicillin sulfoxide acid

(II)

where R is hydrogen or the residue of an acyl group. The alkali metal salts of these penicillins, such as the sodium and potassium salts, can also be used. For reasons of availability and cost, phenoxymethyl penicillin (penicillin V), or its sulfoxide, and benzyl penicillin (penicillin G) and its sulfoxide are preferred. However, it is to be understood that there are literally thousands of penicillins in the prior art to which the process of this invention is applicable in making penicillin and penicillin sulfoxide esters. If desired, this process can also be applied to the penicillin nucleus, (6-APA), if the 6-amino group is suitably protected by known methods.

Numerous penicillins derived by fermentation methods known in the prior art can be esterified by the process of this invention, or first converted to the sulfoxides and esterified by the process of this invention, (e.g., those penicillins disclosed in U.S. Patents Nos. 2,479,295 to 2,479,297; 2,562,407 to 2,562,411; and 2,623,876). Such penicillins are represented by Formulas I and II wherein R in each formula is phenyl, benzyl, phenoxymethyl, phenylmercaptomethyl, and such groups substituted with chlorine, methyl, methoxy, trifluoromethyl, or nitro groups, as well as heptyl and thiophene - 2 - methyl. Penicillins with these representative R groups are examples of the most economically prepared or more readily obtainable by fermentation methods.

Examples of penicillin and penicillin sulfoxide ester products which can be prepared by the process of this invention include:

2, 2, 2 - Trichloroethyl 6 - (phenoxyacetamido), - 2, 2, - dimethylphenam - 3 - carboxylate from 2, 2, 2 - trichloroethanol and penicillin V,

4 - Methoxybenzyl 6 - (phenylacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide from 4 - methoxybenzyl alcohol and benzyl penicillin sulfoxide acid,

Benzyloxymethyl 6 - (phenylmercaptoacetamido) - 2, 2 - dimethylpenam - 3 - caroxylate from benzyloxymethanol and phenylmercaptomethyl penicillin,

4 - Methoxyphenyl 6 - (octanoylamido) - 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide from 4 - methoxyphenol and heptyl penicillin sulfoxide,

2, 2, 2 - Trichloroethyl 6 - (thiophene - 2 - acetamido) - 2, 2 - dimethylpenam - 3 - carboxylate from 2, 2, 2 - trichloroethanol and thiophene - 2 - methyl penicillin,

Bis(4 - methoxyphenyl)methyl 6 - (3' - chlorophenylacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide from bis(4 - methoxyphenyl) methanol and 3 - chlorobenzyl penicillin sulfoxide,

3 - Methoxybenzyl 6 - (2', 4', 6' - trimethylphenoxyacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate from 3 - methoxybenzyl alcohol and 2, 4, 6 - trimethylphenoxymethyl penicillin;

Benzyl 6 - (3', 5' - dichlorophenylmercaptomethyl - 2, 2 - dimethylpenam - 3 -

carboxylate - 1 - oxide from benzyl alcohol and 3, 5 - dichlorophenylmercaptomethyl penicillin sulfoxide;

2 - Methoxybenzyl 6 - (4′ - trifluoromethyl phenylacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate from 2 - methoxybenzyl alcohol and 4 - trifluoromethylbenzyl penicillin;

4 - Methoxybenzyl 6 - (3′, 4′ - dimethylphenylmercaptoacetamido) - 2, 2′dimethylpenam - 3 - carboxylate - 1 - oxide from 4 - methoxybenzyl alcohol and 3, 4 - dimethylphenylmercaptomethyl penicillin sulfoxide;

Benzhydryl 6 - (3′ - trifluoromethylphenoxyacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate from benzhydryl alcohol and 3 - trifluoromethylphenoxymethyl penicillin;

4 - Methoxybenzyl 6 - (4′ - nitrophenylacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide from 4 - methoxybenzyl alcohol and 4 - nitrobenzyl penicillin sulfoxide; and

Bis(3, 5 - dimethoxyphenyl)methyl 6 - (3′ - 4′ - dimethylphenylacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide from bis(3, 5 - dimethoxyphenyl)methyl alcohol and 3, 4 - dimethylbenzyl penicillin sulfoxide.

Benzhydryl 6(4′ - methylphenylacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate from benzhydryl alcohol and 4 - methylbenzyl penicillin.

3, 5 - Dimethoxybenzyl 6 - (4′ - nitrophenoxyacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide from 3, 5 - dimethoxybenzyl alcohol and 4 - nitrophenoxymethyl penicillin.

tert - Butyl 6 - (phenoxyacetamido), 2, 2 - dimethylpenam - 3 - carboxylate from *tert* - butyl alcohol and penicillin V;

Phthalimidomethyl 6 - (phenylacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide from phthalimidomethyl alcohol and penicillin G sulfoxide;

Succinimidomethyl 6 - (3′ - chlorophenoxyacetamido), 2, 2 - dimethylpenam - 3 - carboxylate from succinimidomethanol and 3 - chlorophenoxymethyl penicillin;

Benzyl 6 - (4′ - methylphenylacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide from benzyl alcohol and 4 - methylbenzyl penicillin sulfoxide potassium salt.

The selected alcohol or phenol for penicillin or penicillin sulfoxide ester formation may be any alcohol or phenol which forms a readily cleavable penicillin ester group after the conversion of the sulfoxide ester to a desacetoxycephalosporin antibiotic, or one which forms an orally antibiotically active desacetoxycephalosporanate ester. Preferred easily cleaved esters are, for example, those obtained from 2, 2, 2 - trichloroethanol, benzyl alcohol, benzyloxymethanol, the methoxy - substituted benzyl alcohols such as 4 - methoxybenzyl alcohol, 3 - methoxybenzyl alcohol, 3, 5 - dimethoxybenzyl alcohol, benzylhydrol alcohol, bis(4 - methoxyphenyl) methanol, and the hydroxamic alcohols such as N - hydroxy—succinimide, N - hydroxyphthalimide, as well as phthalimidomethyl alcohol and succinimidomethyl alcohol. Some cephalosporin antibiotics in the acetoxymethyl ester form are orally absorbed, such as the acetoxymethyl 7 - (2′ - thienylacetamido) cephalosporinate. When such an antibiotic is being prepared from penicillin or penicillin sulfoxide ester materials, it will be desirable to use acetoxymethanol as the alcohol. Lower alkanols having from 1 to 6 carbon can also be used, but, in general, they can form esters which are difficult to cleave.

The addition of phosgene or similar materials to the reaction mixture results in an exothermic reaction and the evolution of carbon dioxide. The mixture is generally cooled and stirred or otherwise agitated to distribute the heat of reaction. It is preferred to cool the mixture to which the phosgene is added to from −20°C. to about 40°C., depending upon the size of the reaction mixture and the rate of reaction desired. The low temperatures are maintained until all of the phosgene has been added, and the exothermic reaction has subsided.

When the reaction is completed, as indicated by the cessation of evolution of CO_2, the penicillin or penicillin sulfoxide ester product can be removed from the reaction mixture by adding water in an amount sufficient to precipitate the ester product, and to destroy any excess phosgene in the mixture. The crude ester can be removed by extraction with an appropriate organic solvent or by filtration, and can be purified by methods well known in the art.

The penicillin or penicillin sulfoxide acid or salt is preferably mixed with a slight excess of the selected alcohol in the organic solvent to insure complete reaction of the more expensive penicillin material. An excess of the hydrogen halide acceptor is also preferably used to insure complete reaction of the phosgene and its by-products.

The invention is further illustrated by the following detailed examples which show the preparation of a penicillin sulfoxide before esterification, and the esterification thereof. It is to be understood, however, that the esterification can be carried out before the oxidation to the sulfoxide.

Example 1

Penicillin V Sulfoxide

A suspension of 350 g. (1.0 mole) of penicillin V (phenoxymethyl penicillin) in 1 liter of acetic acid was cooled to 15 to 20°C. and 200 ml. of 35 percent hydrogen peroxide in water (about 2 moles of H_2O_2) was added dropwise at 15 to 20°C. over 90 minutes while stirring the mixture. The penicillin

V slowly dissolved giving a clear, pale yellow solution. After about 2 hours at 15 to 20°C., the penicillin V sulfoxide began to crystallize from the solution. Stirring was maintained for a total reaction time of 4 hours. The mixture was cooled to about 0°C. and 1 liter of water was added dropwise in 60 minutes. The precipitate was filtered, washed with 5 liters of water, and dried for 18 hours at 60°C. There was thus obtained 312 g. (85.5 percent yield) of penicillin V sulfoxide as a white solid, m.p. 167 to 168°C. with dec. The infrared (IR) and nuclear magnetic resonance (NMR) spectra and melting point data were identical with the data of a sample of known penicillin V sulfoxide.

Penicillin V Sulfoxide, 2, 2, 2 - Trichloroethyl Ester

A stirred mixture of 366 g. (1 mole) of penicillin V sulfoxide and 166 g. (1.1 moles) of 2, 2, 2 - trichloroethanol in 1 liter of acetone was cooled to 0 to 5°C. and 240 g. (3 moles) of pyridine was added at such a rate that the temperature did not exceed 10°C. Then 95 ml. (about 140 g., 1.4 moles) of phosgene was added dropwise in 30 minutes from a jacketed dropping funnel which was cooled to approximately −50°C. with a dry ice-acetone mixture. Carbon dioxide evolution was extremely rapid throughout the phosgene addition. Stirring was continued for an additional 30 minutes at 5 to 10°C. to insure completion of the reaction. Then 2 liters of water was added dropwise in 60 minutes at 0 to 10°C. The precipitate which formed was collected, washed with water, air-dried, and then vacuum dried at 65°C. for 2 hours. In this manner there was obtained 402 g. (80 perecent yield) of the crude penicillin V sulfoxide ester [2, 2, 2 - trichloroethyl 6 - (phenoxyacetamide) 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide] as a pale yellow, granular solid, m.p. 141—143°C. The material was slurried in a mixture of 300 ml. of methyl isobutyl ketone and 150 ml. of ethyl ether at about 0°C., collected, washed with a cold 1.5:1 (by volume) mixture of methyl isobutyl ketone and ethyl ether, and dried, yielding 358 g. (71.5 percent yield) of the more highly purified 2, 2, 2 - trichloroethyl penicillin V sulfoxide ester, m.p. 146 to 148°C. The ester was identical, by mixed melting point, IR and NMR analyses with a known sample of the penicillin V sulfoxide ester.

Example 2

Penicillin G, 2, 2, 2 - Trichloroethyl Ester

A suspension of 37.2 g. (0.10 mole) of the potassium salt of penicillin G in 150 ml. of acetone was cooled to approximately 0°C. To this cooled suspension was added 16 g. (0.11 mole) of 2, 2, 2 - trichloroethanol and then 18 g. (0.22 mole) of pyridine. The mixture was stirred and 14 g. (about 0.14 mole) of phosgene was added over 45 minutes at 0—5°C. Stirring was continued for 10 minutes and then 300 ml. of cold water was added in 20 minutes. The oil that separated was extracted into 500 ml. of ethyl acetate. The organic layer containing the ester product was washed with 5 percent sodium bicarbonate solution, and then with 100 ml. of 5N hydrochloric acid. After separation, the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was triturated with 400 ml. of ethyl ether. The white solid produced was collected, washed with ether, and dried, yielding 32.7 g. (70 percent yield) of the 2, 2, 2 - trichloroethyl penicillin G ester [2, 2, 2 - trichloroethyl 6 - phenylacetamido - 2, 2 - dimethylpenam - 3 - carboxylate], m.p. 159—160°C. Infrared (IR) and nuclear magnetic resonance (NMR) spectra of the product so obtained were identical with those obtained from the same ester made by the carbodiimide method.

Example 3

Penicillin V Sulfoxide, 4 - Methoxybenzyl Ester

The 4 - methoxybenzyl penicillin V sulfoxide ester [4 - methoxybenzyl 6 - phenoxyacetamido) - 2, 2 - dimethylpenam - 3 - carboxylate - 1 - oxide] was prepared in a manner similar to that described in Example 1, using 4 - methoxybenzyl alcohol instead of 2, 2, 2 - trichloroethanol.

The oil that separated after the addition of water was extracted with 100 ml. of chloroform, and the organic layer containing the ester product was washed with 5 percent sodium bicarbonate solution, 100 ml. of 1.1 N hydrochloric acid, and 100 ml. of water. The chloroform solution was dried over anhydrous sodium sulfate and then concentrated in a rotary evaporator. The viscous, yellow oil residue was treated with 500 ml. of ether. The yellow, granular solid obtained by such treatment was collected, washed with ether and dried to give 21.6 g. (45 percent yield) of 4 - methoxybenzyl penicillin V sulfoxide ester, m.p. 126—129°C. The IR and NMR spectra confirmed the identity of the product.

Example 4

Penicillin V Sulfoxide, Benzyl Ester

A suspension of 36.6 g. (0.10 mole) of penicillin V sulfoxide in 100 ml. of acetone was added to a 500 ml., round bottomed, three-necked flask equipped with a stirrer, thermometer, dry ice-acetone condenser, and inlet tube for phosgene gas addition. The mixture was cooled to 0°C. with stirring and then 24 g. (0.3 mole) of pyridine was added, followed by the addition of 10.8 g. (0.10 mole) of benzyl alcohol. Phosgene, 12.0 g. (0.12 mole) was introduced via the inlet tube

from a liquid reservoir. The addition required about 30 minutes during which time the temperature was maintained at 0—5°C. Stirring was continued for 10 minutes until carbon dioxide evolution ceased. Then 150 ml. of ice cold water was added in 15 minutes. The white solid produced was collected, washed with a cold 1.5 : 1 water : acetone mixture, air dried and then vacuum dried at 60°C. for 4 hours yielding 40.6 g. (89 percent yield) of the benzyl ester of penicillin V sulfoxide, m.p. 118°—120°C. The IR and NMR spectra for this product were identical with those of a sample of the same ester prepared via the benzyl chloroformate route.

WHAT WE CLAIM IS:—

1. A process for preparing an ester of a penicillin or penicillin sulfoxide which comprises commingling a substance selected from phosgene, carbonyl bromide, thiophosgene and carbonyl fluoride with a liquid mixture of (a) the penicillin or penicillin sulfoxide in the acid form or an alkali metal salt thereof, (b) an alcohol or phenol corresponding to the desired penicillin or penicillin sulfoxide ester, and (c) a hydrogen halide acceptor, in (d) an inert organic liquid diluent at a temperature not above 40°C. to form the corresponding penicillin or penicillin sulfoxide ester.

2. The process of claim 1, wherein the penicillin or penicillin sulfoxide employed has the formula (I) or (II) set forth herein where R is phenyl, benzyl, phenoxymethyl, phenylmercaptomethyl, or such phenyl, benzyl, phenoxymethyl, and phenylmercaptomethyl groups substituted with chlorine, methoxy, methyl or nitro, or heptyl or thiophene - 2 - methyl.

3. The process of claim 1 or 2, wherein the alcohol or phenol employed is 2, 2, 2 - trichloroethanol, benzyl alcohol, tert-butanol, benzyloxy-methanol, a methoxyphenol, a methoxybenzyl alcohol, 3, 5 - dimethoxybenzyl alcohol, benzhydryl alcohol, or bis (4 - methoxyphenyl) methanol.

4. The process of claim 1, 2 or 3, wherein the hydrogen halide acceptor employed is a tertiary amine, and the inert organic liquid diluent employed is a water-miscible organic diluent.

5. The process of claim 1, 2, 3 or 4, wherein the temperature is from —20°C. to 40°C.

6. The process of any of claims 1 to 5, wherein phosgene is commingled with a liquid mixture of (a) phenoxymethyl penicillin sulfoxide, (b) 2, 2, 2 - trichloroethanol, (c) a tertiary amine in an inert organic diluent, to form 2, 2, 2 - trichloroethyl phenoxymethyl penicillin sulfoxide ester.

7. The process of any of claims 1 to 5, wherein phosgene is commingled with a mixture of (a) phenoxymethyl penicillin sulfoxide, (b) 4 - methoxybenzyl alcohol, (c) a tertiary amine, in an inert organic liquid diluent to form the 4 - methoxybenzyl phenoxymethyl penicillin sulfoxide ester.

8. The process of any of claims 1 to 5, wherein phosgene is commingled with a mixture of (a) phenoxymethyl penicillin sulfoxide, (b) benzyl alcohol, (c) a tertiary amine and an organic liquid diluent to form the benzyl phenoxymethyl penicillin sulfoxide ester.

9. The process of any of claims 1 to 5, wherein phosgene is commingled with a liquid mixture of (a) benzyl penicillin, (b) 2, 2, 2 - trichloroethanol, (c) a tertiary amine in an inert organic diluent to form 2, 2, 2 - trichloroethyl benzylpenicillin.

10. The new process for preparing penicillin and penicillin sulfoxide esters, substantially as herein described with particular reference to any one of the specific examples.

11. An ester of a penicillin or penicillin sulfoxide obtained by the process of any of claims 1 to 10.

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from a liquid reservoir. The addition required about 30 minutes during which time the temperature was maintained at 0—5°C. Stirring was continued for 10 minutes until carbon dioxide evolution ceased. Then 150 ml. of ice cold water was added in 15 minutes. The white solid produced was collected, washed with a cold 1.5 : 1 water: acetone mixture, air dried and then vacuum dried at 60°C. for 4 hours yielding 40.6 g. (89 percent yield) of the benzyl ester of penicillin V sulfoxide, m.p. 118°—120°C. The IR and NMR spectra for this product were identical with those of a sample of the same ester prepared via the benzyl chloroformate route.

WHAT WE CLAIM IS:—

1. A process for preparing an ester of a penicillin or penicillin sulfoxide which comprises commingling a substance selected from phosgene, carbonyl bromide, thiophosgene and carbonyl fluoride with a liquid mixture of (a) the penicillin or penicillin sulfoxide in the acid form or an alkali metal salt thereof, (b) an alcohol or phenol corresponding to the desired penicillin or penicillin sulfoxide ester, and (c) a hydrogen halide acceptor, in (d) an inert organic liquid diluent at a temperature not above 40°C. to form the corresponding penicillin or penicillin sulfoxide ester.

2. The process of claim 1, wherein the penicillin or penicillin sulfoxide employed has the formula (I) or (II) set forth herein where R is phenyl, benzyl, phenoxymethyl, phenylmercaptomethyl, or such phenyl, benzyl, phenoxymethyl, and phenylmercaptomethyl groups substituted with chlorine, methoxy, methyl or nitro, or heptyl or thiophene - 2 - methyl.

3. The process of claim 1 or 2, wherein the alcohol or phenol employed is 2, 2, 2 - trichloroethanol, benzyl alcohol, tert-butanol, benzyloxy-methanol, a methoxyphenol, a methoxybenzyl alcohol, 3, 5 - dimethoxybenzyl alcohol, benzhydryl alcohol, or bis (4 - methoxyphenyl) methanol.

4. The process of claim 1, 2 or 3, wherein the hydrogen halide acceptor employed is a tertiary amine, and the inert organic liquid diluent employed is a water-miscible organic diluent.

5. The process of claim 1, 2, 3 or 4, wherein the temperature is from —20°C. to 40°C.

6. The process of any of claims 1 to 5, wherein phosgene is commingled with a liquid mixture of (a) phenoxymethyl penicillin sulfoxide, (b) 2, 2, 2 - trichloroethanol, (c) a tertiary amine in an inert organic diluent, to form 2, 2, 2 - trichloroethyl phenoxymethyl penicillin sulfoxide ester.

7. The process of any of claims 1 to 5, wherein phosgene is commingled with a mixture of (a) phenoxymethyl penicillin sulfoxide, (b) 4 - methoxybenzyl alcohol, (c) a tertiary amine, in an inert organic liquid diluent to form the 4 - methoxybenzyl phenoxymethyl penicillin sulfoxide ester.

8. The process of any of claims 1 to 5, wherein phosgene is commingled with a mixture of (a) phenoxymethyl penicillin sulfoxide, (b) benzyl alcohol, (c) a tertiary amine and an organic liquid diluent to form the benzyl phenoxymethyl penicillin sulfoxide ester.

9. The process of any of claims 1 to 5, wherein phosgene is commingled with a liquid mixture of (a) benzyl penicillin, (b) 2, 2, 2 - trichloroethanol, (c) a tertiary amine in an inert organic diluent to form 2, 2, 2 - trichloroethyl benzylpenicillin.

10. The new process for preparing penicillin and penicillin sulfoxide esters, substantially as herein described with particular reference to any one of the specific examples.

11. An ester of a penicillin or penicillin sulfoxide obtained by the process of any of claims 1 to 10.

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