

PATENT SPECIFICATION

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(54) PROCESS FOR PREPARING CEPHALEXIN AND INTERMEDIATES THEREFOR

(71) We, BRISTOL-MYERS COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of 345 Park Avenue, New York, State of New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to a process for the preparation of cephalexin, and to two intermediates therefor.

Scientists of Toyo Jozo Kabushiki Kaisha appear to have been the first to prepare one penicillin from another by "transacylation", known also as, "the switch reaction". In this synthesis, a readily available, natural penicillin is converted to a chloro-imide or imino-ether (prepared according to U.S. 3,499,909 and 3,676,429) which is then acylated to produce the N,N-diacyl-6-aminopenicillanic acid (as an easily hydrolyzed ester to protect the carboxyl group). The original acyl group of the starting penicillin is then removed along with the esterifying group, for example, by reaction, preferably in dimethylformamide, with a nucleophile such as sodium thiophenolate. Such reactions are described in U.S. patents 3,594,366; 3,658,792 and 3,668,200 and in Farmdoc 14, 183R, 48,229S and 50,298S. Scientists of Yamanouchi Pharmaceutical Company, Ltd. have published related disclosures in patents abstracted in Farmdoc 08,653S, 40,656T, 47,171T and 47,172T and in Yakugaku Zasshi 92(4), 454—458 and 459—464 (1972) which discloses the use of two particular esters of benzylpenicillin in the production of ampicillin.

Cephalexin is an antibacterial agent used in human therapy and marketed as the monohydrate of the free acid (i.e., the zwitterion). It is described, for example, in *J. Med. Chem.* 12, 310—313 (1969), *J. Org. Chem.* 36(9), 1259—1267 (1972) [See Belgium 765,596; Farmdoc 67,511S] and in U.S. 3,507,861, U.K. 1,174,335 and Canada 856,786.

There are numerous disclosures of alternative methods for the production and purification of cephalexin (as the free acid); see for example, U.S. 3,634,416; 3,668,201; 3,668,202; 3,671,449 (Example 3); 3,676,434; 3,676,437; 3,689,483; 3,694,437; 3,714,146; U.K. 1,227,014 and Belgium 768,306 (Farmdoc 80,093S), U.S. Patent No. 3,843,637, and U.K. 1,270,633.

Disclosures relative to crystalline forms and hydrates of cephalexin include for example, *Journal of Pharmaceutical Sciences*, 59(12), 1809—1914 (1970); *Pharmaceutical Journal*, 210—214 (August 22, 1970); U.S. patents 3,502,663, 3,531,481, 3,665,656 and 3,692,781; Belgium patents 753,910 (Farmdoc 8,214S) and 777,789 (Farmdoc 48,556T); and French patent 2,096,117.

The application of the "transacylation" process to cephalosporins developed more slowly and was complicated by the additional functional groups found in the only such compound produced (until recently) by fermentation, that is, cephalosporin C. Fujisawa Pharmaceutical Company, Lt. reported, in Belgium patent 758,587 (Farmdoc 34,689S), application of the "transacylation" process to certain 3-thiolated derivative of cephalosporin C using chloro-imides and imino-ethers of the general type described

in U.S. patents 3,575,970, 3,697,515, 3,573,295 and 3,573,296. Use of this process on certain particular esters of 7-phenoxyacetamido-3-methylceph-3-em-4-carboxylic acid to produce cephalixin, is disclosed in French patent 2,096,117 (Farmdoc 80,093S; Belgium patent 768,306).

The present invention provides the intermediates methoxy-methyl 6-phenoxyacetamido-penicillinate sulfoxide and, methoxymethyl 3-methyl-7- β -phenoxyacetamido-ceph-3-em-4-carboxylate. The invention additionally provides a process for the preparation of the antibacterial agent cephalixin, which process comprises the consecutive steps of

a) reacting methoxymethyl - 3 - methyl - 7 - β - phenoxyacetamido - ceph - 3 - em - 4 - carboxylate in an anhydrous, inert, water-immiscible solvent (preferably, methylene chloride, dichloroethane, chloroform, tetrachloroethane, nitromethane or diethyl ether) in the presence of an acid acceptor (e.g. a deactivating tertiary amine, preferably, trimethylamine, trimethylamine, dimethylaniline, quinoline, lutidine or pyridine) at a temperature of -10°C to -60°C (preferably below -15°C), with at least an equimolar amount of a halogenating agent (preferably, phosphorous pentachloride, phosphorus pentabromide, phosphorus trichloride, phosphorus tribromide, oxalyl chloride, p-toluene-sulfonyl halide, phosphorus oxychloride or phosgene),

b) mixing therewith an aliphatic alcohol containing less than seven carbon atoms (preferably, methanol), while maintaining the temperature at from -20°C to -70°C (preferably, below -30°C),

c) mixing therewith (preferably, in increments) at least an equimolar amount D-(-)-2-phenylglycyl chloride hydrochloride, at a temperature below -30°C ,

d) hydrolysing the reaction product of step c), e.g. by mixing therewith water and a mineral acid, (preferably, sulfuric acid or hydrochloric acid, and preferably at a temperature below 10°C), and

e) basifying the hydrolysed reaction product of step d) to produce the zwitterion, cephalixin.

Preferably, the methoxymethyl 3 - methyl - 7 - β - phenoxyacetamido - ceph - 3 - em - 4 - carboxylate is produced by reacting penicillin V sulfoxide with chloromethyl methyl ether in the presence of an acid acceptor (e.g. an acid deactivating tertiary amine) to produce methoxymethyl 6-phenoxyacetamido-penicillinate sulfoxide, then converting the latter to methoxymethyl 3 - methyl - 7 - β - phenoxyacetamido - ceph - 3 - em - 4 - carboxylate by conventional ring expansion reaction, e.g. by an acid catalysed thermal re-arrangement.

This invention provides a convenient synthetic route for the preparation of cephalixin from the methoxymethyl ester of 3-desacetoxycephalosporin V which in turn is prepared by ring expansion of penicillin V methoxymethyl ester sulfoxide (as described below) or directly from 3-desacetoxycephalosporin V acid and chloromethyl methyl ether (as described below). This ester can also be converted by known side chain cleavage routes into 7-amino-3-desacetoxycephalosporanic acid (7-ADCA). Our new process renders unnecessary the preparation of 7-ADCA and enables one, under essentially anhydrous conditions and in good yield, to simply exchange acyl group sidechains. Moreover, the process can be advantageously conducted in one reaction vessel.

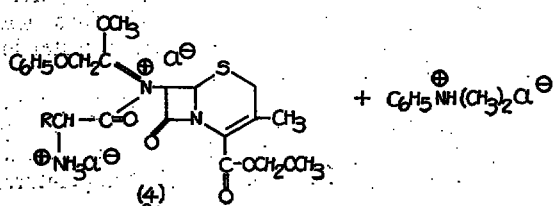
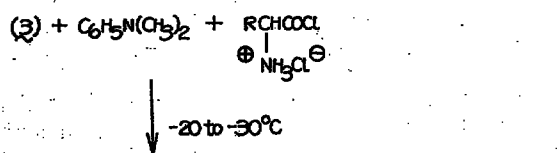
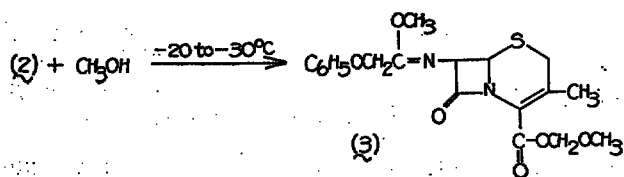
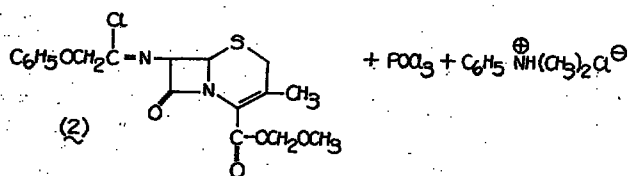
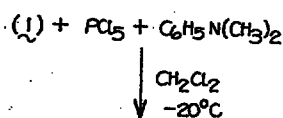
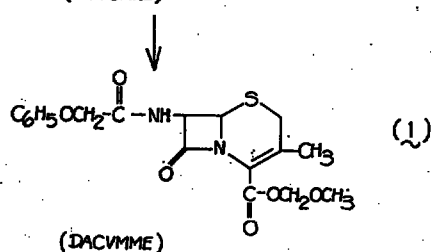
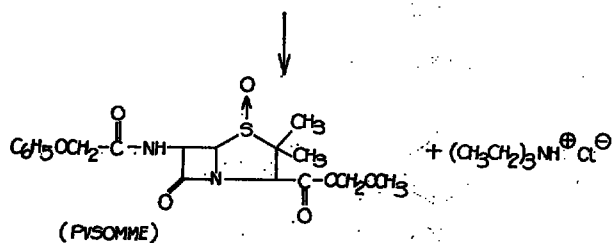
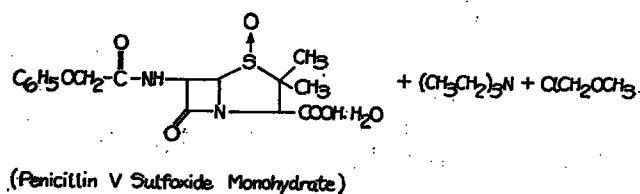
It should be noted that in the disclosure which follows "PVSOMME" means the Pen V sulfoxide methoxymethyl ester viz. methoxymethyl 6-phenoxyacetamido-penicillinate sulfoxide. "DACVMME" means the methoxymethyl ester of desacetoxyceph V viz. methoxymethyl 7- β -phenoxyacetamido-3-methyl ceph-3-em-4-carboxylate. "R" represents phenyl.

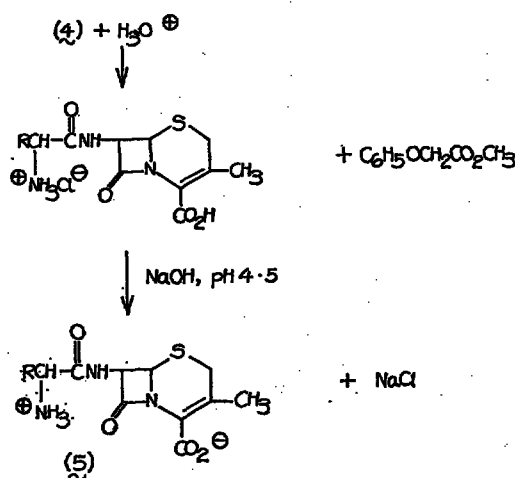
IR data were obtained on a Beckmann (trade mark) IR9. NMR spectra were recorded on a Perkin Elmer R12-B operating at 60MHz with probe temperature at 40°C NMR data are given in units relative to tetramethylsilane. U.V. data were obtained on a Beckmann Acta 3. Rotation data given were obtained at 25°C on a Perkin Elmer PE141 recording polarimeter. The superscript ^{SH} refers to a shoulder on the UV curve. Bioassay data were obtained by turbidimetric methods using S. Aureus 209P.

The process of the invention is illustrated with reference to the following Reaction Scheme.

(14)

Reaction Scheme





Treatment of the methoxymethyl ester (1) with phosphorus pentachloride, in methylene chloride solution, at -20°C and in the presence of *N,N*-dimethylaniline gave rise to the imidoyl chloride (2). This intermediate was sufficiently stable that

the reaction could easily be followed to completion by thin layer chromatography. In an analogous reaction sequence, using phosphorus pentachloride in the presence of d_5 -pyridine in deuteriochloroform solution at 25°C , it was possible to characterize this intermediate fully by the use of NMR (Nuclear Magnetic Resonance) techniques. An NMR spectrum of the chlorination mixture in deuteriochloroform, after 1 hour, revealed that the six line pattern between 5 and 6.3 ppm. (β -lactam; C_6 , C_7 , hydrogen atoms, coupled to amide NH), initially present in the ester, was transformed into a well resolved pair of AB doublets ($J=4.5$ Hz) characteristic of the chloroimide. Furthermore, there was a downfield shift of the sidechain PhOCH_2 signal from 84.70 ppm. to 84.80 ppm., indicative of substitution of chlorine for oxygen at the amide carbonyl group. These data clearly indicate the absence of any amide NH signal, which is generally submerged under the aromatic region center at 87.0 ppm. Finally, integration of the aromatic region revealed detection of only five protons due to C_6H_5O , clearly showing the absence of amide NH signal. Peaks at 83.45 ppm (CH_3O) and 85.70 ppm. (CH_3OCH_2) showed that the ester linkage was intact, and peaks at 82.10 ppm (CH_2-C) and 3.25 ppm ($\text{S}-\text{CH}_2$) were indicative of the dihydrothiazine moiety.

The chlorination mixture in methylene chloride solution was treated with excess methanol at -20°C to -30°C . After two hours, the complete disappearance of the chloroimide was observed by thin layer chromatography. The resulting imino-ether (3) was acylated with *D*-(-)- α -phenylglycyl chloride hydrochloride at -20°C to -30°C giving rise to presumed intermediate (4). The acylation mixture was subsequently hydrolyzed in acidic water for about two hours. High quality solid cephalixin was obtained after adding base to adjust the pH in 1-butanol/water to pH 4.5.

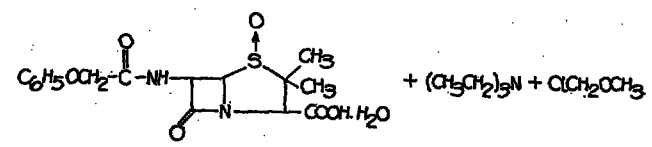
The structure of the cephalixin (5) so produced was confirmed by elemental analysis, infrared, nuclear magnetic resonance and ultraviolet spectral techniques, as well as TLC (Thin Layer Chromatography) comparison with an authentic sample. Biopotency data indicated that the product was more than 90% pure. Slightly lower quality cephalixin obtained during our preliminary investigations was readily recrystallized (with 70% recovery) to analytically pure relatively water-insoluble monohydrate by pH adjustment in 1-butanol/water at 25°C .

The cephalixin produced by the process of the invention can be employed in pharmaceutical compositions together with inert pharmaceutically-acceptable carriers. This invention will now be illustrated by the following examples, which are given by way of illustration and not by way of limitation. All temperatures are given in degrees Centigrade.

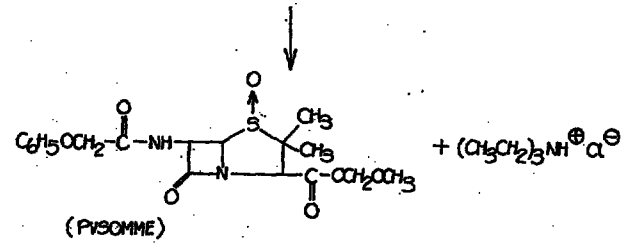
Example 1

Conversion of Penicillin V to Desacetoxy-cephalosporin V via ring expansion of Pen V sulfoxide methoxymethyl ester

A. Preparation of Pen V sulfoxide methoxymethyl ester (PVSOMME) (which is also named at methoxymethyl 6-phenoxyacetamido-penicillinate sulfoxide)

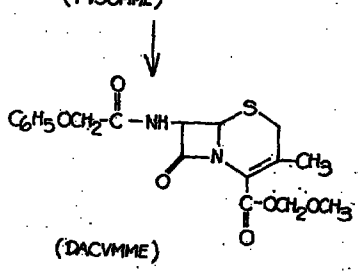
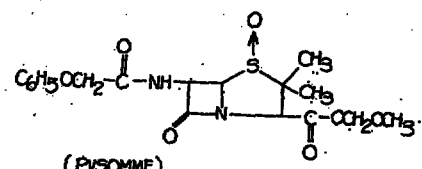


(Penicillin V Sulfoxide Monohydrate)



45 ml. of triethylamine were added to 109.8 g. (0.285 mole) of penicillin V sulfoxide monohydrate (U.S. 3,544,581) slurried in 500 ml. of dichloromethane at 0—5°C. Then sufficient (Linde (trade mark) Type 4A) molecular sieves to take up the water of hydration were added. The mixture was stirred for 20 minutes then 30 ml. of chloromethyl methyl ether were added thereto. The resultant mixture was stirred at 0—5°C. for 2 hours. The molecular sieves were removed by filtration and the solution was washed with two 100 ml. portions of cold water. The organic layer was concentrated under reduced pressure to about 300 ml. then diluted to 1000 ml. with n-heptane. This gave a precipitate. The slurry was stirred for 2 hours at 0—5°C, filtered and the resulting yellow solid redissolved in 500 ml. of 2-propanol at 40—50°C, diluted to 2000 ml. with heptane and cooled to 0—5°C for three hours. The resulting solid was filtered, washed with 600 ml. of 50/50 2-propanol/heptane, and dried at 35°C for 18 hours. 107 g. (93% yield) of white, crystalline PVSOMME (m.p. 113.5—114.5°C) showing one zone on thin layer chromatography, and having infrared and NMR spectra clean and consistent for that structure, were obtained.

B. Ring expansion of Pen V sulfoxide methoxymethyl ester (PVSOMME) to the methoxymethyl ester of desacetoxyceph V (DACVMME) (which is also named as methoxymethyl 7 - phenoxyacetamido - 3 - methylceph - 3 - em - 4 - carboxylate).



Run No. 1

20 gm. (0.050 mole) of PVSOMME, 10 g. of crushed (Linde type 4A) molecular sieves and 2.5 g. of the solid pyridine salt of p-toluenesulfonic acid were added to 200 ml. of dioxane the mixture was stirred and heated at reflux temperature for five hours. After cooling and filtering, the mixture was concentrated under reduced pressure to an oil and taken up in 400 ml. dichloromethane. This solution was washed with three 200 ml. portions of water, filtered through activated charcoal, and the filtrate was dried and then concentrated under reduced pressure to give 15 g. of a foamy solid. Thin layer chromatography showed the methoxymethyl ester of desacetoxy-ceph V (DACVMME) as the predominant product with a substantial amount of decarboxylated material and a trace of unchanged PVSOMME. This solid when subjected to cleavage conditions gave 7-ADCA, assaying 72% pure by chemical assay, in 32% yield.

Run No. 2

The conditions of Run No. 1 were repeated using 2 g. of pyridine tosylate salt and a four hour reaction time. After filtering and stripping, the methylene chloride solution was consecutively washed with 100 ml. of water, 100 ml. of pH 7 buffer solution, and 100 ml. of water. The dried organic solution, in stripping, gave 18 g. of yellow foamy solid. TLC showed about 65% DACVMME. A 100 mg. sample dissolved in 10 ml. of 50/50 acetone and pH 7 buffer solution showed potency of 6100 mcg./ml. in a DACV biological assay.

A 2 g. sample of the foamy solid was dissolved in 60 ml. of dichloromethane at 25°C and treated for 30 minutes with 1 g. of meta-chloroperoxybenzoic acid. The solution was washed with 30 ml. of water and 30 ml. of pH 7 buffer solution. The organic layer was dried, concentrated to an oil and the oil was triturated with ether containing acetone. The resulting crystalline solid was filtered and dried to give 1.1 g. (52% yield) of desacetoxycephalosporin V sulfoxide methoxymethyl ester identical in all respects with the authentic material.

Run No. 3

In a manner similar to the previous Runs, a mixture of 5 g. of PVSOMME, 50 ml. of dioxane, 7.5 g. of molecular sieves and 0.5 g. of pyridine salt of methanesulfonic acid was heated for two hours at reflux temperature. After filtering and stripping, the resulting oil was taken up in 50 ml. dichloromethane. This solution was washed twice with 30 ml. pH 7 buffer solution followed by 30 ml. cold water, treated with activated charcoal, dried and stripped to give 3.5 g. of light yellow foamy solid. On cleaving there was obtained 0.75 g. of 7-ADCA (27% yield) assaying 870 mcg./mg. by chemical assay.

Run No. 4

0.25 g. of pyridine tosylate was added to 10 g. of PVSOMME in 100 ml. of 1,2-dichloroethane. The resultant mixture was heated at reflux temperature for 12 hours. TLC showed that the reaction was incomplete. An additional 0.5 g. of catalyst was added and reflux was continued for four hours. After cooling, the mixture was washed twice with 50 ml. of cold acidified (pH 1.5) water. The organic layer was dried and passed over a 1×60 cm. column of silica gel and the column was eluted with 1250 ml. of dichloromethane. Appropriate fractions of the eluate were combined and stripped to give 2.0 g. (21% yield) of foamy solid, identical with DACVMME.

Run No. 5

The ring expansion was carried out on 5 g. PVSOMME in 50 ml. dioxane with 10 g. of crushed molecular sieves and 0.5 g. of pyridine tosylate at reflux temperature for 18 hours. After cooling and filtering, 20 ml. of 6N HCl solution were added and the resultant mixture was held at about 25°C for approximately 1—2 hours to hydrolyze the methoxymethyl ester group. The mixture was then diluted with 50 ml. of water, extracted three times with 50 ml. of dichloromethane and the combined dichloromethane solution was extracted three times with 50 ml. of pH 7 buffer solution. The combined buffer extracts were adjusted to pH 1.5 with HCl and extracted three times with 30 ml. of ethyl acetate. The combined ethyl acetate layers were stripped to give a foamy solid which was taken up in 30 ml. of methanol and treated with dibenzylamine. After crystallizing 15 hours at 0°C, 2.6 g. (48% yield) of the dibenzylamine salt of DACV (identical with an authentic sample) were obtained.

C. Methoxymethyl 3-methyl-7- β -phenoxyacetamidoceph-3-em-4-carboxylate

A suspension of 20.0 g. (57.4 m. moles) 3-methyl-7- β -phenoxyacetamidoceph-3-em-4-carboxylic acid (Netherlands 72/06193; Farmdoc 76,350T) in 300 ml. dry methylene chloride was cooled to 0–5°C and treated with (7.96 ml., 5.80 g., 57.5 m. moles), triethylamine in one portion and under nitrogen. The resulting solution was then treated with chloromethyl methyl ether (5.0 ml., 5.03 g., 62.5 m. moles) over a 15 minute period, with high speed stirring, and at a temperature of 0–5°C. The resultant mixture was stirred for an additional 2 hours at 0–5°C. At this point, TLC on silica gel F 254, 250 μ ; system 4 acetone/12 benzene/1 acetic acid revealed the absence of any starting acid at R_f 0.5, and the presence of the ester at R_f 0.75, when visualized with 1% potassium permanganate. The mixture was washed with 0–5°C water (100 ml.), followed by 0–5°C pH 7.00 phosphate buffer (100 ml.), dried over anhydrous sodium sulfate, and concentrated to an oil *in vacuo* at 20–25°C. The oil was dissolved in isopropanol (300 ml.) at 25°C, and seed crystals were added. The mixture was cooled to 0–5°C. During the cooling period, the ester crystallized. The slurry was held at 0–5°C for four hours, filtered, and the colorless cake displacement was washed with 100 ml. of 1:1 isopropanol/heptane. The colorless product was oven dried to constant weight at 40°C giving 21.4 g. (95% yield) of colorless rods of the title compound, methoxymethyl 3-methyl-7- β -phenoxyacetamidoceph-3-em-4-carboxylate: m.p. 106–107°C; $[\alpha]_D^{25} + 107^\circ$ (c 1, in methanol); $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ nm (log ϵ) 215^{sh} (3.41), 255 (3.12), 260^{sh} (3.15), 267 (3.16), 274 (3.12); TLC, silica gel F 254, 250 μ , title compound R_f 0.75 (1% KMnO_4); IR 1800 (β -lactam C=O), 1718 (amide C=O), 3315 (NH cm^{-1} in KBr; NMR (CDCl_3) δ 2.20 (s, 3, CH_3 —), δ 3.42 (2d, 2, $J=18$ Hz, S— CH_2), δ 3.45 (s, 3, OCH_3), δ 4.60 (s, 2, PhOCH_2), δ 5.05 (d, 1, C_β β -lactam, $J=5$ Hz), δ 5.40 (s, 2, CH_3OCH_2), δ 5.89 (d, 1, C_γ β -lactam, $J=5$ Hz), 5.89 (d, 1, C_γ β -lactam coupled with NH, $J=15$ Hz), δ 7.2 (m, 6, C_6H_5 , NH).

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_6\text{S}$: C, 55.08; H, 5.13; N, 7.14; S, 8.17.

Found: C, 54.68; H, 5.24; N, 7.07; S, 8.29.

D. 3 - Methyl - 7 - β - [D - 2 - phenylacetamido] - ceph - 3 - em - 4 - carboxylate (cephalexin).

10 g. (25.4 m.moles) Methoxymethyl 3-methyl-7- β -phenoxyacetamidoceph-3-em-4-carboxylate were dissolved in 100 ml. dry methylene chloride and the resultant solution was cooled to –50°C. N,N-Dimethylaniline (7.45 ml., 7.15 g., 59.0 m.moles) was added followed by the addition of 6.20 g. (29.77 m.moles) phosphorus pentachloride with high speed stirring. The mixture was brought to –30°C to –35°C and held at this temperature for two hours. At this point, thin layer chromatography on silica gel F 254, 250 μ ; system—75 benzene/25 ethyl acetate showed the presence of the chloromimide at R_f 0.5, when visualized with 1% potassium permanganate. The chlorination mixture was cooled to –50°C and treated with one portion of dry methanol (30 ml., 23.7 g., 0.74 mole) precooled to a temperature of –30°C. The resultant clear, light yellow solution was allowed to come to –35°C and held at this temperature for two hours. At this point, thin layer chromatography in the above system revealed the complete disappearance of the chloromimide at R_f 0.8. At –35°C, N,N-dimethylaniline (12.0 ml., 11.52 g., 95.07 m.mole) was added and the resultant mixture was brought to –30°C. 5.8 g. (28.15 m.moles) D-(–)- α -phenylglycylchloride hydrochloride, were added portion-wise over a 0.5 hour period at –30°C with high speed stirring. Complete solution was evident within 5 minutes after the addition of the acid chloride. The acylation mixture was held for one hour at –30°C and gradually warmed, over a 0.5 hour period, to 0°C. 20 ml. water at 0–5°C were added with high speed stirring. The pH, initially at 2.5, gradually dropped to 1.3–1.5 after 10 minutes hydrolysis time. The pH was then adjusted to 0.3–0.5 with 6N hydrochloric acid and the reaction was allowed to proceed at 0–5°C for three hours. At this point, thin layer chromatography on silica gel GF 254, 250 μ ; system—50 acetone/15 benzene/10 acetic acid/15 H_2O , visualized with 1% potassium permanganate, revealed the presence of cephalixin at R_f 0.8. The layers were separated and the aqueous phase was layered with an equal volume of 1-butanol. The mixture was adjusted to pH 4.5 with 30% aqueous sodium hydroxide at 0–5°C, then immediately seeded with cephalixin monohydrate. The mixture crystallized within one minute. The slurry was held at 25°C for two hours whereby the crystal structure changed from fine needles to large parallelograms. The mixture was cooled to 0–5°C and held for 16 hours at pH 4.5. The product was collected, washed with cold water/1-butanol, followed by 1-butanol. The colorless product was oven dried to 40°C to constant

weight giving 3.5 g. (38% yield) of cephalixin monohydrate: TLC, silica gel F 254, 250 μ , title compound at R_f 0.8, system-50 acetone/10 acetic acid/15 H_2O (1% $KMnO_4$), no other zones visible; $[\alpha]_D^{25} +125.6^\circ$ (C 1, water); $\lambda_{max}^{H_2O}$ nm (log ϵ) 260 (3.83), 210 (3.97); biopotency 888 $\mu g/mg$; IR 1770 (β -lactam C=O), 1690 amide C=O), 1580 (CO_2^-) cm^{-1} ; NMR (D_2O/d_6 -DMSO/DCI) δ 2.09 (s, 3, CH_3 -), δ 3.40 (2d, 2, J=18 Hz, S- CH_2), δ 5.05 (d, 1, J=5Hz, C_6 β -lactam), δ 5.25 (d, 2, J=5Hz, C_7 β -lactam), δ 7.55 (s, 5, C_6H_5).
 Anal. Calcd. for $C_{16}H_{17}N_3O_4S \cdot H_2O$: C, 52.59; H, 5.24; N, 11.50; S, 8.73; KF, 4.93.

Found: C, 52.49; H, 5.17; N, 10.96; S, 8.73; KF, 5.62.

E. Recrystallization of Cephalixin Monohydrate

1.0 g. cephalixin monohydrate was dissolved in 1:1 water/1-butanol by adjusting the pH to 1.0 with 6 N hydrochloric acid at 25°C. The mixture was warmed to 35–40°C, slowly adjusted to pH 4.5 with 10% aqueous sodium hydroxide, then seeded at pH 3.0. The seeded mixture was crystallized for 30 minutes at 35°C, then cooled to 25°C over a 45 minute period and held at this temperature for one hour. The slurry was cooled to 0–5°C and held at this temperature for 16 hours. The product was collected, washed with 0–5°C 1:1 water/1-butanol, then 1-butanol and oven dried to constant weight at 40°C giving 700 mg. of product (70% recovery) identical in all respects with that obtained in the acylation sequence above. The biopotency ranged between 915 $\mu g/mg$ and 1065 $\mu g/mg$.

Example 2

3-Methyl-7- β -[D-2-amino-2-phenylacetamido] ceph-3-em-4-carboxylate (cephalexin).

5.0 g. (12.7 m.moles) methoxymethyl - 3 - methyl - 7 - β - phenoxyacetamido- ceph - 3 - em - 4 - carboxylate were dissolved in 50 ml. dry methylene chloride and cooled to -50°C. N,N-Dimethylaniline (3.72 ml., 3.58 g., 29.5 m.moles) was added and the resultant mixture was treated with 3.1 g. (14.9 m.moles) pentachloride. The mixture was held at -30°C to -35°C for 2 hours then cooled to -60°C. The mixture was then treated, in one portion, with dry, precooled (-60°C) methanol (20 ml., 15.8 g., 0.49 mole) and then brought to -35°C to -40°C. After two hours at this temperature, N,N-dimethylaniline (6.0 ml., 5.76 g., 47.53 m.moles) was added, followed by the portionwise addition of 2.9 g. (14.08 m.moles) D-(-)- α -phenylglycyl chloride hydrochloride over a 0.5 hour period. The resultant mixture was held at -35°C for one hour then 30 ml. water were added, and the mixture was stirred for 10 minutes at 0–5°C and then for one hour at 25°C. The layers were separated and the aqueous layer was concentrated to about 15–18 ml. 20 ml. acetonitrile were added, and the pH was adjusted to 4.5–5.0 with 20% aqueous sodium hydroxide at 0–5°C. Cephalixin began to crystallize within one minute. The slurry was held at 0–5°C for six hours, the product was collected, washed with water, and acetonitrile then oven dried at 40°C giving 1.75 g. (38% yield) of pale yellow cephalixin: TLC, silica gel F 254, 250 μ , title compound R_f 0.80, system-50 acetone/15 benzene/10 acetic acid/15 H_2O (1% $KMnO_4$), no other zones were visible; NMR (60 MHz), showed traces of acetonitrile. The above product was recrystallized with 69% recovery, by pH adjustment in 1-butanol/water as described previously. The recrystallized product was identical in all respects with that obtained previously.

Example 3

3-Methyl-7- β -[D-2-amino-2-phenylacetamido]-ceph-3-em-4-carboxylate (cephalexin).

10.0 g. (25.4 m.moles) methoxymethyl 3 - methyl - 7 - β - phenoxyacetamido - ceph - 3 - em - 4 - carboxylate were dissolved in 100 ml. dry methylene chloride. The solution was cooled to -20°C then N,N-dimethylaniline (7.54 ml., 7.15 g., 59.0 m.moles) was added followed by the addition of 6.20 g. (29.77 m.moles) phosphorus pentachloride with high speed stirring. The resultant mixture was held at -20°C for two hours, and treated with precooled (-30°C) methanol (30 ml., 23.7 g., 0.74 mole). The mixture was brought to -20°C and held for two hours at this temperature. 5.8 g. (28.15 m.moles) D-(-)- α -phenyl-glycylchloride hydrochloride were added portionwise over a 0.5 hour period, at a temperature of -20°C, and with high speed stirring. The acylation was allowed to proceed for one hour at -25°C and gradually brought to 0°C over a one hour period. 20 ml. water were added to the reaction mixture and the mixture was brought to 25°C. The pH, initially at 2.5, dropped to 1.8

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after 10—15 minutes hydrolysis time. The pH was then adjusted to 0.2 with 6 N HCl and the mixture was stirred at 25°C for three hours. The layers were separated and the aqueous phase was layer with an equal volume of 1-butanol. The mixture was adjusted to pH 4.5 over a 30 minute period and seeded at pH 3.0. The mixture crystallized with two minutes at pH 4. The slurry was allowed to crystallize at 25°C for two hours and then cooled to 0—5°C and held for 16 hours. The product was collected, consecutively washed with 1:1 water/1-butanol, butanol, and isopropanol, then oven dried at 40—45°C giving 3.70 g. (40% yield) of the title compound which was identical in all respects with that obtained earlier. A second crop of slightly less pure cephalixin obtained by evaporation of the mother liquor and cooling for three hours at 0—5°C gave 1.20 g. (13%). Total yield was 53%.

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WHAT WE CLAIM IS:—

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1. A process for the preparation of cephalixin which comprises the steps of
(a) reacting methoxymethyl 3 - methyl - 7 - β - phenoxyacetamido - ceph - 3 - em - 4 - carboxylate, in an inert, water-immiscible solvent, at a temperature of -10°C to -60°C, and in the presence of an acid acceptor, with at least an equimolar amount of a halogenating agent;

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(b) reacting the reaction product of Step (a) with an aliphatic alcohol containing less than 7 carbon atoms while maintaining the temperature at from -20°C to -70°C;

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(c) reacting the reaction product of Step (b) with at least an equimolar amount of D-(-)-2-phenylglycyl chloride hydrochloride, at a temperature below -30°C;

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(d) hydrolyzing the reaction product of Step (c);

(e) then basifying the hydrolyzed reaction product of Step (d) to produce the zwitterion, cephalixin.

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2. A process as claimed in Claim 1 wherein said methoxymethyl - 3 - methyl - 7 - β - phenoxyacetamido - ceph - 3 - em - 4 - carboxylate is produced by reacting penicillin V sulfoxide with chloromethyl methylether in the presence of an acid acceptor to produce methoxymethyl, 6-phenoxyacetamido-penicillinate sulfoxide, then converting same to said methoxymethyl 7-phenoxyacetamido-3-methylceph-3-em-4-carboxylate by conventional ring expansion reaction.

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3. A process as claimed in Claim 1 or 2 wherein said acid acceptor is an acid deactivating tertiary amine and the methoxymethyl 6-phenoxyacetamido-penicillinate sulfoxide is converted by an acid catalyzed thermal rearrangement.

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4. A process as claimed in any one of claims 1 to 3 wherein the solvent in Step (a) is an anhydrous inert water-immiscible solvent selected from methylene chloride, dichloroethane, chloroform, tetrachloroethane, nitromethane and diethylether; the halogenating agent employed in Step (a) is selected from phosphorus pentachloride, phosphorous pentabromide, phosphorus trichloride, phosphorus tribromide, oxalylchloride, p-toluenesulfonyl halide, phosphorus oxychloride and phosgene; and the acid acceptor of Step (a) is an acid deactivating tertiary amine selected from triethylamine, trimethylamine, dimethylaniline, quinoline, lutidine and pyridine.

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5. A process as claimed in any one of Claims 1 to 4 wherein the hydrolysis reaction of Step (d) is carried out by mixing the reaction product of Step (c) with water and a mineral acid and in Step (c) said D-(-)-2-phenylglycyl chloride hydrochloride is reacted incrementally with said reaction product of Step (b).

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6. A process as claimed in any one of Claims 1 to 5 wherein in Step (a) said halogenating agent is phosphorus pentachloride.

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7. A process as claimed in any one of Claims 1 to 6 wherein said reaction of Step (a) is carried out at a temperature below -15°C and in Step (b) said aliphatic alcohol is methanol.

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8. A process as claimed in any one of Claims 1 to 7 wherein in Step (a) said inert solvent is methylene chloride, said acid acceptor is dimethylaniline, said halogenating agent is phosphorus pentachloride and said reaction is carried out at a temperature of below -15°C; in Step (b) said aliphatic alcohol is methanol and said temperature is below -30°C; and in Step (d) the hydrolysis of the reaction product of Step (c) is carried out by mixing same with water and sulfuric acid or hydrochloric acid at a temperature below 10°C.

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9. Methoxymethyl 3 - methyl - 7 - β - phenoxyacetamido - ceph - 3 - em - 4 - carboxylate.

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10. Methoxymethyl 6-phenoxyacetamido-penicillinate sulfoxide.

11. A process for the preparation of cephalixin as claimed in claim 1 and substantially as herein described in any one of the Examples.



after 10—15 minutes hydrolysis time. The pH was then adjusted to 0.2 with 6 N HCl and the mixture was stirred at 25°C for three hours. The layers were separated and the aqueous phase was layer with an equal volume of 1-butanol. The mixture was adjusted to pH 4.5 over a 30 minute period and seeded at pH 3.0. The mixture crystallized with two minutes at pH 4. The slurry was allowed to crystallize at 25°C for two hours and then cooled to 0—5°C and held for 16 hours. The product was collected, consecutively washed with 1:1 water/1-butanol, butanol, and isopropanol, then oven dried at 40—45°C giving 3.70 g. (40% yield) of the title compound which was identical in all respects with that obtained earlier. A second crop of slightly less pure cephalixin obtained by evaporation of the mother liquor and cooling for three hours at 0—5°C gave 1.20 g. (13%). Total yield was 53%.

WHAT WE CLAIM IS:—

1. A process for the preparation of cephalixin which comprises the steps of
 - (a) reacting methoxymethyl 3 - methyl - 7 - β - phenoxyacetamido - cephalixin - 3 - em - 4 - carboxylate, in an inert, water-immiscible solvent, at a temperature of -10°C to -60°C, and in the presence of an acid acceptor, with at least an equimolar amount of a halogenating agent;
 - (b) reacting the reaction product of Step (a) with an aliphatic alcohol containing less than 7 carbon atoms while maintaining the temperature at from -20°C to -70°C;
 - (c) reacting the reaction product of Step (b) with at least an equimolar amount of D-(—)-2-phenylglycyl chloride hydrochloride, at a temperature below -30°C;
 - (d) hydrolyzing the reaction product of Step (c);
 - (e) then basifying the hydrolyzed reaction product of Step (d) to produce the zwitterion, cephalixin.
2. A process as claimed in Claim 1 wherein said methoxymethyl - 3 - methyl - 7 - β - phenoxyacetamido - cephalixin - 3 - em - 4 - carboxylate is produced by reacting penicillin V sulfoxide with chloromethyl methylether in the presence of an acid acceptor to produce methoxymethyl 6-phenoxyacetamido-penicillinate sulfoxide, then converting same to said methoxymethyl 7-phenoxyacetamido-3-methylceph-3-em-4-carboxylate by conventional ring expansion reaction.
3. A process as claimed in Claim 1 or 2 wherein said acid acceptor is an acid deactivating tertiary amine and the methoxymethyl 6-phenoxyacetamido-penicillinate sulfoxide is converted by an acid catalyzed thermal rearrangement.
4. A process as claimed in any one of claims 1 to 3 wherein the solvent in Step (a) is an anhydrous inert water-immiscible solvent selected from methylene chloride, dichloroethane, chloroform, tetrachloroethane, nitromethane and diethylether; the halogenating agent employed in Step (a) is selected from phosphorus pentachloride, phosphorus pentabromide, phosphorus trichloride, phosphorus tribromide, oxalylchloride, p-toluenesulfonyl halide, phosphorus oxychloride and phosgene; and the acid acceptor of Step (a) is an acid deactivating tertiary amine selected from triethylamine, trimethylamine, dimethylaniline, quinoline, lutidine and pyridine.
5. A process as claimed in any one of Claims 1 to 4 wherein the hydrolysis reaction of Step (d) is carried out by mixing the reaction product of Step (c) with water and a mineral acid and in Step (c) said D-(—)-2-phenylglycyl chloride hydrochloride is reacted incrementally with said reaction product of Step (b).
6. A process as claimed in any one of Claims 1 to 5 wherein in Step (a) said halogenating agent is phosphorus pentachloride.
7. A process as claimed in any one of Claims 1 to 6 wherein said reaction of Step (a) is carried out at a temperature below -15°C and in Step (b) said aliphatic alcohol is methanol.
8. A process as claimed in any one of Claims 1 to 7 wherein in Step (a) said inert solvent is methylene chloride, said acid acceptor is dimethylaniline, said halogenating agent is phosphorus pentachloride and said reaction is carried out at a temperature of below -15°C; in Step (b) said aliphatic alcohol is methanol and said temperature is below -30°C; and in Step (d) the hydrolysis of the reaction product of Step (c) is carried out by mixing same with water and sulfuric acid or hydrochloric acid at a temperature below 10°C.
9. Methoxymethyl 3 - methyl - 7 - β - phenoxyacetamido - cephalixin - 3 - em - 4 - carboxylate.
10. Methoxymethyl 6-phenoxyacetamido-penicillinate sulfoxide.
11. A process for the preparation of cephalixin as claimed in claim 1 and substantially as herein described in any one of the Examples.

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12. A process for the preparation of the compound of claim 10 substantially as herein described in part A of Example 1.

13. A process for the preparation of the compound of claim 9 substantially as herein described in any of Runs 1 to 5 of part B, or part C of Example 1.

5. 14. Cephalexin when prepared by the process as claimed in any one of claims 1 to 8, or 11.

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15. A pharmaceutical composition comprising cephalexin as claimed in claim 14 together with an inert pharmaceutically-acceptable carrier.

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