

PATENT SPECIFICATION

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(54) DETHIACEPHALOSPORANIC ACID DERIVATIVES AND THEIR PREPARATION AND USE

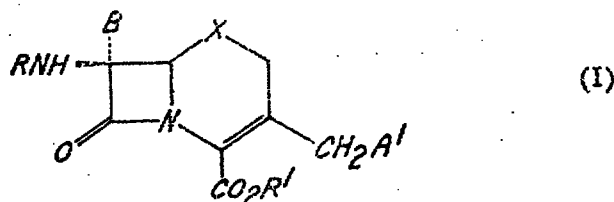
(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with novel antibiotics, processes for preparing them, and novel intermediate compounds produced in the process.

The products are useful in removing susceptible microorganisms from pharmaceutical, medical and dental equipment and as bactericides in industrial applications, for example, in water-based paints and in the white water of paper mills to inhibit the growth of harmful bacteria.

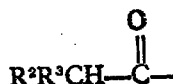
The novel compounds of this invention have the following structural formula:

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in which B is H, OCH₃, CH₃ or SR where R is lower alkyl of 1—6 carbon atoms (e.g., methyl, ethyl, propyl, butyl or hexyl) or aryl (e.g., phenyl):

R is an acyl radical, for example, an aliphatic, aromatic, heterocyclic araliphatic or heterocyclic aliphatic carboxylic acid radical of the formula:



where R² and R³ are as defined below;

R¹ is hydrogen or a protecting group;

A¹ is hydrogen, hydroxy, amino, N-substituted amino, mercapto, C₁₋₆ alkylthio, carbamoyloxy, thiocarbamoyloxy, quaternary ammonium, N-(C₁₋₆ alkyl)-carbamoyloxy such as N-methyl carbamoyloxy, N,N-di-(C₁₋₆ alkyl) carbamoyloxy such as N,N-dimethyl carbamoyloxy, N-(C₁₋₆ alkyl)thio carbamoyloxy or N,N-di(C₁₋₆ alkyl)thio carbamoyloxy, azido, halogen, cyano, quaternary amino such as pyridinium, alkylpyridinium, halopyridinium or aminopyridinium, C₁₋₆ alkanoyloxy such as acetoxy or propionyloxy, aryloxy such as benzoyloxy, or a 5-membered heterocyclic thio group having 1—4 hetero atoms, the latter being S, O and/or N; and

X is —O—, —CH₂—, or —NY— where Y is hydrogen, alkyl of from 1 to 6 carbon atoms such as methyl, ethyl, *i*-propyl, *n*-butyl, *n*-pentyl or *n*-hexyl, formyl or benzyl; or are non-toxic, pharmacologically acceptable salt, ester or amide derivatives of such compounds.

By the phrase a "(5-membered heterocyclic)thio group having 1—4 hetero atoms, the latter being S, O, or N" is meant a group having the formula



where Q is a 5-membered heterocyclic ring having oxa, aza, thia, dioxo, diaza, dithia, trioxo, triaza, trithia, tetra-aza, or mixed hetero atoms in the ring. Included within this definition are the heterocyclic rings, listed above, as well as the following additional rings; 1H-tetrazole; 2H-tetrazole; 3H-1,2,3-oxathiazole; 1,4,2-oxathiazole; 5H-1,2,5-oxathiazole; 3H-1,2,4-dioxazole; 1,3,4-dioxazole; 1,2,4-dithiazole; 1,3,4-dithiazole; 1,2,3-oxadiazole; 1,2,4-oxadiazole; 1,2,5-oxadiazole; 1,3,4-oxadiazole; 1,2,3-thiadiazole; 1,2,4-thiadiazole; 1,2,5-thiadiazole; 1,3,4-thiadiazole; 1H-1,2,3-triazole; 1,2,5-oxadithiole; 1,3,2-dioxathiole; 1,2,3-trioxole; 1,2,4-trioxolane, 1,2,3-trithiole and; 1,2,4-trithiolane. The point of attachment can be in any suitable position of the ring.

Other suitable rings can be found in the literature, including the ACS monograph, *The Ring Index*, Ed. Capell et. al., Second Edition (1957) and supplements (1959), (1963), (1965).

Representative of the hetero groups of interest include furyl, thienyl, thiazolyl, thiadiazolyl, pyrrolyl, pyrazolyl and tetrazolyl or such a substituted heterocyclic group having one or more alkyl, alkoxy, halo, cyano or carboalkoxy substituents. Two heterocyclic thio groups of particular interest are 5-methyl-1,3,4-thiadiazol-2-yl and 1-methyl-tetrazol-5-yl.

Those compounds in which the acyl radical, R, is of the formula:

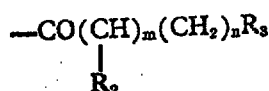


wherein R² and R³ are as defined below, and A¹ is hydrogen, C₁₋₆ alkanoyloxy, heterocyclic thio, carbamoyloxy or pyridinium are preferred because of their generally enhanced antibiotic activity. R² represents hydrogen, halogen, amino, guanidino, phosphono, hydroxy, tetrazolyl, carboxy, sulfo or sulfonamido. R³ represents phenylacetimid-

amido, phenyl, substituted phenyl, a 5- or 6-membered monocyclic heterocyclic ring containing one or more oxygen, sulfur or nitrogen hetero atoms in the ring such as furyl, thienyl, thiazolyl, isothiazolyl, tetrazolyl, oxadiazolyl or thiadiazolyl, a substituted heterocyclic ring, phenylthio, phenyloxy, a heterocyclic thio or substituted heterocyclic thio group or cyano. The substituents can be halo, carboxymethyl, guanidino, guanidinomethyl, carboxamidomethyl, aminomethyl, nitro, methoxy or methyl. Especially preferred are those acyl radicals where R^2 is hydrogen, hydroxy, amino or carboxy and R^3 is a substituted or unsubstituted phenyl group or 5- or 6-membered heterocyclic ring containing from 1 to 4 sulfur, oxygen or nitrogen atoms. Examples of these preferred radicals are phenylacetyl, 3-bromophenylacetyl, *p*-aminomethylphenylacetyl, 4-carboxymethylphenylacetyl, 4-carboxamidomethylphenylacetyl, 2-furylacetyl, 5-nitrofurylacetyl, 3-furylacetyl, 2-thienylacetyl, 3-thienylacetyl, 4-methylthienylacetyl, 3-isothiazolylacetyl, 4-idino-2-thienylacetyl, 3-thienylacetyl, 4-methylthienylacetyl, 3-isothiazolylacetyl, 4-methoxyisothiazolylacetyl, 4-isothiazolylacetyl, 3-methylisothiazolylacetyl, 5-isothiazolylacetyl, 3-chloroisothiazolylacetyl, 3-methyl-1,2,5-oxadiazolylacetyl, 1,2,5-thiadiazolyl-4-acetyl, 3-methyl-1,2,5-thiadiazolyl-4-acetyl, 3-chloro-1,2,5-thiadiazolyl-4-acetyl, 3-methoxy-1,2,5-thiadiazolyl-4-acetyl, phenylthioacetyl, 4-pyridylthioacetyl, cyanoacetyl, 1-tetrazolylacetyl, α -fluorophenylacetyl, *D*-phenylglycyl, 4-hydroxy-*D*-phenylglycyl, 2-thienylglycyl, 3-thienylglycyl, phenylmalonyl, 3-chlorophenylmalonyl, 2-thienylmalonyl, 3-thienylmalonyl, α -phosphonophenylacetyl, α -amino cyclohexadienylacetyl, α -sulfaminophenylacetyl, α -hydroxyphenylacetyl, α -tetrazolylphenylacetyl and α -sulfophenylacetyl.

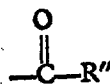
However, it is to be understood that any acyl radical that is conventionally used in the cephalosporin and penicillin antibiotic art may be used in the practice of the invention and is to be considered within the scope of the invention. Additional illustrations of representative acyl residues are as follows:

The acyl radical can be a substituted or unsubstituted aliphatic, aromatic or heterocyclic, araliphatic or heterocyclic aliphatic carboxylic acid radical or a carbothioic acid radical such as the acyl radicals of the known cephalosporins and penicillins. These acyl radicals can be represented by the general formula:



where R_2 is a radical of the group defined below, m and n represent 0, 1, 2, 3 or 4 and R_3 represents R'' or ZR'' , which are defined below.

One group of acyl radicals can be represented by the general formula

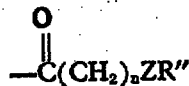


where R'' represents a substituted or unsubstituted straight or branched chain alkyl, alkenyl, or alkynyl group; aryl, aralkyl; cycloalkyl; or a heteroaryl or heteroaralkyl group. These groups can be unsubstituted or can be substituted by radicals such as hydroxy, mercapto, alkylthio, arylthio, alkyl, alkoxy, halo, cyano, carboxy, sulfamoyl, carbamoyl, sulfonyl, azido, amino, substituted amino, haloalkyl, carboxyalkyl, carbamoylalkyl, *N*-substituted carbamoylalkyl, guanidino, *N*-substituted guanidino or guanidinoalkyl. Representative examples of such acyl groups that might be mentioned are those where R'' is benzyl, *p*-hydroxybenzyl, 4-amino-4-carboxybutyl, methyl, cyano-methyl, 2-pentenyl, *n*-amyl, *n*-heptyl, ethyl, 3- or 4-nitrobenzyl, phenethyl, β,β -diphenylethyl, α,α -diphenylethyl, triphenylmethyl, 2-methoxyphenyl, 2,6-dimethoxyphenyl, 2,4,6-trimethoxyphenyl, 3,5-dimethyl-4-isoxazolyl, 3-butyl-5-methyl-4-isoxazolyl, 5-methyl-3-phenyl-4-isoxazolyl, 3-(2-chlorophenyl)-5-methyl-4-isoxazolyl, 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl, *D*-4-amino-4-carboxybutyl, *D*-4-*N*-benzoylamino-4-carboxy-*n*-butyl, *p*-aminobenzyl, *o*-aminobenzyl, *m*-aminobenzyl, (3-pyridyl)methyl, 2-ethoxy-1-naphthyl, 3-carboxy-2-quinolalanyl, 3-(2,6-dichlorophenyl)-5-idyl)methyl, 2-ethoxy-1-naphthyl, 3-carboxy-2-quinolalanyl, 3-(2,6-dichlorophenyl)-5-(2-furyl)-4-isoxazolyl, 3-phenyl-4-isoxazolyl, 5-methyl-3-(4-guanidinophenyl)-4-isoxazolyl, 4-guanidinomethylphenyl, 4-guanidinomethylbenzyl, 4-guanidinobenzyl, 4-guanidinophenyl, 2,6-dimethoxy-4-guanidinophenyl, *o*-sulfobenzyl, *p*-carboxymethylbenzyl, *p*-carbamoylmethylbenzyl, *m*-fluorobenzyl, *m*-bromobenzyl, *p*-chlorobenzyl, 5-isothiazolyl-oxybenzyl, 1-naphthylmethyl, 3-isothiazolylmethyl, 4-isothiazolylmethyl, 5-isothiazolylmethyl, 4-pyridylmethyl, 5-isoxazolylmethyl, 4-methoxy-5-isoxazolylmethyl, 4-methyl-5-isoxazolylmethyl, 1-imidazolylmethyl, 2-benzofuranylmethyl, 2-indolylmethyl, 2-

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phenylvinyl, 2-phenylethynyl, 2-(5-nitrofuranyl)vinyl, phenyl, *o*-methoxyphenyl, *o*-chlorophenyl, *o*-phenylphenyl, *p*-aminomethylbenzyl, 1-(5-cyanotriazolyl)methyl, difluoromethyl, dichloromethyl, dibromomethyl, 1-(3-methylimidazolyl)methyl, 2- or 3-(5-carboxymethylthienyl)methyl, 2- or 3-(4-carbamoylthienyl)methyl, 2- or 3-(5-methylthienyl)methyl, 2- or 3-(5-methoxythienyl)methyl, 2- or 3-(4-chlorothienyl)methyl, 2- or 3-(5-sulfothienyl)methyl, 2- or 3-(5-carboxythienyl)methyl, 3-(1,2,5-thiadiazolyl)methyl, 3-(4-methoxy-1,2,5-thiadiazolyl)methyl, 2-furylmethyl, 2-(5-nitrofuryl)methyl, 3-furylmethyl, 2-thienylmethyl, 3-thienylmethyl, and tetrazolylmethyl.

The acyl group can also be a radical of the formula

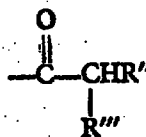


wherein *n* is 0, 1, 2, 3 or 4, Z represents oxygen or sulfur, and R'' is as defined above. Representative members of the substituent



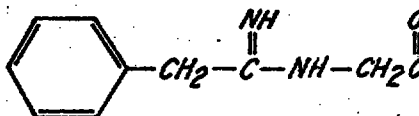
that might be mentioned are allylthiomethyl, phenylthiomethyl, butylmercaptomethyl, α -chlorocrotylmercaptomethyl, phenoxymethyl, phenoxyethyl, phenoxybutyl, dimethylmethoxymethyl, dimethylbutoxymethyl, dimethylphenoxymethyl, 4-guanidinophenoxymethyl, 4-pyridylthiomethyl, *p*-(carboxymethyl)phenoxymethyl, *p*-(carboxymethyl)phenylthiomethyl, 2-thiazolylthiomethyl, *p*-(sulfo)phenoxymethyl, *p*-(carboxy)phenylthiomethyl, *p*-(carboxymethyl)phenoxymethyl, *p*-(carboxymethyl)phenylthiomethyl, 2-pyrimidinylthiomethyl, phenethylthiomethyl, 1-(5,6,7,8-tetrahydronaphthyl)oxymethyl, N-methyl-4-pyridylthio.

Alternatively, the acyl group can be a radical of the formula



where R'' is defined as above and R''' is an amino, hydroxy, azido, carbamoyl, guanidino, acyloxy, halo, sulfamino, tetrazolyl, sulfo, carboxy or alkoxy carbamoyl radical.

Also of interest is the following acyl residue:



Representative members of the substituent



that might be mentioned are α -aminobenzyl, 2-thienyl-aminomethyl, α -methylaminobenzyl, α -amino-methylmercaptopropyl, α -amino-3- or 4-chlorobenzyl, α -amino-3 or 4-hydroxybenzyl, α -amino-2,4-dichlorobenzyl, α -amino-3,4-dichlorobenzyl, β (-)- α -hydroxybenzyl, α -carboxybenzyl, 3-thienyl-aminomethyl, D(-)- α -amino-3-chloro-4-hydroxybenzyl, D(-)-3-thienyl-aminomethyl or 1-aminocyclohexyl, α -(5-tetrazolyl)-benzyl, 2-thienyl-carboxymethyl, 3-thienyl-carboxymethyl, 2-furyl-carboxymethyl, 3-furyl-carboxymethyl, α -sulfaminobenzyl, 3-thienyl-sulfaminomethyl, α -(N-methylsulfamino)benzyl, D(-)-2-thienyl-guanidinomethyl, D(-)- α -guanidinobenzyl, α -guanyluroidobenzyl, α -hydroxybenzyl, α -azidobenzyl, α -fluorobenzyl, 4-(5-methoxy-1,3-oxadiazolyl)-aminomethyl, 4-(5-methoxy-1,3-oxadiazolyl)-carboxymethyl, 4-(5-methoxy-1,3-sulfadiazolyl)-aminomethyl, 4-(5-methoxy-1,3-sulfadiazolyl)-hydroxymethyl, 4-(5-methoxy-1,3-sulfadiazolyl)-carboxymethyl, 2-(5-chlorothienyl)-aminomethyl, 2-(5-chlorothienyl)-hydroxymethyl, 2-(5-

chlorothienyl)-carboxymethyl, 3-(1,2-thiazolyl)-aminomethyl, 3-(1,2-thiazolyl)-hydroxymethyl, 3-(1,2-thiazolyl)-carboxymethyl, 2-(1,4-thiazolyl)-aminomethyl, 2-(1,4-thiazolyl)-hydroxymethyl, 2-(1,4-thiazolyl)-carboxymethyl, 2-benzothienylaminomethyl, 2-benzothienylhydroxymethyl, 2-benzothienylcarboxymethyl, α -sulfobenzyl, α -phosphonobenzyl, α -diethylphosphono, and α -monoethylphosphono.

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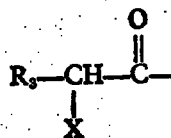
Alternatively, the group R—N can be a sulfonamido group such as phenylsulfonamido, ethylsulfonamido, benzylsulfonamido, 2,5-dimethylbenzenesulfonamido, 4-chlorobenzenesulfonamido or 4-methoxybenzenesulfonamido.

The acyl substituents of the general formula



where R_{10} and R_{11} are as defined below represent a preferred group of substituents because of their generally useful antibiotic activity. R_{10} represents hydrogen, halo, amino, guanidino, phosphono, hydroxy, tetrazolyl, carboxy, sulfo, or sulfonamido. R_{11} represents phenyl, substituted phenyl, a monocyclic substituted or unsubstituted heterocyclic 5- or 6-membered ring containing one or more oxygen, sulfur or nitrogen atoms in the ring, phenylthio, a heterocyclic thio or substituted heterocyclic-thio group; or cyano. The substituents can be halo, carboxymethyl, guanidino.

Of particular interest are acyl groups represented by the formula:



where X is hydrogen, halogen, amino, guanidino, phosphono, hydroxy, tetrazolyl, carboxy, sulfo, or sulfonamido; R_3 is phenyl, substituted phenyl, a substituted or unsubstituted monocyclic heterocyclic 5- or 6-membered ring containing one or more oxygen, sulfur or nitrogen atoms in the ring, phenylthio, phenyloxy, a heterocyclic thio or substituted heterocyclic thio group, C_{1-6} alkyl, or cyano; any substituents on the R_3 group being halogen, carboxymethyl, guanidino, guanidinomethyl, carboxyamidomethyl, aminomethyl, nitro, methoxy or methyl. Particularly preferred are acyl groups in which X is hydrogen, hydroxy, amino or carboxy and R_3 is phenyl, lower alkyl or a 5- or 6-membered heterocyclic ring having one or two sulfur, oxygen or nitrogen hetero atoms. Thus, specific R_3 substituents that might be mentioned as preferred substituents are tetrazolyl, thienyl, furyl and phenyl.

With respect to the term A'; A' can be a halogenator such as chlorine, bromine or fluorine.

When A' is a substituted hydroxy or substituted mercapto group, it can be shown by the formula



where Z is oxygen or sulfur, and R_x is an acyl group, a straight or branched C_{1-6} alkyl, C_{2-6} or C_{3-6} alkynyl group; an aryl group; an aralkyl group; or a heterocyclic group such as heteroaryl or heteroalkyl. The heterocyclic group is preferably a 5- or 6-membered ring containing one or more sulfur, nitrogen or oxygen atoms. These groups can be unsubstituted or can be substituted by radicals such as C_{1-6} alkyl, C_{1-6} alkoxy, halo, cyano, carboxy, carbamoyl, N-substituted carbamoyl, azido, sulfo, amino, substituted amino, haloalkyl, carboxyalkyl, carbamoylalkyl, N-substituted carbamoylalkyl, guanidino, N-substituted guanidino, guanidinoalkyl, sulfamoyl or substituted sulfamoyl.

Representative of the groups $-ZR_x$ thus presented that might be mentioned are isoxazolylthio, pyrrolidinylthio, 1,3,4-thiadiazolylthio, N-oxidopyridylthio, furazanylthio, tetrazolylthio, thienylthio, thiazolylthio, furylthio, pyranlylthio, pyrrolylthio, imidazolylthio, pyrazolylthio, pyridylthio, pyrazinylthio, pyrimidinylthio, pyridazinylthio, isothiazolylthio, methoxy, *n*-propoxy, methylthio, acetoxy, propionyloxy, benzyloxy, (*p*-chlorobenzoyl)oxy, (*p*-methylbenzoyl)oxy, pivaloyloxy, (1-adamantyl)carboxy, isobutanoyloxy, carbamoyloxy, (N-methylcarbamoyl)oxy, (N-ethylcarbamoyl)oxy, [N-(2-chloroethyl)carbamoyl]oxy, (N-phenylcarbamoyl)oxy, (N-*p*-sulphophenylcarbamoyl)oxy, *p*-carboxymethylphenylcarbamoyloxy, methoxycarbonyloxy, isobutanoyloxy, cyclobutylcarbonyloxy, carbamoylthio, (ethoxythiocarbonyl)thio, (N-propoxythiocarbonyl)thio, (cyclopentanoxythiocarbonyl)thio, methylthio, N,N-diethylthiocarbamoylthio, N-methylpiperazinium-1-thiocarbonylthio, N,N-dimethylpiperazinium-1-thiocarbonylthio.

onylthio, 2-furoylthio, isothiuronium, (5-methyl-1,3,4-thiadiazol-2-yl)thio, p-tolylsulfonylthio, mesyloxy, methyl-1,2,3,4-tetrazolyl-5-thio, tosyloxy, sulfamoyloxy, 1-naphthoyloxy, 2-furylacetoxo, cinnamoyloxy, p-hydroxycinnamoyloxy, p-sulfocinnamoyloxy and 1R:2S-epoxypropylphosphonyloxy.

Alternatively, when A' is hydroxy, the cephalosporin can also exist as the lactone, which is formed by internal esterification with the carboxy group.

The substituent A' can also be amino or substituted amino, including nitrogen-containing unsubstituted and substituted heterocyclic groups. Examples of such groups that might be mentioned are amino, acetamido, carbamoylamino, N,N-dimethylamino, N-(2-chloroethyl)amino, 5-cyanotriazol-1-yl and 4-methoxycarbonyltriazol-1-yl.

When A' is amino the cephalosporin compound can also exist as the lactam formed by loss of water with the adjacent carboxy group.

Representative of the quaternary ammonium groups representing A' that might be mentioned are pyridinium, 3-methylpyridinium, 4-methylpyridinium, 3-chloropyridinium, 3-bromopyridinium, 3-iodopyridinium, 4-carbamoylpyridinium, 4-(N-hydroxymethylcarbamoyl)pyridinium, 4-(N-carbomethoxycarbamoyl)pyridinium, 4-(N-cyanocarbamoyl)pyridinium, 4-(carboxymethyl)pyridinium, 4-(hydroxymethyl)pyridinium, 4-(trifluoromethyl)pyridinium, quinolinium, picolinium and lutidinium.

The preferred groups representing A' are hydrogen, halo, azido, cyano, hydroxy, alkoxy, aryloxy, aralkyloxy, heterocycloxy, mercapto, alkylthio, arylthio, aralkylthio, heterocyclicthio, amino, alkylamino, alkanoylamino, hydroxyphenyl, acylthio, acyloxy, isothiuronium, sulfamoyloxy, quaternary ammonium, a heterocyclic tertiary amine, alkylsulfonyloxy and (cis-1,2-epoxypropyl)phosphono. The heterocyclic rings can be a 5 or 6-membered hetero ring containing one or more nitrogen, oxygen or sulfur atoms. The acyl group can be a loweralkanoyl group of 2-6 carbon atoms, carbamoyl, or thio-carbamoyl and N-alkyl or N,N-dialkyl derivatives thereof. The alkyl group of the foregoing substituents contains 1-6 carbon atoms and may be further substituted by radicals such as alkoxy, halo, amino, cyano, carboxy or sulfo.

It may be noted that the substituent at the 3-position of the cephalosporin nucleus may be converted to or readily replaced by other A' substituents pursuant to well known methods. For example, upon treating the 3-acetoxymethyl substituted cephalosporanates of this invention with a suitable reagent or combination of reagents, it is possible to substitute various substituents for acetoxy at the 3-position of the cephalosporin nucleus. Suitable reagents include, for example, isocyanates, alkali metal toluenesulfonates, alkali metal azides, polyhydroxybenzenes, N-(C₁₋₆ alkyl)-indoles, thiourea, mercaptans, thio-cyanates, heterocyclic thiols, cycloalkyl xanthates, pyridine, thiobenzoic acid, N-alkyl and N,N-dialkylthioureas and alkali metal N-alkyl and N,N-dialkylthiocarbamates.

Thus by reaction with a heterocyclic thiol, for example 1-methyl-1,2,3,4-tetrazole-5-thiol or 5-methyl-1,3,4-thiadiazol-2-thiol, the 3-acetoxymethyl-cephalosporin is converted to the corresponding heterothiomethyl compound.

Also, by reaction with a tertiary amine, for example pyridine, the 3-acetoxymethyl-cephalosporin is converted to the corresponding quaternary compound, e.g. a 3-pyridiniummethyl compound. Alternatively, the 3-acetoxymethyl-cephalosporins upon treatment with citrus acetylase are converted to the corresponding 3-hydroxymethyl compounds which can be acylated to produce other 3-acyloxymethyl compound including carbamoyloxymethyl, acylthiomethyl, C₁₋₆ alkanoyl, or aroyl, by using an acylating agent such as a suitable carboxylic acid halide or anhydride, a substituted carbamoyl halide, a C₁₋₆ alkyl isocyanate, or phosgene and a secondary amine.

The 3-acetoxy group may also be converted to other analogs by replacing the acetoxy group with nucleophilic radicals containing nitrogen or sulfur. Many such radicals are well known in the cephalosporin art: they include tertiary amines such as pyridine and, 5-membered heterocyclic thiols such as 5-methyl-1,3,4-thiadiazolyl-2-thiol and N-methyl-tetrazolylthiol. Alternatively, the 3-acetoxy group can be removed by catalytic hydrogenation to afford the 3-methyl compounds.

One method for the introduction of an N,N-di(C₁₋₆ alkyl)carbamoyloxymethyl or heterocyclic aminocarbonyloxyethyl residue at position 3 of the products of the present invention consists in treating a 3-hydroxymethyl analogue such as a 3-hydroxymethyl-7-methoxy-7-(2-thienylacetamido)-1-methylene-dethia-ceph-3-em-4-carboxylic acid with phosgene and a di(C₁₋₆ alkyl)amine in the presence of a base. In this manner the following products can be obtained: sodium dl-3-(N,N-dimethylcarbamoyloxymethyl)-7-methoxy-7-(2-thienylacetamido)-1-methylenedethia-ceph-3-em-4-carboxylate and sodium dl-3-(pyrrolidinyl-carbonyloxymethyl)-7-methoxy-7-(2-thienylacetamido)-1-methylenedethia-ceph-3-em-4-carboxylate.

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ali	35
io-	35
kyl	
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on-	40
yl-	40
yr-	
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hyl	
id-	45
ing	45
oyl	
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or	55
ent	55
yl-	
4-	
In	60
yl-	60
ia-	
l)-	
rb-	65

The N-monosubstituted carbamoyloxyethylcephalosporin products may be obtained by treating a 3-hydroxymethyl-7-amidodecephalosporanate with a suitable isocyanate.

The unsubstituted carbamoyloxymethyl material may be obtained by cleaving an N-substituted carbamoyloxymethyl material such as N,N-di-*p*-methoxybenzylcarbamoyloxymethyl or N-2,2,2-trichloroethyl carbamoyloxymethyl material. An alternative method for obtaining the carbamoyloxymethyl group at the 3-position involves treating the 3-hydroxymethyl analogue with trichloroacetyl isocyanate or chlorosulfonyl isocyanate, followed by hydrolysis.

The carboxy group of the starting material may be blocked or protected, preferably by the use of a group R¹, which can be removed to obtain the free acid without disruption of the β -lactam residue. Protecting groups suitable for this purpose are well known.

The group protecting the carboxyl group may be formed with an alcohol (aliphatic or araliphatic), phenol, silanol, stannanol or acid which may readily be split off at a later stage of the reaction.

Suitable esters thus include compounds containing as the 4-ester group, a group selected from the following list which is representative and not intended to be an exhaustive list of possible ester groups:

(i) —COOCR^aR^bR^c where at least one of R^a, R^b and R^c is an electron-donor, e.g. *p*-methoxyphenyl, 2,4,6-trimethylphenyl, 9-anthryl, methoxy, acetoxy, CH₂SCH₃, tetrahydrofur-2-yl, tetrahydropyran-2-yl or fur-2-yl. The remaining R^a, R^b and R^c groups may be hydrogen or organic substituents. Suitable ester groups of this type include *p*-methoxybenzyloxycarbonyl and 2,4,6-trimethylbenzyloxycarbonyl.

(ii) —COOCR^aR^bR^c where at least one of R^a, R^b and R^c is an electron-attracting group; e.g., benzoyl, *p*-nitrophenyl, 4-pyridyl, trichloromethyl, tribromomethyl, iodomethyl, cyanomethyl, ethoxycarbonylmethyl, arylsulphonylmethyl, 2-dimethylsulphoniummethyl, *o*-nitrophenyl or cyano. The remaining R^a, R^b and R^c groups may be hydrogen or organic substituents. Suitable esters of this type include benzoylmethoxycarbonyl, *p*-nitrobenzyloxycarbonyl, 4-pyridylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl and 2,2,2-tribromoethoxycarbonyl.

(iii) —COOCR^aR^bR^c wherein at least two of R^a, R^b and R^c are hydrocarbon such as alkyl, e.g. methyl or ethyl, or aryl e.g. phenyl and the remaining R^a, R^b and R^c group, if there is one, is hydrogen. Suitable esters of this type include *t*-butoxycarbonyl, *t*-amylxycarbonyl, diphenylmethoxycarbonyl and triphenylmethoxycarbonyl.

(iv) —COOR^d where R^d is adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl or tetrahydropyran-2-yl.

Silyl esters may conveniently be prepared from a halosilane or a silazane of the formula R¹₃SiX; R¹₂SiX₂; R¹₃Si.NR⁴₃; R¹₃SnR⁴₃; R¹₃Si.NH.COR⁴; R¹₃Si.NH.CO.NH.SiR⁴₃; R¹NH.CO.NR⁴.SiR⁴₃; or R¹C(OSiR⁴)₃; NSiR⁴, where X is a halogen and the various groups R⁴, which can be the same or different, represent hydrogen atoms or alkyl radicals, e.g. methyl, ethyl, *n*-propyl, iso-propyl; aryl, e.g. phenyl; or aralkyl, e.g. benzyl groups.

Preferred derivatives of silanols are silyl chlorides, for example trimethylchlorosilane and dimethyldichlorosilane.

Protecting groups of particular interest include esters of alcohols and phenols. R^{''} is preferably an alkyl or aralkyl group containing from 1 to 20 carbon atoms. Thus, R^{''} can be a lower alkyl group such as methyl, ethyl or tertiary butyl, a substituted alkyl group such as phthalimidomethyl, succinimidomethyl, phenacyl, substituted phenacyl such as *p*-bromophenacyl, a β -substituted ethyl group such as 2,2,2-trichloroethyl, 2-methylthioethyl or 2-(*p*-methylphenyl)ethyl, an alkoxyalkyl group such as methoxymethyl, an aryloxyalkyl group such as *p*-methoxyphenoxymethyl, an aralkyloxyalkyl group such as benzyloxymethyl, a substituted benzyl group such as *p*-nitrobenzyl, *p*-methoxybenzyl, 3,5-dinitrobenzyl, 2,4,6-trimethylbenzyl or 3,5-dichloro-4-hydroxybenzyl, benzhydryl or a substituted benzhydryl group such as *p*-methoxybenzhydryl. Preferred blocking groups are methyl, tertiary butyl, phenacyl, *p*-bromophenacyl, 2,2,2-trichloroethyl, *p*-methoxybenzyl, *p*-nitrobenzyl, benzyl, benzhydryl, methoxymethyl and *p*-methoxyphenoxymethyl.

The term "blocking group" herein is used in the same manner and in accordance with the teaching of U.S. Patent 3,697,515.

The carboxyl groups may be regenerated from an ester by any of the usual methods; for example, acid- and base-catalysed hydrolysis (especially for silyl and stannyl esters) is generally applicable, as well as enzymically-catalysed hydrolyses; however, aqueous mixtures may be poor solvents for these compounds and they may cause isomerizations, rearrangements, side-reactions, and general destruction, so that special methods may be desirable. Five suitable methods of deesterification are:

A— Reactions with Lewis acids: Suitable Lewis acids for reaction with the esters include trifluoroacetic acid, formic acid, hydrochloric acid in acetic acid, zinc bromide in benzene and aqueous solutions or suspensions of mercuric compounds. The reaction with the Lewis acid may be improved by addition of a nucleophile such as anisole.

B— Reduction: Suitable systems for effecting reduction are zinc/acetic acid, zinc/formic acid, zinc/lower alcohol, palladium-charcoal and hydrogen, electrolysis and sodium and liquid ammonia.

C— Attack by nucleophiles: Suitable nucleophiles are those containing a nucleophilic oxygen or sulphur atom for example alcohols, mercaptans and water.

D— Oxidative methods: For example, those involving the use of hydrogen peroxide and acetic acid.

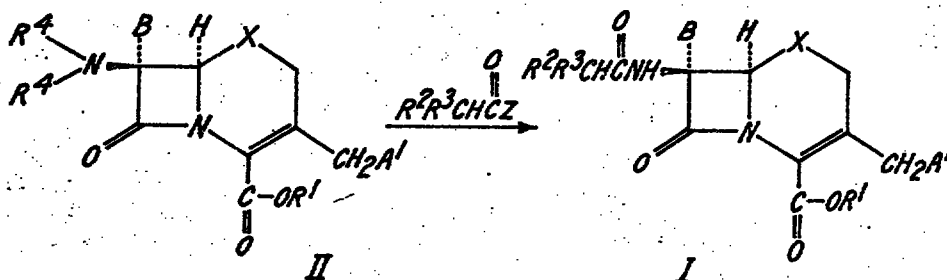
E— Irradiation.

Of particular interest are the procedures involving cleavage of groups such as benzhydryl, tertiary butyl, *p*-bromophenacyl, *p*-methoxybenzyl and *p*-methoxyphenoxymethyl, and methoxymethyl with an acid such as trifluoroacetic acid and cleavage of the 2,2,2-trichloroethyl and phenacyl groups by reaction with zinc and acetic acid.

The process for preparing the 7-acylamino compounds (I, supra) comprises treating the 7-amino or 7-substituted imino compound (II, infra) with an acylating agent, for example, an acyl halide or acyl anhydride such as an aliphatic, aromatic, heterocyclic, araliphatic or heterocyclic aliphatic carboxylic acid halide or anhydride. Other acylating agents may also be used, for example, a mixed acid anhydride with other carboxylic acids and particularly lower alkyl esters of carboxylic acids; also, carboxylic acids in the presence of a carbodiimide such as 1,3-dicyclohexylcarbodiimide, an activated ester of a carboxylic acid such as the *p*-nitrophenyl ester or by enzymatic acylation.

When an imino compound is used increased yields are obtained when the imino compound is first treated with a metal catalyst. The first step comprises dissolving the imino compound in an inert solvent such as tetrahydrofuran, dimethylsulfoxide, dioxane, dimethylformamide, methanol, ethanol, methylene chloride or chloroform. A small amount of water is then added such that the solvent to water ratio is say 5 or 6:1 by weight. The metal catalyst is then added and the reaction mixture stirred at ambient temperature for 1—5 hours. The solvent may be removed or the acylating agent added directly to the reaction mixture. The catalyst is generally of the formula ML_n where M is a metal such as palladium, platinum, nickel, ruthenium, rhodium, cobalt or iron; L is the ligand such as halo, carbonyl, cyclopentadienyl or phenylcyano and *n* is an integer equal to the valence requirements. Palladium chloride ($PdCl_2$) is the preferred catalyst.

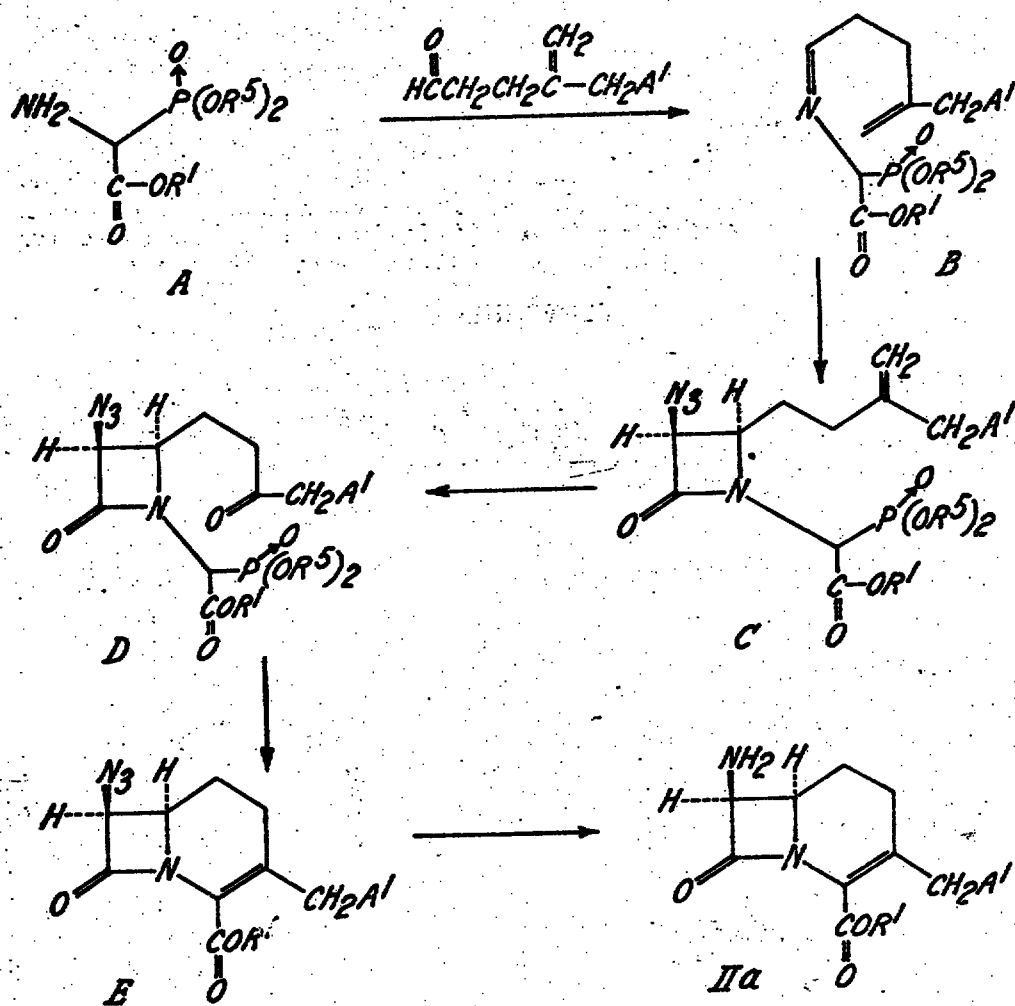
The acylation reaction may be conducted at a temperature in the range of from about $-20^\circ C.$ to about $100^\circ C.$ but is preferably conducted at a temperature in the range of from $0^\circ C.$ to $25^\circ C.$ Any solvent in which the reactants are soluble and that is substantially inert may be used, for example, a hydrocarbon such as benzene or toluene, a tertiary amine, for example, a trialkylamine or heterocyclic amines such as trimethylamine or pyridine, methylene chloride, chloroform, ethylacetate or diethyl ether. The reaction is conducted for a period of from about five minutes to a maximum of three hours, but in general, a reaction time of 30 minutes to one hour is sufficient. The following equation illustrates this process using the carboxylic acid halide; however, it is to be understood that by substituting the corresponding carboxylic acid anhydride or other functionally equivalent acylating agents similar products may be obtained.



where R^1 , R^2 , R^3 , A, B and X are as defined above; and R^4 is hydrogen, or both R^4 groups taken together are benzylidene or substituted benzylidene, and Z is halogen, for example, chlorine, or bromine.

The 7 β -amino and 7 β -substituted imino compounds, (IIa and IIb, respectively, infra) are prepared by various processes depending upon the nature of the X group. When X is methylene, the procedure depicted in Flow Sheet I is used:

Flow Sheet I.



where A' and R^1 are as defined above and R^5 is a C_{1-3} alkyl radical such as methyl, ethyl, propyl or *n*-butyl, or an aryl radical such as phenyl.

In this process the starting material, an ester of α -aminophosphonoacetic acid (**A**) is reacted with a 4-methylene-5-substituted-(or unsubstituted)-valeraldehyde to produce the corresponding imine (**B**). The various phosphono esters of the starting material, **A**, can be used in this process, for example, the di- $(\text{C}_{1-3}$ alkyl)esters and diaryl esters of the phosphonic acid group may be used. This reaction is generally conducted at a temperature in the range of from about 0° – 100°C . This reaction is conducted in a solvent that will azeotrope the water formed during the reaction, with benzene being the preferred solvent. Alternatively, the reaction is conducted in an inert solvent such as CH_2Cl_2 , CHCl_3 or Et_2O and in the presence of a water scavenger such as MgSO_4 or a molecular sieve. The intermediate compound (**B**) is then reacted with azidoacetyl chloride in the presence of an acid scavenger to afford the correspondingly substituted methyleneazetidinone (**C**). This reaction is preferably carried out at low temperatures, for example, at about 0°C . and in the presence of a sufficient amount of base for example a tertiary amine such as triethylamine to serve as an acid scavenger.

The methyleneazetidinone (**C**) is converted to the correspondingly substituted oxoazetidinone (**D**) by treating with an oxidizing agent, for example, ozone. This reaction is preferably effected at low temperatures, for example, a temperature in the range of from -50° to -80°C . Any solvent that is inert or substantially inert to the reactants may be used, such as ethyl acetate, methanol, methylene chloride or chloroform.

The oxoazetidinone (**D**) is then cyclized to afford the azabicyclo(4,2,0)octene (**IIa**). This reaction is conducted with a base such as an alkali metal hydride or alkali metal carbonate, for example, sodium hydride or potassium carbonate. This reaction is

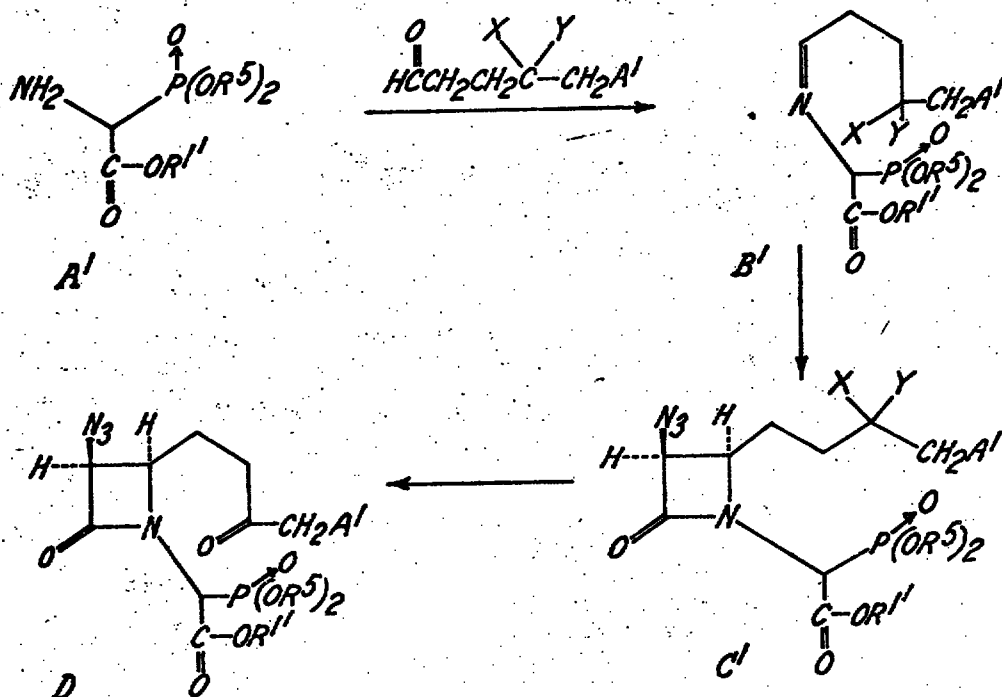
(18)

generally effected at a temperature in the range of from 0°C. to 50°C. in an inert or substantially inert solvent. Suitable solvents include dimethoxyethane, dimethylformamide and dimethylsulfoxide.

The 7β-azido compound (E) is then treated with hydrogen in the presence of a noble metal catalyst such as platinum oxide or palladium on carbon, to obtain the correspondingly substituted 7β-amino compound IIa.

Flow Sheet I' illustrates an alternative method of producing the oxo-azetidinone (D) of Flow Sheet I by utilizing a valeraldehyde containing a 4-carbonyl precursor or 4-masked carbonyl group in place of the 4-methylene valeraldehyde of Flow Sheet I. The conditions of proceeding from A'→B'→C'→D (Flow Sheet I') are identical with those set forth in Flow Sheet I with respect to the reaction of A→B→C→D.

FLOW SHEET I'.



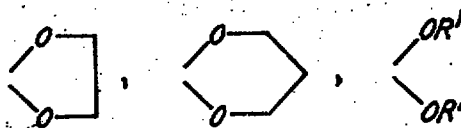
where A¹ and R¹ are as defined above and R⁵ is C₁₋₃ alkyl such as methyl, ethyl, propyl or n-butyl, or an aryl radical such as phenyl, and each of X and Y represents a carbonyl precursor or masked carbonyl group, representative members of which include the following:

I. Carbonyl precursors

X, Y = =CH₂, =CHR*, =CR₂* (R* = lower alkyl)

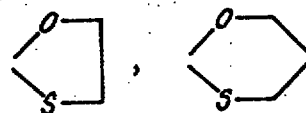
II. Masked carbonyls

A. Ketals X, Y =



(R' = Me, Et)

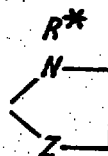
B. Hemithioketals X, Y =



C. Dithioketals X,Y =



D. Oxazolidines and Thiazolidines X,Y =

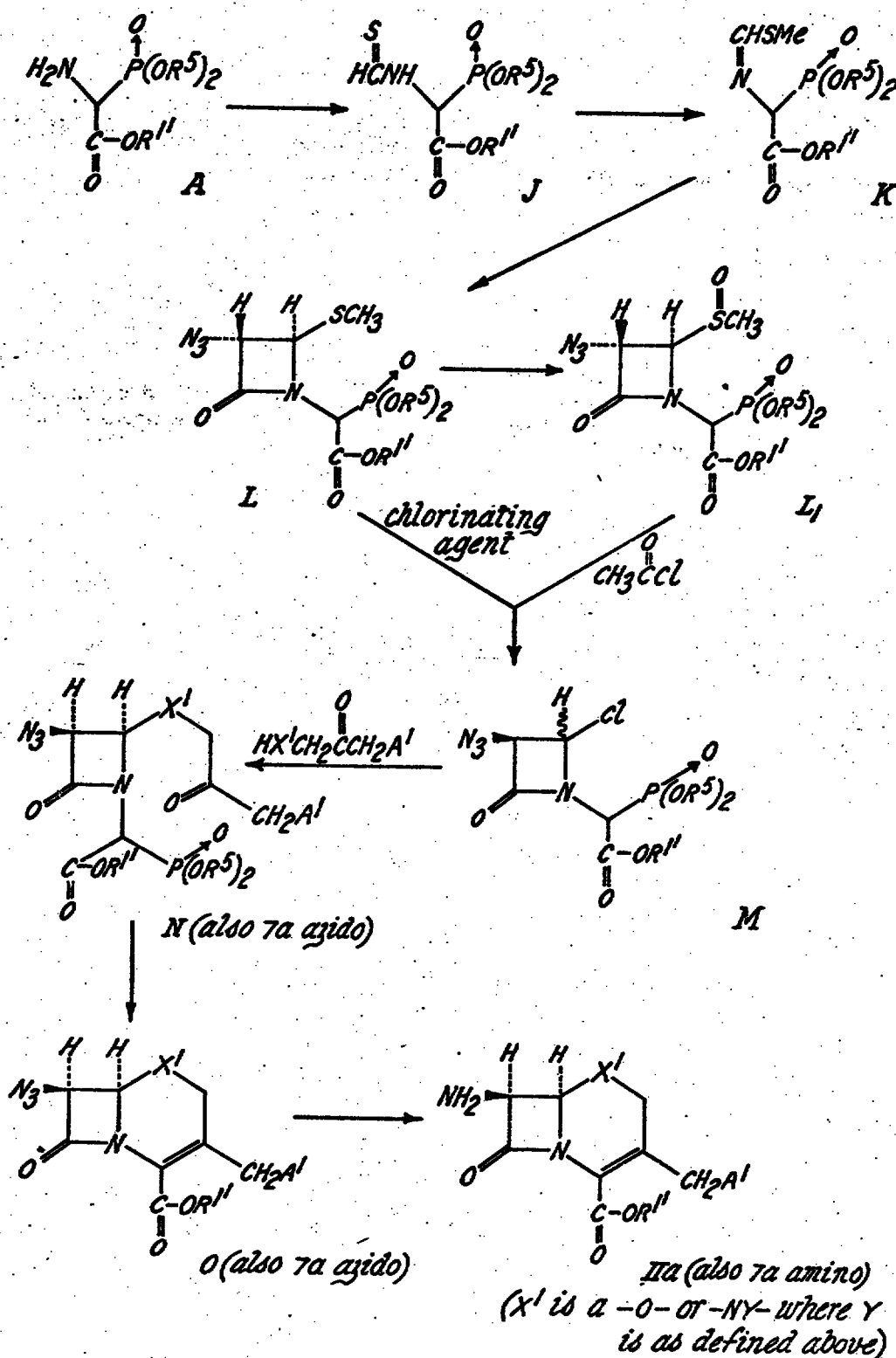


(Z=O,S), (R* = lower alkyl).

Regeneration of the carbonyl group to form the oxo-azetidinone (D) may be effected by treating the azetidinone (C') with an oxidizing agent such as ozone in the case of the carbonyl precursor and by acid hydrolysis where X,Y is a masked carbonyl in accordance with well known techniques.

Another method for preparing the 7β-amino compound (IIa, infra) and one limited to the preparation of those compounds wherein X is —O— or —NY—, where Y is as defined above, is shown in the following Flow Sheet, II.

Flow Sheet II.



In this process the starting material, an ester of α -aminophosphonoacetic acid (A) is reacted with a thionoformate ester to produce the corresponding thioformamido ester (J). The protecting group, R^1 , is as defined above and R^5 is as defined above.

Examples of suitable starting materials that might be mentioned are trichloroethyl α -amino-diethylphosphonoacetate, trichloroethyl α -amino-diphenylphosphonoacetate, phenyl α -amino-dimethylphosphonoacetate, *p*-methoxybenzyl α -amino-diethylphosphonoacetate, benzhydryl α -amino-diphenylphosphonoacetate, *t*-butyl α -amino-dimethylphosphonoacetate, *t*-butyl α -amino-dipropylphosphonoacetate, methyl α -amino-diphenylphosphonoacetate, phenacyl or *p*-bromophenacyl α -amino-diethylphosphonoacetate, methoxymethyl α -amino-dimethylphosphonoacetate, *p*-methoxyphenoxymethyl α -amino-dimethylphosphonoacetate, *p*-nitrobenzyl α -amino-dimethylphosphonoacetate and benzyl α -amino-diethylphosphonoacetate.

The conversion of compound A to the corresponding thioformamido derivative (J) is carried out by reacting the starting material with a C_{1-6} alkyl ester of thionoformic acid. Thus, the reaction is carried out by reaction with ethyl thionoformate at 0°C. Generally, it is preferred to carry out the reaction in an inert solvent such as benzene, carbon tetrachloride, methylene chloride or hexane. Alternatively, the reaction is carried out in the presence of liquid hydrogen sulfide at room temperature under autogenous pressure. After completion of the reaction, the solvent is evaporated to afford the product, J.

The next step comprises treating the thioformamido compound (J) with an alkylating agent such as methyl iodide in the presence of a base such as potassium carbonate. This step is conveniently conducted at room temperature in the presence of a suitable inert solvent such as acetone or dimethylformamide. The S-methyl substituted compound (K) obtained is then treated with azidoacetylchloride and an acid scavenger to afford the azido compound (L). This reaction is preferably conducted at low temperatures, for example, at about 0°C. using a sufficient amount of a base such as a tertiary amine to serve as the acid scavenger and also catalyze the cyclo addition to afford compound (L).

The 4-methylthio compound (L) is converted to the correspondingly substituted 4-chloro compound (M) by either of two alternative processes. The first method comprises treating the 4-methylthio compound (L) with an oxidizing agent such as N-bromoacetamide to afford the 4-methylsulfonyl compound (L₁) which upon treatment with acetylchloride, affords the desired 4-chloro compound (M).

A second method for preparing the 4-chloro compound comprises treating the 4-methylthio compound (L) with a chlorinating agent such as chlorine, in a suitable inert solvent such as methylene chloride, chloroform or benzene at a temperature in the range of from 0° to 40°C.

The next step of the process comprises treating the 4-chloro compound (M) with the appropriately substituted propanone in the optional presence of a dehalogenating agent, for example, silver fluoroborate, silver oxide or silver trifluoromethanesulfonate. Suitable solvents for this reaction include methylene chloride, toluene and chloroform. If the propanone reactant is a liquid at room temperature then an excess may serve as the solvent. The reaction is conveniently conducted at room temperature.

The 4-propyloxy or propylamino compound (N) is then ring-closed by reaction with a base such as an alkali metal carbonate or an alkali metal hydride in a suitable inert solvent such as dimethoxyethane, dimethylformamide, dimethylsulfoxide or acetone, at 0–50°C to afford the desired dethiacephalosporanate (O, supra) which is a mixture of the 7 α and 7 β -azido compound.

The mixture of the 7 α and 7 β -azido-dethiacephalosporanates (O) is converted to its correspondingly substituted 7-amino compound (IIa, supra) by treating the 7-azido compound (O) with hydrogen in the presence of a noble metal catalyst such as platinum oxide, palladium on charcoal, ruthenium or rhodium.

The compounds, —IIa, described in Flow Sheet I, and the compounds, —IIa, as described in Flow Sheet II, since they result from a total synthesis procedure, are racemic mixtures of both *d*- and *l*-forms. The optically active components can be conveniently separated when the compound of Formula IIa is obtained. Alternatively, the compound of Formula II can be acylated to yield the *al*-7 β -acylamino compound of I and then separated using readily available processes. For example, resolution can be accomplished by reaction with an optically active base, separation of the resulting diastereoisomers and reconversion of the diastereoisomers to the free acid or a salt thereof.

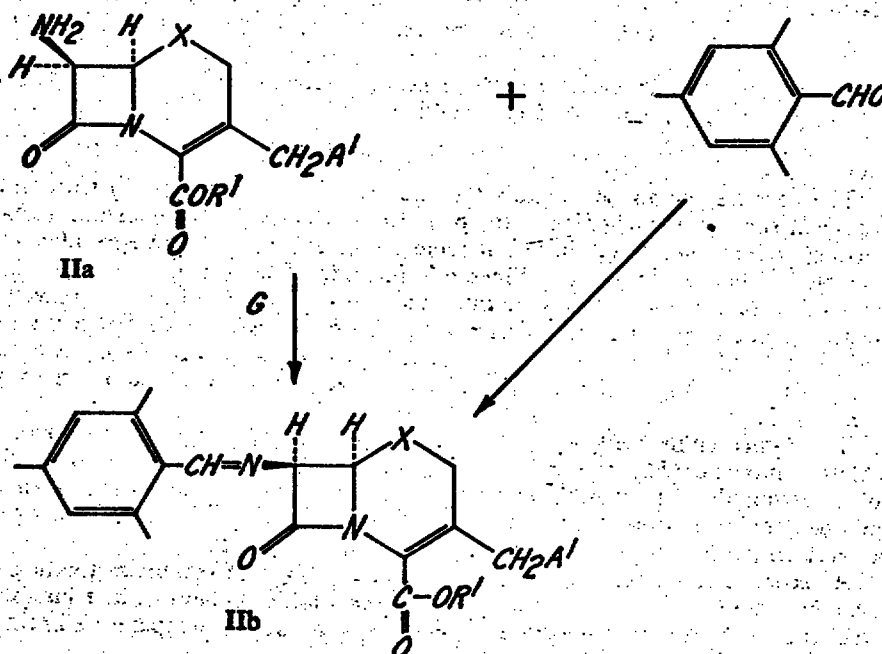
The final 7 β -acylamino products I are valuable antibacterial agents useful against gram-positive and gram-negative bacteria. This activity includes effectiveness against many bacteria, including *in vivo* on *Escherichia coli*, *Proteus vulgaris*, and *Salmonella schottmulleri*, which are gram-negative and *Bacillus subtilis* and *Staphylococcus aureus*, which are gram-positive. Specific bactericidal activity is dependent upon the exact structure of the final product; not all compounds are active against all organisms.

The final active antibiotic agents can be used to combat bacterial infections in

animals or humans. They can be used in dosages and administrative forms similar to those used for commercially available cephalosporins and penicillins. Exact dose levels and modes of administration can be readily determined. Generally, from 0.1—500 mg./kg. body weight gives effective antibacterial control.

The 7 β -amino-7 α -methoxy compounds (IIc) are prepared by treating the 7-amino compound (IIa) with an aromatic aldehyde to form the corresponding imino compound (IIb or IV, *infra*).

The imino compound (IIb or IV) may be prepared as follows: (It may be noted that when X = O or NY IIa and IIb may be a mixture of 7 α and 7 β isomers)



where A¹ and R¹ are as defined above.

The 7-amino compound IIa is reacted with an aromatic aldehyde in which one of the 2, 4 or 6 positions may be substituted with a nitro, halo, cyano, carboxy or hydroxy group. The other two positions can either be one of the above substituents or hydrogen. The preferred aromatic aldehydes are benzaldehyde and *p*-nitrobenzaldehyde. The starting material IIa and the aromatic aldehyde are mixed together in approximately equimolar amounts in an inert solvent, such as ethanol, dioxane, benzene, toluene, methylene chloride or chloroform. The reaction is conducted at room temperature to the reflux temperature of the solvent. It may be noted that in compound IIa when X is O or NY a mixture of 7 α — and 7 β - amino isomers may be present which yield a mixture of 7 α and 7 β imino compounds (IIb). It will be appreciated that both 7 α and 7 β compound IIb may be used for introduction of substituents at C—7.

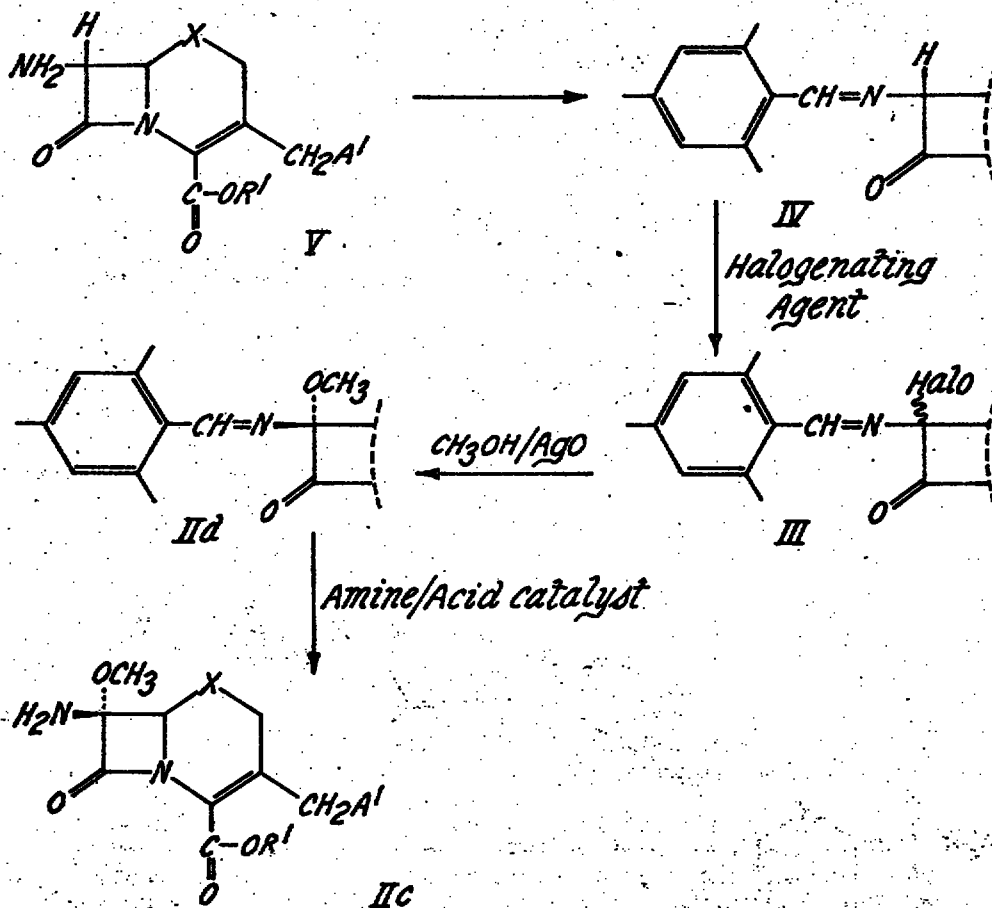
To increase the yields, the water formed during the reaction is removed by any of the known methods including azeotropic distillation, molecular sieves and magnesium sulfate.

The imino compound, IIb or IV, is then activated with a strong base, preferably an inorganic base, for example, an alkali metal hydride such as sodium hydride or an organometallic compound such as phenyl lithium LiN(iPr)₂ or KOtBu *tert*-butyl lithium. The base is added to a solution of the imino compound (IV) at a temperature in the range of from about -100°C. to about -60°C. under an inert atmosphere (e.g. nitrogen) in an inert solvent such as DMF, tetrahydrofuran or acetonitrile.

The activated intermediate is not isolated but treated directly with a halogenating agent such as N-bromosuccinimide, N-bromoacetamide, bromine, *tert*-butyl hypochlorite or perchloromethyl hypochlorite, to afford the 7-imino-7-halo compound (III, *infra*) which upon treatment with methanol in the presence of a base such as silver oxide, barium oxide, calcium oxide, cuprous oxide or triethylamine affords the 7 β -imino-7 α -methoxy compound (IIId) which can be acylated or can be treated with an amine in the presence of an acid catalyst as described above to afford the 7 β -amino-7 α -methoxy compound (IIc, *infra*).

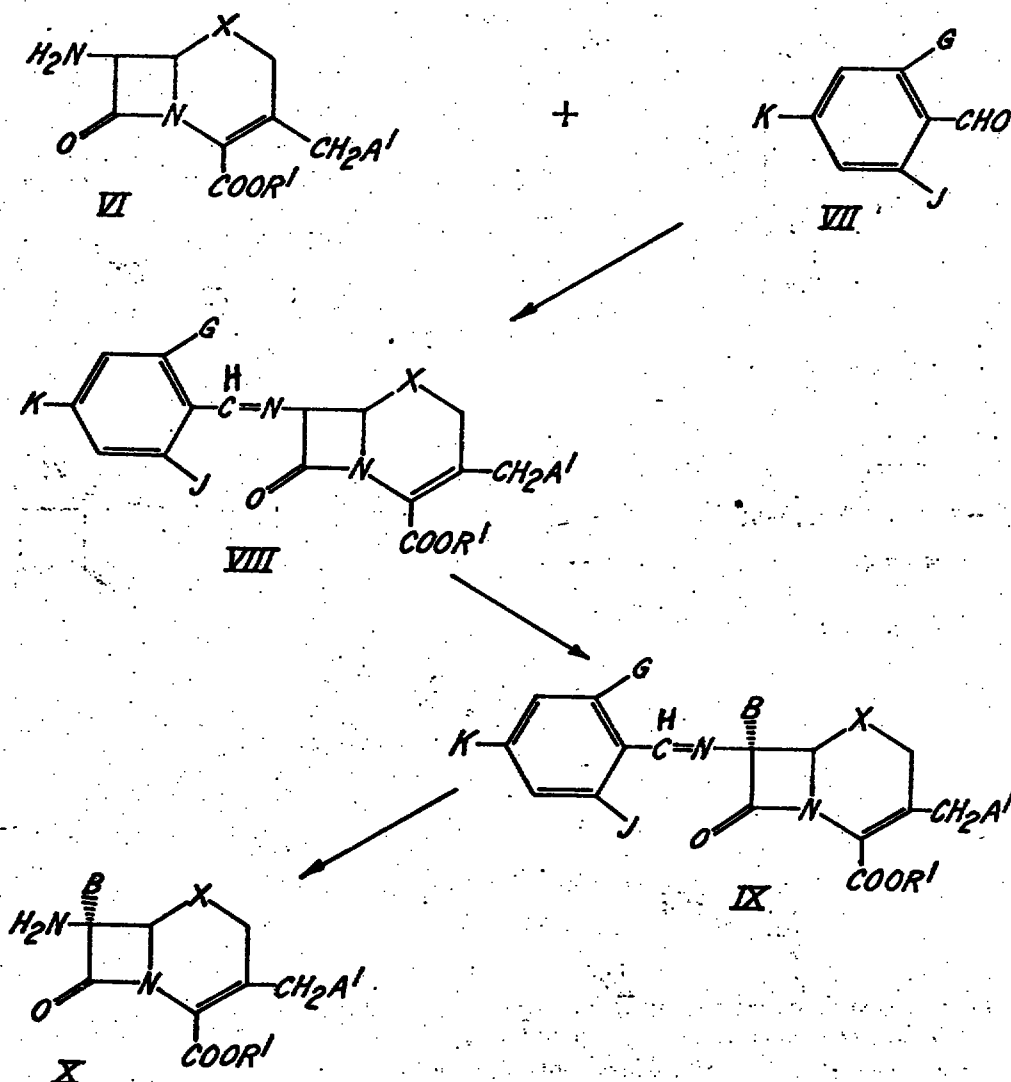
FLOW SHEET III.

The following equation illustrates this process:



wherein A¹, R¹ and X are as defined above and halo is bromo or chloro.

An alternative technique for the preparation of novel 7-substituted antibiotics wherein B = CH₃, OCH₃ or SR (where R is C₁₋₆ alkyl or phenyl) is as follows:



The basic process can be summarized briefly as having three major steps: the first is the preparation of the imino derivative of the 7-amino compound. This imino derivative is then substituted with the chosen reactant supplying the B group desired. The specific reactant depends on the identity of the B group. The third step is then the regeneration of the amino group.

The reactant VII is an aromatic aldehyde optionally having at least one *o*- or *p*-electronegative substituent. In other words, at least one of J, G, and K may be nitro, methyl, halo, sulfonyl, a carboxyl derivative such as an ester or amide or cyano. The other two of J, G, and K can either be one of the above electronegative substituents, or hydrogen. The preferred reactants are *p*-nitrobenzaldehyde, where J = nitro, and G and H = hydrogen, and benzaldehyde.

Other carbonyl containing compounds, e.g., aldehydes and ketones such as acetone, hexafluoroacetone or chloral, which will form stable imino derivatives, will also be operable in this invention. Also, polycyclic aromatic aldehydes can be used, i.e., having 2—3 fused ring nuclei such as 2-hydroxy-1-naphthaldehyde.

The 7-amino starting material VI and the aromatic aldehyde VII are mixed together in approximately equimolar amounts in an inert solvent. Suitable solvents are ethanol, dioxane, acetonitrile, dimethylformamide, dimethylsulfoxide, benzene, toluene, methylene chloride and chloroform. The reaction proceeds readily at temperatures ranging from ambient to reflux. Since this condensation is an equilibrium reaction and since water is one of the products of the reaction, water is removed from active participation in further reactions by any of a number of usual methods, including azeotropic distilla-

tion, molecular sieves, chemical entrapment using potassium carbonate or magnesium sulfate, or borate esters. The particular method is dependent upon the exact parameters of the reaction. The reaction is terminated by evaporation of the solvent. The imino derivative VIII is then recovered and used in the next step.

The latter involves the substitution of the B group at the carbon atom adjacent to the imino nitrogen. This reaction takes place in the presence of an inert solvent, such as THF, DMF or DME, and in the additional presence of an organic or inorganic base as activating agent.

The activating agent can be any of a number of organic or inorganic bases. Tertiary (C_{1-4} alkyl) amines are suitable, such as triethylamine or diisopropyl ethylamine; pyridine is also used. Lithium alkyls and lithium aryls, such as lithium alkyls having 1-4 carbon atoms, e.g., t-butyl lithium or phenyl lithium, could be used. Sodium hydride $LiN(iPr)_2$ and $KOtBu$ may also be used.

The activating agent is added to the solution of compound VIII at a low temperature (-100 to $0^\circ C.$ and preferably -100 to $-60^\circ C.$) and under an inert atmosphere. The amount of activating agent is sufficient to produce a strong color change in the solution. The color is an indicator that the activated form of compound VIII is present.

The activated compound VIII is not isolated, but the next reagent is added directly to the reaction mixture.

The specific reagent used in the reaction with the activated compound VIII to result in the substitution of the chosen B group obviously depends on the B group desired.

The following is of value in defining each reactant in terms of the final B group.

TABLE I.

Reactant	B
methyl sulfate or halide	methyl
phenylsulfenyl halide	phenylthio
methyl peroxide	methoxy
loweralkyl disulfide or lower	loweralkylthio
alkane sulfenyl halide (e.g.	(e.g. methyl thio)
methyl sulfenyl halide)	
lower alkylmethanethiolsulfonate	lower alkylthio

The chosen reagent is added in an amount approximately equivalent to the moles of the activated compound VIII. The reaction proceeds immediately, as evidenced by a color change. The reaction mixture is then permitted to warm up to temperatures ranging from between $0^\circ C.$ to ambient temperatures.

The terms used in Table I and elsewhere in the specification are defined as follows:

"Loweralkyl" refers to an alkyl group having 1-6 carbon atoms.

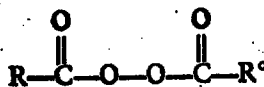
"Loweralkanoyl" and "loweralkoxy" refer to a carbon chain of 1-6 carbon atoms.

"Halide" and "halo" are used to mean chlorine, bromine, fluorine, and iodine. Different halogens can be used in the same residue if more than one is indicated.

"Peroxide" indicates a compound having a $-O-O-$ moiety.

"Disulfide" indicates a $-S-S-$ moiety in a compound.

"Loweralkanoyl peroxide" is used to mean a compound of the formula



where R° is C_{1-6} alkyl.

Once novel compound IX has been prepared, the imino moiety is converted to the amino moiety of compound X.

The regeneration of X from IX takes place by the reaction of IX with an amine in the presence of an acid catalyst. The amine employed can be aniline, hydrazine, or hydrazine derivatives such as phenylhydrazine or 2,4-dinitrophenyl hydrazine. The acid catalyst can be any commonly used strong organic or inorganic acid such as hydrochloric acid or *p*-toluene sulfonic acid. One preferable combination utilizes aniline hydrochloride, which serves as both acid and amine. Another preferred combination is 2,4-dinitrophenyl hydrazine and *p*-toluene sulfonic acid. The reaction conditions of the regeneration are chosen such that no undesired hydrolysis or ring damage occurs, and is preferably carried out in a C_{1-6} alkanol medium, such as methanol or ethanol,

although other solvents including dimethoxyethane or dimethyl formamide may also be used. The temperature is that of the surroundings. The relative amounts of acid and amine depend on the specific aldehyde IV and amine, since the regeneration involves an equilibrium. Other systems that may be used include H₂O in methyl ether or DMF or HCl in H₂O — methyl ether.

In carrying out the reactions it is preferred to protect the 4-carboxy group and also other groups which may be in the nucleus such as other carboxy groups, amino groups or hydroxy groups. Maximum yields are obtained by using these protected compounds. Examples of these protecting groups are trichloroethyl, *tert*-butyl, benzoyl-methyl, *p*-methoxybenzyl, benzyl, benzhydryl, trityl, trimethylsilyl, methoxymethyl and *tert*-butyloxycarbonyl. These ester groups may be removed by known methods: for example, the benzhydryl or *p*-nitrobenzyl groups may be removed by hydrogenation in the presence of a catalyst such as palladium-on-carbon or by treatment with a strong organic or inorganic acid. The *tert*-butyl or methoxymethyl groups may also be removed by treatment with strong organic or inorganic acid. Examples of these acids are hydrochloric acid, sulfuric acid, boron trifluoride etherate, formic acid, trifluoroacetic acid, trichloroacetic acid and nitrobenzoic acid.

Amino protecting groups are well known and are described, for example, in U.S. Patents 2,479,295 through 2,479,297, 2,562,407 through 2,562,411 and 2,623,876. Groups such as triphenylmethyl and trimethylsilyl may be used. In addition, protective groups formed by reagents such as 1-fluoro-2,4-dinitrobenzene, 1-fluoro-2-nitro-4-carbomethoxy-benzene, *p*-toluenesulfonyl chloride, phenylisocyanate and methylchloroformate may be used in the practice of the invention.

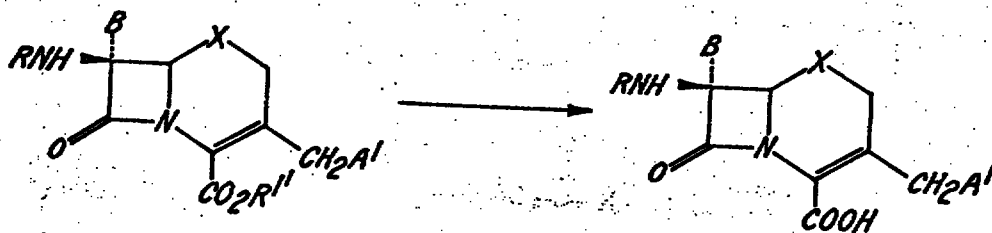
Typical of hydroxy protecting groups include tetrahydropyranyl ether, benzyl ether, *p*-nitrobenzyl ether and *p*-methoxybenzyl ether. These groups may be subsequently converted to the free hydroxy group by mild aqueous hydrolysis or by hydrogenation.

Preparation of 3-Methyl Analogues

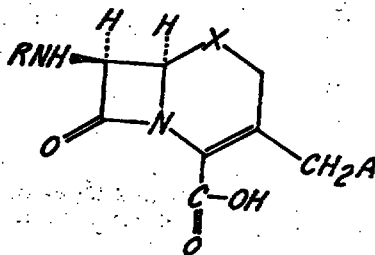
The 3-acetoxy methyl group may be removed to form the 3-hydroxymethyl compound without subsequent lactone formation by enzymatic means, for example, acetyl-esterase. The use of an enzyme allows the hydrolysis of the acetoxy group without the danger of lactone formation. The resulting hydroxy group may be then reacted to form other substituents at the 3-position. For example, the 3-hydroxy group may be re-esterified with a C₁₋₆ alkanolic acid group or with an aryl group by acylating agents such as a suitable acid halide or anhydride, a substituted carbamoyl halide or a C₁₋₆ alkyl isocyanate.

The 3-acetoxy methyl group may also be converted to other analogues by replacing the acetoxy group of I, with nitrogen or sulfur nucleophiles. Many nitrogen and sulfur nucleophiles are well known in the cephalosporin art. Examples are tertiary amines such as pyridine and a 5-membered heterocyclic thiols such as 5-methyl-1,3,4-thiadiazolyl-2-thiol and N-methyl-tetrazolylthiol.

In accordance with the above, deblocking of the 4-carboxy group of 7-amino or 7-acyl cephalosporins prepared in accordance with the invention results in the preparation of the corresponding free acid as follows:



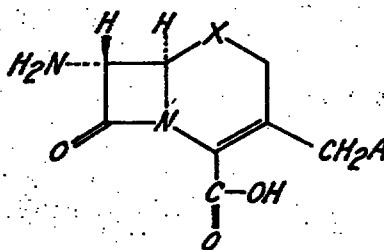
where R is H or acyl; R' is a protecting group; and B and A are as set forth previously. The nomenclature used in this specification is as follows:



is called 3-substituted methyl-7 β -acylamido-1-X-1-dethiacephalosporin.

In this Formula, the dotted lines connecting the two hydrogen atoms to the ring indicate that the hydrogen atoms are below (α) to the plane of the β -lactam ring; the broad line connecting the nitrogen indicates that it is above (β) to the plane of the ring.

There is another possible steric configuration for dethiacephalosporin, which is:



In this formula, the nitrogen and the hydrogen at position 6 is α , or down from the ring; the hydrogen at position 7 is β , or up from the ring. This type of configuration is termed "epi" dethiacephalosporin.

It should be noted that it is unnecessary to specify the configuration of both substituents on the 7-carbon; if the nitrogen configuration is indicated, the other substituent, i.e., the hydrogen, is obviously the other configuration.

The following Examples illustrate the preparation of various compounds in accordance with the present invention and various intermediate compounds and starting materials involved in the processes of the present invention. In the Examples, the words 'Amberlite' and 'Nujol' are trade marks, all parts, percentages and ratios are on a weight basis, temperatures are on the Centigrade scale, and the abbreviation 'mmole' means 'millimole'.

EXAMPLE 1.

Sodium 7 β -(2'-thienylacetamido)-1-methylene-1-dethiacephalosporanate

Step A: Benzyl N-benzylidene- α -amino-diethylphosphonoacetate

Diethyl N-benzylidene-aminomethylphosphonate (21.8 g.) is dissolved in dry tetrahydrofuran (500 ml.) and cooled to -78°C . under a nitrogen atmosphere. Phenyl lithium (58.6 ml.; 2.2 M) in benzene/ether is added dropwise over a 10-minute period and the resulting solution stirred for 5 minutes. Benzyl chloroformate (9.4 ml.) is then added dropwise over a 30-minute period. The reaction mixture is stirred at -78°C . for one hour and then at 0°C . for another half hour. The solvent is evaporated under reduced pressure and the residue is dissolved in ether and washed successively with a phosphate buffer (pH 3) and then with brine. The ethereal solution is dried and the ether removed to afford 36.0 g. of crude product, which is chromatographed on silica gel (1.0 kg.). Elution with ethyl acetate and acetone (9:1) affords 16.5 g. of benzyl N-benzylidene- α -amino-diethylphosphonoacetate.

NMR: τ : 1.64 d (C=N); 4.76, s ($\text{CH}_2\text{---C}_6\text{H}_5$); 5.26, d (CH---P---); 5.9, m ($\text{OCH}_2\text{---CH}_3$); 8.8, t ($\text{CH}_3\text{---CH}_2\text{---O}$).

IR: μ : 572 (ester C=O); 6.1 (C=N); 9.7 (P=O).

Step B: Benzyl α -amino-diethylphosphonoacetate

Benzyl N-benzylidene- α -amino-diethylphosphonoacetate (16.5 g.) is dissolved in ether (50 ml.) and added dropwise to an ice-cold solution of *p*-toluenesulfonic acid monohydrate (8.08 g.) in ether (300 ml.). After the addition is complete, the reaction mixture is stirred for an additional 20 minutes. The ethereal solution is decanted from the oily product. The oily product is triturated with an ether/petroleum ether solution (1:1) and the soluble material is again decanted. The residual oil is dissolved in dichloromethane (300 ml.) and washed with dipotassium phosphate (1 equivalent of a 1 M solution). The organic solution is dried and the solvent removed to afford 9.6 g. of benzyl α -amino-diethylphosphonoacetate.

NMR: τ : 2.84, s (C_6H_5); 4.77, s ($C_6H_5-CH_2$); 5.88, m ($P-O-CH_2-CH_3$)

6.4 d ($CH-P$); 8.06, NH_2 ; 8.73 t (CH_3-CH_2-O).
 IR: μ : 2.95 (NH); 5.72 (ester); 9.7 (P=O).

Step C: 1-Chloro-2-methylene-3-acetoxypropane

Sodium hydride (4.5 g.; 57% in mineral oil) is placed under a nitrogen atmosphere and the mineral oil removed with petroleum ether. Dimethylsulfoxide (30 ml.) is then added and the mixture is stirred at 70°C. for two hours and then cooled to 10°C. Methyltriphenylphosphonium bromide (35.7 g.) dissolved in dimethylsulfoxide (50 ml.) is added dropwise under nitrogen to afford a yellowish-orange ylide solution. 1-Chloro-3-acetoxy-2-propanone (15 g.) in dimethylsulfoxide (20 ml.) is then added and the reaction mixture is stirred until the color of the ylide disappears and then is stirred for an additional hour at room temperature. The reaction mixture is dissolved in hexane (200 ml.) and washed three times with water. The organic phase is filtered to remove triphenylphosphine oxide and then dried over magnesium sulfate. The solvent is evaporated and the residue is distilled under vacuum to afford 1-chloro-2-methylene-3-acetoxypropane.

Step D: 4,4,6 - Trimethyl - 5,6 - dihydro - 2 - (4' - acetoxy - 3' - methylene)butyl - 1,3 - (4H - oxazine

2,4,4,6 - Tetramethyl - 5,6 - dihydro - 1,3 - (4H - oxazine (14.1 g.) is dissolved in tetrahydrofuran (100 ml.), cooled to -78°C. under a nitrogen atmosphere and treated with *n*-butyllithium (100 ml.; 1N) in hexane. The reaction mixture is stirred for two hours at -78°C. and then 1-chloro-2-methylene-3-acetoxypropane (14.8 g.) in tetrahydrofuran (50 ml.) is added dropwise. The reaction mixture is allowed to come to room temperature gradually. The solvent is removed under reduced pressure and the residue dissolved in ether (200 ml.) and washed with water. The ethereal solution is dried and removed by evaporation to afford the crude product which is purified by chromatography on silica gel to afford 4,4,6 - trimethyl - 5,6 - dihydro - 2 - (4' - acetoxy - 3' - methylene)butyl - 1,3 - (4H) - oxazine.

Step E: 4-Methylene-5-acetoxyvaleraldehyde

4,4,6 - Trimethyl - 5,6 - dihydro - 2 - (4' - acetoxy - 3' - methylene)butyl - 1,3 - (4H) - oxazine (12.5 g.) is dissolved in tetrahydrofuran (100 ml.) and water is then added until a slightly turbid solution results. The mixture is cooled to -30°C. and sodium borohydride (10 g) is added in 4 equal amounts. After being stirred for half an hour at -30°C. the reaction mixture is allowed to come to room temperature and is then treated with dilute hydrochloric acid. The reaction mixture is diluted with ether (300 ml.) and then washed successively with water and brine. The ethereal solution is dried and the solvent removed to afford the tetrahydro-oxazine which is then refluxed with oxalic acid (100 ml.; 5%) for half an hour. The reaction mixture is extracted with ether and the ethereal solution dried and the solvent removed to afford 4-methylene-5-acetoxyvaleraldehyde.

Step F: Benzyl α - (5' - acetoxy - 4' - methylene) - valeraldiminodiethyl phosphonoacetate

Benzyl α -aminodiethylphosphonoacetate (3 g.) is mixed with 4-methylene-5-acetoxyvaleraldehyde (1.56 g.). Benzene (150 ml.) is added and the benzene is distilled off over a 45-minute period until the volume is 10 ml. The remaining benzene is evaporated off under reduced pressure and the residue of benzyl α - (5' - acetoxy - 4' - methylene) - valeraldiminodiethylphosphonoacetate is used immediately in Step G.

Step G: 1 - (Benzylloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - cis - (3' - methylene - 4' - acetoxy) - butyl - 2 - azetidinone

The product of Step F (4.39 g.) is dissolved in methylene chloride (80 ml.) under a nitrogen atmosphere and a solution of azidoacetyl chloride (1.2 g.) in methylene chloride (10 ml.) is added dropwise over a half-hour period. Triethylamine (distilled from calcium hydride) (1.2 g.) in methylene chloride (10 ml.) is then added dropwise over a 45-minute period and the reaction mixture is stirred at room temperature for another 15 minutes. The reaction mixture is washed with pH 7 phosphate buffer,

dried and the solvent removed to afford a crude product which is chromatographed on silica gel (200 g.) to afford 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - (cis - (3' - methylene - 4' - acetoxy) - butyl - 2 - azetidinone).

Step H: 1 - (Benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - cis - (3' - oxo - 4' - acetoxy) - butyl - 2 - azetidinone

1 - (Benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - cis - (3' - methylene - 4' - acetoxy) - butyl - 2 - azetidinone (2.61 g.) is dissolved in ethyl acetate (25 ml.), cooled to -78°C . and then treated with ozone until the solution shows a blue color. The reaction mixture is stirred at -78°C . for five minutes and then nitrogen is passed into the solution to remove the ozone. The reaction mixture is allowed to come to room temperature and then treated with a 2% solution of potassium iodide and a few drops of acetic acid. The aqueous phase is separated, the organic phase is washed with sodium thiosulfate and dried, and the solvent is removed. Chromatography on silica gel affords 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - cis - (3' - oxo - 4' - acetoxy) - butyl - 2 - azetidinone.

Step I: Benzyl 7- β -azido-1-methylene-1-dethiacephalosporanate

Sodium hydride (0.112 g., 57% in mineral oil) is placed under a nitrogen atmosphere and the mineral oil removed with pentane. Anhydrous dimethoxyethane (10 ml.) is added and the mixture is cooled to 0°C . 1 - (Benzyloxycarbonyl - diethylphosphono) - methyl - 3 - azido - 4 - cis - (3' - oxo - 4' - acetoxy) butyl - 2 - azetidinone (1.3 g.) in dimethoxyethane (10 ml.) is added dropwise to the sodium hydride suspension and the mixture is stirred for one hour. The reaction mixture is diluted with benzene, washed twice with water and dried, and the solvent is removed to afford the crude product, which is purified by chromatography on silica gel to afford benzyl 7- β -azido-1-methylene-1-dethiacephalosporanate.

Step J: Benzyl 7- β -amino-1-methylene-1-dethiacephalosporanate

Benzyl 7- β -azido-1-methylene-1-dethiacephalosporanate (1.85 g.) is dissolved in dioxane (30 ml.). Platinum oxide (1.8 g.) is added and the reaction mixture is reduced with hydrogen at atmospheric pressure for three hours. The dioxane is removed under reduced pressure and the residue is dissolved in chloroform and filtered through a short column of silica gel G to remove the catalyst. Evaporation of the solvent affords benzyl 7- β -amino-1-methylene-1-dethiacephalosporanate.

Step K: Benzyl 7- β -(2'-thienylacetamido)-1-methylene-1-dethiacephalosporanate

Benzyl 7- β -amino-1-methylene-1-dethiacephalosporanate (0.5 g.) is dissolved in 20 ml. methylene chloride and cooled to 0°C . Pyridine (0.5 ml.) is added and then 2-thienylacetyl chloride (0.25 g.) is added dropwise and the mixture is stirred at 0°C . for half an hour. The reaction mixture is washed once with a pH 2 phosphate buffer and then with a pH 8 phosphate buffer. The organic phase is dried and evaporated to afford a residue which is chromatographed on silica gel to give benzyl 7- β -(2'-thienylacetamido) - 1 - methylene - 1 - dethiacephalosporanate.

Step L: Sodium 7- β -(2'-thienylacetamido)-1-methylene-1-dethiacephalosporanate

Benzyl 7- β -(2'-thienylacetamido) - 1 - methylene - 1 - dethiacephalosporanate (0.300 g.) is dissolved in ethanol (15 ml.), water is added to turbidity and then 0.300 g. of the catalyst (10% Pd/C) is added. The mixture is reduced under hydrogen at 40 atm. for half an hour. The catalyst is filtered off. The filtrate is evaporated under reduced pressure to remove most of the ethanol and then treated with sodium bicarbonate (0.1 g.) and the solution is freeze-dried to afford sodium 7- β -(2'-thienylacetamido) - 1 - methylene - 1 - dethiacephalosporanate.

EXAMPLE 2.

Benzyl 7- β -benzaldimino-1-methylene-1-dethiacephalosporanate

Benzyl 7- β - amino - 1 - methylene - 1 - dethiacephalosporanate (1.72 g.) is treated with benzaldehyde (0.55 g.). The mixture is dissolved in benzene (30 ml.) and magnesium sulfate (2.0 g.) is added. The reaction mixture is allowed to stand at room temperature for two hours. The magnesium sulfate is removed by filtration and the filtrate is evaporated to afford benzyl 7- β - benzaldimino - 1 - methylene - 1 - dethiacephalosporanate.

EXAMPLE 3.

Sodium 7- α - (2' - thienylacetamido) - 1 - oxa - 1 - dethiacephalosporanate and sodium 7- β - (2' - thienylacetamido) - 1 - oxa - 1 - dethiacephalosporanate
Benzyl α -aminodiethylphosphonoacetate (0.594 g.) is dissolved in carbon tetra-

chloride (5.0 ml.) and added to ethyl thionoformate (0.1 g.) in carbon tetrachloride (5 ml.) cooled to 0°C. After the addition the reaction mixture is stirred at room temperature overnight. The solvent is removed under reduced pressure to afford 0.602 g. of benzyl α -thioformamido-diethylphosphonoacetate as an oil.

5 I.R.: 3.1 μ (NH); 5.71 μ (C=O); 7.0 (C=S), 9.75 (P—O). 5

NMR: (CCl₄) τ : -0.1 (NH); 0.6, s (H—C—^S); 2.73, s (C₆H₅); 3.98, d (j=10 c.p.s.) (CH—P); 4.8 (—CH₂—C₆H₅); 5.93, m (O—CH₂—CH₃); 2.75, m (CH₃CH₂—O).

10 Step B: Benzyl α -(S-methylthioimidato)-diethylphosphonoacetate 10

Benzyl α -thioformamido-diethylphosphonoacetate (0.6 g.) is dissolved in acetone (20 ml.). Methyl iodide (0.5 ml.) and potassium carbonate (0.276 g.) are added and the mixture is stirred under N₂ overnight. The insoluble salts are filtered off, the filtrate is evaporated, and the residue is dissolved in chloroform and filtered again. The filtrate is evaporated to afford 0.536 g. of benzyl α -(S-methylthioimidato)-diethylphosphonoacetate as an oil. 15

IR: 5.72 μ (C=O); 6.25 μ (C=N); 9.75 μ (P—O).

NMR: τ : 1.6, d (H—C—^S); 2.7 s (C₆H₅); 4.83, s (CH₂—C₆—H₅); 5.43,

d (HC—^O); 5.93, m (O—CH₂—CH₃); 7.6, s (CH₃—S—); 8.73, t (CH₃—CH₂—O).

20 Step C: 1 - (Benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - (methylthio) - 2 - azetidinone 20

Benzyl α -(S-methylthioimidato)-diethylphosphonoacetate (0.53 g.) is dissolved in dry methylene chloride (25 ml.) and placed under N₂. Azidoacetyl chloride (0.180 ml.) is then added dropwise over two minutes. The mixture is stirred for three minutes and triethylamine (0.264 ml.) in dry methylene chloride (4.0 ml.) is added dropwise over 10 minutes. The resulting solution is stirred for another 10 minutes and is then washed with a pH 7 buffer, dried and evaporated. The residue (0.745 g.) is chromatographed on silica gel using 50% ethyl acetate/benzene to afford 0.349 g. of 1 - (benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - (methylthio) - 2 - azetidinone. 25 30

IR: 4.75 μ (azide); 5.6 μ (β -lactam C=O); 5.72 μ (ester C=O); 9.72 μ (P—O).

NMR: (CCl₄) τ : 2.73 s (C₆H₅); 4.83 s (CH₂—C₆H₅); 5.1 to 5.66 (β -lactam protons and CH—P—O); 5.91 (O—CH₂—CH₃); 7.9 (S—CH₃); 8.73 (CH₃—CH₂—O).

35 Step D: 1 - (Benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - methylsulfonyl - 2 - azetidinone 35

1 - (Benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - (methylthio) - 2 - azetidinone (0.44 g.) is dissolved in methanol (20 ml.) and treated with N-bromoacetamide (0.52 g.) for two hours. Sodium thiosulfate (10 ml.; 0.1N) is then added and the mixture is stirred for five minutes. At the end of this time, the reaction mixture shows no positive reaction to starch iodide paper. The reaction mixture is saturated with sodium chloride and extracted with methylene chloride. The methylene chloride extract is dried and evaporated. The residue is chromatographed to afford 1 - (benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - methylsulfonyl - 2 - azetidinone. 40

45 Step E: 1 - (Benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - chloro-2 - azetidinone 45

1 - (Benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - methylsulfonyl - 2 - azetidinone (0.446 g.) is dissolved in acetyl chloride (5 ml.). The mixture is allowed to stand for 10 minutes and the acetyl chloride is removed under reduced pressure to

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afford 1 - (benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - chloro - 2 - azetidinone.

IR: 4.75 μ (azide); 5.6 μ (β -lactam C=O); 5.72 μ (ester C=O); 9.72 μ (P=O).

The product of Step E can also be prepared by dissolving 1 - (benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - (methylthio) - 2 - azetidinone (0.44 g.) in methylene chloride (10 ml.) and treating with chlorine (0.110 g.) in methylene chloride (2.0 ml.). The mixture is allowed to stand for 10 minutes at room temperature. The solvent is removed under reduced pressure to afford the 1 - (benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - chloro - 2 - azetidinone as described in Step E.

n.m.r.; (CDCl₃) τ : 2.6 (C₆H₅); 3.82, $\begin{array}{c} \text{Cl} \\ | \\ \text{---} \text{H} \text{ (cis)} \end{array}$; 4.26 $\begin{array}{c} \text{Cl} \\ | \\ \text{---} \text{H} \text{ (trans)} \end{array}$; 4.76 $\begin{array}{c} \text{N} \\ | \\ \text{H} \text{---} \text{S} \end{array}$ and $\begin{array}{c} \text{H} \\ | \\ \text{C} \text{---} \text{P} \end{array}$; 5.84 (O-CH₂-CH₃); 8.73 (O-CH₂-CH₃).

Step F: *Cis* and *Trans* 1 - (benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - (3' - acetoxy - 2' - oxo)propyloxy - 2 - azetidinone

1 - (Benzyloxycarbonyl - diethylphosphono)methyl - 3 - azido - 4 - chloro - 2 - azetidinone (0.43 g.) is dissolved in methylene chloride (10 ml.), 1,3-dihydroxy-2-propanone monoacetate (0.5 g.) and silver fluoroborate (0.3 g) are added and the mixture is stirred at room temperature for 0.5 hour. The mixture is diluted with CH₂Cl₂ (20 ml) and the silver salts are filtered off. The filtrate is washed once with 5% sodium bicarbonate and then with brine, dried and evaporated. The residue is chromatographed on silica gel to afford *cis* and *trans* 1 - (benzyloxycarbonyl - diethylphosphono)methyl - 3 - azido - 4 - (3' - acetoxy - 2' - oxo)propyloxy - 2 - azetidinone.

i.r. 4.71 (azide); 5.59 (β -lactam C=O); 5.72 (esters and ketone carbonyls).

Step G: Benzyl 7 α - (and β)-azido-1-oxadethiacephalosporanate

Cis and *trans* 1 - (benzyloxycarbonyl - diethylphosphono)methyl - 3 - azido - 4 - (3' - acetoxy - 2' - oxo)propyloxy - 2 - azetidinone (0.526 g.) is dissolved in anhydrous dimethoxyethane (20 ml.) under N₂ and treated with sodium hydride (0.047 g.; 57% in mineral oil). The reaction mixture is stirred for three hours at room temperature, taken up in benzene and washed once with a pH 7 buffer, and then with brine. The organic phase is dried and evaporated to give a residue, which is chromatographed on silica gel to afford benzyl 7 β -azido-1-oxadethiacephalosporanate.

i.r. 4.71 (azide); 5.58 (β -lactam C=O); 5.75 (ester C=O), 6.09 (C=C).

n.m.r. τ (CDCl₃): 2.56 (C₆-H₅); 4.69 (C₆H₅CH₂O); 4.8-5.6 (β -lactam,

$\begin{array}{c} \text{O} \\ || \\ \text{---CH}_2\text{O---C---CH}_3 \text{ and C-2 proton)} \end{array}$; 7.95 ($\begin{array}{c} \text{O} \\ || \\ \text{CH}_3\text{---C} \end{array}$) (J=3.5 c.p.s for β -lactam protons).

and Benzyl 7 α -azido-1-oxadethiacephalosporanate

i.r. 4.71 (azide); 5.58 (β -lactam C=O), 5.75 (ester C=O) 6.09 (C=C).

n.m.r. τ (CDCl₃): 2.59 (C₆H₅); 4.66 (C₆H₅.CH₂O); 4.8-5.6 (β -lactam,

$\begin{array}{c} \text{O} \\ || \\ \text{CH}_2\text{---O---C---CH}_3 \text{ and C-2 proton)} \end{array}$; 7.96 ($\begin{array}{c} \text{O} \\ || \\ \text{CH}_3\text{---C} \end{array}$) (J=1 c.p.s for β -lactam proton).

Step H: Benzyl 7 α -(and β)-amino-1-oxadethiacephalosporanate

Benzyl 7 α - (and β)-azido-1-oxadethiacephalosporanate (0.733 g.) is dissolved in dioxane (30 ml.). Platinum oxide (0.5 g.) is added and the mixture is reduced under hydrogen at atmospheric pressure until the infrared spectrum of a portion shows the

absence of the azide function. The dioxane is removed under reduced pressure, the residue is taken up in chloroform and filtered through a short column of silica gel G to remove the catalyst. The filtrate is evaporated to afford benzyl 7 α -(and β)-amino-1-oxadethiacephalosporanate.

5 **Step I:** Benzyl 7 α - (2' - thienylacetamido) - 1 - oxadethiacephalosporanate and benzyl 7 β - (2' - thienylacetamido) - 1 - oxadethiacephalosporanate 5

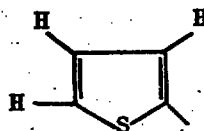
10 Benzyl 7 α -(and β)-amino-1-oxadethiacephalosporanate (0.692 g.) is dissolved in methylene chloride (25 ml.), cooled to 0°C. and treated with pyridine (0.7 ml.) followed by 2-thienylacetyl chloride (0.33 g.). The mixture is stirred at 0°C. for 30 minutes and then washed once with a pH 2 phosphate buffer and then with a pH 7 phosphate buffer. The organic phase is dried and evaporated to give a residue which, on chromatography on silica gel, affords benzyl 7 β - (2 - thienylacetamido) - 1 - oxadethiacephalosporanate and benzyl 7 α - (2 - thienylacetamido) - 1 - oxadethiacephalosporanate. 10

15 **Step J:** Sodium 7 α - (2' - thienylacetamido) - 1 - oxadethiacephalosporanate and Sodium 7 β - (2' - thienylacetamido) - 1 - oxadethiacephalosporanate 15

20 Benzyl 7 β - (2' - thienylacetamido) - 1 - oxadethiacephalosporanate (0.5 g) is dissolved in methanol (10 ml.). Water (3 ml.) is added, followed by 10% palladium-on-carbon catalyst (0.5 g.), and the mixture reduced under 40 lbs. of hydrogen pressure for one hour. The catalyst is filtered off, the filtrate is evaporated to about 2 ml. and diluted to 10 ml. with water, one equivalent of sodium bicarbonate is added and the resulting solution is freeze-dried to afford sodium 7 β - (2' - thienylacetamido) - 1 - oxadethiacephalosporanate. 20

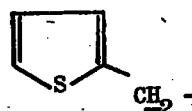
n.m.r. (D₂O, DSS) τ : 2.73 and 3.03

25



25

4.56 (C—7H) 4.83 (C—6H, J = 4 c.p.s); 5.66 (CH₂—OAc); 6.16



6.32 (C—2 H); 8.19 (CH₃—C=O).

30 Similar reductive cleavage of the benzyl ester of benzyl 7 α - (2' - thienylacetamido) - 1 - oxadethiacephalosporanate affords sodium 7 α - (2' - thienylacetamido) - 1 - oxadethiacephalosporanate. 30

EXAMPLE 3A.

7 β -Amino-1-oxadethiacephalosporanic acid

35 Benzyl 7 β -azido-1-oxadethiacephalosporanate (0.100 g) is dissolved in 4 ml. of dioxane and 2 ml. of H₂O and 0.020 g. of 10% Pd/C (Bolhofer) catalyst is added and the mixture is reduced under 40 lbs H₂ for 55 minutes. The catalyst is filtered off and the filtrate is freeze-dried to give 7 β -amino-1-oxadethiacephalosporanic acid. 35

i.r. 5.63 β -lactam, 5.71 (shoulder, ester carbonyl), 6.0 (amide); 6.25 (carboxylate).

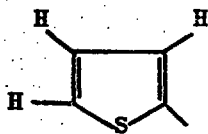
EXAMPLE 3B.

7 β -(2-Thienylacetamido)-1-oxadethiacephalosporanic acid

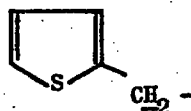
40 7 β -Amino-1-oxadethiacephalosporanic acid (0.070 g) is dissolved in 4 ml. acetone and 2 ml. H₂O and 0.047 g. of NaHCO₃ is added and the mixture is cooled to 0°. 2-Thienylacetyl chloride (0.045 g.) is added and the mixture is stirred at 0° for half an hour. The acetone is removed under reduced pressure and the residue is diluted with 10 ml H₂O and extracted twice with ethyl acetate. The EtOAc extract is washed once with water and the combined aqueous layers are taken to pH 2 with pH 2 phosphate 45

buffer and extracted twice with ethyl acetate. The ethyl-acetate extract is dried and evaporated to give 0.068 g of 7 β -(2-thienylacetamido)-1-oxadethiacephalosporanic acid.

i.r. 5.60 (β -lactam); 5.78 (ester carbonyl); 6.03 (amide); 6.5 (amide II).
n.m.r. τ (CDCl₃); 2.71 and 3.03



4.36 (C—7 H) 4.95 (C—6 H); 5.70 (CH₂—O—C(=O)—CH₃); 6.08 and 6.1



and C—2H); 8.0 CH₃—C(=O)

EXAMPLE 4.

Sodium 7 β - (2' - thienylacetamido) - 1 - methylene - 1 - dethia - 3 - methyl - 3 - cephem - 4 - carboxylate

By substituting for the 4-methylene-5-acetoxy-valeraldehyde of Step F of Example 1, an equimolar quantity of 4-methylenevaleraldehyde and by following substantially the procedures described in Steps F—L of Example 1, there is obtained sodium 7 β -(2 - thienylacetamido) - 1 - methylene - 1 - dethia - 3 - methyl - 3 - cephem - 4 - carboxylate.

Preparation of 4-methylenevaleraldehyde:

Step A: 4-Methylenevaleronitrile

Dry acetonitrile (5.0 g.) is placed in a 1-liter flask under N₂, dry tetrahydrofuran (200 ml.) is added and the mixture is cooled to -78°C. 38 ml. of a 23.1% solution of *n*-butyllithium is then added dropwise over 15 min. to the reaction mixture and stirring is continued for another 40 minutes. The reaction mixture is allowed to warm to -25°C, cuprous iodide (23.8 g.) is then added and stirring is continued for another 15 minutes at -25°C. Methallyl chloride (11.3 g.) in tetrahydrofuran (20 ml.) is then added dropwise over 5 minutes and the mixture is stirred at -25°C. for one hour. Aqueous ammonium chloride is then added and the product is extracted with ether. The ethereal extract is washed once with brine, dried and evaporated under a Vigreux column at atmospheric pressure. The residue is then distilled to afford 10.2 g. of 4-methylenevaleronitrile b.p. 165°—173°C.

IR: 4.45 μ (C $\equiv$ N); 6.02 μ (C=C); 11.1 μ (C=C).

NMR: τ : 5.2 m (C=CH₂); 7.63, m (—CH₂—CH₂—); 8.2, (CH₂—).

Step B: 4-methylenevaleraldehyde

4-Methylenevaleronitrile (3.0 g.) is dissolved in benzene (10 ml.) and placed under N₂. 25 ml. of a 20% solution of diisobutylaluminum hydride in hexane is added dropwise so that the reaction mixture is maintained at 40°—45°C. After the addition, the reaction is maintained at 40°C. for half an hour and then poured into ice-cold 2.5 *N* hydrochloric acid. The organic phase is separated and the aqueous phase is washed with ether 3 times. The combined organic extract is dried and evaporated using a Vigreux column. The residue is distilled at atmospheric pressure through a short Vigreux column to afford 2.45 g. of 4-methylenevaleraldehyde b.p. 135°—142°C.

IR: 3.7 μ (C=O); 5.75 μ (C=O); 6.02 μ (C=C) and 11.1 μ (C=C).

EXAMPLE 5.

Sodium 7 β - (2' - thienylacetamido) - 3 - carbamoyloxymethyl - 1 - methylene - 1-dethia - 3 - cephem - 4 - carboxylate

5 *Step A:* 4,4,6 - Trimethyl - 5,6 - dihydro - 2 - (4' - hydroxy - 3' - methylene)-butyl - 1,3(4 H) - oxazine

4,4,6 - Trimethyl - 5,6 - dihydro - 2 - (4' - acetoxy - 3' - methylene) - butyl-1,3(4 H) - oxazine (12.5 g.) is dissolved in tetrahydrofuran (100 ml.). Water (50 ml.) is added and then 20 ml. of 2.5 N sodium hydroxide is added dropwise for over one hour. The reaction mixture is stirred at room temperature for another four hours. Ether (200 ml.) is then added and the aqueous layer is separated and extracted once with ether (100 ml.). The combined ethereal extract is washed with brine, dried and evaporated to afford 4,4,6 - trimethyl - 5,6 - dihydro - 2 - (4' - hydroxy - 3' - methylene)-butyl - 1,3 (4 H) - oxazine.

15 *Step B:* 4,4,6 - Trimethyl - 5,6 - dihydro - 2 - (4' - carbamoyloxy - 3' - methylene)-butyl - 1,3(4 H) - oxazine

4,4,6 - Trimethyl - 5,6 - dihydro - 2 - (4' - hydroxy - 3' - methylene) - butyl-1,3(4 H) - oxazine (21.1 g.) is dissolved in benzene (100 ml.). Sodium cyanate (13.0 g.) is added and then trifluoroacetic acid (22.8 g.) is added dropwise for over one hour. The reaction mixture is stirred for another two hours. Water (20 ml.) is added and the aqueous phase is separated. The organic phase is dried and evaporated to afford 4,4,6 - trimethyl - 5,6 - dihydro - 2 - (4' - carbamoyloxy - 3' - methylene)-butyl - 1,3(4 H) - oxazine.

Step C: 4-Methylene-5-carbamoyloxyvaleraldehyde

4,4,6 - Trimethyl - 5,6 - dihydro - 2 - (4' - carbamoyloxy - 3' - methylene)-butyl - 1,3(4 H) - oxazine (12.5 g.) is dissolved in tetrahydrofuran (100 ml.). Water is added until a slight turbidity results. The mixture is cooled to -30°C. and sodium borohydride (1.0 g.) is added in four equal amounts. After being stirred for half an hour at -30°C. the reaction mixture is allowed to warm to room temperature and treated with dilute hydrochloric acid. The reaction mixture is diluted with ether (300 ml.) and washed once with water and then with brine. The organic phase is dried and evaporated to afford the tetrahydro-oxazine which is refluxed with 100 ml. of 5% oxalic acid solution for half an hour. The reaction mixture is extracted with ether and the ethereal extract is dried and evaporated to afford 4-methylene-5-carbamoyloxyvaleraldehyde.

35 *Step D:* Sodium 7 β - (2' - thienylacetamido) - 3 - carbamoyloxymethyl - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate

By substituting for the 4-methylene-5-acetoxyvaleraldehyde of Example 1, Step F, an equimolar quantity of 4-methylene-5-carbamoyloxyvaleraldehyde and by the following substantially the procedures described in Example 1, Steps F—L, there is obtained sodium 7 β - (2' - thienylacetamido) - 3 - carbamoyloxymethyl - 1 - methylene - 1-dethia - 3 - cephem - 4 - carboxylate.

By substituting for the sodium cyanate and trifluoroacetic acid of Example 5, Step B, an equimolar quantity of methylisocyanate or N,N-diethylcarbamoyl chloride, and by following substantially the procedures described in Example 5, Steps B—D, there are obtained respectively sodium 7 β - (2' - thienylacetamido) - 3 - (N - methylcarbamoyloxymethyl) - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate and sodium 7 β - (2' - thienylacetamido) - 3 - (N,N - diethylcarbamoyloxymethyl) - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate.

EXAMPLE 6.

50 Sodium 7 β - (2' - thienylacetamido) - 3 - carbamoyloxymethyl - 1 - oxa - 1 - dethia - 3 - cephem - 4 - carboxylate

Step A: 1-Acetoxy-3-carbamoyloxy-2-propanone

To a stirred mixture of 1-acetoxy-3-hydroxy-2-propanone (10.8 g., 0.1 mole) and sodium cyanate (13.0 g., 0.2 mole) in benzene (50 ml.) is slowly added trifluoroacetic acid (15.5 ml., 0.21 mole). The reaction mixture is stirred for three hours, then water (15 ml.) is added. The organic layer is separated and dried and the solvent removed under reduced pressure to afford 1-acetoxy-3-carbamoyloxy-2-propanone.

Step B: 1-Hydroxy-3-carbamoyloxy-2-propanone

Aqueous sodium hydroxide (35 ml. of a 2.5 N solution) is added dropwise over 30 minutes to a stirred solution of 1-acetoxy-3-carbamoyloxy-2-propanone (14.9 g., 0.085 g.) in methanol (10 ml.). The methanol is evaporated under reduced pressure and the aqueous residue extracted with chloroform (3 x 25 ml.). The combined extracts are dried, and the solvent is removed *in vacuo* to afford 1-hydroxy-3-carbamoyloxy-2-propanone.

Step C: Sodium 7 β - (2' - thienylacetamido) - 3 - carbamoyloxymethyl - 1 - oxy-1 - dethia - 3 - cephem - 4 - carboxylate

By substituting for the 1,3-dihydroxy-2-propanone monoacetate of Example 3, Step F, an equimolar quantity of 1-hydroxy-3-carbamoyloxy-2-propanone and by following the procedures described in Example 3, Steps F—J, there is obtained sodium 7 β - (2' - thienylacetamido) - 3 - carbamoyloxymethyl - 1 - oxa - 1 - dethia - 3 - cephem - 4 - carboxylate.

EXAMPLE 7.

Sodium 7 β - (2' - thienylacetamido) - 3 - acetoxymethyl - 1 - aza - 1 - dethia - 3 - cephem - 4 - carboxylate

Step A: 1-Azido-3-acetoxyacetone

1-Chloro-3-acetoxyacetone (15.05 g.) is dissolved in tetrahydrofuran (50 ml.) and water (25 ml.) is added. Sodium azide (8.7 g.) is added and the mixture is stirred overnight at room temperature. The reaction mixture is diluted with ether (200 ml.) and the aqueous phase is separated. The organic phase is washed once with brine, then dried and evaporated to give 1-azido-3-acetoxyacetone.

Step B: 1-Amino-3-acetoxyacetone

1-Azido-3-acetoxyacetone (15.7 g.) is dissolved in ethylacetate (200 ml.). Then 10% palladium on carbon catalyst (1.0 g.) is added; the mixture is reduced under hydrogen at atmospheric pressure until the infrared spectrum of a portion indicates the absence of the azide. The catalyst is filtered off and the filtrate is evaporated to afford 1-amino-3-acetoxy acetone.

Step C: Sodium 7 β - (2' - thienylacetamido) - 3 - acetoxymethyl - 1 - aza - 1 - dethia - 3 - cephem - 4 - carboxylate

By substituting for the 1,3-dihydroxy-2-propanone monoacetate of Example 3, Step F, an equimolar quantity of 1-amino-3-acetoxyacetone and by following substantially the procedures described in Example 3, Steps F—J, there is obtained sodium 7 β - (2' - thienylacetamido) - 3 - acetoxymethyl - 1 - aza - 1 - dethia - 3 - cephem - 4 - carboxylate.

EXAMPLE 8.

Sodium 7 β - (2' - thienylacetamido) - 3 - acetoxymethyl - N - methyl - 1 - aza - 1 - dethia - 3 - cephem - 4 - carboxylate

Step A: 1-(N-methyl)amino-3-acetoxyacetone

To 1-amino-3-acetoxyacetone (13.1 g.) is added benzaldehyde (10.6 g.) dropwise with cooling; 10 minutes after the addition, benzene (300 ml.) is added and the solution is dried over MgSO₄ for two hours. The MgSO₄ is removed and the solvent is evaporated to afford 1-benzaldimino-3-acetoxyacetone. This is redissolved in benzene (200 ml.) and treated with 15 g. of dimethyl sulfate, added dropwise. The resulting solution is heated slowly to reflux and then refluxed for one hour. The benzene is removed under reduced pressure. The residue is taken up in water (200 ml.) and treated with 1 equivalent of 1 N sodium hydroxide, added at such a rate that the pH remains between 4 and 8. After the addition is complete, the reaction mixture is extracted with ether and the ethereal extract is dried. Anhydrous hydrochloric acid is then bubbled into the ethereal extract and the precipitated amine hydrochloride is separated. The amine hydrochloride is dissolved in water and the solution is taken to pH 7.5 and extracted with ether. The ethereal extract is dried and evaporated to afford 1-(N-methyl)-amino-3-acetoxyacetone.

Step B: Sodium 7 β - (2' - thienylacetamido) - 3 - acetoxymethyl - N - methyl - 1 - aza - 1 - dethia - 3 - cephem - 4 - carboxylate

By substituting for the 1,3-dihydroxy-2-propanone monoacetate of Example 3, Step F, an equimolar quantity of 1-(N-methyl)amino-3-acetoxyacetone and by following substantially the procedures described in Example 3, Steps F—J, there is obtained

sodium 7 β - (2' - thienylacetamido) - 3 - acetoxymethyl - N - methyl - 1 - aza - 1 - dethia - 3 - cephem - 4 - carboxylate.

EXAMPLE 9.

Sodium 7 β - (2' - thienylacetamido) - 3 - hydroxymethyl - 1 - methylene 1 - dethia - 3 - cephem - 4 - carboxylate

To a solution of sodium 7 β - (2' - thienylacetamido) - 3 - acetoxymethyl - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate (1.0 g.) in water (15.0 ml.) is added acetylesterase. The pH is adjusted to 6.0 and maintained around this level for 15 hours. The solution is then passed through a column containing phenolic amine (in the acetate form) and eluted with aqueous 0.1 M acetic acid that has been adjusted to pH 5.5 by addition of pyridine. The fractions collected are adjusted to pH 8 by the addition of sodium hydroxide and this alkaline mixture is evaporated *in vacuo* to afford sodium 7 β - (2' - thienylacetamido) - 3 - hydroxymethyl - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate.

EXAMPLE 10.

Sodium 7 β - (2' - thienylacetamido) - 3 - (pyridinium - methyl) - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate

A solution of sodium 7 β - (2' - thienylacetamido) - 3 - hydroxymethyl - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate (1.0 g.) is brought to pH 2.5. Pyridine (8.0 ml.) is added and the solution is allowed to stand overnight at 45°C. The reaction mixture is then lyophilized and the residue is dissolved in water and passed through a polystyrene trimethylbenzylammonium anion-exchange resin (43% H₂O). Selected fractions are diluted with water and lyophilized to afford substantially pure sodium 7 β - (2' - thienylacetamido) - 3 - (pyridinium - methyl) - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate.

EXAMPLE 11.

Sodium 7 β - (2' - thienylacetamido) - 3 - (5 - methyl - 1,3,4 - thiadiazol - 2 - ylthio - methyl) - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate

A mixture of benzyl 7 β - (2' - thienylacetamido) - 1 - methylene - 1 - dethia - cephalosporanate (0.654 g.) and 5-methyl-1,3,4-thiadiazolyl-2-thiol (0.37 ml.) in a mixture of one part acetone and one part water (10 ml.) is stirred at room temperature and 10% sodium hydroxide solution (2.0 ml.) is added with stirring. The mixture is then heated in a sealed tube for 100 hours and the resulting mixture is concentrated *in vacuo* to afford the substantially pure product.

By substituting for 5-methyl-1,3,4-thiadiazolyl-2-thiol an equimolar quantity of N-methyl tetrazolylthiol and by following substantially the procedure described above there is obtained sodium 7 β - (2' - thienylacetamido) - 3 - (N - methyltetrazolylthiomethyl) - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate.

EXAMPLE 12.

Benzyl 7 β - amino - 1 - benzyloxycarbonylamino - dethiacephalosporanate and benzyl 7 α - amino - 1 - benzyloxycarbonylamino - dethiacephalosporanate

A. 2,2-Dimethyl-4-azidomethyl-1,3-dioxolane

15.05 g. of 2,2-dimethyl-4-chloromethyl-1,3-dioxolane is dissolved in 100 ml. DMF and 6.5 g. of NaN₃ is added. The mixture is stirred at 50° overnight, cooled to room temperature, diluted with 300 ml. C₆H₆ and washed 5 times with water. The organic phase is dried and evaporated under reduced pressure to give 2,2-dimethyl-4-azidomethyl-1,3-dioxolane.

B. 2,2-dimethyl-4-aminomethyl-1,3-dioxolane

15.7 g. of 2,2-dimethyl-4-azidomethyl-1,3-dioxolane is dissolved in 200 ml. C₆H₆. 1.5 g. of PtO₂ is added and the mixture is reduced under hydrogen at 40 lbs. pressure, until i.r. of a portion shows absence of azide.

The catalyst is filtered off and the filtrate is evaporated to give 2,2-dimethyl-4-aminomethyl-1,3-dioxolane.

C. 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methylamino - azetidin - 2 - one

0.156 g. of potassium is dissolved in 10 ml. of *t*-butanol under N₂. To this is added 0.524 g. of 2,2-dimethyl-4-aminomethyl-1,3-dioxolane and the mixture is stirred at room temperature for 1/2 hour. 1.722 g. of 1 - (benzyloxycarbonyldiethylphosphono) -

za - 1-			methyl - 3 - azido - 4 - chloro - azetidin - 2 - one dissolved in 10 ml. of <i>t</i> -butanol is added dropwise over 15 minutes and the mixture is stirred at room temperature until a portion shows a neutral reaction to pH paper.	
dethia-	5	5	The reaction mixture is diluted with 100 ml. C_6H_6 and washed once with pH 3 buffer and then with pH 7 phosphate buffer. The organic phase is dried and evaporated. The residue is chromatographed on silica gel to give 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methylamino - azetidin - 2 - one.	5
yl - 1-	10	10	D. 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2,2 - dimethyl - 1,3 - dioxolan - 4 - ylmethyl) - benzyloxycarbonylamino - azetidin - 2 - one	10
0 ml.)			1.05 g. of 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methylamino - azetidin - 2 - one is dissolved in 50 ml. CH_2Cl_2 , cooled to 0° and treated with 0.474 g. (3 eq.) pyridine. Benzyloxycarbonyl chloride (0.680, 2 eq.) is then added and the mixture is stirred at 0° for 15 minutes and then at room temperature for 3 hours. The reaction mixture is	15
vel for	15	15	diluted with CH_2Cl_2 , washed once with pH 7 phosphate buffer, then pH 3 phosphate buffer and then again with pH 7 phosphate buffer. The organic phase is dried and evaporated. The residue is chromatographed on silica gel (60 g.) to give 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2,2 - dimethyl - 1,3 - dioxolan - 4 - ylmethyl) - benzyloxycarbonylamino - azetidin - 2 - one.	20
ine (in	20	20	E. 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2,3 - dihydroxypropyl) - benzyloxycarbonylamino - azetidin - 2 - one	25
sted to	25	25	1 - (Benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2,2 - dimethyl - 1,3 - dioxolan - 4 - ylmethyl) - benzyloxycarbonylamino - azetidin - 2 - one (1 g.) is dissolved in 10 ml. of THF, 2 ml. H_2O is added and then 0.5 ml. of 7% aqueous $HClO_4$ is added. The mixture is allowed to stand at room temperature for $2\frac{1}{2}$ hours. The mixture is diluted with $CHCl_3$ (50 ml.), washed once with	30
by the	30	30	pH 7 buffer and then with brine, dried and evaporated to give a residue, which is 1 - benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2,3 - dihydroxypropyl) - benzyloxycarbonylamino - azetidin - 2 - one.	35
afford	35	35	F. 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2 - hydroxy - 3 - acetoxypropyl) - benzyloxycarbonylamino - azetidin - 2 - one	40
dethia-	40	40	0.619 g. of 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2,3 - dihydroxypropyl) - benzyloxycarbonylamino - azetidine - 2 - one is dissolved in 15 ml. of CH_2Cl_2 and cooled to $0^\circ C$. Pyridine (0.158 g., 2 eq.) and acetic anhydride (0.102 g., 1.1 eq.) are added and the mixture is stirred at $0^\circ C$. for 15 minutes and then at room temperature for one hour. The reaction mixture is diluted with CH_2Cl_2 and washed once with pH 7 buffer, then with pH 3 buffer and once again with pH 7 buffer. The organic phase is dried and evaporated. The residue is chromatographed on silica gel to give 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - (N - 2 - hydroxy - 3 - acetoxypropyl) - benzyloxycarbonylamino - azetidin - 2 - one.	45
ne - 1-	45	45	G. 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2 - oxo - 3 - acetoxypropyl) - benzyloxycarbonylamino - azetidin - 2 - one	50
l - 1-	50	50	1 - (Benzyloxycarbonyldiethylphosphono) methyl - 3 - azido - 4(N - 2 - hydroxy - 3 - acetoxypropyl) - benzyloxycarbonylamino - azetidin - 2 - one (0.661 g.) is dissolved in 2 ml. of CH_2Cl_2 . Chromium trioxide (0.6 g.) is added to a magnetically stirred solution of 0.949 g. pyridine in 15 ml. of methylene chloride under N_2 . The solution is stirred for 15 minutes at room temperature, at the end of which the solution of the alcohol in CH_2Cl_2 prepared above is added in one portion. Stirring is continued for 16 minutes and the solution is decanted from the black residue, which is washed with 20 ml. of CH_2Cl_2 . The combined organic phase is washed once with pH 3 buffer then with pH 7 buffer and then dried and evaporated. The residue is chromatographed on silica gel to give 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2 - oxo - 3 - acetoxypropyl) - benzyloxycarbonylamino - azetidin - 2 - one.	55
H 2.5.	55	55	H. benzyl - 7 α - azido - 1 - (benzyloxycarbonylamino) - dethiacephalosporanate and its 7 β -azido epimer	60
45°C.	60	60	1 - (Benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4(N - 2 - oxo - 3 - acetoxypropyl) - benzyloxycarbonylamino - azetidin - 2 - one (0.65 g.) is dissolved in 20 ml. of anhydrous DMF under N_2 and treated with 0.047 g. of sodium	
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hydride (57% in mineral oil). The reaction mixture is stirred for 3 hours at room temperature. The reaction mixture is diluted with C_6H_6 and washed once with pH 7 buffer and then with brine. The organic phase is dried and evaporated to give a residue which, on chromatography on silica gel, gives benzyl - 7 α - azido - 1 - (benzyloxycarbonylamino)dethiacephalosporanate and its 7 β -azido epimer.

1. benzyl 7 β - amino - 1 - (benzyloxycarbonylamino) - dethiacephalosporanate and benzyl 7 α - amino - 1 - (benzyloxycarbonylamino) - dethiacephalosporanate

0.800 g. of the benzyl 7 β - azido - 1 - (benzyloxycarbonylamino) - dethiacephalosporanate is dissolved in 50 ml. of C_6H_6 . 0.400 g. of PtO_2 is added and the mixture is reduced under H_2 at 40 lbs. pressure until a portion shows absence of azide by its i.r. spectrum.

The catalyst is filtered off and the filtrate is evaporated to give benzyl 7 β - amino - 1 - (benzyloxycarbonylamino) - dethiacephalosporanate.

Similarly, benzyl 7 α - azido - 1 - (benzyloxycarbonylamino) - dethiacephalosporanate is reduced to benzyl 7 α - amino - 1 - (benzyloxycarbonylamino) - dethiacephalosporanate.

EXAMPLE 13.

benzyl 7 β -(2-thienylacetamido)-1-benzyloxycarbonylamino-dethiacephalosporanate
0.479 g. of benzyl 7 β - amino - 1 - (benzyloxycarbonyl) - dethiacephalosporanate is dissolved in 25 ml. of CH_2Cl_2 , cooled to 0°C. and treated with 0.160 ml. of pyridine and 0.160 g. of thienylacetyl chloride.

The reaction mixture is stirred at 0°C. for 15 minutes then diluted with CH_2Cl_2 and washed once with pH 7 buffer then with pH 3 buffer and then with pH 7 buffer. The organic phase is dried and evaporated to give a residue which is chromatographed on silica gel to give benzyl 7 β - (2 - thienylacetamido) - 1 - benzyloxycarbonylamino-dethiacephalosporanate.

EXAMPLE 14.

7 β -(2-thienylacetamido)-1-aminodethiacephalosporanic acid

0.400 g. of benzyl 7 β - (2 - thienylacetamido) - 1 - benzyloxycarbonylamino-dethiacephalosporanate is dissolved in 5 ml. of dioxane and 2 ml. of H_2O is added. 0.400 g. of 10% Pd/C (Böcher catalyst) is added and the mixture is reduced under 40 lbs. hydrogen pressure for 1 hour. The catalyst is filtered off and washed with water. The filtrate and washings are extracted with $CHCl_3$ and the aqueous phase is freeze-dried to give 7 β - (2 - thienylacetamido) - 1 - aminodethiacephalosporanic acid.

EXAMPLE 15.

benzyl 7 α -(4-nitrobenzaldimino)-1-benzyloxycarbonylamino-dethiacephalosporanate

Benzyl 7 α - amino - 1 - (benzyloxycarbonylamino) - dethiacephalosporanate (0.489 g.) is dissolved in 20 ml. $CHCl_3$ and treated with 0.151 g. of *p*-nitrobenzaldehyde. 3 g. of anhydrous $MgSO_4$ is added and the mixture is stirred at room temperature for 2 hours and filtered. The filtrate is evaporated to give benzyl 7 α - (4 - nitrobenzaldimino) - 1 - benzyloxycarbonylamino-dethiacephalosporanate.

EXAMPLE 16.

benzyl 7 β - (4 - nitrobenzaldimino) - 1 - benzyloxycarbonylamino-dethiacephalosporanate and benzyl 7 α - (4 - nitrobenzaldimino) - 1 - benzyloxycarbonylamino-dethiacephalosporanate

0.612 g. of the benzyl 7 α - (4 - nitrobenzaldimino) - 1 - benzyloxycarbonylamino-dethiacephalosporanate is dissolved in 25 ml. of anhydrous THF under N_2 and cooled to -78°C. 0.5 ml. of a 2 M solution of phenyl lithium in C_6H_6/Et_2O is added dropwise over 2 minutes. The mixture is stirred a further 2 minutes and 20 ml. of DMF are added dropwise over 3 minutes followed by 0.066 g. of HOAc and 0.100 ml. of H_2O in 5 ml. of THF. The reaction mixture is diluted with C_6H_6 and washed once with pH 7 phosphate buffer and then with water, and then 4 times with brine. The organic phase is dried and evaporated to give a mixture of benzyl 7 β - (4 - nitrobenzaldimino) - 1 - benzyloxycarbonylamino-dethiacephalosporanate and its epimer at C-7.

EXAMPLE 17.

benzyl 7 β - amino - 1 - benzyloxycarbonylamino-dethiacephalosporanate and benzyl 7 α - amino - 1 - benzyloxycarbonylamino-dethiacephalosporanate

2,4-Dinitrophenylhydrazine (0.198 g.) and *p*-toluenesulfonic acid monohydrate (0.190 g.) are added to 5 ml. of EtOH and the mixture is stirred at room temperature for 1 hour. The mixture of benzyl 7 β - (4 - nitrobenzaldimino) - 1 - benzyloxycarbonylamino-dethiacephalosporanate and its epimer at C-7 (0.612 g.) is dissolved in 2 ml. EtOH and added to the above mixture and stirred for half an hour. The orange solid is

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filtered off and the filtrate is evaporated under reduced pressure. The residue is taken up in CH₂Cl₂ and washed with pH 8 phosphate buffer, dried and evaporated to give benzyl 7 β - amino - 1 - benzyloxycarbonylamino - dethiacephalosporanate and its C—7 epimer.

EXAMPLE 18.

benzyl 7 β - (2 - thienylacetamido) - 1 - benzyloxycarbonylamino - dethiacephalosporanate and benzyl 7 α - (2 - thienylacetamido) - 1 - benzyloxycarbonylamino - dethiacephalosporanate

The mixture of benzyl 7 β - amino - 1 - benzyloxycarbonylamino - dethiacephalosporanate and its C—7 epimer is acylated with thienyl-acetyl chloride and pyridine as described for the 7 β -isomer and the resulting mixture is chromatographed on silica gel to give benzyl 7 β - (2 - thienylacetamido) - 1 - benzyloxycarbonylamino - dethiacephalosporanate and benzyl 7 α - (2 - thienylacetamido) - 1 - benzyloxycarbonylamino - dethiacephalosporanate.

EXAMPLE 19.

7 β -(2-thienylacetamido)-1-methylamino-dethiacephalosporanic acid
0.524 g. of 7 β - (2 - thienylacetamido) - 1 - amino - dethiacephalosporanic acid is dissolved in 4.5 ml. of AcOH, 2.5 ml. of H₂O, 0.4 g. of 35% HCHO and 0.3 g. of PtO₂ are added and the mixture is reduced under H₂ at 40 lbs. pressure for half an hour. The catalyst is filtered off and the filtrate is freeze-dried to give 7 β - (2 - thienylacetamido) - 1 - methylamino - dethiacephalosporanic acid.

EXAMPLE 20.

cis- and *trans* - 1 - (1 - benzyloxycarbonyl - 2 - chloromethyl - 3 - acetoxy - prop - 1 - enyl) - 3 - azido - 4 - chloroazetidin - 2 - one
To a solution of 388 mg. of benzyl-7-azidocephalosporanate (mixture of C—7 epimers) in 10 ml. of anhydrous carbon tetrachloride is added 2.2 equivalents of chlorine in CCl₄. After half an hour at room temperature, the solvent is removed *in vacuo* to give a mixture of *cis*- and *trans* - 1 - (1 - benzyloxycarbonyl - 2 - chloromethyl - 3 - acetoxy - prop - 1 - enyl) - 3 - azido - 4 - chloroazetidin - 2 - one.

EXAMPLE 21.

benzyl 7 α - azido - 1 - benzylamino - dethiacephalosporanate and benzyl 7 β - azido - 1 - benzylamino dethiacephalosporanate

A solution of 107 mg. (1 mmole) of benzylamine in 2 ml. of N,N-dimethylformamide is added to a suspension of 276 mg. (2 mmoles) of potassium carbonate in 5 ml. of N,N-dimethylformamide containing 427 mg. (1 mmole) of 1 - (1 - benzyloxycarbonyl - 2 - chloromethyl - 3 - acetoxy - prop - 1 - enyl) - 3 - azido - 4 - chloro - azetidin - 2 - one. The reaction mixture is stirred at room temperature overnight under nitrogen and poured onto 100 g. of ice. The organic matter is extracted with 5 x 20 ml. of a 1:1 mixture of ether and petroleum ether. Removal of the solvent from the extracts and drying over anhydrous magnesium sulfate gives a residue, which, on chromatography on silica gel, gives benzyl 7 α - azido - 1 - benzylamino - dethiacephalosporanate and benzyl 7 β - azido - 1 - benzylamino - dethiacephalosporanate.

EXAMPLE 22.

benzyl 7 α - azido - 1 - methylamino - dethiacephalosporanate and benzyl 7 β - azido - 1 - methylamino - dethiacephalosporanate

A solution of 1 equivalent of methylamine in anhydrous N,N-dimethylformamide is added to a solution of 427 mg. (1 mmole) of 1 - (1 - benzyloxycarbonyl - 2 - chloromethyl - 3 - acetoxy - prop - 1 - enyl) - 3 - azido - 4 - chloro - azetidin - 2 - one in 5 ml. of N,N-dimethylformamide, containing 2 equivalents of potassium carbonate. The reaction mixture is stirred under nitrogen at room temperature for 1 day, poured into ice-cold water and extracted with a mixture of ether and petroleum ether. The combined organic layers are dried over anhydrous magnesium sulfate. The residue obtained by removing the solvent is chromatographed on silica gel to give benzyl 7 α - azido - 1 - methylamino - dethiacephalosporanate and benzyl 7 β - azido - 1 - methylamino - dethiacephalosporanate.

Example 23.

benzyl 7 α -amino-1-benzylamino-dethiacephalosporanate
246 mg. of benzyl 7 α - azido - 1 - benzylamino - dethiacephalosporanate is reduced under hydrogen in benzene, using 59 mg. of platinum oxide as catalyst, at atmospheric pressure, until the azide band in the i.r. spectrum disappears. The catalyst is filtered

and washed with benzene. The solvent removal from the filtrate gives benzyl 7 α -amino-1-benzylamino-dethiacephalosporanate.

Similarly, benzyl 7 α -azido-1-methylamino-dethiacephalosporanate is reduced to give benzyl 7 α -amino-1-methylamino-dethiacephalosporanate.

Analogously, benzyl 7 β -azido-1-benzylamino-dethiacephalosporanate is reduced to give benzyl 7 β -amino-1-benzylamino-dethiacephalosporanate.

Also, benzyl 7 β -azido-1-methylamino-dethiacephalosporanate gives benzyl 7 β -amino-1-methylamino-dethiacephalosporanate.

EXAMPLE 24.

benzyl 7 α -p-nitrobenzaldimino-1-benzylamino-dethiacephalosporanate

To a solution of 152 mg. (1 mmole) of p-nitrobenzaldehyde in 4 ml. of chloroform is added a solution of 435 mg. (1 mmole) of benzyl 7 α -amino-1-benzylamino-dethiacephalosporanate in 6 ml. of chloroform. 1.5 g. of anhydrous magnesium sulfate is added and the mixture is stirred for 2 hours. The solid is filtered and washed with chloroform. The solvent removal from the filtrate gives benzyl 7 α -p-nitrobenzaldimino-1-benzylamino-dethiacephalosporanate.

Similarly, condensation of benzyl 7 α -amino-1-methylaminodethiacephalosporanate with p-nitrobenzaldehyde gives benzyl 7 α -p-nitrobenzaldimino-1-methylamino-dethiacephalosporanate.

EXAMPLE 25.

benzyl 7 α -p-nitrobenzaldimino-1-benzylamino-dethiacephalosporanate and benzyl 7 β -nitrobenzaldimino-1-benzylamino-dethiacephalosporanate

To a solution of 523 mg. of benzyl 7 α -p-nitrobenzaldimino-1-benzylamino-dethiacephalosporanate in 10 ml. of anhydrous tetrahydrofuran is added under nitrogen 0.435 ml. of 2.3 M solution of phenyl lithium at -78°C. 10 ml. of N,N-dimethylformamide is slowly added followed by a mixture of 30 μ l. of water and 76 μ l. of glacial acetic acid in 2 ml. of tetrahydrofuran. The reaction mixture is allowed to warm to room temperature, diluted with benzene and washed with water and brine. Evaporation of the solvent gives a mixture of the starting material and its C-7 epimer.

Similarly, a mixture of starting Schiff base and its epimer at C-7 is obtained from benzyl 7 α -p-nitrobenzaldimino-1-methylamino-dethiacephalosporanate.

EXAMPLE 26.

benzyl 7 α -amino-1-benzylamino-dethiacephalosporanate and benzyl 7 β -amino-1-benzylamino-dethiacephalosporanate

To a solution of 198 mg. (1 mmole) of 2,4-dinitrophenylhydrazine in 10 ml. of ethanol is added 190 mg. (1 mmole) of p-toluenesulfonic acid monohydrate and the mixture is stirred for half an hour at room temperature. A solution of 523 mg. (1 mmole) of benzyl-7-p-nitrobenzaldimino-1-benzylamino-dethiacephalosporanate (C-7 α and β epimeric mixture) in 10 ml. of ethanol is then added. The reaction mixture is stirred for 0.5 hour at room temperature, filtered and the filtrate evaporated. The residue is taken up in 100 ml. of methylene chloride, washed with 2 $\times$ 50 ml. of brine, dried over anhydrous magnesium sulfate and evaporated to give benzyl-7-amino-1-benzylamino-dethiacephalosporanate (α and β epimers at C-7).

Similarly, C-7 epimeric mixture of benzyl-7-amino-1-methylaminodethiacephalosporanate is obtained from benzyl-7-p-nitrobenzaldimino-1-methylamino-dethiacephalosporanate (mixture of α and β epimers at C-7).

EXAMPLE 27.

benzyl 7 β -thienylacetamido-1-benzylamino-dethiacephalosporanate, and benzyl 7 α -thienylacetamido-1-benzylaminodethiacephalosporanate

143 μ l. (2 mmoles) of pyridine is added to an ice-cold solution of 435 mg. (1 mmole) of a mixture of C-7 epimers of benzyl-7-amino-1-benzylamino-dethiacephalosporanate in 20 ml. of methylene chloride. 134 μ l (1 mmole) of thienyl acetyl chloride is added dropwise and the mixture is stirred for 30 minutes at 0°C. The reaction mixture is washed with 20 ml. of water and 20 ml. of pH 2 buffer to remove excess of base and then with 20 ml. of brine. The resulting solution is dried over anhydrous magnesium sulfate and the solvent is evaporated to give a residue, which is chromatographed on silica gel to give benzyl 7 β -thienylacetamido-1-benzylamino-dethiacephalosporanate and benzyl 7 α -thienylacetamido-1-benzylamino-dethiacephalosporanate.

Similarly, acylation of a mixture of C-7 epimers of benzyl-7-amino-1-methylamino-dethiacephalosporanate and subsequent chromatography gives benzyl

amino-		7 β - thienylacetamido - 1 - methylamino - dethiacephalosporanate and benzyl 7 α -thienylacetamido - 1 - methylamino - dethiacephalosporanate.	
to		Analogously, acylation of benzyl 7 β - amino - 1 - benzylamino - dethiacephalosporanate with thienyl acetyl chloride gives benzyl 7 β - thienylacetamido - 1 - benzylamino - dethiacephalosporanate.	
reduced	5	Also, acylation of benzyl 7 β - amino - 1 - methylamino - dethiacephalosporanate with thienyl acetyl chloride gives benzyl 7 β - thienylacetamido - 1 - methylamino - dethiacephalosporanate.	5
yl 7 β -			
	10	EXAMPLE 28. sodium 7 β -thienylacetamido-1-amino-dethiacephalosporanate	10
chloro-		203 mg. of benzyl 7 β - thienylacetamido - 1 - benzylamino - dethiacephalosporanate is hydrogenated in a mixture of dioxane and water, using 50 mg. of 10% palladium on carbon as catalyst in an atmosphere of hydrogen at 45 p.s.i. The catalyst is filtered and washed with a mixture of dioxane and water. The filtrate is concentrated and 1 equivalent of sodium bicarbonate is added. The resulting solution is freeze-dried to give sodium 7 β - thienylacetamido - 1 - amino - dethiacephalosporanate.	10
lamino-		Similarly, benzyl 7 α - thienylacetamido - 1 - benzylamino - dethiacephalosporanate is hydrogenated to give 7 α - thienylacetamido - 1 - amino - dethiacephalosporin, which, after neutralization and freeze-drying, gives its sodium salt.	15
sulfate	15		15
ed with			
dimino-			
oranate	20	EXAMPLE 29. sodium 7 β -thienylacetamido-1-methylamino-dethiacephalosporanate	20
-dethia-		483 mg. (1 mmole) of benzyl 7 β - thienylacetamido - 1 - methylamino - dethiacephalosporanate is dissolved in 10 ml. of dioxane and 84 mg. (1 mmole) of sodium bicarbonate in 2 ml. of water and 50 mg. of 10% palladium on carbon are added. The mixture is reduced in a hydrogen atmosphere at 45 p.s.i. for 1 hour. The catalyst is filtered and washed with 5 ml. dioxane and 5 ml. water. The filtrate is freeze-dried to give sodium 7 β - thienylacetamido - 1 - methylamino - dethiacephalosporanate.	20
	25	Similarly, benzyl 7 α - thienylacetamido - 1 - methylamino - dethiacephalosporanate is hydrogenolysed to give, after neutralization, sodium 7 α - thienylacetamido - 1 - methylamino - dethiacephalosporanate.	25
	30	EXAMPLE 30. sodium 7 β -thienylacetamido-1-formamido-dethiacephalosporanate	30
		379 mg. (1 mmole) of 7 β - thienylacetamido - 1 - amino - dethiacephalosporin is dissolved in 15 ml. of methylene chloride and 72 μ l. (1 mmole) of dry pyridine and 96 mg. (1 mmole) of N-formylimidazole are added. The reaction mixture is stirred for 3 hours at room temperature, then washed with pH 2 buffer and with brine. The organic phase is dried over anhydrous magnesium sulfate and the solvent removed to give 7 β -thienylacetamido - 1 - formamido - dethiacephalosporin, which on neutralization with sodium bicarbonate and freeze-drying gives sodium 7 β - thienylacetamido - 1 - formamido - dethiacephalosporanate.	35
	40		40
		EXAMPLE 31. <i>p</i> -methoxybenzyl <i>dl</i> -7 β -(2-thienylacetamido)-1-oxa-dethiacephalosporanate	40
	45	Oxalyl chloride (0.5 ml.) and dimethylformamide (0.02 ml.) are added to a stirring suspension of <i>dl</i> - 7 β - (2 - thienylacetamido) - 1 - oxa - dethiacephalosporanic acid (1.04 g.) in dry methylene chloride (75 ml.). The reaction mixture is stirred at room temperature for 20 minutes to give an orange solution. The solvent and excess of oxalyl chloride are removed <i>in vacuo</i> . The residue is diluted with dry benzene and evaporated <i>in vacuo</i> to afford the crude acid chloride.	45
		The acid chloride is dissolved in dry methylene chloride (40 ml.), and the solution is treated with <i>p</i> -methoxybenzyl alcohol (1.45 g.) and <i>dl</i> - α -pinene (0.61 g.). The solution is stirred at room temperature for 40 minutes. Evaporation of the solvent <i>in vacuo</i> leaves a dark oil, which is chromatographed on silica gel (75 g.). Elution with 20% ethylacetate in benzene affords <i>p</i> -methoxybenzyl <i>dl</i> - 7 β - (2 - thienylacetamido) - 1 - oxa - dethiacephalosporanate.	50
	50		50
	55	EXAMPLE 32. <i>p</i> -Methoxybenzyl <i>dl</i> -7 α -methoxy-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate	55
		Phenyllithium (2.6 ml of a 2.3 M solution) and anhydrous methanol (5 ml) are added with stirring to ice-cold anhydrous tetrahydrofuran (50 ml) under nitrogen. The resulting solution is cooled to -78°C. (dry ice-acetone) and treated with a solution of <i>p</i> -methoxybenzyl <i>dl</i> - 7 β - (2 - thienylacetamido) - 1 - oxa - dethiacephalosporanate (1.00 g) in dry tetrahydrofuran (15 ml). After being stirred for 2 minutes, the cold	60
	60		60

reaction mixture is treated with *t*-butyl hypochlorite (0.29 ml) and stirred for an additional 10 minutes. Glacial acetic acid (5 ml) is then added and the reaction mixture is concentrated *in vacuo*. The residue is dissolved in methylene chloride and the solution is washed with dilute aqueous sodium thiosulfate, aqueous sodium bicarbonate, and saturated brine. The methylene chloride solution is dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield *p*-methoxybenzyl *dl*-7 α -methoxy-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate.

EXAMPLE 33.

Sodium *dl*-7 α -methoxy-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate

To an ice-cold mixture of *p*-methoxybenzyl *dl*-7 α -methoxy-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate (0.86 g) and anisole (4 ml) is added ice-cold trifluoroacetic acid (20 ml). The mixture is swirled to make homogeneous and then kept at 0° for 3 minutes. The trifluoroacetic acid is evaporated *in vacuo* at 0°, and the residue is warmed to 35° *in vacuo*. The remaining oil is diluted with water (50 ml) containing sodium bicarbonate (1.35 g) and extracted with methylene chloride (2 $\times$ 25 ml). The aqueous portion is acidified to pH 2.6 with 6 *N* hydrochloric acid and extracted with ethyl acetate (3 $\times$ 25 ml). The combined ethyl acetate extracts are dried over magnesium sulfate, filtered, and evaporated *in vacuo* to provide *dl*-7 α -methoxy-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanic acid.

A portion of the above free acid (0.41 g) is stirred with sodium bicarbonate (0.09 g) in water (30 ml) for 20 minutes. The resulting mixture is washed with ethyl acetate (2 $\times$ 10 ml). The aqueous phase is separated, concentrated *in vacuo* to remove dissolved ethyl acetate, and lyophilized to afford sodium *dl*-7 α -methoxy-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate.

EXAMPLE 34.

Potassium *dl*-7 α -methoxy-7-(2-thienylacetamido)-3-hydroxymethyl-1-oxa-dethiaceph-3-em-4-carboxylate

A solution of sodium *dl*-7 α -methoxy-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate (0.41 g) in citrus acetyl esterase (13 ml) is placed in a thermostated 30° bath and stirred at that temperature. The pH of the reaction mixture is maintained at 6.7 $\pm$ 0.1 by the periodic addition of 1 *N* sodium hydroxide. After 16 hrs. at 30°, the rate of base addition is very slow and the reaction is stopped. The mixture is brought to room temperature, treated with powdered sodium chloride (4.5 g), and stirred. The resulting thin suspension is overlaid with ethylacetate (20 ml) and, with vigorous stirring, acidified to pH 2.1 with 6 *N* hydrochloric acid. The layers are separated and the aqueous portion is extracted with more ethyl acetate (2 $\times$ 5 ml). The combined ethylacetate solution is backwashed with water (2 $\times$ 10 ml) and then layered with water (50 ml). The mixture is stirred vigorously while 6 *N* potassium hydroxide is added to pH 5.4. The aqueous phase is separated, pumped under vacuum to remove dissolved ethyl acetate, and lyophilized to yield potassium *dl*-7 α -methoxy-7-(2-thienylacetamido)-3-hydroxymethyl-1-oxa-dethiaceph-3-em-4-carboxylate.

EXAMPLE 35.

Sodium *dl*-7 α -methoxy-7-(2-thienylacetamido)-3-carbamoyloxymethyl-1-oxa-dethiaceph-3-em-4-carboxylate

Potassium *dl*-7 α -methoxy-7-(2-thienylacetamido)-3-hydroxymethyl-1-oxy-dethiaceph-3-em-4-carboxylate (0.27 g) is dissolved in 0.05 *M* pH 7 phosphate buffer (8 ml). The aqueous solution is layered with ethyl acetate (8 ml), cooled in an ice-bath, and, with vigorous stirring, acidified to pH 2.2 with 2.5 *N* hydrochloric acid. The layers are separated and the aqueous portion is extracted with more ethyl acetate (2 $\times$ 8 ml). The combined ethyl acetate solution is washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated *in vacuo* to yield *dl*-7 α -methoxy-7-(2-thienylacetamido)-3-hydroxymethyl-1-oxa-dethiaceph-3-em-4-carboxylic acid.

The above free acid is dissolved in anhydrous tetrahydrofuran (15 ml) and the solution is cooled to -40° (dry ice-tetrachloroethane) under nitrogen. Chlorosulfonyl isocyanate (0.07 ml) is added to the solution via a syringe. The resulting mixture is stirred at -40° for 4 hrs. and then treated with 0.1 *M* pH 7 phosphate buffer (1.2 ml) at that temperature. The tetrahydrofuran is removed *in vacuo* and the wet residue is treated with 0.1 *M* pH 7 phosphate buffer (8 ml) and ethyl acetate (8 ml). The resulting mixture is stirred at room temperature for 1 hour. The pH of the aqueous layer is brought to 8 with 2.5 *N* sodium hydroxide and 5% aqueous trisodium phosphate. The organic layer is then separated and extracted with 0.1 *M* pH 7 phosphate buffer (8 ml).

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The combined aqueous solution is acidified to pH 2.3 with 2.5 N hydrochloric acid and extracted with ethyl acetate (2 × 20 ml). The ethyl acetate extracts are washed with saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated *in vacuo* to afford *dl*-7α-methoxy-7-(2-thienylacetamido)-3-carbamoyloxymethyl-1-oxa-dethiaceph-3-em-4-carboxylic acid.

A portion of the above free acid is dissolved in water containing 1.05 equivalents of sodium bicarbonate. The solution is washed with ethyl acetate, pumped under vacuum to remove dissolved ethyl acetate, and lyophilized to yield sodium *dl*-7α-methoxy-7-(2-thienylacetamido)-3-carbamoyloxymethyl-1-oxa-dethiaceph-3-em-4-carboxylate.

EXAMPLE 36.

p-Methoxybenzyl *dl*-7α-methylthio-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate

A solution of *p*-methoxybenzyl *dl*-7β-(2-thienylacetamido)-1-oxa-dethiacephalosporanate (0.50 g) in anhydrous tetrahydrofuran (25 ml) is stirred and cooled to -78° (dry ice-acetone) under nitrogen. Phenyllithium (0.44 ml of a 2.3 M solution) and, after 2 minutes, *t*-butyl hypochlorite (0.14 ml) are added to the cold solution. The reaction mixture is warmed to -17° and treated with a solution of methyl mercaptan (0.10 g) in dry tetrahydrofuran (2 ml). The reaction mixture is then concentrated *in vacuo* and the residue is dissolved in methylene chloride. The solution is washed with dilute aqueous sodium thiosulfate, water, and saturated brine, dried over magnesium sulfate, and evaporated *in vacuo*. Chromatographic purification of the residue on silica gel provides *p*-methoxybenzyl *dl*-7α-methylthio-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate.

EXAMPLE 37.

Sodium *dl*-7α-methylthio-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate

Ice-cold trifluoroacetic acid (7.5 ml.) is added to an ice-cold mixture of *p*-methoxybenzyl *dl*-7α-methylthio-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate (0.33 g.) and anisole (1.5 ml.). After swirling to make it homogeneous, the reaction mixture is kept at 0° for 5 minutes. The trifluoroacetic acid is removed *in vacuo* at 0°, and the residue is then warmed to 30° *in vacuo*. The resulting oil is partitioned between water (40 ml.) containing sodium bicarbonate (0.50 g.) and methylene chloride (20 ml.). The aqueous phase is separated, acidified to pH 2.5, and extracted with ethyl acetate. The extracts are dried over magnesium sulfate, filtered, and evaporated *in vacuo* to afford *dl*-7α-methylthio-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanic acid.

The free acid is stirred with a solution of sodium bicarbonate (0.05 g.) in water (20 ml.) for 15 minutes at room temperature. The resulting mixture is washed with ethyl acetate (2 × 10 ml.). The aqueous phase is separated and lyophilized to afford sodium *dl*-7α-methylthio-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate.

EXAMPLE 38.

7β-Amino-3-(2-methyl-1,3,4-thiadiazolyl)-5-thiomethyl-1-oxa-dethia-3-cephem-4-carboxylic acid

To a mixture of 1 g. 7β-amino-1-oxa-dethiacephalosporanic acid, 10 ml. water and 5 ml. acetone is added NaHCO₃ until the pH of the solution is 7.9. A solution of 1.5 equivalents 2-methyl-1,3,4-thiadiazole-5-thiol in 10 ml. acetone is added and the reaction kept in an 80°C. water bath for 3 hours. The mixture is then cooled to 10° and the pH adjusted to 3.9 with 6 N hydrochloric acid. 7β-amino-3-(2-methyl-1,3,4-thiadiazolyl)-5-thiomethyl-1-oxa-dethia-3-cephem-4-carboxylic acid crystallizes, and is filtered and dried.

7β-amino-3-(1-methyl-1,2,3,4-tetrazolyl)-5-thiomethyl-1-oxa-dethia-3-cephem-4-carboxylic acid is made in accordance with the above process, using 1-methyl-1,2,3,4-tetrazole-5-thiol in place of 2-methyl-1,3,4-thiadiazole-5-thiol.

EXAMPLE 39.

7β-(*D*-2-phenyl-2-hydroxyacetamido)-3-(1-methyl-1,2,3,4-tetrazolyl)-5-thiomethyl-1-oxa-dethia-3-cephem-4-carboxylic acid

To a solution of 10 mmoles 7β-amino-3-(1-methyl-1,2,3,4-tetrazolyl)-5-thiomethyl-1-oxa-dethia-3-cephem-4-carboxylic acid in 100 ml water and 100 ml acetone containing 5 g NaHCO₃ is added 20 mmoles *D*-phenyl-formyloxycarbonyl chloride in 40 ml acetone at 0°C. After 1 hr stirring at 0° and 2 hrs at 25° the acetone is pumped off *in vacuo* and the aqueous solution added to 100 ml water and 20 ml EtOAc. The pH is adjusted to 2.0 with HCl and the ethyl acetate layer dried with

MgSO₄, filtered and evaporated. The residue is stirred for 3 hrs in 50 ml water containing 2.5 g NaHCO₃ and its pH adjusted at 0°C. to 2.0 with HCl. 7β - (D - 2-phenyl - 2 - hydroxyacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5 - thiomethyl) - 1 - oxa - dethia - 3 - cephem - 4 - carboxylic acid is extracted into ethyl acetate and isolated by drying the solution with MgSO₄, filtering and evaporating the solvent.

EXAMPLE 40.

7β - (2 - tetrazolylacetamido) - 3 - (2 - methyl - 1,3,4 - thiadiazolyl - 5 - thiomethyl) - 1 - oxa - dethia - 3 - cephem - 4 - carboxylic acid

To a solution of 10 mmoles 7β - amino - 3 - (2 - methyl - 1,3,4 - thiadiazolyl - 5 - thiomethyl) - 1 - oxa - dethia - 3 - cephem - 4 - carboxylic acid in 100 ml water and 100 ml acetone containing 5 g NaHCO₃ is added 20 mmoles 2-tetrazolylacetyl chloride in 40 ml acetone at 0°C. After 1 hr stirring at 0° and 2 hrs at 25° the acetone is pumped off *in vacuo* and the aqueous solution added to 100 ml water and 200 ml EtOAc. The pH is adjusted to 2 with HCl and the ethyl acetate layer separated, dried with MgSO₄, filtered and evaporated, affording 7β - (2 - tetrazolylacetamido) - 3 - (2 - methyl - 1,3,4 - thiadiazolyl - 5 - thiomethyl) - 1 - oxa - dethia - 3 - cephem - 4 - carboxylic acid.

EXAMPLE 41.

Benzyl 7-(2'-thienylacetamido)-7α-methoxy-1-methylene-1-dethiacephalosporanate

Step A: Benzyl 7-benzaldimino-7-bromo-1-methylene-1-dethiacephalosporanate

Benzyl 7β - benzaldimino - 1 - methylene - 1 - dethiacephalosporanate (527 mg.) is dissolved in 20 ml. of dry tetrahydrofuran. At -78°C., under nitrogen, 0.435 ml. of 2.3 M phenyl lithium is added. The reaction mixture is stirred at -78°C. for 5 minutes. 0.2 g. of N-bromosuccinimide in 3 ml. of anhydrous tetrahydrofuran is then added. The cooling bath is removed and the reaction mixture allowed to come to 0°C. The solvent is removed under reduced pressure and the residue taken up in methylene chloride (30 ml.), washed with pH 7 phosphate buffer and then with water, dried, and evaporated to a volume of about 12 ml. This solution of benzyl 7 - benzaldimino - 7 - bromo - 1 - methylene - dethiacephalosporanate is used directly in the next step.

Step B: Benzyl 7-benzaldimino-7α-methoxy-1-methylene-1-dethiacephalosporanate

Silver oxide (0.2 g.) is suspended in 20 ml. of methanol. The solution of the 7-bromoderivative obtained in Step A is added dropwise over 10 minutes to the silver oxide suspension. The reaction mixture is stirred for another 15 minutes. The silver salts are removed by filtration, the filtrate evaporated, and the residue taken up in benzene and washed twice with pH 7 phosphate buffer, then dried and evaporated to afford benzyl 7 - benzaldimino - 7α - methoxy - 1 - methylene - 1 - dethiacephalosporanate.

Step C: Benzyl 7 - (2' - thienylacetamido) - 7α - methoxy - 1 - methylene - 1 - dethiacephalosporanate

50 mg. of benzyl 7 - benzaldimino - 7α - methoxy - 1 - methylene - 1 - dethiacephalosporanate is dissolved in 4 ml. of methylene chloride and cooled to 0°C., and 0.08 ml. of thienylacetyl chloride is added. To this is added 0.4 ml. of a 1% solution of water in tetrahydrofuran and the mixture stirred at 0°C. for two minutes. 0.2 ml. of pyridine is then added dropwise over 30 minutes. The reaction mixture is washed with pH 2 phosphate buffer followed by pH 7 buffer, then dried and evaporated to yield the desired product, after purification using preparative TLC on silica gel using 2% methanol/chloroform as eluant, to afford benzyl 7 - (2' - thienylacetamido) - 7α - methoxy - 1 - methylene - 1 - dethiacephalosporanate.

By proceeding in an analogous manner but starting with benzyl 7 - benzaldimino - 1 - methylene - 1 - dethiocephalosporanate, benzyl 7 - (2' - thienylacetamido) - 1 - methylene - 1 - dethiocephalosporanate is produced.

By proceeding in an analogous manner but starting with benzyl 7 - benzaldimino - 3 - carbamoyloxymethyl - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate and then treating the resulting benzyl 7 - (2' - thienylacetamido) - 3 - carbamoyloxymethyl - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate by the procedures of Example 1 Step L, sodium 7β - (2' - thienylacetamido) - 3 - carbamoyloxymethyl - 1 - methylene - 1 - dethia - 3 - cephem - 4 - carboxylate is produced.

EXAMPLE 42.

Benzyl 7β-phenylacetamido-7-methoxy-1-methylene-1-dethiacephalosporanate

Benzyl 7 - benzaldimino - 7α - methoxy - 1 - methylene - 1 - dethiacephalospor-

anate (0.14 g.) is dissolved in 6 ml. tetrahydrofuran. 1 ml. of water is added and then 0.025 g. of PdCl_2 . The mixture is stirred at room temperature for 3 hours. The solvent is removed under reduced pressure at ambient temperature. The residue is triturated with petroleum ether and the soluble material is discarded. The residue is taken up in 25 ml. methylene chloride, dried over MgSO_4 and evaporated to afford the residue containing the 7-amino metal complex which is taken up in 4 ml. of methylene chloride, cooled to 0°C . and treated with 0.142 g. of pyridine and then with 0.042 ml. of phenylacetylchloride. The reaction mixture is stirred at 0°C . for 15 minutes. The reaction mixture is diluted with methylene chloride and washed once with pH 2 buffer and then with pH 7 buffer. The organic phase is dried and evaporated to afford the crude product which is purified by thin-layer chromatography.

EXAMPLE 43.

1 - (Benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - (2' - oxo)propyloxy - 2 - azetidinone

0.860 g. of 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - chloro - 2 - azetidinone is dissolved in 8 ml. of hydroxyacetone. 0.800 g. of silver fluoroborate is added and the mixture is stirred at room temperature for 15 minutes. The excess of hydroxy acetone is removed under reduced pressure and the residue is taken up in CH_2Cl_2 and filtered. The filtrate is washed once with 5% NaHCO_3 and then with brine. The organic phase is dried and evaporated. Chromatography on silica gel (45 g) using 50% EtOAc in C_6H_6 as eluant gives 0.231 g 1 - (benzyloxycarbonyldiethylphosphono) - methyl - 3 - azido - 4 - (2' - oxo)propyloxy - 2 - azetidinone as a mixture of *cis* and *trans* isomers.

i.r. 4.74 (azide); 5.62 (β -lactam); 4.75 (ester and ketone carbonyl).
n.m.r. τ 2.66 (C_6H_5 —); 4.75 (C_6H_5 —CH—); 5.0—6.1 multiplets
(β -lactam, $\text{C}-\text{CH}_2-\text{O}$ and $\text{O}-\text{CH}_2-\text{CH}_2$ protons)

7.85 ($\text{CH}_2-\text{C}-$); 8.73 (CH_2-CH_2-).

EXAMPLE 44.

Cis and *Trans* 4-Benzyloxycarbonyl-3-methyl-7-azido-1-oxa-dethia-3-cephem
0.468 g. of *cis* and *trans* 1 - benzyloxycarbonyl - diethylphosphono)methyl - 3 - azido - 4 - (2' - oxo) - propyloxy - 2 - azetidinone is dissolved in 20 ml. anhydrous DME under N_2 and treated with 0.047 g. sodium hydride (57% in mineral oil). The reaction mixture is stirred for 2 hours and then taken up in C_6H_6 , washed once with pH 7 buffer and then with brine. The organic phase is dried and evaporated to give a residue which on chromatography on silica gel using 10% ethylacetate in C_6H_6 as eluant gives *cis* and *trans* 4 - benzyloxycarbonyl - 3 - methyl - 7 - azido - 1 - oxa-dethia - 3 - cephem.

i.r. 4.72 (azide); 5.60 (β -lactam) 5.80 (ester carbonyl) 6.09 ($\text{C}=\text{C}$).

EXAMPLE 45.

Cis and *trans* 4-benzyloxycarbonyl-3-methyl-7-amino-1-oxadethia-3-cephem
0.300 g. of *cis* and *trans* 4 - benzyloxycarbonyl - 3 - methyl - 7 - azido - 1 - oxa - dethia - 3 - cephem is dissolved in 20 ml C_6H_6 , 0.150 g. of PtO_2 is added and the mixture is reduced under 40 lbs. H_2 pressure for half an hour. The catalyst is filtered off and the filtrate is evaporated to give *cis* and *trans* 4 - benzyloxycarbonyl - 3 - methyl - 7 - amino - 1 - oxadethia - 3 - cephem.

EXAMPLE 46.

4 - Benzyl - oxycarbonyl - 3 - methyl - 7 α - (D - α - azido) - phenylacetamido - 1 - oxadethia - 3 - cephem and 4 - benzyloxycarbonyl - 3 - methyl - 7 β - (D - α - azido) - phenylacetamido - 1 - oxadethia - 3 - cephem

0.274 g. *cis* and *trans* 4 - benzyloxycarbonyl - 3 - methyl - 7 - amino - 1 - oxadethia - 3 - cephem is dissolved in 25 ml CH_2Cl_2 and cooled to 0° . 0.195 g. of D- α -azidophenylacetyl chloride and 0.196 g. of pyridine are added and the mixture is stirred for 15 minutes. The reaction mixture is washed once with pH 7 phosphate buffer, then pH 3 phosphate buffer and then once again with pH 7 phosphate buffer. The organic

phase is dried and evaporated. The residue is chromatographed on silica gel to give 4-benzyl - oxycarbonyl - 3 - methyl - 7 α - (D - α - azido) - phenylacetamido - 1 - oxadethia - 3 - cephem and 4 - benzyloxycarbonyl - 3 - methyl - 7 β - (D - α - azido) - phenylacetamido - 1 - oxadethia - 3 - cephem.

EXAMPLE 47.

3-Methyl-7 β -(D- α -amino)-phenylacetamido-1-oxa-dethia-3-cephem-4-carboxylic acid
0.150 g. of 4 - benzyloxycarbonyl - 3 - methyl - 7 β - (D - α - azido) - phenylacetamido - 1 - oxa - dethia - 3 - cephem is dissolved in 5 ml. dioxane and 5 ml. H₂O is added followed by 0.075 g. of 10% Pd/C (Borhofer catalyst). The mixture is reduced under 40 lbs H₂ pressure for half an hour. The catalyst is filtered off and the filtrate is freeze-dried to give 3 - methyl - 7 β - (D - α - amino) - phenylacetamido - 1 - oxa - dethia - 3 - cephem - 4 - carboxylic acid.

EXAMPLE 48.

4-Pentenoyl chloride

Into a solution of 10 g. (0.1 mole) of commercial 4-pentenoic acid in 40 ml. of ether is dropped slowly a solution of 10 ml. of oxalyl chloride in 10 ml. of dry ether. Effervescence stops after 0.5 hour. After 3 hours further stirring, the reaction mixture is distilled slowly to give 92% of 4-pentenoyl chloride, boiling at 126—9°C.

n.m.r. (CDCl₃) δ : 2.51 (m, 2H, $\text{—}\overset{|}{\text{C}}\text{—CH}_2\text{—}$)
3.00 (t, 2H, O=C—CH₂—)
4.90—6.20 (m, 3H, CH₂=CH—)

i.r. (film) λ : 5.55 ($>\text{C}=\text{O}$)
6.06 ($>\text{C}=\text{C}<$)

EXAMPLE 49.

1-Diazo-5-hexen-2-one

A solution of diazomethane in 1000 ml of ether is prepared from 0.75 mole of N-nitrosomethylurea. To this solution, cooled to 5°C., is added dropwise a solution of 0.1 mole of 4-pentenoyl chloride in 100 ml. of dry ether. The resulting solution, protected from light with aluminium foil, is kept overnight at room temperature. Concentration of the crude solution gives yellow 1-diazo-5-hexen-2-one in almost quantitative yield.

i.r. (film): λ 4.72 (—N_2)
6.06 ($>\text{C}=\text{C}<$ and $>\text{C}=\text{O}$)

EXAMPLE 50.

1-Acetoxy-5-hexen-2-one

Into 35 ml of glacial acetic acid at 60—70°C. is dropped slowly 12.4 g. (0.1 mole) of 1-diazo-5-hexen-2-one. After the nitrogen evolution has stopped, the reaction mixture is heated to reflux for one hour. The resulting mixture is extracted with 3 $\times$ 50 ml of methylene chloride. The organic layer is dried over anhydrous magnesium sulfate. Concentration of the filtrate gives 1-acetoxy-5-hexen-2-one as a brown oil in 90% yield, based on the starting 4-pentenoyl chloride.

n.m.r. (CDCl₃) δ : 2.17 ($\text{—}\overset{\text{O}}{\parallel}{\text{C}}\text{CH}_3$, S, 3H)

4.67 ($\text{—}\overset{\text{O}}{\parallel}{\text{C}}\text{CH}_2\text{—OAc}$, S, 2H)
2.47 ($\text{—CH}_2\text{—CH}_2\text{—}$, m, 4H)
4.82—6.17 ($\text{CH}_2=\text{CH—}$, m, 3H)

i.r. (film), λ : 5.70 ($\text{—}\overset{\text{O}}{\parallel}{\text{C}}\text{CH}_3$)
5.74 ($>\text{C}=\text{O}$)
6.08 ($>\text{C}=\text{C}<$)

EXAMPLE 51.

2-Acetoxyethyl-2-(3-buten-1-yl)-1,3-dioxolane

A mixture of 15.6 g. (0.1 mole) of 1-acetoxy-5-hexen-2-one and 18.6 g. (0.3 mole) of ethylene glycol in 250 ml. of benzene containing 1.56 g. of *p*-toluenesulfonic acid monohydrate is heated to reflux using a Dean-Stark water separator. After 2 hours, the reaction mixture is shaken well with 250 ml. of cold water. The aqueous layer is washed with 3 x 25 ml. of ether. The combined organic layers are dried over anhydrous magnesium sulfate. Evaporation of the solvent gives 2-acetoxyethyl-2-(3-buten-1-yl)-1,3-dioxolane in 90% yield as a light brown oil.

n.m.r. (CDCl₃) δ: 2.03 (s, OCCH_3)
1.7—2.15 (m, $-\text{CH}_2-\text{CH}_2-$)
3.95 (s, $-\text{OCH}_2\text{CH}_2\text{O}-$)
4.00 (s, $-\text{CH}_2\text{OAc}$)
4.80—6.1 (m, $\text{CH}_2=\text{CH}-$)

i.r. (film) λ: 5.70 ($-\text{OCCH}_3$)
6.06 ($\text{CH}_2=\text{CH}-$)

EXAMPLE 52.

2-Acetoxyethyl-2-(3-propanal-1-yl)-1,3-dioxolane

To a well stirred mixture of 5.0 g. (25 mmoles) of 2-acetoxyethyl-2-(3-buten-1-yl)-1,3-dioxolane and 300 mg. of osmium tetroxide in 75 ml. of ether and 75 ml. of water is added portionwise 11.6 g. (54 mmoles) of sodium metaperiodate so that the reaction temperature remains 24—27°C. After the addition of the periodate, a voluminous white solid starts precipitating out. After 2½ hours, the reaction mixture is extracted with 3 x 50 ml. of methylene chloride. Drying over anhydrous magnesium sulfate and solvent removal affords crude 2-acetoxyethyl-2-(3-propanal-1-yl)-1,3-dioxolane which soon darkens. Chromatography of the crude product on silica gel (30 g. per gm. of the crude material) using a 50:50 mixture of ethyl acetate and benzene as eluent gives 2-acetoxyethyl-2-(3-propanal-1-yl)-1,3-dioxolane in 60% yield. Pure aldehyde is stable only at the freezer-temperatures.

n.m.r. (CDCl₃) δ: 2.10 (s, OCCH_3)
2.04—2.60 (m, $-\text{CH}_2\text{CH}_2-$)
4.0 ($-\text{OCH}_2\text{CH}_2\text{O}-$, s)
4.03 (s, CH_2OAc)
9.73 (t, $\text{O}=\text{C}-\text{H}$)

i.r. (film) λ: 3.66 ($\text{C}=\text{H}$)
5.70 ($\text{OC}=\text{O}$)
5.79 ($\text{H}-\text{C}=\text{O}$)

EXAMPLE 53.

cis and *trans* - benzyl - α - [5 - acetoxy - 4,4 - ethylenedioxy-pentanalaldimino] - diethylphosphonoacetate

To a solution of 75 mg. (0.25 mmole) of benzyl-α-amino-diethylphosphonoacetate in 5 ml. of ether under nitrogen is added 2 g. of anhydrous magnesium sulfate and then a solution of 50 mg. (0.25 mmole) of 5-acetoxy-4,4-ethylenedioxy-pentanal in 5 ml. of ether. The mixture is stirred for 50 minutes. Filtration and concentration of the filtrate gives a mixture of *cis* and *trans* benzyl - α - [5 - acetoxy - 4,4 - ethylenedioxy - pentan-

aldimino] - diethylphosphonoacetate in almost quantitative yield. This Schiff base is very unstable and hence is used soon after its preparation.

n.m.r. (CDCl_3): δ 1.27 (t, OCH_2CH_3);
2.08 (s, OCCH_3);



5

3.96 and 4.02 (singlets; $\text{---OCH}_2\text{CH}_2\text{O---}$ and $\text{---CH}_2\text{OAc}$)

5

4.5 (d, $J = 20$ cps; HC---P---)

5.25 (s, $\text{OCH}_2\phi$)
7.38 ($\text{---}\phi$, s)

7.82 (d, d, one of the isomeric $\text{---}\overset{\text{H}}{\underset{|}{\text{C}}}=\text{N---}$)

10

i.r. (film) λ : 5.72 (OCCH_3 and $\text{O}=\text{C}=\text{O}$);
6.00 ($>\text{C}=\text{N---}$)

10

EXAMPLE 54.

Cis - 1 - (benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - (3 - ethylenedioxy - 4 - acetoxy)butyl - 2 - azetidinone

15

15

A solution of 0.075 ml. of anhydrous triethylamine in 2 ml. of anhydrous ether is added dropwise under nitrogen to a solution of 0.04 ml. of azidoacetyl chloride in 2 ml. of anhydrous ether at -60°C . (acetone-water-dry ice bath). After stirring for an hour, to this white solid suspension in ether at -60°C . under nitrogen is added slowly a solution of 115 mg. of freshly prepared benzyl - α - [5 - acetoxy - 4,4 - ethylenedioxy-pentanalidimino] - diethylphosphonoacetate in 2 ml. of anhydrous ether. The resulting mixture is stirred as it warms up to room temperature over a period of 3-4 hours. After continued stirring of the reaction mixture overnight at room temperature, it is diluted with 20 ml. of methylene chloride and washed with ~ 15 ml. of brine. The organic layer is dried over anhydrous magnesium sulfate and concentrated to give 130 mg. of a dark residue. This is purified on silica gel preparative TLC to give 40 mg. of *cis* - 1 - (benzyloxycarbonyldiethylphosphono)methyl - 3 - azido - 4 - (3 - ethylenedioxy - 4 - acetoxy)butyl - 2 - azetidinone.

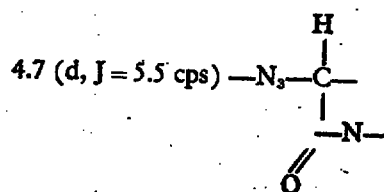
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20

25

25

n.m.r. (CDCl_3) (100 mc) δ : 2.08 (s, OCCH_3);



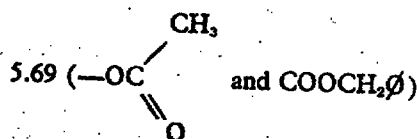
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30

5.00 (d; HC---P--- ; $J = 24$ cps)

5.22 (s, $\text{CH}_2\phi$); 7.34 (s, aromatic)

i.r. (film) λ : 4.70 (---N_3); 5.52 (β -lactam $\text{---}\overset{|}{\underset{|}{\text{N}}}\text{---C=O}$)



EXAMPLE 55.

Cis - 1 - (benzyloxycarbonyl - diethylphosphono)methyl - 3 - azido - 4 - (3 - oxo - 4 - hydroxy)butyl - 2 - azetidinone

A suspension of 100 mg. of *cis* - 1 - (benzyloxycarbonyl - diethylphosphono)-methyl - 3 - azido - 4 - (3 - ethylenedioxy - 4 - acetoxy)butyl - 2 - azetidinone in 8 ml. of aqueous 10% sulfuric acid and 1 ml. glacial acetic acid is heated for 2 hours with stirring at 50°C. The reaction mixture is then cooled to room temperature and extracted with 3 × 15 ml. of methylene chloride. The combined organic layers are washed with 2 × 5 ml. of brine and dried over anhydrous magnesium sulfate. The solvent is removed to give 89% of *cis* - 1 - (benzyloxycarbonyl - diethylphosphono)methyl - 3 - azido - 4 - (3 - oxo - 4 - hydroxy)butyl - 2 - azetidinone as a light-brown gum.

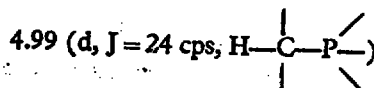
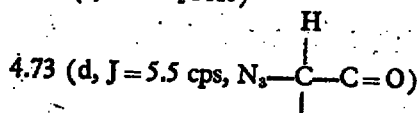
i.r. (film) λ : 2.56 (OH)
4.70 ($-\text{N}_3$)
5.62 (β -lactam $>\text{C}=\text{O}$)
5.72—5.80 ($>\text{C}=\text{O}$ and $-\text{COOCH}_2\phi$).

EXAMPLE 56.

Cis - 1 - (benzyloxycarbonyl - diethylphosphono) - methyl - 3 - azido - 4 - (3 - oxo - 4 - acetoxy)butyl - 2 - azetidinone

To a solution of 26 mg. of *cis* - 1 - (benzyloxycarbonyl - diethylphosphono)-methyl - 3 - azido - 4 - (3 - oxo - 4 - hydroxy)butyl - 2 - azetidinone in 1 ml. of anhydrous methylene chloride under nitrogen are added 8 μl of acetyl chloride and subsequently 8.5 μl of anhydrous pyridine. The clear solution is allowed to stand overnight at room temperature, diluted with 10 ml. of methylene chloride and washed with 3 × 5 ml. of brine. The resulting organic layer is dried over anhydrous magnesium sulfate and concentrated to give 82.5% of *cis* - 1 - (benzyloxycarbonyl - diethylphosphono) - methyl - 3 - azido - 4 - (3 - oxo - 4 - acetoxy)butyl - 2 - azetidinone as light-brown gum.

n.m.r. (CDCl_3) δ : 2.14 (s, $-\text{OCCH}_3$)
(100 Mc) 1.25 (m, OCH_2CH_3)
4.13 (m, OCH_2CH_3)
4.63 (s, $-\text{CH}_2\text{OAc}$)



7.32 and 7.34 (aromatic protons)

i.r. (film) λ : 4.70 ($-\text{N}_3$)
5.62 (β -lactam $>\text{C}=\text{O}$)
5.70 ($-\text{OCCH}_3$ and COOCH_2O)

EXAMPLE 57.

Benzyl-7 β -azido-1-methylene-dethiacephalosporanate

3.7 mg. of sodium hydride (57% in paraffin oil) is added to a solution of 40 mg. of *cis* - 1 - (benzyloxycarbonyl - diethylphosphono) - methyl - 3 - azido - 4 - (3 - oxo - 4 - acetoxy) - butyl - 2 - azetidinone in 0.5 ml. of freshly distilled anhydrous dimethoxyethane under nitrogen. After 15 minutes stirring at room temperature, the reaction mixture is heated for 1.5 hrs. at 50°C. The residue after solvent removal is shaken well with 2 ml. of brine and extracted with 3 × 5 ml. of methylene chloride. The combined organic layers are dried over anhydrous magnesium sulfate. Removal of the solvent from the filtrate gives 30 mg. of crude material, which is purified on silica gel preparative TLC with 1:1 ethyl acetate-benzene to give benzyl - 7 β - azido - 1 - methylene - dethiacephalosporanate in ~62% yield.

n.m.r. (CDCl_3) δ : 1.98 (s, OCCH_3)
 (100 Mc) 3.72 (m, $\text{C}-\text{C}-\text{N}-$
 H)
 4.91 (AB quartet, CH_2OAc)
 4.85 (d, $J=5.5$ cps; $\text{N}_3-\text{C}-\text{H}$)
 5.20 (s, $\text{CH}_2\phi$)
 7.21 (m, aromatic protons)
 i.r. (film) λ : 4.70 ($-\text{N}_3$)

5.62 (β -lactam $\text{C}=\text{O}$)
 5.73 ($\text{COOCH}_2\phi$ and OCCH_3)
 6.09 ($>\text{C}=\text{C}<$)

EXAMPLE 58.

7 β -Amino-1-methylenedethiacephalosporanic acid

A mixture of 74 mg. of benzyl - 7 β - azido - 1 - methylenedethiacephalosporanate and 10 mg. of 10% palladium on carbon (Bolhoff catalyst) in 4 ml. of dioxane and 2 ml. of water is hydrogenated for half an hour in an atmosphere of hydrogen at 45 psi and at room temperature. The catalyst is filtered and washed with 4×2 ml. of water. The solvent is removed from the filtrate to give 55 mg. of an amorphous solid, 7 β - amino - 1 - methylenedethiacephalosporanic acid.

i.r. (Nujol) λ : 2.94 ($-\text{NH}_2$ and OH of COOH)
 5.57 (β -lactam $>\text{C}=\text{O}$)
 5.74 (COOH and OCCH_3)

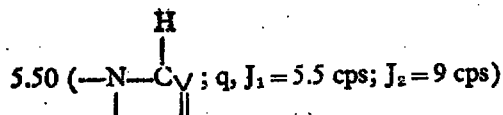
EXAMPLE 59.

7 β -(2-Thienyl)acetamido-1-methylene-dethiacephalosporanic acid

A suspension of 50.8 mg. of 7 β - amino - 1 - methylene - dethiacephalosporanic acid in 6 ml. of aqueous 67% acetone is cooled in an ice bath. 33.6 mg. of sodium bicarbonate and then 26.8 μl . of thienylacetyl chloride are added. After stirring for an hour at 0°C , acetone is removed and the residual aqueous layer is diluted with 10 ml of brine. The resulting solution is washed with 3×10 ml. of methylene chloride, then acidified with 2.5 N hydrochloric acid solution. The acidified aqueous phase is extracted with 3×10 ml. of ethyl acetate. The combined organic layers are dried over anhydrous magnesium sulfate. The solvent is removed from the filtrate to afford 52 mg. of crude material, which is triturated with 2×2 ml. of anhydrous ether to give 27 mg. of 7 β - (2 - thienyl)acetamido - 1 - methylene - dethiacephalosporanic acid as a white amorphous powder.

n.m.r. (D_2 -acetone) δ : 2.03 (s, OCCH_3)

3.89 (s, NCCH_2-)

4.97 (AB quartet, $-\text{CH}_2\text{OAc}$)8.00 (d, NH; $J = 9 \text{ cps}$)

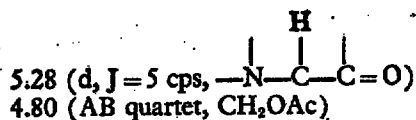
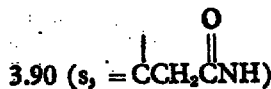
i.r. (Nujol) λ : 5.70 (β -lactam $>\text{C}=\text{O}$)
5.80 (COOH and $\text{OC}=\text{O}$)



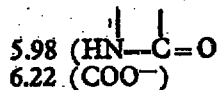
EXAMPLE 60.

Sodium 7 β -(2-thienyl)acetamido-1-methylene-dethiacephalosporanate
19 Mg. of 7 β -(2-thienyl)acetamido-1-methylene-dethiacephalosporanic
acid is suspended in 2 ml. of distilled water. 4.10 mg. of sodium bicarbonate is added.
The resulting solution is freeze-dried to give the sodium salt as a white foam.

n.m.r. (D_2O) δ : 2.07 (s, $-\text{OC}(=\text{O})\text{CH}_3$)

4.80 (AB quartet, CH_2OAc)

i.r. (Nujol) λ : 5.67 (β -lactam $>\text{C}=\text{O}$)
5.75 ($\text{OC}=\text{O}$)

6.22 (COO^-)

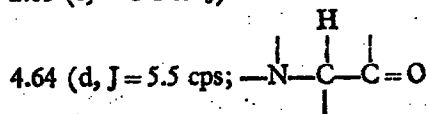
u.v. $\lambda_{\text{H}_2\text{O}}$: 238 ($\epsilon = 320$)
max and 255 ($\epsilon = 261$)

EXAMPLE 61.

Benzyl-7 β -amino-1-methylene-dethiacephalosporanate

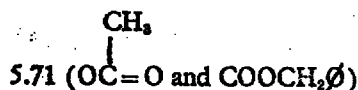
To an ice-cooled solution of 18 mg. of benzyl-7 β -azido-1-methylene-dethiacephalosporanate in 0.5 ml. of anhydrous chloroform is added 14 μl . of anhydrous triethylamine under nitrogen. Hydrogen sulfide is slowly passed into this stirred solution. Colloidal yellow precipitate is formed instantaneously. After 5 minutes introduction of hydrogen sulfide, the solvent is removed to give benzyl-7 β -amino-1-methylene-dethiacephalosporanate.

n.m.r. (CDCl_3): 2.03 (s, $-\text{OC}(=\text{O})\text{CH}_3$)

4.90 (AB quartet, $-\text{CH}_2\text{OAc}$)5.22 (s, $-\text{CH}_2\phi$)

7.33 (s, aromatic protons)

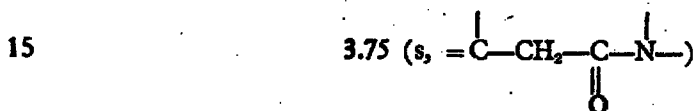
i.r. (film) λ : 2.86 ($-\text{NH}_2$)
5.65 (β -lactam $>\text{C}=\text{O}$)



EXAMPLE 62.

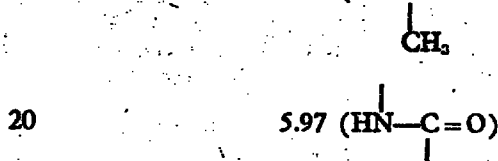
5 Benzyl-7 β -(2-thienyl)acetamido-1-methylene-dethiacephalosporanate
17.5 mg. of benzyl-7 β -amino-1-methylene-dethiacephalosporanate is dis-
solved in 2 ml. of anhydrous methylene chloride under nitrogen. 7 μ l. of anhydrous tri-
ethylamine and 5.8 μ l. of thienylacetyl chloride are added. After letting the reaction
10 mixture stand for 6 hrs. at room temperature, it is diluted with 5 ml. of methylene
chloride and washed with 2×4 ml. of brine. The organic layer is dried over anhydrous
magnesium sulfate. The solvent is removed from the filtrate to give crude benzyl-7 β -
(2-thienyl)acetamido-1-methylene-dethiacephalosporanate, which is purified by
silica gel preparative TLC. 10

n.m.r. (CDCl_3) δ : 1.95 (s, OCCH_3)



4.94 (AB quartet, $-\text{CH}_2\text{OAc}$)
7.03 (phenyl ring protons)

i.r. (film) λ : 5.62 (β -lactam $>\text{C}=\text{O}$)
5.70 ($-\text{OC}=\text{O}$ and COOCH_2)



EXAMPLE 63.

7 β -(D- α -azido)-phenylacetamido-1-methylene-dethiacephalosporanic acid
1.016 g. of 7 β -amino-1-methylene-dethiacephalosporanic acid is dissolved
in 5 ml. of acetone and 10 ml. of H_2O containing 0.672 g. of sodium bicarbonate. The
25 mixture is cooled to 0°C . and treated with 0.784 g. of D- α -azido-phenyl-acetyl chloride
in 5 ml. acetone. The mixture is stirred at 0°C . for 15 minutes and the acetone is re-
moved under reduced pressure. The residual aqueous solution at pH 8 is extracted once
with ethyl acetate and then acidified to pH 2 with pH 2 phosphate buffer and extracted
30 with ethyl acetate. The ethyl acetate extract is dried and evaporated to give 7 β -(D- α -
azido)-phenylacetamido-1-methylene-dethiacephalosporanic acid. 30

EXAMPLE 64.

sodium 7 β -(D- α -azido)-phenylacetamido-3-hydroxymethyl-1-methylene-
dethia-3-cephem-4-carboxylate
7 β -(D- α -azido)-phenylacetamido-1-methylene-dethiacephalosporanic
35 acid (1 g.) is dissolved in 100 ml. of a solution of citrus acetyl esterase (J. D. A. Jeffery,
et al., Biochem. J. (1961) 81, 591). The pH is adjusted to 6.6 and the mixture is main-
tained at 30°C . 1 N NaOH is added dropwise to maintain the pH at 6.6 as the reac-
tion proceeds and the reaction is continued until no further pH change occurs. 10 g.
NaCl is added and the mixture is layered with 50 ml. EtOAc, the pH is adjusted to 2.1
40 with HCl and the mixture is stirred vigorously. The EtOAc layer is separated and
washed once with water and then layered with water and stirred, and the pH of the
aqueous phase is adjusted to 5.9 with 6 N NaOH. The aqueous layer is separated and
freeze-dried to give sodium 7 β -(D- α -azido)-phenylacetamido-3-hydroxy-
methyl-1-methylene-dethia-3-cephem-4-carboxylate.

EXAMPLE 65.

7 β - (D - α - azido) - phenylacetamido - 3 - carbamoyloxymethyl - 1 - methylene-dethia - 3 - cephem - 4 - carboxylic acid

0.464 g. of the sodium 7 β - (D - α - azido) - phenylacetamido - 3 - hydroxymethyl - 1 - methylene - dethia - 3 - cephem - 4 - carboxylate is dissolved in 10 ml. of 0.05 M NaH₂PO₄ and the pH is adjusted to 2.2 with 2.5 N HCl. The mixture is extracted with ethyl acetate 3 times and the combined ethyl acetate extract is dried and evaporated to 2 ml. This is diluted with 20 ml. THF and cooled to -78°C. and treated with 0.141 g. of chlorosulfonylisocyanate. The reaction mixture is stirred for 1½ hours at -78°C. and then treated with 0.1 M pH 2 phosphate buffer (2 ml.) and the THF buffer (10 ml.) are added and the mixture is stirred for 1 hour at room temperature. The pH of the aqueous layer is adjusted to 8, the mixture is shaken and the organic phase is separated. The aqueous phase is adjusted to pH 2 and extracted with ethyl acetate, 3 x 30 ml. The ethyl acetate extract is dried and evaporated to give 7 β - (D - α - azido) - phenylacetamido - 3 - carbamoyloxymethyl - 1 - methylene - dethia - 3 - cephem - 4 - carboxylic acid.

EXAMPLE 66.

7 β - (D - α - amino) - phenylacetamido - 3 - carbamoyloxymethyl - 1 - methylene-dethia - 3 - cephem - 4 - carboxylic acid

0.300 g. of 7 β - (D - α - azido) - phenylacetamido - 3 - carbamoyloxymethyl - 1 - methylene - dethia - 3 - cephem - 4 - carboxylic acid is dissolved in 5 ml. H₂O and 5 ml. dioxane, 0.150 g. of 10% Pd/C (Bolhofer catalyst) is added and the mixture is reduced under 40 lbs H₂ pressure for half an hour. The catalyst is filtered off and the filtrate is freeze-dried to give 7 β - (D - α - amino) - phenylacetamido - 3 - carbamoyloxymethyl - 1 - methylene - dethia - 3 - cephem - 4 - carboxylic acid.

EXAMPLE 67.

benzyl 7-amino-1-benzylloxycarbonylamino-dethiacephalosporanate
A solution of 505 mg. (1 mmole) benzyl 7 - azido - 1 - benzylloxycarbonylamino-dethiacephalosporanate in 20 ml. of benzene is stirred in an atmosphere of hydrogen in the presence of 50 mg. of platinum oxide at atmospheric pressure and room temperature until the azide band in the i.r. spectrum disappears. The catalyst is filtered and washed with 3 x 4 ml. of benzene. The filtrate is concentrated to give benzyl 7 - amino-1 - benzylloxycarbonylamino - dethiacephalosporanate.

EXAMPLE 68.

benzyl 7-(p-nitrobenzaldimino)11-benzylloxycarbonylamino-dethiacephalosporanate
To a solution of 152 mg. (1 mmole) of p-nitrobenzaldehyde in 5 ml. of chloroform is added a solution of 479 mg. (1 mmole) of benzyl 7 - amino - 1 - benzylloxycarbonylamino - dethiacephalosporanate in 5 ml. of chloroform. 2 g. of anhydrous magnesium sulfate is added and the mixture is stirred for 2 hours. The solid is filtered and washed with 3 x 5 ml. of chloroform. The solvent removal from the filtrate gives benzyl 7 - (p - nitrobenzaldimino) - 1 - benzylloxycarbonylamino - dethiacephalosporanate.

EXAMPLE 69.

benzyl 7 α - methyl - 7 - p - nitrobenzaldimino - 1 - benzylloxycarbonylamino - dethiacephalosporanate

To a solution of 306 mg. (0.5 mmole) of benzyl 7 - p - nitrobenzaldimino - 1 - benzylloxycarbonylamino - dethiacephalosporanate in 10 ml. of anhydrous tetrahydrofuran at -78°C. is added under nitrogen 0.22 ml. of 2.3 M phenyllithium (0.5 mmole) slowly. 0.4 ml. of methyl iodide in 10 ml. of N,N-dimethylformamide is added dropwise. The reaction mixture is allowed to warm to room temperature, poured into ice water and extracted with 3 x 20 ml. of ethyl acetate. The mixed organic layers are washed with 2 x 10 ml. brine and dried over anhydrous magnesium sulfate. The solvent removal from the filtrate gives benzyl 7 α - methyl - 7 - p - nitrobenzaldimino - 1 - benzylloxycarbonylamino - dethiacephalosporanate.

EXAMPLE 70.

benzyl 7 α -methyl-7-amino-1-benzylloxycarbonylamino-dethiacephalosporanate
To a solution of 99 mg. (0.5 mmole) of 2,4-dinitrophenylhydrazine in 5 ml. of ethanol is added 95 mg. (0.5 mmole) of p-toluene sulfonic acid monohydrate and the mixture is stirred for half an hour at room temperature. A solution of 313 mg. (0.5 mmole) of benzyl - 7 α - methyl - 7 β - p - nitrobenzaldimino - 1 - benzylloxycarb-

5 onylamino - dethiacephalosporanate in 5 ml. of ethanol is then added. The reaction mixture is stirred for half an hour at room temperature and filtered, and the filtrate is evaporated. The residue is taken up in 50 ml. methylene chloride, washed with 2 x 20 ml. brine, dried over anhydrous magnesium sulfate and evaporated to give benzyl 7 α - methyl - 7 - amino - 1 - benzyloxycarbonylamino - dethiacephalosporanate. 5

EXAMPLE 71.

10 benzyl 7 α - methyl - 7 - (2 - thienyl)acetamido - 1 - benzyloxycarbonylamino - dethiacephalosporanate
72 μ l. of pyridine is added to an ice-cold solution of 247 mg. of benzyl 7 α - methyl - 7 β - amino - 1 - benzyloxycarbonylamino - dethiacephalosporanate in 10 ml. of methylene chloride. 67 μ l. of 2-thienylacetyl chloride is added and the mixture is washed with 10 ml. of water, 10 ml. of pH 2 buffer and then with 10 ml. of pH 7 buffer. The resulting solution is dried over anhydrous magnesium sulfate and the solvent is evaporated to give a residue, which is chromatographed on silica gel to give benzyl 7 α - methyl - 7 - (2 - thienyl)acetamido - 1 - benzyloxycarbonylamino - dethiacephalosporanate. 15

EXAMPLE 72.

20 sodium 7 α -methyl-7 β -(2-thienyl)-acetamido-1-amino-dethiacephalosporanate
256 mg. of benzyl 7 α - methyl - 7 β - (2 - thienyl) - acetamido - 1 - benzyloxycarbonylamino - dethiacephalosporanate is hydrogenated in a mixture of dioxane and water, using 59 mg. of 10% palladium on carbon as catalyst in an atmosphere of hydrogen at 45 p.s.i. The catalyst is filtered and washed with a mixture of dioxane and water. The filtrate is concentrated and one equivalent of sodium bicarbonate is added. The resulting solution is freeze-dried to give sodium 7 α - methyl - 7 β - (2 - thienyl) - acetamido - 1 - amino - dethiacephalosporanate. 25

EXAMPLE 73.

30 7 β - (2 - thienyl) - acetamido - 3 - (1 - pyridyl) - methyl - 1 - formamido - dethia-3 - cephem - 4 - carboxylic acid betaine
A solution of 407 mg. (1 mmole) of 7 β - (2 - thienyl) - acetamido - 1 - formamido - dethiacephalosporanic acid, 217 mg. (2.25 mmoles) of potassium thiocyanate, and 0.216 mg. (2.70 mmole) of pyridine in 1.1 ml. of water is adjusted to pH 6.5 with 85% phosphoric acid and heated for 5.5 hours with stirring at 58°-61°C. The solution is cooled to room temperature and extracted with 25% Amberlite-LA-1 (acetate form) in methyl isobutyl ketone and washed with methyl isobutyl ketone. The aqueous solution is allowed to stand 15 hours below 5°C. to give 7 β - (2 - thienyl) - acetamido - 3 - (1 - pyridyl) - methyl - 1 - formamido - dethia - 3 - cephem - 4 - carboxylic acid betaine. 35

EXAMPLE 74.

40 7 - methoxy - 7 - (α - carboxy - 3 - thienyl)acetamido - 3 - carbamoyloxy methyl - 1 - methylene - dethia - ceph - 3 - em - 4 - carboxylic acid disodium salt 40

A. benzhydryl 7 β -amino-1-methylene-dethiacephalosporanate.

45 1.54 g. of 7 - β - amino - 1 - methylene - dethiacephalosporanic acid is stirred for 5 minutes at 25°C. in 70 ml. of dioxane with 1.7 g. of *p*-toluenesulfonic acid hydrate. Methanol (20 ml.) is added and the solvents are removed *in vacuo*. The residue is dissolved in 80 ml. of dioxane and 2.9 g. of diphenyldiazomethane are added. After evolution of nitrogen is complete the dioxane is removed under reduced pressure and the residue is stirred with methylene chloride (100 ml.) and water (100 ml.) containing sufficient dipotassium hydrogen phosphate to bring the pH to 8. The layers are separated and the aqueous portion is extracted with methylene chloride. The combined organic layers are dried over magnesium sulfate, filtered and evaporated leaving benzhydryl 7 β - amino - 1 - methylene - dethiacephalosporanate. 50

B. benzhydryl 7 β -(*p*-nitrobenzylideneamino)-1-methylene-dethiacephalosporanate

55 A mixture of *p*-nitrobenzaldehyde (0.58 g.), anhydrous magnesium sulfate (9 g.) and benzhydryl 7 β - amino - 1 - methylene - dethiacephalosporanate (1.14 g.) in 70 ml. of methylene chloride is stirred at room temperature for 15 hours. The mixture is filtered and the filtrate is evaporated under reduced pressure to give benzhydryl 7 β -(*p* - nitrobenzylideneamino) - 1 - methylene - dethiacephalosporanate. 55

C. benzhydryl 7 α - methylthio - 7 - (*p* - nitrobenzylideneamino) - 1 - methylenethiacephalosporanate

60 A solution of benzhydryl 7 β - (*p* - nitrobenzylideneamino) - 1 - methylene- 60

The and she give date.	5	5	dethiacephalosporanate (1.98 g.) in anhydrous tetrahydrofuran (70 ml.) is stirred at -78°C. under a nitrogen atmosphere. Phenyllithium (1.9 ml. of a 2.3 M solution in 7:3 benzene-ether) is added followed by anhydrous dimethylformamide (88 ml.) dropwise over a six-minute period. Freshly prepared methylsulfonyl chloride (470 mg.) in tetrahydrofuran (8 ml.) is then added. The reaction mixture is stirred for 45 minutes allowing it to gradually warm to room temperature. The resulting red-brown solution is diluted with 1.4 liters of benzene and washed successively with 600-ml. portions of water, 0.5 M pH 3 phosphate buffer, water, 0.5 M dipotassium hydrogen phosphate, water and saturated brine. The benzene solution is dried with magnesium sulfate and filtered and the filtrate is evaporated under reduced pressure to give an orange oil. Chromatography of the crude product on silica gel (110 g) using 1:9 ethyl acetate-benzene as eluting solvent gives substantially pure benzhydryl 7- α -methylthio-7-(<i>p</i> -nitrobenzylideneamino)-1-methylenedethiacephalosporanate.	5
thia-7 α -ml. re is H 7 sol-give thia-	10	10		10
oxy-and dro-ater. The acet-	20	20	D. benzhydryl 7-amino-7 α -methylthio-1-methylene-dethiacephalosporanate To a suspension of 300 mg. of 2,4-dinitrophenylhydrazine <i>p</i> -toluenesulfonate in 8 ml. of tetrahydrofuran is added a solution of benzhydryl 7- α -methylthio-7-(<i>p</i> -nitrobenzylideneamino)-1-methylene-dethiacephalosporanate (400 mg.) in 12 ml. of tetrahydrofuran. After being stirred for 90 minutes at room temperature, the reaction mixture is filtered and the filtrate is evaporated under reduced pressure. The crude residue is taken up in 40 ml. of methylene chloride and the solution is shaken vigorously for 4 minutes with aqueous dipotassium hydrogen phosphate (272 mg. in 10 ml. of water). The organic phase is separated, washed with saturated brine, dried with magnesium sulfate and filtered. The filtrate is evaporated under reduced pressure to give benzhydryl 7-amino-7 α -methylthio-1-methylene-dethiacephalosporanate.	15
thia-	25	25	E. 7 α -methylthio-7 β -(α -carboxy-3-thienyl)acetamido-1-methylene-dethiacephalosporanic acid bis-benzhydryl ester. To a solution of 584 mg. of benzhydryl-3-thienyl malonic acid in 4 ml. of dry acetonitrile cooled to 0°C is added 340 mg. of dicyclohexylcarbodiimide followed immediately by a cooled solution of 250 mg. of benzhydryl 7-amino-7 α -methylthio-1-methylene-dethiacephalosporanate in 2 ml. of acetonitrile. The mixture is stirred at 0°C. for 25 minutes. The acetonitrile is rapidly evaporated <i>in vacuo</i> and to the residue is added 10 ml. of chloroform and 5 ml. of 10% sodium dihydrogen phosphate. The mixture is separated by centrifugation and the chloroform is extracted twice with N pH 7 phosphate buffer. The organic phase is filtered, dried over anhydrous magnesium sulfate and evaporated. The residual oil is chromatographed on silica gel using 5% ethylacetate-chloroform as eluting solvent giving 7- α -methylthio-7- β -(α -carboxy-3-thienyl)acetamido-1-methylene-dethiacephalosporanic acid bis-benzhydryl ester.	25
-1-thio-0 pH 1°C. LA-1 The nyl)-carb-	30	30	F. disodium salt of 7 α -methoxy-7 β -(α -carboxy-3-thienyl)acetamido-1-methylene-dethiacephalosporanic acid To a solution of 7- α -methylthio-7- β -(α -carboxy-3-thienyl)acetamido-1-methylene-dethiacephalosporanic acid bis-benzhydryl ester (195 mg.) in methanol (3 ml.) and tetrahydrofuran (0.5 ml.) is added a solution of thallium trinitrate trihydrate (132 mg.) in methanol (1.5 ml.). The resulting mixture is stirred at room temperature for 10 minutes and then treated with sodium bicarbonate (65 mg.). After stirring for two minutes, the mixture is filtered and the filtrate is evaporated <i>in vacuo</i> to dryness. The residue is dissolved in methylene chloride (10 ml.) and the solution is filtered. The filtrate is washed with 5-ml. portions of water, 5% aqueous dipotassium hydrogen phosphate and water, dried with magnesium sulfate and filtered, and the filtrate is evaporated under reduced pressure to give 7- α -methoxy-7 β -(α -carboxy-3-thienyl)acetamido-1-methylene-dethiacephalosporanic acid bis-benzhydryl ester.	30
1-1-	40	40	The ester is dissolved in a mixture of 1 ml. of anisole and 5 ml. of trifluoroacetic acid at 0°C. and stirred for 8 minutes. The reagents are removed under reduced pressure and the residue is triturated with chloroform, which is removed under reduced pressure. The residue is stirred with a mixture of 10 ml. of chloroform and 40 mg. of sodium bicarbonate in 10 ml. of water. The aqueous layer is separated by centrifugation, filtered and lyophilized to give the disodium salt of 7 α -methoxy-7 β -(α -carboxy-3-thienyl)acetamido-1-methylene-dethiacephalosporanic acid.	40
stirred acid residue After e and ntains are bined benz-	45	45		45
	50	50		50
re (9 g.) in 7 β -	55	55		55
thia-	60	60		60

G. disodium salt of 7 α - methoxy - 7 β - (α - carboxy - 3 - thienyl)acetamido - 3 - hydroxymethyl - 1 - methylene - dethiaceph - 3 - em - 4 - carboxylic acid

2.0 g. of disodium 7 - α - methoxy - 7 - β (α - carboxy - 3 - thienyl)acetamido - 1 - methylene - dethiacephalosporanate dissolved in 200 ml. of citrus acetylase solution is adjusted to pH 6.6 with N sodium hydroxide solution. The mixture is stirred and heated at 32°C. for six hours while the pH is maintained between 6.5 and 6.7 by the addition of N sodium hydroxide solution under the control of a pH-stat. Sodium chloride (20 g.) is added and the solution is filtered. The filtrate is over-layered with ethyl acetate, cooled to 5°C. and acidified to pH 2 with hydrochloric acid. The emulsion that forms is separated by centrifugation and the aqueous phase is extracted twice with ethyl acetate. The ethyl acetate solutions are washed once with water and extracted with sodium bicarbonate solution at pH 5.6. The sodium bicarbonate extract is freeze-dried leaving the disodium salt of 7 α - methoxy - 7 β - (α - carboxy - 3 - thienyl)acetamido - 3 - hydroxymethyl - 1 - methylene - dethiaceph - 3 - em - 4 - carboxylic acid.

H. disodium salt of 7 α - methoxy - 7 β - (α - carboxy - 3 - thienyl)acetamido - 3 - carbamoyloxymethyl - 1 - methylene - dethiacephalosporanic acid

A solution of 1 g. of disodium 7 α - methoxy - 7 β - (α - carboxy - 3 - thienyl)acetamido - 3 - hydroxymethyl - 1 - methylene - dethiaceph - 3 - em - 4 - carboxylic acid in 20 ml. of ice-water is acidified to pH 2 and extracted with three 20 ml. portions of cold ethyl acetate. The ethyl acetate solutions are washed with cold saturated brine, dried with magnesium sulfate and rapidly evaporated under reduced pressure. The residue is dissolved in 50 ml. of dry tetrahydrofuran and the solution is cooled to -40°C. in a dry-ice bath. Chlorosulfonyl isocyanate (0.4 ml.) is added and the reaction mixture is stirred at -40°C. for two hours. 10 ml. of 0.1 N pH 7 phosphate buffer is added and the tetrahydrofuran is removed under reduced pressure. Ethyl acetate is added and the solution is brought to pH 2 by the addition of phosphate buffer. The mixture is stirred for one hour at room temperature, then the pH is adjusted to 7.5 by the addition of 1 N sodium hydroxide solution. The organic phase is separated and the aqueous phase is extracted with ethyl acetate. The combined ethyl acetate extracts are washed with water, then extracted with aqueous sodium bicarbonate solution at pH 5.6. The sodium bicarbonate extract is lyophilized leaving the disodium salt of 7 α - methoxy - 7 β - (α - carboxy - 3 - thienyl)acetamido - 3 - carbamoyloxymethyl - 1 - methylene - dethiacephalosporanic acid.

EXAMPLE 75.

7 α - methoxy - 7 - (D - 2 - hydroxy - 2 - phenylacetamido) - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - 1 - methylene - dethia - 3 - cephem - 4 - carboxylic acid sodium salt

A. 7 β - amino - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5 -)thiomethyl - 1 - methylene - dethia - ceph - 3 - em - 4 - carboxylic acid

A saturated solution of sodium bicarbonate is added with stirring to a mixture of 2.54 g. of 7 β - amino - 1 - methylene - dethiacephalosporanic acid in 20 ml. of water and 10 ml. of acetone until the pH is 7.9. The solution is placed in a bath at 80°C. and a solution of 1.74 g. of 1 - methyl - 1,2,3,4 - tetrazole - 5 - thiol is added. The mixture is stirred at 80°C. for 3 hours then cooled to 10°C. whereupon the pH is adjusted to 3.9 by the addition of 6 N hydrochloric acid. The mixture is chilled for one hour and the precipitate is recovered by filtration and washed with acetone and dried affording 7 - β - amino - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5 -)thiomethyl - 1 - methylene - dethia - ceph - 3 - em - 4 - carboxylic acid.

B. Benzhydryl 7 β - amino - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5 -)thiomethyl - 1 - methylene - dethia - ceph - 3 - em - 4 - carboxylate

3.09 g. of 7 β - amino - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5 -)thiomethyl - 1 - methylene - dethia - ceph - 3 - em - 4 - carboxylic acid is stirred for 5 minutes at 25°C. in 70 ml. of dioxane with 1.7 g. of *p*-toluenesulfonic acid hydrate. Methanol (20 ml.) is added and the solvents are removed *in vacuo*. The residue is flushed twice with dioxane, then dioxane (80 ml.) is added followed by 2.9 g of diphenyldiazomethane. After evolution of nitrogen is complete, the dioxane is removed under reduced pressure and the residue is stirred with methylene chloride (100 ml.) and water (100 ml.) containing sufficient K₂HPO₄ to bring the pH to 8. The layers are separated and the aqueous portion extracted with methylene chloride. The combined organic layers are dried over magnesium sulfate, filtered and evaporated leaving benzhydryl 7 β -

amino - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5) - thiomethyl - 1 - methylene - dethia -
ceph - 3 - em - 4 - carboxylate.

C. Benzhydryl 7 β - (p - nitrobenzylideneamino) - 3 - (1 - methyl - 1,2,3,4 - tetra -
zolyl - 5)thiomethyl - 1 - methylene - dethiaceph - 3 - em - 4 - carboxylate

A mixture of p-nitrobenzaldehyde (1.07 g.), anhydrous magnesium sulfate (18.0 g.) and benzhydryl 7 - β - amino - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5) -
thiomethyl - 1 - methylene - dethiaceph - 3 - em - 4 - carboxylate (3.37 g.) in
140 ml. of methylene chloride is stirred at room temperature for a period of 15 hours.
The mixture is filtered and the filtrate is evaporated under reduced pressure to give
benzhydryl 7 β (p - nitrobenzylideneamino) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5) -
thiomethyl - 1 - methylene - dethiaceph - 3 - em - 4 - carboxylate as a yellow oil.

D. benzhydryl 7 α - methylthio - 7 β - (p - nitrobenzylideneamino) - 3 - (1 - methyl -
1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylene - dethia - ceph - 3 - em - 4 -
carboxylate

A solution of benzhydryl 7 β - (p - nitrobenzylideneamino) - 3 - (1 - methyl -
1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylene - thiaceph - 3 - em - 4 - carboxylate
(1.33 g.) in anhydrous tetrahydrofuran (35 ml.) is stirred at -78°C. under a nitrogen
atmosphere. Phenyllithium (0.95 ml. of a 2.3 M solution in 7:3 benzene:ether) is
added followed by anhydrous dimethylformamide (44 ml.) dropwise during a six -
minute period. Freshly prepared methylsulfonyl chloride (235 mg.) in tetrahydrofuran
(4 ml.) is then added. The reaction mixture is stirred for 45 minutes, allowing it to
gradually warm to room temperature. The resulting solution is diluted with 700 ml. of
benzene and washed successively with 300-ml. portions each of water, 0.5 M pH 3 phos -
phate buffer, water, 0.5 M dipotassium hydrogen phosphate, water and saturated brine.
The benzene solution is dried over magnesium sulfate and filtered and the filtrate is
evaporated under reduced pressure to give benzhydryl - 7 - α - methylthio - 7 β -
(p - nitrobenzylideneamino) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl -
1 - methylene - dethia - ceph - 3 - em - 4 - carboxylate. The crude product is chro -
matographed on silica gel (58 g.) using 1:9 ethylacetate-benzene as eluting solvent.

E. Benzhydryl 7 - amino - 7 α - methylthio - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl -
5)thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylate

To a suspension of 300 mg. of 2,4-dinitrophenylhydrazine p-toluene sulfonate in
8 ml. of tetrahydrofuran is added a solution of benzhydryl 7 α - methylthio - 7 - (p -
nitrobenzylideneamino) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 -
methylenedethia - ceph - 3 - em - 4 - carboxylate (512 mg) in 12 ml. of tetra -
hydrofuran. After being stirred for 90 minutes at room temperature, the reaction mixture
is filtered and the filtrate is evaporated under reduced pressure. The crude residue is
taken up in 40 ml. of methylene chloride and the solution is shaken vigorously for 4
minutes with aqueous dipotassium hydrogen phosphate (272 mg. in 10 ml. of water).
The organic phase is separated, washed with saturated brine, dried with magnesium
sulfate and filtered. The filtrate is evaporated under reduced pressure to give benzhydryl
7 - amino - 7 α - methylthio - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 -
methylenedethia - ceph - 3 - em - 4 - carboxylate.

F. Benzhydryl 7 - α - methylthio - 7 - (D - 2 - formyloxy - 2 - phenylacetamido) -
3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylenedethia - ceph -
3 - em - 4 - carboxylate

A solution of benzhydryl 7 - amino - 7 α - methylthio - 3(1 - methyl - 1,2,3,4 -
tetrazolyl - 5)thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylate
(430 mg.) in 10 ml of methylene chloride is cooled in an ice-bath. D - 2 - Formyloxy -
2 - phenylacetylchloride (243 mg.) and pyridine (150 ml.) are added and the resulting
solution is stirred for 25 minutes. Cold water (10 ml.) is added and the mixture is
stirred for 5 minutes. The organic phase is separated and washed with cold 10-ml. por -
tions of 1 M pH 3 phosphate buffer, water, 5% dipotassium hydrogen phosphate, water
and saturated brine. It is then dried with magnesium sulfate and filtered, and the filtrate
is evaporated under reduced pressure to give an oil. Chromatography of the crude prod -
uct on silica gel (34 g.) using 1:4 ethyl acetate-benzene as eluting solvent gives sub -
stantially pure benzhydryl 7 - α - methylthio - 7 - (D - 2 - formyloxy - 2 - phenyl -
acetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylenedethia -
ceph - 3 - em - 4 - carboxylate.

G. Benzhydryl 7 α - methoxy - 7(D - 2 - formyloxy - 2 - (phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylate

To a solution of benzhydryl 7 α - methylthio - 7 - (D - 2 - formyloxy - 2 - phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylate (170 mg.) in methanol (3 ml.) and tetrahydrofuran (0.5 ml.) is added a solution of thallium trinitrate trihydrate (132 mg.) in methanol (0.5 ml.). The resulting mixture is stirred at room temperature for a period of 10 minutes and then treated with sodium bicarbonate (65 mg.). After being stirred for an additional two minutes, the mixture is filtered and the filtrate is evaporated *in vacuo* to dryness. The residue is dissolved in 10 ml. of methylene chloride and the solution is filtered. The filtrate is washed with 5-ml. portions of water, 5% aqueous dipotassium hydrogen phosphate and water, dried with magnesium sulfate and filtered, and the filtrate is evaporated under reduced pressure to give an oil. Chromatography of the crude product on silica gel (10.5 g.) using 15% ethyl acetate/benzene as eluting solvent gives substantially pure benzhydryl 7 α - methoxy - 7(D - 2 - formyloxy - 2 - phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylate.

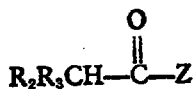
H. 7 α - Methoxy - 7 - (D - 2 - formyloxy - 2 - phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylic acid

Trifluoroacetic acid (0.5 ml.) is added to a cold solution of benzhydryl 7 α - methoxy - 7 - (D - 2 - formyloxy - 2 - phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylate (60 mg.) and anisole (0.5 ml.). The resulting solution is stirred for 5 minutes at 0°C. and then the excess of trifluoroacetic acid is removed *in vacuo*. The residue is partitioned between aqueous sodium bicarbonate (15 mg. in 5 ml. of water) and methylene chloride (5 ml.). The aqueous phase is separated and extracted again with methylene chloride. The aqueous phase is then layered with ethyl acetate (5 ml.) and acidified to pH 2.6. The aqueous phase is separated and extracted with ethyl acetate (2 x 5 ml.). The combined ethyl acetate solutions are dried on magnesium sulfate and filtered and the filtrate is evaporated under reduced pressure to give 7 α - methoxy - 7 - (D - 2 - formyloxy - 2 - phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylic acid.

I. 7 α - Methoxy - 7 - (D - 2 - hydroxy - 2 - phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5)thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylate sodium salt

A solution of 7 - α - methoxy - 7 - (D - 2 - formyloxy - 2 - phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5) - thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylic acid (30 mg.) in aqueous sodium bicarbonate (30 mg. in 0.4 ml. of water) is stirred at room temperature for three hours. The solution is diluted with 2 ml. of water, layered with 2 ml. of ethyl acetate and then acidified to pH 2.6 with pH 2 phosphate buffer. The aqueous phase is separated and extracted with ethyl acetate (2 x 3 ml. The combined ethyl acetate solutions are dried with magnesium sulfate and filtered, and the filtrate is evaporated under reduced pressure. The residue is dissolved in 1 ml. of acetone and aqueous sodium bicarbonate (4.2 mg. in 3.2 ml. water) is added. The acetone is removed *in vacuo* and the aqueous solution remaining is lyophilized to give 7 α - methoxy - 7 - (D - 2 - hydroxy - 2 - phenylacetamido) - 3 - (1 - methyl - 1,2,3,4 - tetrazolyl - 5) - thiomethyl - 1 - methylenedethia - ceph - 3 - em - 4 - carboxylate sodium salt as a white powder.

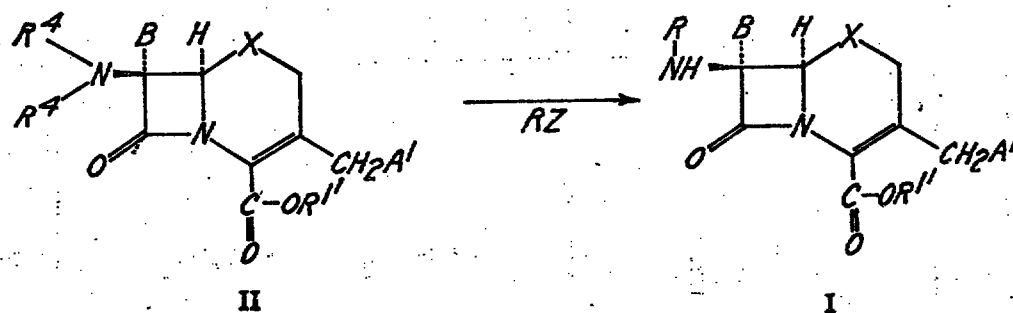
By following the procedures illustrated in the Flow Sheets and described in detail in the Examples and by using an appropriately substituted 2-aminophosphonate there is obtained the 7 β -amino or 7-substituted imino compound II which, upon treatment with an acylating agent such as an acylating agent of the formula



by known techniques, affords those compounds in which A' is as defined above. These compounds can be further treated if desired, by the methods described above to form other 3-substituted analogs described in the following Table I. The following equation

89

and Table I together with Flow Sheets I and II illustrate the various products embraced by this invention:



5
 10
 15
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 form
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TABLE I

Ex. No.	R	R ¹	A	X
76		-C(CH ₃) ₃	H	O
77		-C(CH ₃) ₃	-OCONH ₂	-CH ₂ -
78		-CH(φ) ₂	-OCOCH ₃	-NH-
79		-CH(φ) ₂	H	-CH ₂ -
80		-CH ₂ C(Cl) ₃		O
81		-CH ₂ -	-OCOCH ₃	
82		-CH(φ) ₂		
83		-CH(φ) ₂	-OCOCH ₃	-NH-
84		-C(CH ₃) ₃	-OCOCH ₃	O
85		-CH ₂ -C(=O)-φ		-CH ₂ -

TABLE I

Ex. No.	R	R ¹	A	X
86		-C(CH ₃) ₃		-CH ₂ -
87		-CH(φ) ₂	-OCOCH ₃	-O-
88		-CH(φ) ₂	-OCOCH ₃	-NH-
89		-CH ₂ -	-OCOCH ₃	O
90		-CH ₂ C(Cl) ₃		
91		-CH ₂ C(=O)-φ	-OCOCH ₃	-CH ₂ -
92		-C(CH ₃) ₃	-OCOCH ₃	
93		-CH(φ) ₂	H	-NH-
94		-CH(φ) ₂	-OCONH ₂	-O-
95		-CH ₂ -	H	-CH ₂ -

X

O

CH₂-

NH-

CH₂-

O

-NH-

O

-CH₂-

TABLE I

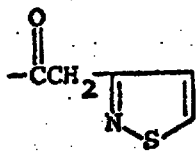
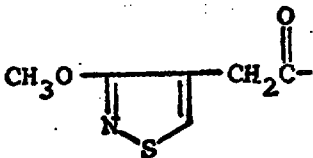
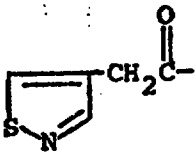
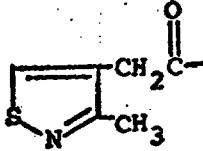
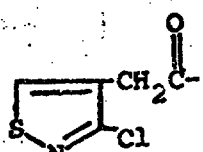
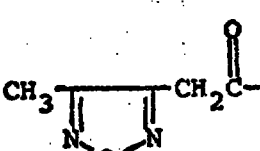
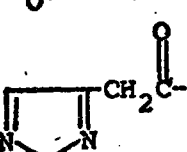
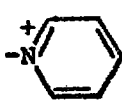
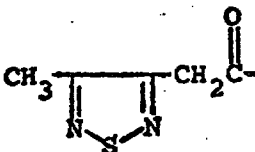
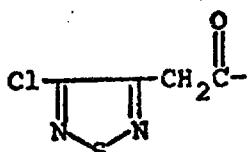
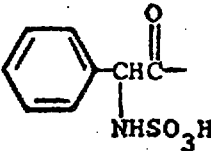
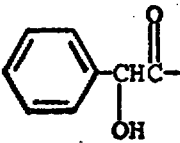
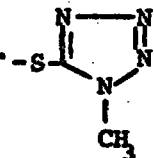
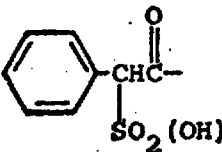
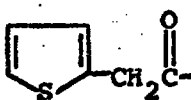
Ex. No.	R	R ¹	A	X
96		$-\text{CH}_2\text{C}(\text{Cl})_3$	$-\text{OCOCH}_3$	O
97		$-\text{CH}_2\text{C}(\text{Cl})_3$	H	$\begin{matrix} \text{CH}_3 \\ \\ -\text{N}- \end{matrix}$
98		$-\text{C}(\text{CH}_3)_3$	$-\text{OCONH}_2$	$-\text{CH}_2-$
99		$-\text{CH}(\phi)_2$	H	$-\text{NH}-$
100		$-\text{CH}_2-\text{C}_6\text{H}_4-\text{OCH}_3$	$-\text{OCH}_3$	$-\text{NH}-$
101		$-\text{CH}_2\text{C}(=\text{O})-\phi$	$-\text{OCH}_3$	$\begin{matrix} \text{CH}_3 \\ \\ -\text{N}- \end{matrix}$
102		$-\text{CH}_2\text{C}(=\text{O})-\phi$		O
103		$-\text{CH}_2\text{C}(\text{Cl})_3$	H	$-\text{CH}_2-$
104		$-\text{CH}(\phi)_2$	$-\text{OCONH}_2$	$-\text{CH}_2-$

TABLE I

Ex. No.	R	R ¹	A	X
105		-CH(φ) ₂	H	
106		-C(CH ₃) ₃	-OCH ₃	-CH ₂ -
107		-C(CH ₃) ₃		-O-
108		-CH(φ) ₂	-OCOCH ₃	-CH ₂ -
109		-CH(φ) ₂		-O-
110		-CH(φ) ₂	-OCOCH ₃	-NH-
111		-CH ₂ C(=O)φ	H	-CH ₂ -
112		-CH ₂ -	H	-NH-
113		-C(CH ₃) ₃	-OCOCH ₃	
114		-CH ₂ C(Cl) ₃	-OCONH ₂	-NH-

TABLE I

Ex. No.	R	R ¹	A	X
115		-CH(φ) ₂	-OCOCH ₃	
116		-CH(φ) ₂		-CH ₂ -
117		-CH(φ) ₂	-OCONH ₂	-NH-
118		-CH ₂ OCH ₃	-OCOCH ₃	-O-

It will be appreciated that the products illustrated in the chart above, in which B=H, are merely representative of the compounds embraced by this invention. Corresponding novel useful antibiotic compounds in which B=OCH₃, CH₃ or SR may also be obtained in accordance with the teachings of the invention.

The products of this invention (I) form a wide variety of pharmacologically acceptable salts with inorganic and organic bases; these include, for example, metal salts derived from alkali metal or alkaline earth metal hydroxides, carbonates or bicarbonates, and salts derived from primary, secondary or tertiary amines such as monoalkylamines, dialkylamines, trialkylamines, C₁₋₆ alkanolamines, di-(C₁₋₆ alkanol)amines, C₂₋₆ alkylenediamines, N,N-diaralkyl C₂₋₆ alkylenediamines, aralkylamines, amino-substituted C₁₋₆ alkanols, N,N-di-(C₁₋₆ alkyl)amino-substituted C₁₋₆ alkanols, amino-, polyamino- and guanidino-substituted C₁₋₆ alkanolic acids and nitrogen-containing heterocyclic amines. Representative examples include salts derived from sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium hydroxide, calcium carbonate, trimethylamine, triethylamine, piperidine, morpholine, quinine, lysine, proline, arginine, procaine, ethanolamine, morphine, benzylamine, ethylenediamine, N,N'-dibenzylethylenediamine, diethanolamine, piperazine, dimethylaminoethanol, 2-amino-2-methyl-1-propanol, theophylline and N-methylglucamine.

The salts can be mono-salts such as the monosodium salt obtained by treating one equivalent of sodium hydroxide with one equivalent of the product (I); mixed di-salts may be obtained by treating one equivalent of a mono-salt with one equivalent of a different base. Alternatively, salts may be obtained by treating one equivalent of a base having a bivalent cation, such as calcium hydroxide, with one equivalent of the product (I). In addition, mixed salts and esters such as those obtained by treating the product (I) with one equivalent of sodium hydroxide and then with one equivalent of lactic acid are also within the scope of this invention.

The salts of this invention are pharmacologically acceptable nontoxic derivatives

which can be used as the active ingredient in suitable unit-dosage pharmaceutical forms. Also, they may be combined with other drugs to provide compositions having a broad spectrum of activity. In addition, the salts and, also the corresponding ester and amide derivatives, have utility as intermediate compounds in preparing the carboxylic acid products illustrated by formula I, supra.

The products (I) may also be converted to their corresponding mono- and di-esters and mono- and di- amides for example, the pivaloyloxymethyl or dibenzhydryl esters or alkyl, cycloalkyl, aryl or aralkyl esters, for example, the methyl, ethyl, cyclohexyl, phenyl and benzyl esters or amides, diamides, N-(C₁₋₆ alkyl)amides, N,N-di-(C₁₋₆ alkyl)amides, N-aralkylamides, N,N-diaralkylamides or heterocyclic amides such as the N-methyl and N-ethylamide, N,N-dimethylamide, N,N-diethylamide, N-benzylamide, N,N-dibenzylamide, piperidide, pyrrolidide and morpholide.

Of particular interest are the following esters:

2-thienyl,
methylthiobutyl,
methylallyl,
3-penten-1-yl,
4-penten-1-yl,
3-pentyn-1-yl,
methylthioethyl,
benzyl,
3-buten-1-yl and
2-buten-1-yl.

Methods for the preparation of the esters and amide derivatives include the reaction of the carboxylic acid product (I) or corresponding acid halide with an alcohol or phenol, for example, methanol, ethanol, cyclohexanol, phenol, benzyl, alcohol or dibenzhydrol. The amide derivatives may be obtained by treating the corresponding acid halide with ammonia or with an appropriate alkylamine, dialkylamine, aralkylamine or heterocyclic amine. These and other conventional methods for the preparation of the esters and amides will be obvious to those skilled in the art.

Thus the novel cephalosporins are valuable anti-microbial substances and are active against various gram-positive and gram-negative pathogens such as *Bacillus subtilis*, *Salmonella schottmuelleri* and *Proteus vulgaris*. Thus, the free acid and especially the salts thereof such as amine and metal salts, particularly the alkali metal and alkaline-earth metal salts, are useful bactericides and can be used for removing susceptible pathogens from dental and medical equipment, for separating microorganisms, and for therapeutic use in humans and animals. For this latter purpose pharmacologically acceptable salts with inorganic and organic bases such as those known in the art and used for the administration of penicillins and cephalosporins can be utilized. For example, salts such as alkali metal and alkaline-earth metal salts, and primary, secondary and tertiary amine salts can be used for this purpose. These salts can be combined with pharmaceutically acceptable liquid and solid vehicles to form suitable dosage unit forms such as pills, tablets, capsules, suppositories, syrups and elixirs which can be prepared in accordance with well known procedures.

Pharmaceutically acceptable salts, which may be formed using known procedures from the compounds of the invention, include (a) inorganic base salts such as alkali metal, e.g. sodium and potassium, alkaline-earth e.g. calcium, and organic base, e.g. procaine and dibenzylethylene diamine, salts and (b) acid-addition salts e.g. with hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, toluene-*p*-sulphonic and methanesulphonic acids. In addition to salts, the novel cephalosporins of the invention may be administered in the form of esters, including those discussed above. Examples of esters that might be mentioned are esters of alcohols, phenols, mercaptans, and thiophenols of the general formula —COXR, where R, represents the radical of an alcohol or a thiol such as methyl, ethyl, tertiary butyl, substituted alkyl such as phthalimidomethyl, succinimidomethyl, phenacyl, substituted phenacyl for example *p*-bromophenacyl, β -substituted ethyl such as 2,2,2-trichloroethyl, 2-(*p*-methylphenyl)ethyl, 2-(*p*-methylphenyl)sulfonyl, 2-methylaminoethyl or 2-chloro- (or bromo) ethyl, benzyl, substituted benzyl such as *p*-nitrobenzyl, *p*-methoxybenzyl, 3,5-dinitrobenzyl, 2,4,6-trimethylbenzyl or 3,5-dichloro-4-hydroxybenzyl, benzhydryl or substituted benzhydryl such as *p*-methoxybenzhydryl, acyloxyalkyl such as acetoxymethyl or pivaloyloxymethyl, alkoxy alkyl such as methoxymethyl, or monocyclic aryl for example phenyl or substituted phenyl such as *p*-nitrophenyl or 3,5-dinitrophenyl; of interest are the alkenyl esters (e.g. 3-buten-1-yl). These esters are readily prepared in accordance with known processes.

The novel cephalosporins are valuable antibiotics active against various gram-

positive and gram negative bacteria and, accordingly, find utility in human and veterinary medicine. The compounds of this invention can therefore be used as antibacterial drugs for treating infections caused by gram-positive or gram-negative bacteria, for example against *Staphylococcus aureus* (penicillin resistant), *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella typhosa*, *Pseudomonas* and *Bacterium proteus*. The antibacterial cephalosporins of the invention may further be utilized as additives to animal feedingstuffs, for preserving foodstuffs and as disinfectants. For example, they may be used in aqueous compositions in concentrations ranging from 0.1 to 100 parts of antibiotic per million parts of solution in order to destroy and inhibit the growth of harmful bacteria on medical and dental equipment and as bactericides in industrial applications, for example in water-based paints and in the white water of paper mills to inhibit the growth of harmful bacteria.

The products of this invention may be used alone or in combination as the active ingredient in any one of a variety of pharmaceutical preparations. These antibiotics and their corresponding salts may be employed in capsule form or as tablets, powders or liquid solutions or as suspensions or elixirs. They may be administered orally, intravenously or intramuscularly.

The compositions are preferably presented in a form suitable for absorption by the gastro-intestinal tract. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; lubricants, for example, magnesium stearate, talc, polyethylene glycol, silica; disintegrants, for example, potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to known methods. Oral liquid preparations may be in the form of aqueous or oily suspension, solution, emulsions, syrups or elixirs or may be presented as a dry product, for reconstitution with water or other suitable vehicles before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate or acacia; non-aqueous vehicles which may include edible oils, for example, almond oil, fractionated coconut oil, oily esters, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoates or sorbic acid. Suppositories will contain conventional suppository bases, e.g. cocoa butter or other glyceride.

Compositions for injection may be presented in unit dose form in ampoules, or in multidose containers with an added preservative. The compositions may take such forms as suspensions, solutions and emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The compositions may also be prepared in suitable forms for absorption through the mucous membranes of the nose and throat or bronchial tissues and may conveniently take the form of powder or liquid sprays or inhalents, lozenges or throat paints. For medication of the eyes or ears, the preparations may be presented as individual capsules, in liquid or semi-solid form, or may be used as drops. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints or powders.

Also, in addition to a carrier, the compositions may include other ingredients such as stabilizers, binders, antioxidants, preservatives, lubricators, suspending agents, viscosity agents or flavoring agents. In addition, there may also be included in the compositions other active ingredients to provide a broader spectrum of antibiotic activity.

For veterinary medicine the composition may, for example, be formulated as an intramammary preparation in either long-acting or quick-release bases.

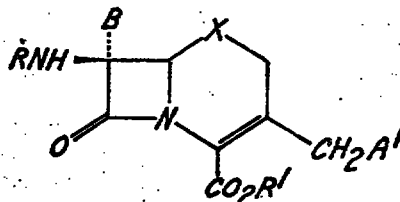
The dosage to be administered depends to a large extent upon the condition of the subject being treated and the weight of the host, the route and frequency of administration, the parenteral route being preferred for generalized infections and the oral route for intestinal infections. In general, a daily oral dosage consists of from 15 to 600 mg. of active ingredient per kg. of body weight of the subject in one or more applications per day. A preferred daily dosage for adult humans lies in the range of from 80 to 120 mg. of active ingredient per kg. of body weight. The preferred daily dosage for the compounds of the invention range from 80 to 120 mg. of active ingredient per kg. of body weight.

The instant compositions may be administered in several unit dosage forms as, for example, in solid or liquid orally ingestible dosage form. The compositions per unit

dosage, whether liquid or solid may contain from 0.1% to 99% of active material, the preferred range being from about 10—60%. The composition will generally contain from 15 mg. to 1500 mg. by weight of the active ingredient based upon the total weight of the composition; however, in general, it is preferable to use a dosage in the range of from 250 mg. to 1000 mg. In parenteral administration the unit dosage is usually the pure compound in a slightly acidified sterile water solution or in the form of a soluble powder intended for solution.

WHAT WE CLAIM IS:—

1. A compound of the formula:

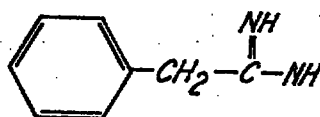


and its isomers, in which R is an acyl radical; B is H, OCH₃, CH₃, or SR where R is alkyl of 1—6 carbon or aryl; R¹ is hydrogen or a protecting group; A¹ is hydrogen, azido, halogen, cyano, quaternary ammonium, hydroxy, carbamoyloxy, N-(C₁₋₆ alkyl)-carbamoyloxy, N,N-di-(C₁₋₆ alkyl)carbamoyloxy, thiocarbamoyloxy, N-(C₁₋₆ alkyl)-thiocarbamoyloxy, N,N-di-(C₁₋₆ alkyl)thiocarbamoyloxy, amino, N-substituted amino, mercapto, C₁₋₆ alkylthio, quaternary amino, C₁₋₆ alkanoyloxy, aroyloxy or a 5-membered heterocyclic thio radical having from 1 to 4 hetero atoms, the latter being S, O and/or N, and X is —O—, —CH₂— or —NY— where Y is hydrogen, benzyl, formyl or C₁₋₆ alkyl; or a non-toxic pharmacologically acceptable salt, ester or amide derivative of such a compound.

2. A compound according to Claim 1 in which R is of the formula:



where R² is hydrogen, halogen, amino, guanidino, phosphono, hydroxy, tetrazolyl, carboxy, sulfo or sulfonamido; and R³ is phenylacetimidamido, i.e.



phenyl, substituted phenyl, a substituted or unsubstituted 5- or 6-membered monocyclic heterocyclic ring containing one or more oxygen, sulfur or nitrogen hetero atoms, phenylthio, phenyloxy, heterocyclic-thio, substituted heterocyclic thio or cyano; R¹ is hydrogen or a protecting group and A¹ is hydrogen, C₁₋₆ alkanoyloxy, carbamoyloxy, pyridinium or heterocyclic-thio.

3. A compound according to Claim 2 in which R is of the formula:



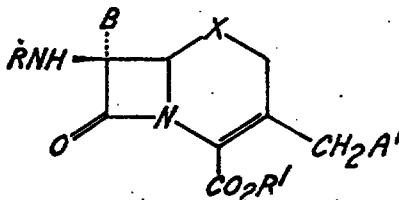
where R² is hydrogen, amino, hydroxy or carboxy and R³ is substituted or unsubstituted phenyl or a substituted or unsubstituted 5- or 6-membered heterocyclic ring.

4. A compound according to Claim 3 in which R is 2-thienylacetyl, 2-furylacetyl, 3-thienylacetyl, 2-tetrazolylacetyl, D-phenylglycyl, phenylmalonyl, 3-thienylmalonyl, or α-hydroxyphenylacetyl; R¹ is hydrogen, methyl, 2,2,2-trichloroethyl, tert-butyl, benzoylmethyl, p-methoxybenzyl, benzyl, benzhydryl, trimethylsilyl or methoxymethyl; A is hydrogen, acetoxy, carbamoyloxy, N-methyltetrazolylthio, 2-methyl-1,3,4-thiadiazol-5-yl-thio, or pyridine and X is a divalent radical selected from —O—, —CH₂—, or —NY— where Y is hydrogen, benzyl, formyl, or methyl.

dosage, whether liquid or solid may contain from 0.1% to 99% of active material, the preferred range being from about 10—60%. The composition will generally contain from 15 mg. to 1500 mg. by weight of the active ingredient based upon the total weight of the composition; however, in general, it is preferable to use a dosage in the range of from 250 mg. to 1000 mg. In parenteral administration the unit dosage is usually the pure compound in a slightly acidified sterile water solution or in the form of a soluble powder intended for solution.

WHAT WE CLAIM IS:—

1. A compound of the formula:

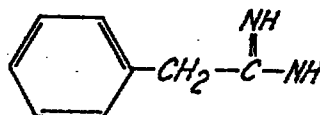


and its isomers, in which R is an acyl radical; B is H, OCH₃, CH₃, or SR where R is alkyl of 1—6 carbon or aryl; R¹ is hydrogen or a protecting group; A¹ is hydrogen, azido, halogen, cyano, quaternary ammonium, hydroxy, carbamoyloxy, N-(C₁₋₆ alkyl)-carbamoyloxy, N,N-di-(C₁₋₆ alkyl)carbamoyloxy, thiocarbamoyloxy, N-(C₁₋₆ alkyl)-thiocarbamoyloxy, N,N-di-(C₁₋₆ alkyl)thiocarbamoyloxy, amino, N-substituted amino, mercapto, C₁₋₆ alkylthio, quaternary amino, C₁₋₆ alkanoyloxy, aroyloxy or a 5-membered heterocyclic thio radical having from 1 to 4 hetero atoms, the latter being S, O and/or N, and X is —O—, —CH₂— or —NY— where Y is hydrogen, benzyl, formyl or C₁₋₆ alkyl; or a non-toxic pharmacologically acceptable salt, ester or amide derivative of such a compound.

2. A compound according to Claim 1 in which R is of the formula:



where R² is hydrogen, halogen, amino, guanidino, phosphono, hydroxy, tetrazolyl, carboxy, sulfo or sulfonamido; and R³ is phenylacetimidamido, i.e.



phenyl, substituted phenyl, a substituted or unsubstituted 5- or 6-membered monocyclic heterocyclic ring containing one or more oxygen, sulfur or nitrogen hetero atoms, phenylthio, phenyloxy, heterocyclic-thio, substituted heterocyclic thio or cyano; R¹ is hydrogen or a protecting group and A¹ is hydrogen, C₁₋₆ alkanoyloxy, carbamoyloxy, pyridinium or heterocyclic-thio.

3. A compound according to Claim 2 in which R is of the formula:



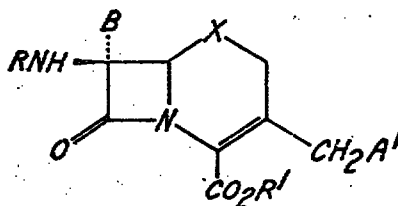
where R² is hydrogen, amino, hydroxy or carboxy and R³ is substituted or unsubstituted phenyl or a substituted or unsubstituted 5- or 6-membered heterocyclic ring.

4. A compound according to Claim 3 in which R is 2-thienylacetyl, 2-furylacetyl, 3-thienylacetyl, 2-tetrazolylacetyl, D-phenylglycyl, phenylmalonyl, 3-thienylmalonyl, or α-hydroxyphenylacetyl; R² is hydrogen, methyl, 2,2,2-trichloroethyl, tert-butyl, benzoylmethyl, p-methoxybenzyl, benzyl, benzhydryl, trimethylsilyl or methoxymethyl; A is hydrogen, acetoxy, carbamoyloxy, N-methyltetrazolylthio, 2-methyl-1,3,4-thiadiazol-5-yl-thio, or pyridine and X is a divalent radical selected from —O—, —CH₂—, or —NY— where Y is hydrogen, benzyl, formyl, or methyl.



5. Sodium 7 β -(2'-thienylacetamido)-1-methylene-1-dethiacephalosporanate.
 6. Benzyl 7 β -(2'-thienylacetamido)-1-methylene-1-dethiacephalosporanate.
 7. Sodium 7 β -(2'-thienylacetamido)-1-oxa-1-dethiacephalosporanate.
 8. Sodium 7 β -(2'-thienylacetamido)-1-methylene-1-dethia-3-methyl-3-cephem-4-carboxylate. 5
 9. Sodium 7 β -(2'-thienylacetamido)-3-carbamoyloxymethyl-1-methylene-1-dethia-3-cephem-4-carboxylate.
 10. Sodium 7 β -(2'-thienylacetamido)-3-carbamoyloxymethyl-1-oxa-1-dethia-3-cephem-4-carboxylate. 10
 11. Sodium 7 β -(2'-thienylacetamido)-3-acetoxymethyl-1-aza-1-dethia-3-cephem-4-carboxylate.
 12. Sodium 7 β -(2'-thienylacetamido)-3-acetoxymethyl-N-methyl-1-aza-1-dethia-3-cephem-4-carboxylate.
 13. Sodium 7 β -(2'-thienylacetamido)-3-(pyridinium-methyl)-1-methylene-1-dethia-3-cephem-4-carboxylate. 15
 14. Sodium 7 β -(2'-thienylacetamido)-3-hydroxymethyl-1-methylene-1-dethia-3-cephem-4-carboxylate.
 15. Sodium 7 β -(2'-thienylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-ylthio-methyl)-1-methylene-1-dethia-3-cephem-4-carboxylate. 20
 16. 7 β -(2-Thienylacetamido)-1-aminodethiacephalosporanic acid. 20
 17. 7 β -(2-Thienylacetamido)-1-methylamino-dethiacephalosporanic acid.
 18. Benzyl 7 β -thienylacetamido-1-benzylamino-dethiacephalosporanate.
 19. Sodium 7 β -thienylacetamido-1-amino-dethiacephalosporanate.
 20. Sodium 7 β -thienylacetamido-1-methylamino-dethiacephalosporanate.
 21. Sodium 7 β -thienylacetamido-1-formamido-dethiacephalosporanate. 25
 22. *p*-Methoxybenzyl 7 β -(2-thienylacetamido)-1-oxa-dethiacephalosporanate.
 23. *p*-Methoxybenzyl 7 α -methoxy-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate.
 24. Sodium 7 α -methoxy-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate. 30
 25. Potassium 7 α -methoxy-7-(2-thienylacetamido)-3-hydroxymethyl-1-oxa-dethia-ceph-3-em-4-carboxylate. 30
 26. Sodium 7 α -methoxy-7-(2-thienylacetamido)-3-carbamoyloxy-methyl-1-oxa-dethiaceph-3-em-4-carboxylate.
 27. *p*-Methoxybenzyl 7 α -methylthio-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate. 35
 28. Sodium 7 α -methylthio-7-(2-thienylacetamido)-1-oxa-dethiacephalosporanate.
 29. 7 β -(*D*-2-Phenyl-2-hydroxyacetamido)-3-(1-methyl-1,2,3,4-tetrazolyl-5-thio-methyl)-1-oxa-dethia-3-cephem-4-carboxylic acid.
 30. 7 β -(2-Tetrazolylacetamido)-3-(2-methyl-1,3,4-thiadiazolyl-5-thiomethyl)-1-oxa-dethia-3-cephem-4-carboxylic acid. 40
 31. Benzyl 7-(2'-thienylacetamido)-7 α -methoxy-1-methylene-1-dethiacephalosporanate.
 32. Benzyl 7 β -phenylacetamido-7-methoxy-1-methylene-1-dethiacephalosporanate.
 33. 3-Methyl-7 β -(*D*- α -amino)-phenylacetamido-1-oxa-dethia-3-cephem-4-carboxylic acid. 45
 34. 7 β -(2-Thienyl)acetamido-1-methylene-dethiacephalosporanic acid.
 35. Sodium 7 β -(2-thienyl)acetamido-1-methylene-dethiacephalosporanate.
 36. Benzyl 7 β -(2-thienyl)acetamido-1-methylene-dethiacephalosporanate.
 37. 7 β -(*D*- α -azido)-phenylacetamido-1-methylene-dethiacephalosporanic acid.
 38. Sodium 7 β -(*D*- α -azido)-phenylacetamido-3-hydroxymethyl-1-methylene-dethia-3-cephem-4-carboxylate. 50
 39. 7 β -(*D*- α -azido)-phenylacetamido-3-carbamoyloxymethyl-1-methylene-dethia-3-cephem-4-carboxylic acid.
 40. 7 β -(*D*- α -amino)-phenylacetamido-3-carbamoyloxymethyl-1-methylene-dethia-3-cephem-4-carboxylic acid. 55
 41. 7 β -(2-Thienyl)-acetamido-3-(1-pyridyl-methyl-1-formamido-dethia-3-cephem-4-carboxylic acid betaine).
 42. 7 α -Methoxy-7-(α -carboxy-3-thienyl)acetamido-3-carbamoyloxy-methyl-1-methylene-dethia-ceph-3-em-4-carboxylic acid disodium salt.
 43. 7 α -Methoxy-7-(*D*-2-hydroxy-2-phenylacetamido)-3-[5-(1-methyl-1,2,3,4-tetrazolylthiomethyl)-1-methylene-dethia-3-cephem-4-carboxylic acid sodium salt. 60
 44. A process for preparing a compound as claimed in Claim 1, that comprises treating a compound of the formula:





in which A', B and X are as defined in Claim 1, R' is a blocking group and both R's is hydrogen or are joined to form benzylidene or substituted benzylidene group, with an acylating agent and, if necessary, removing the blocking group to form the free acid, to produce the desired product.

45. A process according to Claim 44 in which both R's are joined to form a benzylidene group and the starting imino compound is first treated with a metal catalyst and then acylated.

46. A process according to Claim 45 in which the metal catalyst is ML_n where M is palladium, platinum, nickel, ruthenium, rhodium, cobalt or iron; L is a ligand selected from halo, carbonyl, cyclopentadienyl or phenylcyano and n is an integer equal to the valence requirements.

47. A process according to Claim 46 in which the metal catalyst is palladium chloride.

48. A process according to any one of Claims 44 to 47 in which the acylating agent is of the formula:



in which R^2 and R^3 are as defined in Claim 2 and Z is a halogen atom.

49. A process according to Claim 48 in which A is hydrogen, C_{1-n} alkanoyloxy, carbamoyloxy or pyridinium.

50. A process according to Claim 49 in which the radical



is 2-thienylacetyl, 2-furylacetyl, 3-thienylacetyl, 2-tetrazolylacetyl, N-protected D-phenylglycyl, O-protected phenylmalenyl, 3-thienylmalonyl, or α -protected hydroxy phenylacetyl and R^1 is hydrogen, methyl, 2,2,2-trichloroethyl, *tert*-butyl, benzoylmethyl, *p*-methoxybenzyl, benzyl, *p*-nitrobenzyl, benzhydryl, trimethylsilyl or methoxymethyl.

51. A process according to Claim 50 in which benzyl 7 β -(2'-thienylacetamido)-1-methylene-1-dethiacephalosporanate is produced by treating benzyl 7-benzaldimino-1-methylene-1-dethiacephalosporanate with 2-thienylacetyl chloride.

52. A process according to Claim 50 in which benzyl 7 β -(2'-thienylacetamido)-1-methylene-1-dethiacephalosporanate is produced by treating benzyl 7 β -amino-1-methylene-1-dethiacephalosporanate with 2-thienylacetyl chloride.

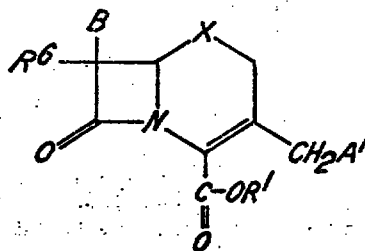
53. A process according to Claim 50 in which benzyl 7 β -(2'-thienylacetamido)-1-oxa-dethiacephalosporanate is produced by treating benzyl 7 β -amino-1-oxa-dethiacephalosporanate with 2-thienylacetyl chloride.

54. A process according to Claim 44 in which sodium 7 β -(2'-thienylacetamido)-3-carbamoyloxymethyl-1-methylene-1-dethia-3-cephem-4-carboxylate is produced by treating benzyl 7-benzaldimino-3-carbamoyloxymethyl-1-methylene-1-dethia-3-cephem-4-carboxylate with 2-thienylacetyl chloride, removing the benzyl group by hydrogenation in the presence of a catalyst and finally treating the free acid with sodium bicarbonate.

55. A process according to Claim 44 in which sodium 7 β -(2'-thienylacetamido)-3-carbamoyloxymethyl-1-oxa-1-dethia-3-cephem-4-carboxylate is produced by treating benzyl 7 β -amino-3-carbamoyloxymethyl-1-oxa-1-dethia-3-cephem-4-carboxylate with 2-thienylacetyl chloride followed by removal of the benzyl group by hydrogenation in the presence of a catalyst and finally treating with sodium bicarbonate.



56. A compound of the formula:



in which A¹, R¹, B and X are as defined in Claim 1 and R⁶ is azido, amino, benzaldimino or substituted benzaldimino.

- 5 57. A compound according to Claim 56 in which A¹ is hydrogen, C₁₋₆ alkanoyloxy, heterocyclic thio, or carbamoyloxy. 5
58. A compound according to Claim 57 in which B is hydrogen and R⁶ is amino, benzaldimino or substituted benzaldimino.
- 10 59. A compound according to Claim 58 in which R⁶ is 7β-amino. 10
60. A compound according to Claim 59 in which R¹ is hydrogen and A¹ is acetoxy.
61. A compound according to Claim 58 in which R⁶ is benzaldimino or substituted benzaldimino in the α or β configuration.
62. A compound according to Claim 57 in which B is methyl and R⁶ is amino, benzaldimino or substituted benzaldimino.
- 15 63. A compound according to Claim 62 in which R⁶ is 7β-amino. 15
64. A compound according to Claim 62 in which R⁶ is benzaldimino or substituted benzaldimino and is in the α or β configuration.
65. A compound according to Claim 57 in which B is methoxy and R⁶ is amino, benzaldimino or substituted benzaldimino.
- 20 66. A compound according to Claim 65 in which R⁶ is 7β-amino. 20
67. A compound according to Claim 65 in which R⁶ is benzaldimino or substituted benzaldimino and is in the α or β configuration.
68. A compound according to Claim 56 in which B is C₁₋₆ alkyl thio or phenyl thio and R⁶ is amino, benzaldimino or substituted benzaldimino.
- 25 69. A compound according to Claim 68 in which R⁶ is 7β-amino. 25
70. A compound according to Claim 68 in which R⁶ is benzaldimino or substituted benzaldimino and is in the α or β configuration.
71. Benzyl 7β-amino-1-methylene-1-dethiacephalosporanate.
72. Benzyl 7-amino-1-oxadethiacephalosporanate.
- 30 73. 7β-Amino-1-oxadethiacephalosporanic acid. 30
74. Benzyl 7-amino-1-benzylamino-dethiacephalosporanate.
75. 7β-Amino-3-(1-methyl-1,2,3,4-tetrazolyl-5-)thiomethyl-1-methylene-dethia-ceph-3-em-4-carboxylic acid.
76. Benzhydryl 7β-amino-3-(1-methyl-1,2,3,4-tetrazolyl-5)thiomethyl-1-methylene-dethia-ceph-4-em-4-carboxylate.
- 35 77. Benzhydryl 7-amino-7-α-methylthio-3-(1-methyl-1,2,3,4-tetrazolyl-5)thio-methyl-1-methylenedethia-ceph-3-em-4-carboxylate. 35
78. Benzhydryl 7-α-methylthio-7-β-(p-nitrobenzylideneamino)-3-(1-methyl-1,2,3,4-tetrazolyl-5)thiomethyl-1-methylenedethia-ceph-3-em-4-carboxylate.
- 40 79. 7β - Amino - 3 - (2 - methyl - 1,3,4 - thiadiazolyl - 5 - thiomethyl) - 1 - oxa-dethia - 3 - cephem - 4 - carboxylic acid. 40
80. 4-Benzylloxycarbonyl-3-methyl-7-amino-1-oxadethia-3-cephem.
81. 7β-Amino-1-benzylamino-dethiacephalosporanic acid.
82. 7β-Amino-1-benzylamino-dethiacephalosporanic acid.
- 45 83. 7β-Amino-1-methylamino-dethiacephalosporanic acid. 45
84. 7β-Amino-1-amino-dethiacephalosporanic acid.
85. Benzyl 7β-benzaldimino-1-methylene-1-dethiacephalosporanate.
86. Benzyl 7-p-nitrobenzaldimino-1-benzylamino-dethiacephalosporanate.
87. Benzhydryl 7β - (p - nitrobenzylideneamino) - 1 - methylene - dethia-cephalosporanate.
- 50 88. Benzhydryl 7β-(p-nitrobenzylideneamino)-3-(1-methyl-1,2,3,4-tetrazolyl-5)-thiomethyl-1-methylene-dethia-ceph-3-em-4-carboxylate. 50
89. Benzhydryl 7-α-methylthio-7-β-(p-nitrobenzylideneamino)-3-(1-methyl-1,2,3,4-tetrazolyl-5)thiomethyl-1-methylene-dethia-ceph-3-em-4-carboxylate.



90. Benzhydryl 7- α -methylthio-7-(p-nitrobenzylideneamino)-1-methylene-1-dethiacephalosporanate.

91. Benzyl 7-benzaldimino-7 α -methoxy-1-methylene-1-dethiacephalosporanate.

92. Benzyl 7 β -azido-1-methylene-1-dethiacephalosporanate.

93. Benzyl 7-azido-1-oxadethiacephalosporanate.

94. Benzyl 7-azido-1-benzylamino-dethiacephalosporanate.

95. Benzyl 7-azido-1-methylamino-dethiacephalosporanate.

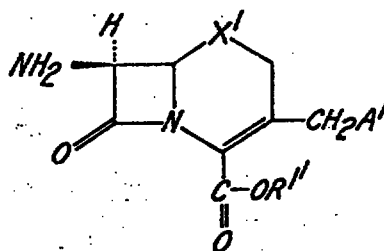
96. 4-benzyloxycarbonyl-3-methyl-7-azido-1-oxa-dethia-3-cephem.

97. A compound according to Claim 63 in which R¹ is hydrogen and A¹ is acetoxy.

98. A compound according to Claim 66 in which R¹ is hydrogen and A¹ is acetoxy.

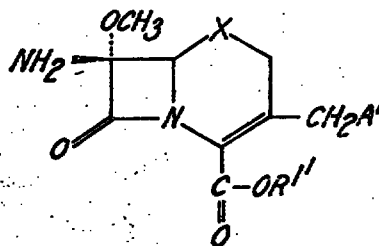
99. A compound according to Claim 69 in which R¹ is hydrogen and A¹ is acetoxy.

100. A process for preparing a compound of the formula:



and its 7 α -isomer where A¹ is as defined in Claim 1, R¹ is a protecting group and X¹ is —O— or —NY— where Y is as defined in Claim 1, that comprises treating the corresponding 7 β or 7 α azido compound with hydrogen in the presence of a noble metal catalyst followed by separation of the isomers.

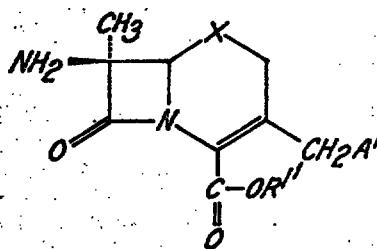
101. A process for preparing a compound of the formula:



in which A¹ and X are as defined in Claim 1 and R¹ is a protecting group, that comprises first treating the corresponding 7-halo-7-imino compound with methanol in the presence of a base to form the 7 β -imino-7 α -methoxy compound and treating the latter with an amine in the presence of an acid catalyst to afford the desired product.

102. A process according to Claim 69 in which the base is silver oxide, barium oxide, cuprous oxide or triethylamine.

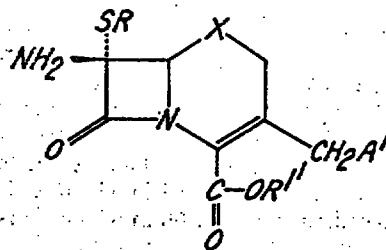
103. A process for preparing a compound of the formula:



in which A¹ and X are as defined in Claim 1 and R¹ is a protecting group, that comprises first treating the corresponding 7-imino compound with an activating agent and a methyl halide to form the 7 β -imino-7 α -methyl compound and treating the latter with an amine in the presence of an acid catalyst to afford the desired product.

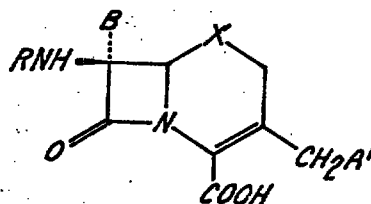


104. A process for preparing a compound of the formula:

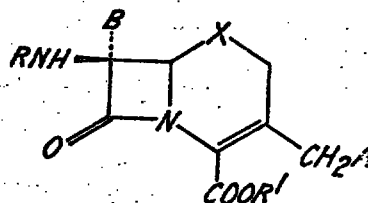


in which R, A' and X are as defined in Claim 1 and R' is a protecting group, that comprises first treating the corresponding 7-imino compound with an activating agent and a C₁₋₆ alkyl or phenyl sulfonyl halide to form the 7β-imino-7α-SR compound and treating the latter with an amine in the presence of an acid catalyst to afford the desired product.

105. A method for preparing a compound of the formula:



and its isomers in which A', B, R and X are as defined in Claim 1 that comprises de-blocking a compound of the formula:



where R' is a protecting group.

106. A method according to Claim 105 in which A and R are as defined in Claim

107. A method according to Claim 106 in which R is as defined in Claim 3.

108. A method according to Claim 107 in which R is as defined in Claim 4.

109. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-1-methylene-1-dethiacephalosporanic acid is produced.

110. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-3-carbamoyloxymethyl-1-methylene-1-dethia-3-cephem-4-carboxylic acid is produced.

111. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-1-oxa-1-dethiacephalosporanic acid is produced.

112. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-1-methylene-1-dethia-3-methyl-3-cephem-4-carboxylic acid is produced.

113. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-3-carbamoyloxymethyl-1-oxa-1-dethia-3-cephem-4-carboxylic acid is produced.

114. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-3-acetoxymethyl-1-aza-1-dethia-3-cephem-4-carboxylic acid is produced.

115. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-3-acetoxymethyl-N-methyl-1-aza-1-dethia-3-cephem-4-carboxylic acid is produced.

116. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-3-(pyridinium-methyl)-1-methylene-1-dethia-3-cephem-4-carboxylic acid is produced.

117. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-3-hydroxymethyl-1-methylene-1-dethia-3-cephem-4-carboxylic acid is produced.

118. A method according to Claim 105 in which 7β-(2'-thienylacetamido)-3-(2-methyl-1,3,4-thiadiazol-5-ylthiomethyl)-1-methylene-1-dethia-3-cephem-4-carboxylic acid is produced.



119. A method according to Claim 105 in which 7 β -(2'-thienylacetamido)-1-aminodethiacephalosporanic acid is produced.

120. A method according to Claim 105 in which 7 β -(2'-thienylacetamido)-1-methylamino-dethiacephalosporanic acid is produced.

121. A method according to Claim 105 in which 7 β -(2'-thienylacetamido)-1-benzylamino-dethiacephalosporanic acid is produced.

122. A method according to Claim 105 in which 7 β -(2'-thienylacetamido)-1-amino-dethiacephalosporanic acid is produced.

123. A method according to Claim 105 in which 7 β -(2'-thienylacetamido)-1-methylamino-dethiacephalosporanic acid is produced.

124. A method according to Claim 105 in which 7 β -(2'-thienylacetamido)-1-formamido-dethiacephalosporanic acid is produced.

125. A method according to Claim 105 in which 7 β -(2'-thienylacetamido)-1-oxa-dethiacephalosporanic acid is produced.

126. A method according to Claim 105 in which 7 α -methoxy-7-(2'-thienylacetamido)-1-oxa-dethiacephalosporanic acid is produced.

127. A method according to Claim 105 in which 7 α -methoxy-7-(2'-thienylacetamido)-3-hydroxymethyl-1-oxa-dethiaceph-3-em-4-carboxylic acid is produced.

128. A method according to Claim 105 in which 7 α -methoxy-7-(2'-thienylacetamido)-3-carbamoyloxymethyl-1-oxa-dethiaceph-3-em-4-carboxylic acid is produced.

129. A method according to Claim 105 in which 7 α -methylthio-7-(2'-thienylacetamido)-1-oxa-dethiacephalosporanic acid is produced.

130. A method according to Claim 105 in which 7 β -(D-2-phenyl-2-hydroxyacetamido)-3-(1-methyl-1,2,3,4-tetrazolyl-5-thiomethyl)-1-oxa-dethia-3-cephem-4-carboxylic acid is produced.

131. A method according to Claim 105 in which 7 β -(2-tetrazolylacetamido)-3-(2-methyl-1,3,4-thiadiazolyl-5-thiomethyl)-1-oxa-dethia-3-cephem-4-carboxylic acid is produced.

132. A method according to Claim 105 in which 7-(2'-thienylacetamido)-7 α -methoxy-1-methylene-1-dethiacephalosporanic acid is produced.

133. A method according to Claim 105 in which 7 β -phenylacetamido-7-methoxy-1-methylene-1-dethiacephalosporanic acid is produced.

134. A method according to Claim 105 in which 3-methyl-7 β -(D- α -amino)-phenylacetamido-1-oxa-dethia-3-cephem-4-carboxylic acid is produced.

135. A method according to Claim 105 in which 7 β -(2'-thienylacetamido)-1-methylene-dethiacephalosporanic acid is produced.

136. A method according to Claim 105 in which 7 β -(D- α -azido)-phenylacetamido-1-methylene-dethiacephalosporanic acid is produced.

137. A method according to Claim 105 in which 7 β -(D- α -azido)-phenylacetamido-3-hydroxymethyl-1-methylene-dethia-3-cephem-4-carboxylate is produced.

138. A method according to Claim 105 in which 7 β -(D- α -azido)-phenylacetamido-3-carbamoyloxymethyl-1-methylene-dethia-3-cephem-4-carboxylic acid is produced.

139. A method according to Claim 105 in which 7 β -(D- α -amino)-phenylacetamido-3-carbamoyloxymethyl-1-methylene-dethia-3-cephem-4-carboxylic acid is produced.

140. A method according to Claim 105 in which 7 β -(2'-thienylacetamido)-3-(1-pyridinium-methyl-1-formamido-dethia-3-cephem-4-carboxylic acid is produced.

141. A pharmaceutical composition containing as active ingredient a compound as claimed in any one of Claims 1-43 together with a pharmaceutical diluent or carrier.

142. A veterinary composition containing as active ingredient a compound as claimed in any one of Claims 1-43 together with a suitable diluent or carrier.

143. An antibacterial composition containing as active ingredient a compound as claimed in any one of Claims 1-43 together with a diluent or carrier.

144. A composition as claimed in Claim 141 in solid or liquid orally administrable form.

145. A composition as claimed in Claim 144 in the form of a pill, tablet, capsule, syrup, elixir, lozenge, or an aqueous or oily solution, suspension or emulsion.

146. A composition as claimed in Claim 141 in injectable form.

147. A composition as claimed in Claim 146 in the form of an aqueous or oily solution, suspension or emulsion.

148. A composition as claimed in Claim 146 or 147 made up in ampoules.

149. A composition as claimed in Claim 141 in topically administrable form.

150. A composition as claimed in Claim 149 in the form of a paint, powder, spray, inhalant, drops, ointment, cream or lotion.



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151. A composition as claimed in Claim 141 in the form of a suppository.
152. A composition as claimed in Claim 142 in the form of an intramammary preparation.
153. A method of killing microorganisms or pharmaceutical, medical or dental equipment, that comprises applying to the equipment a composition as claimed in Claim 143.
154. A method of killing microorganisms in the white water of paper mills that comprises incorporating a compound as claimed in any one of Claims 1 to 43 into the white water.
155. A water-based paint containing a compound as claimed in any one of Claims 1 to 43.
156. A process for producing a compound as claimed in Claim 1, substantially as hereinbefore described in any appropriate foregoing Example.
157. A compound as claimed in Claim 1 when prepared by a process as claimed in any one of Claims 44 to 55 and 156.
158. A compound as claimed in Claim 1 when prepared by a method as claimed in any one of Claims 105 to 140.
159. A process for producing a compound as claimed in Claim 56, substantially as hereinbefore described in any appropriate foregoing Example.
160. A compound as claimed in Claim 56, when prepared by a process as claimed in any one of Claims 100 to 104 and 159.

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