

PATENT SPECIFICATION

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(54) NEW PROCESS FOR THE PREPARATION OF CEPHALOSPORANIC ACID DERIVATIVES

(71) We, KONINKLIJKE NEDERLANDSCHE GIST-EN SPIRITUS FABRIEK N.V., a Dutch Body Corporate of 1 Wateringseweg, Delft, The Netherlands, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new process for the preparation of cephalosporanic acid derivatives, and to compounds employed in the process.

It is known, for example from United States Patent No. 3,275,626 granted on Sept. 27, 1966 to R. B. Morin and B. G. Jackson, and entitled "Penicillin conversion via Sulphoxide" that 7-aminocepham derivatives can be prepared by heating analogous 6-amino-penicillanic sulphoxide derivatives in solution to temperatures of about 80° to 175°C. under acid conditions, which may be promoted by, for example, acetic anhydride or toluene-*p*-sulphonic acid. This known process involving heating under acid conditions results in a rearrangement of the heterocyclic ring structure, leading to the enlargement of the thiazolidine ring of the penicillanic sulphoxide and the formation, among others, of a thiazine ring, which is a structural part of cephalosporin compounds. Several of these cephalosporin compounds possess useful antibiotic activity and are, therefore, very important as therapeutics.

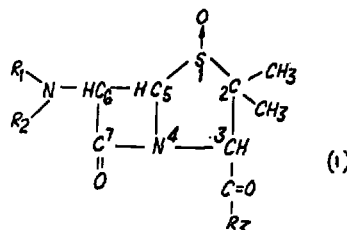
On the other hand it has been disclosed by R. B. Morin *et al* in J.A.C.S. 91 (1969), 1401—7, that heating esters of 6-aminopenicillanic sulphoxide derivatives, e.g. the cyanomethyl and methyl esters of phenoxymethylpenicillin sulphoxide, in the presence of bases such as triethylamine and pyridine causes fission of the bicyclic ring system and results in the formation of isothiazolone derivatives

It has now unexpectedly been found as a result of research and experimentation that 6-substituted - amino - penicillanic sulphoxides can be rearranged to form 7 - amino - desacetoxyccephalosporin derivatives by heating

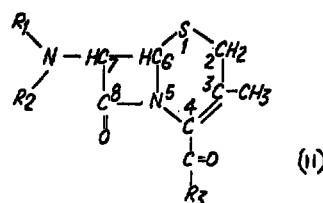
the sulphoxides in the presence of a considerable excess of a nitrogen-containing organic base provided the rearrangement is carried out also in the presence of a silicon compound having a silicon-halogen bond.

The present invention thus provides a new process for the preparation of 7-substituted amino - desacetoxyccephalosporanic derivatives from 6-substituted amino-penicillanic sulphoxides in the form of acids or derivatives thereof, including thiocarboxylic acids, salts, esters and amides, by rearrangement of the sulphoxides by heating up to a temperature not greater than 160°C. Under anhydrous conditions in the presence of at least one nitrogen-containing organic base and a silicon compound having a silicon-halogen bond, at least five moles of base being present for each mole of penicillanic sulphoxide, optionally in an inert organic solvent. Preferably the nitrogen-containing organic base is one with a secondary or tertiary nitrogen atom which has a pKa value of 4 to 10 measured in water at 25°C.

The new process may be applied generally to 6-substituted aminopenicillanic sulphoxides of the general formula:—



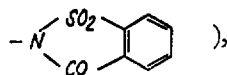
to yield 7 - substituted - amino - desacetoxyccephalosporanic derivatives of the general formula:—



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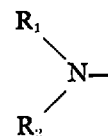
- wherein R_1 represents a group linked to the nitrogen atom by a carbon or sulphur atom, R_2 represents hydrogen or a lower alkyl or phenyl(lower)alkyl group, or R_1 and R_2 together with the nitrogen atom to which they are attached represent a heterocyclic group, e.g. a succinimido, phthalimido, oxazolidinyl or imidazolidinyl group, which may carry one or more substituents, and R_3 represents (a) a radical linked to the carbon atom by nitrogen, the nitrogen atom having attached to it atoms or groups selected from hydrogen, lower alkyl and aryl (e.g. phenyl or naphthyl) groups, or a combination of sulphonyl and carbonyl groups or a combination of two carbonyl groups on the nitrogen atom may be joined through the agency of an optionally substituted phenyl group (e.g.



- examples of such a nitrogen-containing radical being primary amino, mono(lower)alkylamino, di(lower)alkylamino, anilino, saccharyl or succinimido; or R_3 represents (b) a group $-SR_4$ wherein R_4 is hydrogen, or a lower alkyl or phenyl group; or R_3 represents (a) a group $-OR_5$ wherein R_5 is hydrogen or a cation which is preferably pharmaceutically-acceptable (e.g. an alkali metal or alkaline earth metal atom such as sodium, potassium or calcium, or a cation derived from an amine such as triethylamine or cyclohexylamine), or R_5 represents a lower alkyl group (e.g. methyl, *t*-butyl or trichloroethyl), a cycloalkyl radical containing 4 to 7 carbon atoms, phenyl, a phenylalkyl (e.g. benzyl), diphenyl-alkyl (e.g. benzhydryl) or aroylalkyl (e.g. phenacyl) group, the alkyl radicals of which contain 1 or 2 carbon atoms, or a stannyl group ($R_6R_7R_8\equiv Sn-$ [wherein R_6 , R_7 and R_8 represent lower alkyl groups, phenyl, or a phenylalkyl group containing 1 or 2 carbon atoms in the alkyl radical], or a silyl group ($R_9R_{10}R_{11}\equiv Si-$, wherein R_9 , R_{10} and R_{11} each represent a halogen atom, a lower alkyl group, phenyl or a phenylalkyl group containing 1 or 2 carbon atoms in the alkyl radical, or one of R_9 , R_{10} and R_{11} represents the group connected to symbol R_3 in formula II and linked via oxygen to the silicon atom.
- The aforementioned alkyl and aryl groups within the definitions of symbols R_2 and R_3 may optionally carry as substituents halogen atoms and, in the case of aryl groups, lower alkyl, lower alkoxy or di(lower)alkylamino groups.

The group represented by R_1 may be any group hitherto disclosed in relation to penicillins and cephalosporins, or analogous thereto. Thus, R_1 can represent, for example an

alkanoyl group containing up to 20 carbon atoms, a phenyl(lower alkanoyl, phenoxy-(lower)alkanoyl, phenyl(lower)alkyloxycarbonyl, (lower)alkanoylaminocarbonyl, salicyl optionally substituted by one or two halogen atoms, phenoxyphenyl(lower)alkanoyl, isoxazolylicarbonyl, benzoyl, naphthoyl, formyl, oxazolidinyl, phenyl - α - amino(lower)-alkanoyl, thienyl- or furyl-(lower)alkanoyl, phenylthio(lower)alkanoyl, 2-benzofuranyl-(lower)alkanoyl, benzenesulphonyl or 1-piperidinosulphonyl group. The phenyl and heterocyclyl radicals of such groups may carry substituents such as halogen atoms, and lower alkyl, carboxy, phenyl(lower)alkoxy, amino, nitro, cyano, trifluoromethyl and methylthio groups. The symbol R_2 may represent, for example, a hydrogen atom or a methyl, ethyl, isobutyl or benzyl group. Moreover, the symbols R_1 and R_2 together with the nitrogen atom to which they are attached may represent a heterocyclic group (e.g. phthalimido). Suitable groups represented by



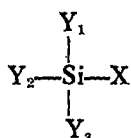
in formulae I and II are benzyloxycarbamoyl, phenylacetamido, phenoxyacetamido, 3-acetylureido, (3,5-dichlorosalicyl)amino, 2-phenoxypropionamido, 2-phenoxybutyramido, 2-phenoxyphenylacetamido, 5 - methyl - 3 - phenyl - 4 - isoxazolecarboxamido, 5 - methyl - 3 - (o - chlorophenyl) - 4 - isoxazolecarboxamido, 5 - methyl - 3 - (2,6 - dichlorophenyl) - 4 - isoxazolecarboxamido, 2,6 - dimethoxybenzamide, 2 - ethoxy - 1 - naphthamide, 2 - (o - aminobenzamide) - phenylacetamido - N - methyl, 2 - (2 - amino - 5 - nitrobenzamide) - phenylacetamido - N - methyl, N-benzylformamido, N - methyl - 2 - phenoxyacetamido, N - methyl - 2 - phenylacetamido, N - ethyl - 2 - phenyl - acetamido, N - isobutyl - 2 - phenoxyacetamido, 2 - benzylidene - 4,5 - dioxo - 3 - oxazolidinyl, 2-butylsuccinimido, 2,2 - dimethyl - 5 - oxo - 4 - phenyl - 1 - imidazolidinyl, phthalimido, α -aminophenylacetamido, 2-thienylacetamido, 3-thienylacetamido, 2-furylacetamido, 4-chlorophenylacetamido, 3-bromophenylacetamido, 3-nitrophenylacetamido, 4-nitrophenylacetamido, 3 - trifluoromethyl - phenylacetamido, 4-cyanophenylacetamido, 4-methylthiophenylacetamido, 3-chlorophenylthioacetamido, 2-benzofuranylacetamido, benzenesulphonamido, *p*-bromobenzenesulphonamido, and 1-piperidinosulphonamido. Preferred groupings represented by R_1R_2N- are phenylacetamido, phenoxyacetamido, α -aminophenylacetamido and 2-ethoxynaphthamido. When it is desired to obtain a desacetoxyccephalosporanic derivative of general formula

II in which R_1R_2N — is α -aminophenylacetamido, the amino group of the corresponding 6-substituted aminopenicillanic sulphoxide starting material should be protected during the ring enlargement by, for example, a benzyloxycarbonyl group, which can readily be removed subsequently to leave the free amino group.

By the term "lower" as applied herein to alkyl, alkoxy and alkanoyl groups is meant that the group in question contains at most 6, and preferably not more than 4, carbon atoms.

The nitrogen-containing organic base necessarily present when the penicillanic sulphoxide derivative is heated is a secondary or tertiary aliphatic, cycloaliphatic, aromatic or heterocyclic amine, preferably having a pK_a in water between 4 and 10. Suitable bases are hexamethylenetetramine, N-methylaniline, dimethylaniline, pyridine and pyridine substituted by, for example, one or more lower alkyl or mono- or di(lower)alkylamino groups, such as the picolines, 2-ethylpyridine, 2-propylpyridine, 2,3-dimethylpyridine, 2,5-dimethylpyridine, 2,6-dimethylpyridine, collidines and 2-dimethylaminopyridine, or quinoline or 3-methylisoquinoline. Preferred bases are α -picoline, 2,5-dimethylpyridine, 2-dimethylaminopyridine and 3-methylisoquinoline.

The silicon-containing compound necessarily present in the reaction mixture is preferably a silicon-halogen compound of the general formula:—



III

wherein Y_1 , Y_2 and Y_3 may be the same or different and each represents a halogen atom (preferably chlorine), or a lower alkyl group, a phenyl or phenylalkyl group containing 1 or 2 carbon atoms in the alkyl radical, the said alkyl and phenyl groups optionally carrying as substituents halogen atoms and, in the case of phenyl groups lower alkyl, lower alkoxy or di(lower)alkylamino groups, and X represents a halogen (preferably chlorine) atom. Examples of suitable silane compounds of formula III are trimethylchlorosilane, dimethyldichlorosilane, triethylchlorosilane, methyltrichlorosilane, triethylbromosilane, tri-*n*-propylchlorosilane, triethylbromosilane, tri-*n*-propylbromosilane, bromomethyl-dimethylchlorosilane, tri-*n*-butyl-chlorosilane, methyl-diethylchlorosilane, dimethylethylchlorosilane, phenyldimethylbromosilane, benzylmethyl-ethylchlorosilane, phenylethylmethyl-chlorosilane, triphenylchlorosilane, tri-*o*-tolyl-

chlorosilane and tri-*p*-dimethylamino-phenyl-chlorosilane. Of the silicon compounds that are most widely used in chemistry trimethylchlorosilane and dimethyldichlorosilane are preferred.

The process of the invention may be carried out in an inert organic solvent medium. Suitable solvents are acetonitrile, chlorobenzene, dimethylformamide, acetonitrile, dioxane, nitrobenzene, anisole, benzene, carbon tetrachloride, and especially benzyl cyanide and halogenoalkanes such as 1,2-dichloroethane, 1,1-dichloroethane, 1-bromo-1-chloroethane, 1,2,3-trichloropropane and chloroform. The process can be carried out using the nitrogen-containing organic base (e.g. pyridine) itself as reaction medium. Good combinations of organic bases and solvents are α -picoline or 2,5-dimethylpyridine with benzyl cyanide or one of the above-mentioned halogenoalkanes, such as 1,2-dichloroethane, 1-bromo-1-chloroethane or chloroform.

The process may be carried out at a temperature between 50° and 160°C. and is advantageously carried out at a temperature between 60° and 130°C., and preferably within the range 70° to 100°C. The reaction temperature should be kept below 160°C. in order to minimize the formation of decomposition products. Generally, the reaction temperature and reaction times are linked together to obtain good yields of the desacetoxycephalosporanic derivatives; lower temperatures require longer reaction times and higher temperatures require shorter reaction times, e.g. 70°, 80° and 90°C., the reaction may be 70 hours, 20–24 hours, and 10 hours respectively.

In order to obtain good yields of the desacetoxycephalosporanic derivatives by the ring enlargement of the 6-substituted aminopenicillanic sulphoxides a large molar excess of the nitrogen-containing organic base is preferably used, for example ten to seventy moles of base for each mole of sulphoxide employed.

The amount of silicon compound in the reaction mixture may be from half a mole per mole of sulphoxide to a considerable molar excess. Preferably a molar excess of silicon compound is employed and this excess may range from 3 moles to 15 moles per mole of sulphoxide, the amount giving the best results varying according to the silicon compound and the solvent (if any) employed. By appropriate selection of organic base, silicon compounds and solvent medium, yields as high as 75% of the theoretical yield of 7-amino-desacetoxycephalosporanic derivatives can be obtained from the penicillanic sulphoxide starting materials.

After completion of the ring enlargement reaction the resulting reaction mixture may be treated to separate the 7-amino-des-

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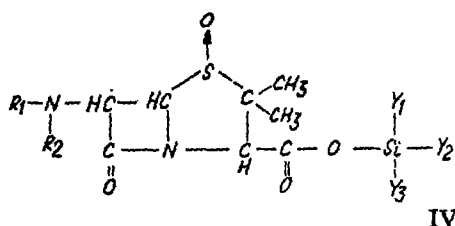
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acetoxycephalosporanic derivative therefrom by any convenient method such as extraction, for example with ethyl acetate or chloroform, and/or crystallisation. The 7-substituted amino-desacetoxycephalosporanic derivative so obtained (e.g. of general formula II) may, if desired, be converted by methods known *per se* into another desacetoxycephalosporanic derivative by appropriate modification of the 7-amino substituent and/or the substituent in the 4-position.

The substituent R_3 in the 6-substituted amino-penicillanic sulphoxide starting material of general formula I is advantageously a group $—OR_3$, in which R_3 represents a hydrogen atom or a pharmaceutically-acceptable cation (e.g. sodium, potassium or calcium) or a lower alkyl (e.g. trichloroethyl) or benzyl group, or a benzhydryl group optionally substituted in the benzene ring by one or more methoxy groups, preferably in the *para*-positions. The advantage arising when the 6 - amino - penicillanic sulphoxide is in the form of free acid or salt lies in the fact that the process of the invention can then give readily a biologically active 7 - amino - desacetoxycephalosporanic acid by carrying out just after the ring enlargement reaction a very easy and mild hydrolysis, thereby splitting off from the reaction product the silyl group which has esterified the carboxy group under the conditions of the ring enlargement reaction. When R_3 in the 6-substituted aminopenicillanic sulphoxide is a benzyloxy or benzhydryloxy group, the benzyl and benzhydryl groups can be removed from the resulting desacetoxycephalosporanic esters (e.g. by hydrogenation or hydrolysis) without affecting the bicyclic heterocyclic ring system.

When a 6-aminopenicillanic sulphoxide of general formula I is employed as starting material wherein R_3 represents a group OR_3 , (R_3 being as hereinbefore defined), the silicon-halogen compound, e.g. trimethylchlorosilane or dimethyldichlorosilane, present in the reaction mixture can silylate the carboxy group of the sulphoxide to form, for example, the 6-aminopenicillanic sulphoxide silyl esters of the general formula:—



wherein the various symbols are as hereinbefore defined, or one of Y_1 , Y_2 and Y_3 represents the 6-substituted amino - penicillanylcarbonyloxy group attached to the silicon

atom in formula IV. Such new silyl esters, for example the trimethylsilyl ester of benzylpenicillin sulphoxide (i.e. 6 - phenylacetamido - penicillanic acid sulphoxide), the dimethylchlorosilyl ester of benzylpenicillin sulphoxide, di(benzylpenicillin sulphoxide)dimethylsilyl ester, the trimethylsilyl ester of phenoxymethylpenicillin sulphoxide, the dimethylchlorosilyl ester of phenoxymethylpenicillin sulphoxide and di(phenoxymethylpenicillin sulphoxide)dimethylsilyl ester, form a feature of the invention. The silyl group $—SiY_1Y_2Y_3$ can be easily split off from such products by simple hydrolysis to yield the corresponding 7-substituted amino-desacetoxycephalosporanic acids.

The 6-aminopenicillanic sulphoxide derivatives of formula I employed as starting materials in the process of the present invention can be obtained by treatment of the corresponding 6-aminopenicillanic acid derivatives with an oxidizing agent by known methods. For this purpose the 6-aminopenicillanic acid derivative is treated with a substance affording active oxygen such as sodium periodate, a peracid, hydrogen peroxide or iodosobenzene, in a proportion sufficient to oxidise the thiazolidine sulphur atom to an $—SO—$ group. The initial compound can be the free acid, a salt, ester or amide thereof, suitably dissolved in a solvent which is inert under the reaction conditions used. The resulting sulphoxide can be readily recovered from the reaction mixture by methods known *per se*.

When the 6-aminopenicillanic acid derivative includes a group which would also be affected by the oxidizing agent, it is possible to obtain the desired sulphoxide by starting with a 6-aminopenicillanic acid derivative that can be sulphoxidised without affecting an alternative group present thereon, and then to replace the unaffected group after sulphoxidation of the thiazolidine ring by the desired but more sensitive group. For example, a 6N-acylamidopenicillanic sulphoxide derivative obtained directly by sulphoxidation can be converted into another 6N-acylsulphoxide derivative with a more sensitive acyl group by deacylation in manner known *per se* leading to 6-aminopenicillanic acid sulphoxide, or salt, ester or amide thereof, followed by reacylation of the free 6-amino group with the appropriate acyl group by methods known *per se*. Alternatively, the required 6-aminopenicillanic sulphoxide derivative can be prepared by protecting in a suitable manner a labile group of the starting 6-aminopenicillanic acid derivative, followed by oxidation to the sulphoxide derivative and removal of the protecting group.

Deacylation of an N-acylamido group or the removal of a protecting group on the amino nitrogen atom of the 6-aminopenicill-

lanic sulphoxide derivative is preferably effected after the ring enlargement reaction.

A preferred method is to start from an aminopenicillanic sulphoxide derivative, obtained from a penicillin which can easily be prepared by fermentation, such as benzylpenicillin or phenoxymethylpenicillin. After the ring enlargement to the corresponding desacetoxycephalosporanic derivative its 7-N-acyl group can be replaced by another desired one by deacylation and reacylation of the resulting amino group by methods known *per se*.

The following Examples illustrate the invention.

EXAMPLE 1

Preparation of the potassium salt of 7-phenylacetamidodesacetoxycephalosporanic acid

20 g. (0.057 mol) of benzylpenicillin sulphoxide, 14 ml. (0.116 mol) of dimethyldichlorosilane and 112 ml. (1.39 mol) of pyridine were dissolved in 280 ml. of acetonitrile and stirred for 1 hour at room temperature. A mixture of the dimethylchlorosilyl ester of benzylpenicillin sulphoxide and di(benzylpenicillin sulphoxide) dimethylsilyl ester was formed *in situ*. The mixture was then heated at 70°C. for 75 hours. Afterwards the reaction mixture was evaporated to dryness in vacuo. The residue was dissolved in a mixture of 400 ml. of water and 400 ml. of ethyl acetate and the pH adjusted to 1.5 with hydrochloric acid. The ethyl acetate layer was removed, stirred with water and the pH adjusted to 8 with a potassium hydroxide solution, and the aqueous layer washed several times with ethyl acetate. After adjusting the pH of the aqueous solution to 3.3 with hydrochloric acid, it was extracted with ethyl acetate and the ethyl acetate layer was then extracted several times with water in order to remove unreacted benzylpenicillin sulphoxide. From the ethyl acetate layer the potassium salt of 7-phenylacetamidodesacetoxycephalosporanic acid was obtained by stirring with water, adjustment of the pH to 7 with a potassium hydroxide solution, treatment of the aqueous layer with decolorizing charcoal and removal of the water by azeotropic distillation with *n*-butanol; it crystallized when the butanol solution was concentrated. Yield 4.15 g. (0.011 mol). The mother liquor contained more of the final product.

The structure was confirmed by IR and PMR spectra. The analysis of the PMR spectrum was as follows:

PMR (as the potassium salt in D₂O, values in ppm):

δ: 1.93 (s, 3); 3.15 (d, J=18 Hz, 1); 3.50 (d, J=18 Hz, 1); 3.67 (s, 2); 5.04 (d, J=4.5 Hz, 1); 5.61 (d, J=4.5 Hz, 1); 7.41 (s, 5).

The sodium salt of 2,2 - dimethyl - 2 - silapentyl - 5 - sulphonate was used as an internal standard.

EXAMPLE 2

Preparation of the potassium salt of 7-phenylacetamidodesacetoxycephalosporanic acid

A mixture of 20 g. (0.057 mol) of benzylpenicillin sulphoxide, 43 ml. (0.34 mol) of trimethylchlorosilane, 112 ml. (1.39 mol) of pyridine and 280 ml. of acetonitrile was heated at a temperature of 85°C. for 20 hours. The reaction mixture was evaporated under reduced pressure to dryness. The residue was dissolved in a mixture of 200 ml. of water and 200 ml. of ethyl acetate and the pH adjusted to 1.5 with hydrochloric acid. The ethyl acetate layer was removed, stirred with water and the pH adjusted to 8 with a potassium hydroxide solution, and the aqueous layer washed several times with ethyl acetate. After adjusting the pH of the aqueous solution to 3.3 with hydrochloric acid, it was extracted with ethyl acetate and the ethyl acetate layer was then extracted several times with water in order to remove unreacted benzylpenicillin sulphoxide. From the ethyl acetate layer potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid was obtained by stirring with water, adjustment of the pH to 7 with potassium hydroxide solution, treatment of the aqueous layer with decolorizing charcoal and removal of the water by azeotropic distillation with *n*-butanol; it crystallized when the butanol solution was concentrated. Yield 2.7 g. (0.005 mol). The mother liquor contained more of the final product.

The structure was confirmed by IR and PMR spectra.

EXAMPLE 3

Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid.

2.5 g. (0.0075 mol) of benzylpenicillin sulphoxide, 1.7 ml. (0.014 mol) of dimethyldichlorosilane and 24 ml. (0.19 mol) of dimethylaniline were dissolved in 35 ml. of chlorobenzene, and the mixture was heated at 85°C. for 8 hours. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in a mixture of 50 ml. of water and 50 ml. of ethyl acetate and the pH adjusted to 1.5 with hydrochloric acid. The ethyl acetate layer was removed, stirred with water and the pH adjusted to 8 with a potassium hydroxide solution, and the aqueous layer washed several times with ethyl acetate. After adjustment of the pH of the aqueous solution to 3.3 with hydrochloric acid, it was extracted with ethyl acetate and the ethyl acetate layer was then extracted several times with water in order to remove unreacted benzylpenicillin sulphoxide. From the

ethyl acetate layer the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid was obtained by stirring with water, adjustment of the pH to 7 with a potassium hydroxide solution, treatment of the aqueous layer with decolorizing charcoal and removal of the water by azeotropic distillation with *n*-butanol.

- 10 The potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid was filtered off. The structure was confirmed by the NMR spectrum.

EXAMPLE 4

- 15 Preparation of the benzyl ester of 7 - phenylacetamido - desacetoxycephalosporanic acid

A solution composed of 4.4 g. (0.01 mol) of the benzyl ester of benzylpenicillin sulphoxide, 17 ml. (0.21 mol) of pyridine, 3.0 ml. (0.025 mol) of dimethyldichlorosilane and 50 ml. of acetonitrile was heated for 16 hours in a water bath maintained at a temperature of 80°C. The reaction mixture was then concentrated under reduced pressure. The residue obtained was taken up in ethyl acetate. The resulting solution was washed with 1N hydrochloric acid and water, and evaporated to dryness.

- 20 According to thin layer chromatography, the residue consisted of the starting compound and an apolar product. It was dissolved in chloroform. By adding some diethyl ether, the starting compound was precipitated, and it was filtered off. After addition of some more diethyl ether another compound was precipitated, which according to the PMR and the UV spectra was the benzyl ester of 7 - phenylacetamido - desacetoxycephalosporanic acid.

- 40 The analysis of the PMR spectrum was as follows:

PMR (in CDCl₃, values in ppm):

- 45 δ : 2.10 (s, 3); 3.20 (d, J=18 Hz, 1); 3.40 (d, J=18 Hz, 1); 3.63 (s, 2); 4.93 (d, J=5 Hz, 1); 5.28 (s, 2); 5.78 (q, J=5 and 9.5 Hz, 1); 6.63 (d, J=9.5 Hz, 1); 7.35 (s, 5); 7.41 (s, 5).

Tetramethylsilane was used as an internal standard.

- 50 The data are in accordance with those of a reference compound, prepared by reacting 7 - phenylacetamido - desacetoxycephalosporanic acid with benzyl bromide in dimethyl formamide as solvent.

EXAMPLE 5

- 55 Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

- 60 (a) Preparation of the trimethylsilyl ester of 6 - phenylacetamido - penicillanic acid sulphoxide

To a suspension of 2.5 g. (7.15 mmol) of benzylpenicillin sulphoxide in 30 ml. of dry tetrachloromethane was added rapidly a solution of 1 ml. (7.2 mmol) of triethylamine in 10 ml. of carbon tetrachloride. After stirring for 15 minutes, a solution of 1 ml. (7.9 mmol) trimethylchlorosilane in 10 ml. of tetrachloromethane was added slowly at room temperature. After further stirring for 90 minutes at room temperature, the reaction mixture was concentrated to a volume of about 20 ml. and filtered. The precipitate containing triethylamine hydrochloride was washed three times with dry tetrachloromethane. From the combined filtered tetrachloromethane solutions a PMR spectrum was recorded. The analysis of this spectrum was as follows:

PMR (in tetrachloromethane, values in ppm):

- 80 δ : 0.32 (s, 9); 1.13 (s, 3); 1.63 (s, 3); 3.53 (s, 2); 4.54 (s, 1); 4.95 (d, 1, J=5 Hz); 5.90 (q, 1, J=5 Hz and 11 Hz); 7.27 (d, 1, J=11 Hz); 7.30 (s, 5).

Tetramethylsilane was used as an internal standard.

By totally evaporating the filtrate the compound 6 - phenyl - acetoamidopenicillanic trimethylsilyl ester sulphoxide was obtained in an amorphous state.

- (b) Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid.

A mixture of 1.22 g. (0.0029 mol) of the trimethylsilyl ester of benzylpenicillin sulphoxide, 6 ml. (0.075 mol) of pyridine, 0.35 ml. (0.0029 mol) of dimethyldichlorosilane and 14 ml. of acetonitrile was heated at a temperature of 80°C. for 16 hours. Then the reaction mixture was diluted with 13 ml. of water and 37 ml. of 2N hydrochloric acid and the pH adjusted to 1.5.

After following a procedure similar to that described in Example 1, the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid was obtained; its presence was detected by a bio-autogram.

EXAMPLE 6

- Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

A mixture composed of 2.5 g. (0.0072 mol) of benzylpenicillin sulphoxide, 1.7 ml. (0.014 mol) of dimethyldichlorosilane and 35 ml. (0.43 mol) of pyridine was heated for 7 hours at a temperature of 85°C. The reaction mixture was evaporated under reduced pressure to dryness. The residue was dissolved in a mixture of 50 ml. of water and 50 ml. of ethyl acetate and the pH adjusted to 1.5 with hydrochloric acid. The ethyl acetate layer was removed, and the same procedure as is described in Examples 1 and 2 was followed

to yield 130 mg. of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid.

- 5 The structure was confirmed by IR and PMR spectra.

EXAMPLE 7

Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

- 10 20 g. (0.057 mol) of benzylpenicillin sulphoxide, 14 ml. (0.116 mol) of dimethyldichlorosilane and 140 ml. (1.40 mol) of α -picoline were dissolved in 280 ml. of 1,2-dichloroethane and the mixture was heated at 80°C. for 24 hours. A mixture of a sulphoxide dimethylchlorosilyl ester and a di-sulphoxide dimethylsilyl ester was formed *in situ*. The reaction mixture was cooled to 0°C. and stirred with an aqueous phosphate buffer solution of pH 7. The pH of the mixture was then adjusted to 7.2 with a potassium hydroxide solution. The aqueous layer was separated, adjusted to a pH of 1.5 with 4N hydrochloric acid and extracted with ethyl acetate.
- 25 The ethyl acetate layer was extracted with water of pH 7.2. The water from the aqueous extract was removed by azeotropic distillation *in vacuo* with *n*-butanol. The final volume of the remaining solution was about 200 ml.
- 30 After standing overnight at 0°C., 12.6 g. of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid had been precipitated; the product, as analysed by NMR spectroscopy, contained 10–20% by weight of *n*-butanol.

EXAMPLE 8

Preparation of the potassium salt of 7 - phenoxyacetamido - desacetoxycephalosporanic acid

- 40 2.6 g. (0.0072 mol) of phenoxymethylpenicillin sulphoxide, 1.75 ml. (0.014 mol) of dimethyldichlorosilane and 17.2 ml. (0.17 mol) of α -picoline were dissolved in 35 ml. of 1,2-dichloroethane and stirred for 1 hour at room temperature. A mixture of the dimethylchlorosilyl ester of phenoxymethylpenicillin sulphoxide and di(phenoxymethylpenicillin sulphoxide)dimethylsilyl ester was formed *in situ*. The mixture was then heated at 80°C. for 16 hours. Afterwards the reaction mixture was cooled to 0°C. and stirred with an aqueous phosphate buffer solution of pH 7. The pH of the mixture was then adjusted to 7.2 with a potassium hydroxide solution.
- 55 The aqueous layer was separated, adjusted to a pH of 1.5 with 4N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was extracted with water of pH 7.2. The water from the aqueous extract was removed by azeotropic distillation *in vacuo* with *n*-butanol. The final volume of the remaining solution was about 25 ml. After

standing overnight at 0°C., 0.46 g. of the potassium salt of 7 - phenoxyacetamido - desacetoxycephalosporanic acid had been precipitated.

The structure was confirmed by IR and PMR spectra. The analysis of the PMR spectrum was as follows:

PMR (in D₂O values in ppm): 70
 8: 2.00 (s, 3); 3.05 (d, J=18 Hz, 1); 3.52 (d, J=18 Hz, 1); 4.58 (s, 2); 5.08 (d, J=4.5 Hz, 1); 5.71 (d, J=4.5 Hz, 1); 6.7–7.4 (m, 5).

The sodium salt of 2,2 - dimethyl - 2 - silapentyl - 5 - sulphonate was used as an internal standard.

EXAMPLE 9

Preparation of 7 - (α - aminophenylacetamido) - desacetoxycephalosporanic acid 80

- (a) Preparation of the potassium salt of 7 - (α - benzyloxycarbamoyl - phenylacetamido) - desacetoxycephalosporanic acid. 85
 2.6 g. (0.0072 mol) of 6 - (α - benzyloxycarbamoylphenylacetamido) - penicillanic acid sulphoxide (prepared as described in Procedure C hereinafter), 1.75 ml. (0.014 mol) of dimethyldichlorosilane and 17.2 ml. (0.17 mol) of α -picoline were dissolved in 35 ml. of 1,2-dichloroethane, and the mixture was heated at 80°C. for 24 hours. The reaction mixture was then concentrated to dryness *in vacuo*. The residue was dissolved in a mixture of 400 ml. of water and 100 ml. of ethyl acetate and the pH was adjusted to 8.0 with a potassium hydroxide solution. The aqueous layer was separated, treated with decolorising charcoal and extracted with ethyl acetate at pH 1.5. The ethyl acetate layer was stirred with water of pH 7.2. From the aqueous extract the water was removed by azeotropic distillation *in vacuo* with *n*-butanol. The final volume was 10 ml. After standing overnight at 0°C., 62 mg. of the potassium salt of 7 - (α - benzyloxycarbamoyl - phenylacetamido) - desacetoxycephalosporanic acid had been precipitated.

The structure was confirmed by IR and PMR spectra. The analysis of the PMR spectrum was as follows: 110

PMR (in dimethylsulphoxide—D₆ values in ppm):
 8=1.94 (s, 3); 2.95 (d, J=18 Hz, 1); 3.33 (d, J=18 Hz, 1); 4.82 (d, J=5 Hz, 1); 5.06 (s, 2); 5.2–5.7 (m, 2); 7.30 (s, 10); 7.93 (d, J=8 Hz, 1); 9.06 (d, J=8 Hz, 1).

Tetramethylsilane was used as an internal standard. 120

- (b) The preparation of 7 - (α - aminophenylacetamido) - desacetoxycephalosporanic acid.

5 A suspension of 2.0 g. of a 30% palladium-barium carbonate catalyst in 25 ml. of an aqueous phosphate buffer of 7.5 was stirred in a hydrogen atmosphere. After one hour a suspension of 0.5 g. of the potassium salt of 7 - (α - benzyloxycarbamoyl - phenylacetamido) - desacetoxycephalosporanic acid in 20 ml. of acetone was added. The mixture was stirred in the hydrogen atmosphere for 4 hours. The catalyst was removed by filtration. A thin layer chromatogram on silica gel of the filtrate developed by a mixture of butyl acetate, butanol, acetic acid, methanol and water (16:3:8:1:5) on an *Escherichia coli* inoculated agar plate treated with penicillinase showed one single biologically active spot which had exactly the same Rf value as an authentic sample of 7 - (α - aminophenylacetamido) - desacetoxycephalosporanic acid.

EXAMPLE 10

25 Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

30 A mixture of 2.5 g. (0.0071 mol) of benzylpenicillin sulphoxide, 35 ml. of 1,2-dichloroethane, 1.75 ml. (0.014 mol) of dimethyldichlorosilane and about 14 ml. (0.174 mol) of a base as specified below was heated at 80°C. for 24 hours. The reaction mixture was cooled and treated with water. After adjusting the pH to 7.2 with a potassium hydroxide solution, the organic layer was extracted with a phosphate buffer solution of pH 7.2.

35 The amount of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid in the combined aqueous layers was determined by a direct microbiological assay using *Escherichia coli* as the test micro-organism and is expressed in the table hereafter in mol percentages related to the quantity of starting material and according to the base employed:

	Base	mol percentage
	2-dimethylaminopyridine	49%
	α -picoline	47%
50	3-methylisoquinoline	47%
	2,5-dimethylpyridine	46%
	hexamethylenetetramine	19%

EXAMPLE 11

55 Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

60 The experiment described in Example 10 was repeated with the difference that 35 ml of chloroform, 5.8 ml. (0.0458 mol) of trimethylchlorosilane and N-methylaniline (15.6 ml) were used. The yield of the potassium salt of 7 - phenylacetamido - desacetoxy-

cephalosporanic acid was 13% as expressed in a mol percentage.

EXAMPLE 12

65 Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

70 A mixture of 2.5 g. (0.0071 mol) of benzylpenicillin sulphoxide, 2.5 ml. (0.035 mol) of pyridine, 4.4 ml. (0.035 mol) of trimethylchlorosilane and 40 ml. of benzylocyanide was heated at 80°C. for 24 hours. The yield of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid, determined by microbiological assay as mentioned in Example 10, was 10%.

EXAMPLE 13

80 Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

85 A mixture of 1.05 g. (3 mmol) of benzylpenicillin sulphoxide, 14 ml. of acetonitrile, 6 ml. (0.074 mol) of pyridine and 0.5 g. (2.8 mmol) of dichloromethyldimethylchlorosilane was stirred at a temperature of 80°C. for 16 hours. The mixture was then poured into a cold mixture of 75 ml. of a 1 molar solution of hydrochloric acid and 25 ml. of ethyl acetate. The ethyl acetate layer was separated and the aqueous layer extracted twice with 25 ml of ethyl acetate. The combined ethyl acetate layers were washed twice with 25 ml. of water.

90 The potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid was obtained from the ethyl acetate solution by stirring with water adjusting the pH to 7 with a potassium hydroxide solution, treatment of the aqueous layer with charcoal and removal of the water by azeotropic distillation with *n*-butanol. The potassium salt crystallized upon concentration. Yield 130 mg (0.35 mmol).

EXAMPLE 14

105 Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

110 The experiment described in Example 13 was repeated with 0.5 g. (3.1 mmol) of methylpropyldichlorosilane instead of dichloromethyldimethylchlorosilane. Yield 140 mg (0.38 mmol) of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid.

EXAMPLE 15

120 Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

The experiment described in Example 13 was repeated with 0.6 ml (2.9 mmol) of diphenyldichlorosilane instead of dichloromethyldimethylchlorosilane. Yield 120 mg

(0.32 mmol) of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid.

7 - phenoxyacetamido - desacetoxycephalosporanic acid had been precipitated. Its structure was confirmed by IR and PMR spectra.

EXAMPLE 16

5 Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

A mixture of 90 g. (0.257 mol) of benzylpenicillin sulphoxide, 210 ml. (1.66 mol) of trimethylchlorosilane, 900 ml. (9 mol) of α -picoline and 900 ml. of chloroform was heated for 20 hours at a temperature of 83°C. The reaction mixture was cooled and stirred with water. The pH of the mixture was adjusted to 7.5 with a potassium hydroxide solution. The amount of the potassium salt of phenylacetamido-desacetoxycephalosporanic acid obtained was 55 mol % as determined by microbiological assay using *Escherichia coli* as the test microorganism.

The aqueous layer was separated, adjusted to a pH of 1.5 with 4N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate was then replaced by *n*-propanol (925 ml.) and the propanol solution cooled to about 0°C. Addition of 3.5 ml. of water and 100 ml. of a 1.25 molar solution of the potassium salt of 2-ethylcaproic acid in butyl acetate gave a precipitate of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid. Yield 57 g. (0.15 mol) consisting of 78% of the potassium salt of Δ^3 - 7 - phenylacetamido - desacetoxycephalosporanic acid and about 12% of the potassium salt of Δ^2 - 7 - phenylacetamido - desacetoxycephalosporanic acid. The mother liquor contained more of the desacetoxycephalosporanic derivatives. After separation of the Δ^3 -compound, Δ^2 -compound can be converted into the Δ^3 -product by usual methods.

EXAMPLE 17

45 Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

1.3 g. (0.036 mol) of phenoxymethylpenicillin sulphoxide, 1.4 ml. (0.011 mol) of dimethyldichlorosilane and 13 ml. (0.13 mol) of α -picoline were dissolved in 13 ml. of chloroform and the mixture was heated at 80°C for 24 hours. The reaction mixture was cooled and stirred with an aqueous phosphate buffer solution of pH 7. The pH was then adjusted to 7.2 with a potassium hydroxide solution. The aqueous layer was separated, adjusted to a pH of 1.5 with a hydrochloric acid solution and extracted with ethyl acetate. The ethyl acetate was then replaced by 16 ml. of *n*-propanol. To the cooled solution was added 4 ml. of a 1.25 molar solution of potassium 2-ethylcaproate in butyl acetate. After standing overnight at 0°C. 0.62 g. (0.0016 mol) of the potassium salt of

EXAMPLE 18

Preparation of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid

A mixture of 2.5 g. (0.0071 mol) of benzylpenicillin sulphoxide, 35 ml. of a solvent as specified below, 14 ml. (0.172 mol) of pyridine and 1.75 ml. (0.014 mol) of dimethyldichlorosilane was heated at 80°C for 8 hours. The reaction was then terminated and the resulting reaction mixture was cooled and treated with water. After adjusting the pH to 7.2 with a potassium hydroxide solution, the organic layer was extracted with a phosphate buffer solution of pH 7.2.

The amount of the potassium salt of 7 - phenylacetamido - desacetoxycephalosporanic acid in the combined aqueous layers was determined by a microbiological assay using *Escherichia coli* as the testing microorganism and is expressed in the table hereafter in mol percentages related to the quantity of the starting material and according to the solvent employed.

Solvent	Yield	
1,2-dichloroethane	20—22%	
benzylcyanide	20—22%	
dimethylformamide	16%	
acetonitrile, dioxane, nitrobenzene, pyridine, anisole, benzene, benzonitrile and carbon tetrachloride	13—16%	95

EXAMPLE 19

Preparation of 7 - (2 - ethoxynaphthamido) - desacetoxycephalosporanic acid

A mixture of 2.6 g. (6 mmol) of 2 - ethoxynaphthylpenicillin sulphoxide, 20 ml. of chloroform, 20 ml. (200 mmol) of α -picoline and 4.8 ml. (36 mmol) of trimethylchlorosilane was refluxed for 16 hours. The reaction mixture was then poured into a cold mixture of 50 ml. of water and 30 ml. of chloroform. After adjusting the pH to 1.5 with a hydrochloric acid solution, the aqueous layer was extracted with 50 ml. of chloroform and the combined chloroform extracts washed with water and evaporated to dryness. The residue (1.4 g.) was analysed by NMR, using 2,6-dichloroacetophenone as an internal standard; it contained 21% of unchanged sulphoxide, 45% of the desired 7 - (2 - ethoxynaphthamido) - desacetoxycephalosporanic acid and 8% of the corresponding Δ^2 -compound.

EXAMPLE 20

Preparation of 7 - phenylacetamidodesacetoxycephalosporanic acid

A mixture of 5.2 g. (10 mmol) of the saccharimide of benzylpenicillin sulphoxide,

40 ml. of chloroform, 10 ml. (102 mmol) of α -picoline and 1.1 ml. (10 mmol) of dimethyldichlorosilane was heated at a temperature of 80°C. for 16 hours, after which
 5 60 ml of chloroform and 100 ml. of water were added. The pH was adjusted to 1.5 with a hydrochloric acid solution, the organic layer was separated, washed with water and evaporated to dryness. The residue thus obtained was taken up in 60 ml of tetrahydrofuran and a solution of 4 g. of sodium bicarbonate in 60 ml. of water was added to cause splitting of the saccharimide group.
 10 After stirring the mixture for 2 hours in a nitrogen atmosphere, 100 ml. of water were added. The tetrahydrofuran was removed by evaporation. The remaining solution was adjusted to pH 7 and washed with ethyl acetate. The presence of 7 - phenylacetamido - desacetoxycephalosporanic acid in the solution was detected by means of an bioautogram.

The saccharimide of benzylpenicillin sulphoxide employed as starting material was prepared as follows:—

25 17.6 g. (50 mmol) of benzylpenicillin sulphoxide was dissolved in 750 ml. of dichloromethane and 5 g. (50 mmol) of triethylamine. The solution was cooled to 3°C. 10.1 g. (50 mmol) of γ -saccharin chloride was added and the mixture stirred for 30 minutes.
 30 After standing overnight in a refrigerator, the solution was washed two times with 350 ml. of cold water, 500 ml. of a pH 7 phosphate buffer, dried over sodium sulphate and at 40°C. evaporated to dryness.

35 According to NMR analysis the residue was the saccharide of benzylpenicillin sulphoxide; yield 33.7 g.

EXAMPLE 21

40 Preparation of 7 - phenoxyethyl - desacetoxycephalosporanic acid

A mixture of 36.6 g. (0.1 mol) of phenoxyethylpenicillin sulphoxide, 360 ml. (3.6 mol) of α -picoline and 81 ml. (0.64 mol) of trimethylchlorosilane in 360 ml. of chloroform was stirred at room temperature for 1 hour. The trimethylsilyl ester of phenoxyethylpenicillin sulphoxide was formed *in situ*. The mixture was heated at 80°C. for
 45 24 hours, poured into water and the pH adjusted to 7.9 by addition of a sodium hydroxide solution. The aqueous layer was washed with 500 ml. of ethyl acetate, treated with charcoal and, after filtration in the presence of 250 ml. of ethyl acetate, the pH was
 50 adjusted to 1.5. The aqueous layer was extracted once more with 250 ml. of ethyl acetate and the ethyl acetate layers after washing with 500 ml. of water evaporated to dryness. The residue was triturated with ethyl acetate giving 8.31 g. (25% yield) of phenoxyethyl - desacetoxycephalosporanic acid.

The following Procedures illustrate the preparation of penicillanic acid sulphoxide start-

ing materials can be employed in the process of the present invention. 65

Procedure A

Preparation of benzylpenicillin sulphoxide.

A mixture of 75 g. (0.19 mol) of the potassium salt of benzylpenicillin, 1 l. of water and 45.5 g. (0.20 mol) of sodium metaperiodate was stirred for 2 hours at 25°C. temperature. After cooling to 0°C., the reaction mixture was extracted at pH 1 with chloroform. The chloroform layer was concentrated to a volume of about 150 ml. and 400 ml. of diethyl ether were added. The precipitated benzylpenicillin sulphoxide was filtered off, washed with diethyl ether and dried under reduced pressure. The yield was 64 g. (90%). Decomposition temperature: 142.5—143.5°C.

Analysis of the PMR spectrum was as follows:

PMR (as a sodium salt in D₂O, values in ppm):

8: 1.24 (s, 3), 1.67 (s, 3); 3.67 (s, 2); 4.42 (s, 1); 5.21 (d, J=4.5 Hz, 1); 5.94 (d, J=4.5 Hz, 1); 7.39 (s, 5).

The sodium salt of 2,2 - dimethyl - 2 - silapentyl - 5 - sulphonate was used as an internal standard. 90

Procedure B

Preparation of 6 - (α - aminophenylacetamido) - penicillanic acid sulphoxide

(a) Preparation of the toluene - *p* - sulphonic acid addition salt of 6-aminopenicillanic sulphoxide. 95

A mixture of 56 g. (0.16 mol) of benzylpenicillin sulphoxide, 500 ml. of methylene chloride, 71.5 ml. (0.57 mol) of dimethyldichlorosilane and 16 ml. (0.13 mol) of dimethyldichlorosilane was stirred for 2 hours at room temperature. The reaction mixture was then cooled to -50°C. and 36 g. (0.17 mol) of phosphorus pentachloride were added. The mixture was stirred for 2.5 hours at a temperature of -30°C. The temperature was lowered to -70°C., and 250 ml. (2.8 mol) of 2-butanol were added; then the mixture was stirred for 75 minutes at -40°C. To the solution 86 g. (0.45 mol) of toluene - *p* - sulphonic acid monohydrate in 170 ml. of methanol were added. The temperature was maintained at 0°C. for 15 minutes, and this lead to the crystallization of 6-aminopenicillanic acid sulphoxide toluene - *p* - sulphonate. The precipitate was filtered off, washed with acetone and diethyl ether and dried under reduced pressure. The yield was 43 g.

The analysis of the PMR spectrum was as follows: 120

PMR (in CDCl₃/dimethyl sulphoxide-d₆).
 8: 1.27 (s, 3); 1.67 (s, 3); 2.37 (s, 3); 4.55 (s, 1); 5.23 (d, J=5 Hz, 1); 5.35 (d, J=5 Hz, 1); 7.1—7.9 (m, 8). 125

Tetramethylsilane was used as an internal standard.

(b) Preparation of 6-aminopenicillanic acid sulphoxide.

5 A mixture composed of 1.0 g. (0.0025 mol) of 6-aminopenicillanic acid sulphoxide toluene - *p* - sulphonate, 0.34 ml. (0.0025 mol) of triethylamine and 3 ml. of a 85% solution of isopropanol was stirred for 30 minutes at 20°C. The precipitated 6-aminopenicillanic acid sulphoxide was filtered off. The yield amounted to 552 mg. of product (96%). The decomposition temperature was 185—187°C.

15 The analysis of the PMR spectrum was as follows:

PMR (as the sodium salt in D₂O):

8: 1.29 (s, 3); 1.69 (s, 3); 4.39 (s, 1); 4.89 (d, 1, J=4.5 Hz); 5.27 (d, 1, J=4.5 Hz).

The sodium salt of 2,2 - dimethyl - 2 - silapentyl - 5 - sulphonate was used as an internal standard.

(c) Preparation of 6 - (α - aminophenylacetamido)penicillanic acid sulphoxide.

25 5.3 ml. (0.044 mol) of dimethyldichlorosilane were added to a mixture of 5 g. (0.021 mol) of 6 - aminopenicillanic acid sulphoxide, 5.9 ml. (0.042 mol) of triethylamine, 3.1 ml. (0.024 mol) of dimethylaniline and 65 ml. of methylene chloride. After stirring at 25°C. for 1 hour, the mixture was cooled to 16°C. and 4.25 g. of α-phenylglycyl chloride hydrochloride (0.021 mol) were added in portions over a period of 15 minutes. After stirring for 2.5 hours at 16°C., the reaction mixture was poured into 160 ml. of ice-water. The aqueous layer was brought to pH 3.5 with triethylamine and 6 g. (0.027 molo) of β-naphthalene sulphonic acid in water were added. The pH was brought to 2.0 with sulphuric acid. After concentration the precipitate was filtered off and dried. The resulting solid was suspended in 90% aqueous isopropanol and triethylamine was added until the pH was 5.8. The solid material was filtered off and stirred with diethyl ether. Yield 1.1 g. of crystalline 6 - (α - aminophenylacetamido) - penicillanic acid sulphoxide (confirmed by NMR).

Procedure C

Preparation of 6 - (α - benzyloxycarbamoylphenylacetamido) - penicillanic acid sulphoxide

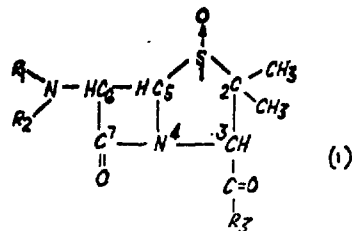
55 483 mg. (1 mmol) of benzyloxycarbonyl-ampicillin (i.e. α - benzyloxycarbamoyl - benzylpenicillin), the preparation of which has been described in J. Chem. Soc. 1962 II, 1440, were dissolved in 5 ml. of a 3% solution of sodium bicarbonate in water. A solu-

tion of 0.34 g. (1.5 mmol) of periodic acid in 2.3 ml. of water, the pH of which was brought to 5.5 with a 4N sodium hydroxide solution, was added. After stirring for 15 hours at room temperature, the formed sodium iodate precipitate was filtered off and washed with water. To the aqueous layer 20 ml. of ethyl acetate were added and the pH was adjusted to 2.0 with 4N hydrochloric acid. The ethyl acetate layer was separated and the aqueous layer was extracted twice with 10 ml. of ethyl acetate. The collected ethyl acetate extracts were washed three times with 5 ml. of water and dried on Drierite. After filtration, the ethyl acetate solution was concentrated to a volume of about 1 or 2 ml. and diethyl ether was added until no more crystalline solid precipitated. The precipitate was filtered off and washed with diethyl ether. The yield amounted to 400 mg. of benzyloxycarbonyl-ampicillin sulphoxide, i.e. 6 - (α - benzyloxycarbamoylphenylacetamido)penicillanic acid sulphoxide. The structure was confirmed by NMR analysis.

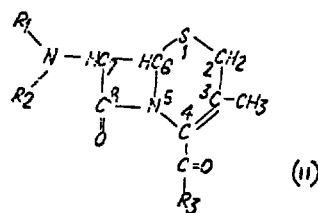
WHAT WE CLAIM IS:—

1. Process for the transformation of a 6-substituted amino-penicillanic sulphoxide in the form of acid or derivative thereof, including a thiocarboxylic acid derivative, salt, ester or amide, into a 7-substituted amino-desacetoxycephalosporanic derivative characterised in that the penicillanic sulphoxide compound is heated up to a temperature not greater than 160°C. under anhydrous conditions in the presence of at least one nitrogen-containing organic base and a silicon compound having a silicon-halogen bond, at least five moles of base being present for each mole of penicillanic sulphoxide compound.

2. Process according to claim 1 wherein the penicillanic sulphoxide starting material is of the general formula:—



and the 7-substituted amino-desacetoxycephalosporanic acid derivative obtained as product is of the general formula:—



Tetramethylsilane was used as an internal standard.

(b) Preparation of 6-aminopenicillanic acid sulphoxide.

- 5 A mixture composed of 1.0 g. (0.0025 mol) of 6-aminopenicillanic acid sulphoxide toluene - *p* - sulphonate, 0.34 ml. (0.0025 mol) of triethylamine and 3 ml. of a 85% solution of isopropanol was stirred for 30 minutes at 20°C. The precipitated 6-amino-
10 penicillanic acid sulphoxide was filtered off. The yield amounted to 552 mg. of product (96%). The decomposition temperature was 185—187°C.

- 15 The analysis of the PMR spectrum was as follows:

PMR (as the sodium salt in D₂O):

- 8: 1.29 (s, 3); 1.69 (s, 3); 4.39 (s, 1);
20 4.89 (d, 1, J=4.5 Hz); 5.27 (d, 1, J=4.5 Hz).

The sodium salt of 2,2 - dimethyl - 2 - silapentyl - 5 - sulphonate was used as an internal standard.

- 25 (c) Preparation of 6 - (α - aminophenylacetamido)penicillanic acid sulphoxide.

- 5.3 ml. (0.044 mol) of dimethyldichlorosilane were added to a mixture of 5 g. (0.021 mol) of 6 - aminopenicillanic acid sulphoxide, 5.9 ml. (0.042 mol) of triethylamine, 3.1 ml. (0.024 mol) of dimethylaniline and 65 ml. of methylene chloride. After stirring at 25°C. for 1 hour, the mixture was cooled to 16°C. and 4.25 g. of α-phenylglycyl chloride hydrochloride (0.021 mol) were added in portions over a period of 15 minutes. After stirring for 2.5 hours at 16°C., the reaction mixture was poured into 160 ml. of ice-water. The aqueous layer was brought to pH 3.5 with triethylamine and 6 g. (0.027 molo) of β-naphthalene sulphonic acid in water were added. The pH was brought to 2.0 with sulphuric acid. After concentration the precipitate was filtered off and dried. The resulting solid was suspended in 90% aqueous isopropanol and triethylamine was added until the pH was 5.8. The solid material was filtered off and stirred with diethyl ether. Yield 1.1 g. of crystalline 6 - (α - aminophenylacetamido) - penicillanic acid sulphoxide (confirmed by NMR).
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Procedure C

Preparation of 6 - (α - benzyloxycarbamoylphenylacetamido) - penicillanic acid sulphoxide

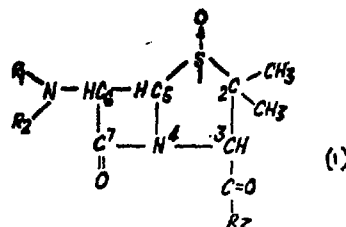
- 55 483 mg. (1 mmol) of benzyloxycarbonyl-ampicillin (i.e. α - benzyloxycarbamoyl - benzylpenicillin), the preparation of which has been described in J. Chem. Soc. 1962 II, 1440, were dissolved in 5 ml. of a 3% solution of sodium bicarbonate in water. A solu-
60

tion of 0.34 g. (1.5 mmol) of periodic acid in 2.3 ml. of water, the pH of which was brought to 5.5 with a 4N sodium hydroxide solution, was added. After stirring for 15 hours at room temperature, the formed sodium iodate precipitate was filtered off and washed with water. To the aqueous layer 20 ml. of ethyl acetate were added and the pH was adjusted to 2.0 with 4N hydrochloric acid. The ethyl acetate layer was separated and the aqueous layer was extracted twice with 10 ml. of ethyl acetate. The collected ethyl acetate extracts were washed three times with 5 ml. of water and dried on Drierite. After filtration, the ethyl acetate solution was concentrated to a volume of about 1 or 2 ml. and diethyl ether was added until no more crystalline solid precipitated. The precipitate was filtered off and washed with diethyl ether. The yield amounted to 400 mg. of benzyloxycarbonyl-ampicillin sulphoxide, i.e. 6 - (α - benzyloxycarbamoylphenylacetamido)penicillanic acid sulphoxide. The structure was confirmed by NMR analysis.

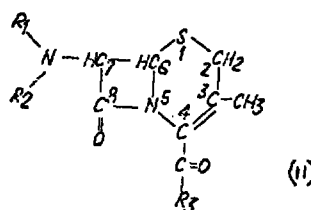
WHAT WE CLAIM IS:—

1. Process for the transformation of a 6-substituted amino-penicillanic sulphoxide in the form of acid or derivative thereof, including a thiocarboxylic acid derivative, salt, ester or amide, into a 7-substituted amino-desacetoxycephalosporanic derivative characterised in that the penicillanic sulphoxide compound is heated up to a temperature not greater than 160°C. under anhydrous conditions in the presence of at least one nitrogen-containing organic base and a silicon compound having a silicon-halogen bond, at least five moles of base being present for each mole of penicillanic sulphoxide compound.

2. Process according to claim 1 wherein the penicillanic sulphoxide starting material is of the general formula:—



and the 7-substituted amino-desacetoxycephalosporanic acid derivative obtained as product is of the general formula:—





wherein R_1 represents a group linked to the nitrogen atom by a carbon or sulphur atom, R_2 represents a hydrogen or a lower alkyl or phenyl(lower)alkyl group, or R_1 and R_2 together with the nitrogen atom to which they are attached represent a heterocyclic group which may carry one or more substituents, and R_3 represents (a) a radical linked to the carbon atom by nitrogen, the nitrogen atom having attached to it atoms or groups selected from hydrogen, lower alkyl and aryl groups, or a combination of sulphonyl and carbonyl groups or a combination of two carbonyl groups on the nitrogen atom may be joined through the agency of a phenyl group; or R_3 represents (b) a group $-SR_4$ wherein R_4 is hydrogen, or a lower alkyl or phenyl group; or R_3 represents (c) a group $-OR_5$ wherein R_5 is hydrogen, a cation which is preferably pharmaceutically-acceptable a lower alkyl group, a cycloalkyl radical containing 4 to 7 carbon atoms, phenyl, a phenylalkyl or diphenyl-alkyl or aroylalkyl group, the alkyl radicals of which contain 1 or 2 carbon atoms, or a stannyl group $(R_6R_7R_8)Sn-$ [wherein R_6 , R_7 and R_8 each represent a lower alkyl group, phenyl, or a phenylalkyl group containing 1 or 2 carbon atoms in the alkyl radical], or a silyl group

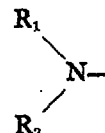


wherein R_9 , R_{10} and R_{11} each represent a halogen atom, a lower alkyl group, phenyl or a phenylalkyl group containing 1 or 2 carbon atoms in the alkyl radical, or one of R_9 , R_{10} and R_{11} represents the group connected to symbol R_3 in formula II and linked via oxygen to the silicon atom, the alkyl and aryl groups within the definitions of symbols R_2 and R_3 optionally carrying as substituents halogen atoms and, in the case of aryl groups, lower alkyl, lower alkoxy or di(lower)alkylamino groups.

3. Process according to claim 2 wherein R_1 represents an alkanoyl group containing up to 20 carbon atoms, a phenyl(lower)alkanoyl, phenoxy(lower)alkanoyl, phenyl(lower)alkyloxycarbonyl, (lower)alkanoylaminocarbonyl, salicyl optionally substituted by one or two halogen atoms, phenoxyphenyl(lower)alkanoyl, isoxazolylcarbonyl, benzoyl, naphthoyl, formyl, oxazolidinyl, phenyl - α - amino(lower)alkanoyl, thienyl- or furyl-(lower)alkanoyl, phenylthio(lower)alkanoyl, 2-benzofuranyl-(lower)alkanoyl, benzene-sulphonyl or 1-piperidinosulphonyl group, the phenyl and heterocyclic radicals of such groups optionally carrying one or more substituents selected from halogen atoms, and lower alkyl, carboxy, phenyl(lower)alkoxy, amino, nitro, cyano, trifluoromethyl and methylthio groups, and R_2 represents hydrogen or a methyl, ethyl, isobutyl or benzyl group, or R_1 and R_2 together

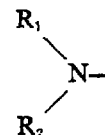
with the nitrogen atom to which they are attached represent a heterocyclic group.

4. Process according to claim 2 or 3 wherein the grouping



represents benzyloxycarbamoyl, phenylacetamido, phenoxyacetamido, 3-acetylureido, (3,5-dichlorosalicyl)amino, 2-phenoxypropionamido, 2-phenoxybutyramido, 2-phenoxyphenylacetamido, 5 - methyl - 3 - phenyl - 4 - isoxazolecarboxamido, 5 - methyl - 3 - (o - chlorophenyl) - 4 - isoxazolecarboxamido, 5 - methyl - 3 - (2,6 - dichlorophenyl) - 4 - isoxazolecarboxamido, 2,6-dimethoxy benzamido, 2 - ethoxy - 1 - naphthamido, 2 - (o - aminobenzamido) - phenylacetamido - N - methyl, 2 - (2 - amino - 5 - nitrobenzamido)phenylacetamido - N - methyl, N-benzylformamido, N - methyl - 2 - phenoxyacetamido, N - methyl - 2 - phenylacetamido, N - ethyl - 2 - phenylacetamido, N - isobutyl - 2 - phenoxyacetamido, 2 - benzylidene - 4,5 - dioxo - 3 - oxazolidinyl, 2-butylsuccinimido, 2,2 - dimethyl - 5 - oxo - 4 - phenyl - 1 - imidazolidinyl, phthalimido, α -aminophenylacetamido, 2-thienylacetamido, 3-thienylacetamido, 2-furylacetamido, 4-chlorophenylacetamido, 3-bromophenylacetamido, 3-nitrophenylacetamido, 4-nitrophenylacetamido, 3 - trifluoromethyl - phenylacetamido, 4-cyanophenylacetamido, 4-methylthiophenylacetamido, 3-chlorophenylthioacetamido, 2-benzofuranylacetamido, benzenesulphonamido, p-bromobenzenesulphonamido, or 1-piperidinosulphonamido.

5. Process according to claim 2, 3 or 4 wherein the grouping



in the penicillanic sulfoxide starting material is phenylacetamido, phenoxyacetamido, α - benzyloxycarbamoyl - phenylacetamido or 2-ethoxynaphthamido, and when the grouping is α - benzyloxycarbamoyl - phenylacetamido removing from the resulting des-acetoxycephalosporanic acid product the benzyloxycarbonyl group on the amino radical.

6. Process according to any one of claims 2 to 5 wherein R_3 represents a grouping OR_6 , wherein R_6 represents a hydrogen atom or a pharmaceutically-acceptable cation, or a lower alkyl or benzyl group, or a benzhydryl group optionally substituted in the benzene ring by one or more methoxy groups.



7. Process according to any one of the preceding claims in which transformation of the penicillanic sulphoxide into the 7-substituted amino-desacetoxycephalosporanic derivative is effected by heating at a temperature between 50°C and 160°C.

8. Process according to claim 7 in which the temperature is between 60° and 130°C.

9. Process according to claim 7 in which the temperature is from 70° to 100°C.

10. Process according to any one of the preceding claims in which the nitrogen-containing organic base has a pKa value of 4 to 10 measured in water at 25°C.

11. Process according to claim 10 in which the base is a secondary or tertiary aliphatic, cycloaliphatic aromatic or heterocyclic amine.

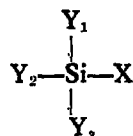
12. Process according to any one of the preceding claims in which the nitrogen-containing base present in the reaction mixture is hexamethylenetetramine, N-methylaniline, dimethylaniline, pyridine or pyridine substituted by one or more lower alkyl or mono- or di-(lower)alkylamino groups, a collidine or quinoline.

13. Process according to any one of claims 1 to 11 in which the nitrogen-containing base present in the reaction mixture is a picoline, 2-ethylpyridine, 2-propylpyridine, 2,3-dimethylpyridine or 2,6-dimethylpyridine.

14. Process according to any one of claims 1 to 11 in which the nitrogen-containing base present in the reaction mixture is α -picoline, 2,5-dimethylpyridine, 2-dimethylaminopyridine or 3-methylisoquinoline.

15. Process according to any one of claims 1 to 14 in which the amount of nitrogen-containing base present in the reaction mixture is ten to seventy moles for each mole of penicillanic sulphoxide.

16. Process according to any one of the preceding claims in which the silicon-halogen compound is of the general formula:—



wherein Y_1 , Y_2 and Y_3 may be the same or different and each represents a halogen atom, a lower alkyl group, or a phenyl or phenyl-alkyl group containing 1 or 2 carbon atoms in the alkyl radical, the said alkyl and phenyl groups optionally carrying substituents such as halogen atoms and, in the case of phenyl groups, lower alkyl, lower alkoxy or di(lower)-alkylamino groups.

17. Process according to claim 16 in which the silicon-halogen compound is one in which X represents a chlorine atom.

18. Process according to claim 16 in which the silicon-halogen compound is triethylchlorosilane, methyltrichlorosilane, triethyl-

bromosilane, tri - n - propylchlorosilane, triethylbromosilane, tri - n - propyl - bromosilane, bromomethyl - dimethylchlorosilane, tri - n - butyl - chlorosilane, methyldiethylchlorosilane, dimethylethylchlorosilane, phenyldimethylbromosilane, benzylmethylethylchlorosilane, phenylethylmethylchlorosilane, triphenylchlorosilane, tri - o - tolyl - chlorosilane and tri - p - dimethylaminophenyl - chlorosilane.

19. Process according to claim 16 or 17 in which the silicon-halogen compound is trimethylchlorosilane or dimethyldichlorosilane.

20. Process according to any one of the preceding claims in which the silicon-halogen compound is present in molar excess in relation to the penicillanic sulphoxide.

21. Process according to claim 20 in which 3 to 15 moles of silicon-halogen compound is present per mole of penicillanic sulphoxide.

22. Process according to any one of claims 1 to 21 in which the transformation of the penicillanic sulphoxide is carried out in an inert organic solvent medium.

23. Process according to claim 22 in which the organic solvent is benzyl cyanide or a halogenoalkane.

24. Process according to claim 23 in which the halogenoalkane is 1,2-dichloroethane, 1,1-dichloroethane, 1 - bromo - 1 - chloroethane, 1,2,3-trichloropropane or chloroform.

25. Process according to claim 22, 23 or 24 in which the solvent employed is benzyl cyanide, 1,2-dichloroethane, 1 - bromo - 1 - chloroethane or chloroform, and the base present in the reaction mixture is α -picoline or 2,5-dimethylpyridine.

26. Process according to any one of claims 2 to 25 followed by the step of converting a substituent R_1R_2N — in the 7-position, and/or a substituent $—COR_3$ in the 4-position of the 7-substituted amino-desacetoxycephalosporanic product into another group R_1R_2N — or $—COR_3$ respectively by methods known *per se*.

27. Process for the preparation of 7 - substituted - amino - desacetoxycephalosporanic derivatives according to claim 1 substantially as hereinbefore described.

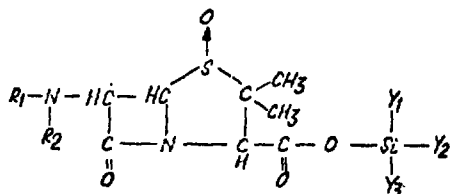
28. Process for the preparation of 7 - substituted - amino - desacetoxycephalosporanic derivatives substantially as hereinbefore described in any one of Examples 1 to 21.

29. 7 - Substituted amino - desacetoxycephalosporanic derivatives when prepared by the process claimed in any one of claims 1 to 28.

30. 7-Phenylacetamido-, 7-phenoxyacetamido-, 7 - α - aminophenylacetamido - and 7 - (2 - ethoxynaphthamido) - desacetoxycephalosporanic acid and salts, esters and amides thereof, when prepared by the process claimed in any one of claims 1 to 28.



31. 6-Aminopenicillanic sulphoxide silyl esters of the general formula:—



5 wherein R_1 and R_2 are as defined in claim 2, 3, 4 or 5, and Y_1 , Y_2 and Y_3 are as defined in claim 16, or one of Y_1 , Y_2 and Y_3 represents the 6-aminopenicillanylester group attached to the silicon atom in the depicted formula.

32. Benzylpenicillin sulphoxide trimethylsilyl ester, benzylpenicillin sulphoxide dimethylchlorosilyl ester, di(benzylpenicillin sulphoxide)dimethylsilyl ester, phenoxy-methylpenicillin sulphoxide trimethylsilyl ester, phenoxymethylpenicillin sulphoxide dimethylchlorosilyl ester and di(phenoxymethylpenicillin sulphoxide)dimethylsilyl ester.

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