

PATENT SPECIFICATION

(11) 1 551 931

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- (21) Application No. 33597/76 (22) Filed 12 Aug. 1976
 (31) Convention Application No. 10822/75
 (32) Filed 20 Aug. 1975 in
 (33) Switzerland (CH)
 (44) Complete Specification published 5 Sept. 1979
 (51) INT CL² C07D 501/20; A61K 31/545//C07D 499/44
 (52) Index at acceptance



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(54) CEPHALOSPORINS CONTAINING AN ALKYLSULPHONYLAMINO GROUP

(71) We, CIBA-GEIGY AG, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, 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 7β - [D - 2-amino - 2 - (lower alkylsulphonylamino-phenyl) - acetyl-amino] - 3 - R - 3 - cephem-4 - carboxylic acids (I), wherein R denotes lower alkoxy or halogen with an atomic number of up to 35, and their salts, processes for the manufacture of such compounds and also pharmaceutical formulations which contain these compounds as the active compound and to the use of these compounds, preferably in the form of pharmacological formulations.

Lower alkyl in lower alkylsulphonylamino preferably contains up to 4 carbon atoms and denotes, for example, ethyl, n-propyl, isopropyl, n-butyl or isobutyl and above all methyl. Lower alkylsulphonylamino can be in any position in the phenyl radical but above all is in the 3-position.

Lower alkoxy R preferably contains up to 4 carbon atoms and denotes, for example, ethoxy, n-propoxy, isopropoxy, n-butoxy or isobutoxy and, above all, methoxy, whilst halogen represents fluorine or bromine, but above all represents chlorine.

Salts are, in particular, non-toxic salts which can be used pharmaceutically, such as metal salts or ammonium salts, especially alkali metal salts and alkaline earth metal salts, for example sodium salts, potassium salts, magnesium salts or calcium salts, as well as ammonium salts with ammonia or suitable organic amines and compounds

which can be used for forming the salts are, above all, aliphatic, cycloaliphatic, cycloaliphatic-aliphatic and araliphatic primary, secondary or tertiary monoamines, diamines or polyamines, as well as heterocyclic bases, such as lower alkylamines, for example triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, basic aliphatic esters of carboxylic acids, for example 4-amino-benzoic acid 2-diethylamino-ethyl ester, lower alkyleneamines, for example 1-ethylpiperidine, cycloalkylamines, for example bicyclohexylamine, or benzylamines, for example N,N'-dibenzyl-ethylenediamine, and also bases of the pyridine type, for example pyridine, collidine or quinoline. The new compounds can also form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulphuric acid or phosphoric acid, or with suitable organic carboxylic or sulphonic acids, for example trifluoroacetic acid or 4-methylphenylsulphonic acid. The new compounds are preferably in the form of their inner salts, that is to say in the zwitterionic form.

The new compounds of the present invention display valuable pharmacological properties. Thus, in the free form or in the form of their salts they are active in vitro in a dosage range of 0.05 to 100 mcg/ml against cocci, such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus haemolyticus*, *Streptococcus faecalis*, *Diplococcus pneumoniae*, *Neisseria gonorrhoeae* and *Neisseria meningitidis*, in a dosage range of 0.8 to 50 mcg/ml against enterobacteria, such as *Escherichia coli*, *Salmonella* species, *Shigella flexneri*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Proteus rettgeri* and *Proteus*

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mirabilis and in a dosage range of 0.4 to 12.5 mcg/ml against other pathogenic germs, such as *Haemophilus influenzae* and *Pasteurella multocida*. On parenteral or, in particular, oral administration, they are active against micro-organisms, such as Gram-positive bacteria, for example *Staphylococcus aureus*, *Streptococcus pyogenes* and *Diplococcus pneumoniae* (for example in mice in doses of about 0.5 to about 100 mg/kg, given subcutaneously or perorally) and Gram-negative bacteria, for example *Escherichia coli*, *Salmonella typhimurium*, *Shigella flexneri*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Proteus rettgeri* and *Proteus mirabilis* (for example in mice in doses of about 3.0 to about 200 mg/kg, given subcutaneously or perorally) and especially also against penicillin-resistant bacteria, and are of low toxicity.

Compared with the 3-substituted 3-phenyl-glycylamino-3-cephem-4-carboxylic acids which are known from German Offenlegungsschriften 2,331,133 and 2,408,698 and which do not contain a lower alkylsulphonylamino group in the phenyl nucleus, the compounds of the present invention are distinguished by a higher *in vitro* activity against many of the strains of enterobacteria. *In vivo*, in mice, they are distinctly superior to these known formulations, both against many infections by cocci and against infections by enterobacteria. Compared with the 3-substituted 7β-[2-(lower alkylsulphonylaminophenyl)-glycylamino]-3-cephem-4-carboxylic acids which are known from German Offenlegungsschriften 2,422,385 and 2,432,190, the new compounds are distinguished by an increased *in vitro* and *in vivo* (mice) activity, especially against strains of enterobacteria. Moreover, they are highly soluble in water and urine and this makes the possibility of crystalluria appear slight. The new compounds can be used, for example in the form of formulations having an antibiotic action, for the treatment of the infections mentioned.

The invention relates above all to 7β-[D-2-amino-2-(3-methylsulphonylamino-phenyl)-acetylaminol-3-R'-3-cephem-4-carboxylic acids, wherein R' represents methoxy or chlorine, and their salts, especially their non-toxic salts which can be used pharmaceutically and in particular their inner salts.

The new compounds are manufactured in a manner which is in itself known. Thus, for example, they can be obtained when the hydroxyl group in a 7β-[D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetylaminol-3-hydroxy-3-cephem-4-carboxylic acid (II), wherein the carboxyl group is in a protected form, the 2-amino group is optionally in a protected form and

the lower alkylsulphonylamino group is optionally in a N-acylated form, is converted into the radical R and, if necessary, in a resulting compound a protected 2-amino group and/or a N-acylated lower alkylsulphonylamino group are converted into the free amino group and into the lower alkylsulphonylamino group respectively, and/or the protected carboxyl group is converted into a free carboxyl group, and, if desired, a resulting salt is converted into the free compound or into another salt, and/or a free compound is converted into a salt.

In the above starting material, the carboxyl group is in a protected form and the amino group is usually in a protected form and possible protective groups are, in particular, the radicals used in penicillin and cephalosporin chemistry and in peptide chemistry.

The carboxyl group is usually protected in an esterified form and an ester grouping of this type can be split easily under mild conditions. Possible groups which are suitable as protected carboxyl groups are, in particular, lower alkoxy-carbonyl, especially tert.-lower alkoxy-carbonyl, for example tert.-butoxycarbonyl, polycycloalkoxy-carbonyl, for example adamantyloxycarbonyl, arylmethoxycarbonyl, wherein aryl preferably represents one or two phenyl radicals, which are optionally monosubstituted or polysubstituted, for example by lower alkyl, especially tert.-lower alkyl, for example tert.-butyl, lower alkoxy, such as methoxy, hydroxyl, halogen, for example chlorine, and/or nitro, such as benzyloxycarbonyl which is optionally substituted, for example as mentioned above, for example 4-nitro-benzyloxycarbonyl, or diphenylmethoxycarbonyl which is substituted, for example as mentioned above, for example benzhydryloxycarbonyl or di-(4-methoxyphenyl)-methoxycarbonyl, or 2-halogeno-lower alkoxy-carbonyl, for example 2,2,2-trichloroethoxycarbonyl or 2-bromo- or 2-iodo-ethoxycarbonyl, or acyl-methoxycarbonyl, especially aroyl-methoxycarbonyl, wherein the aroyl group preferably represents benzoyl which is optionally substituted, for example by halogen, such as bromine, for example phenacyloxycarbonyl. Esterified carboxyl groups are also corresponding silyloxy-carbonyl groups, especially organic silyloxy-carbonyl groups. In these groups, the silicon atom preferably has lower alkyl, especially methyl, and also lower alkoxy, for example methoxy, and/or halogen, for example chlorine, as substituents. Suitable silyl protective groups are, above all, tri-lower alkylsilyl, especially trimethylsilyl, and also dimethyl-tert.-butylsilyl, lower alkoxy-lower alkyl-halogeno-silyl, for example methoxy-methyl-chloro-silyl, or di-lower alkyl-

halogeno-silyl, for example dimethyl-chloro-silyl. Silyl protective groups, especially those which contain a halogen atom as a substituent, can at the same time protect the carboxyl groups in two different molecules of the starting material; that is to say in groups of this type such a halogen atom has been replaced by the carbonyl group of a further molecule of the starting material.

A preferred protected carboxyl group is, in particular, benzoyloxycarbonyl which is optionally substituted, for example as mentioned, for example 4-nitrobenzyloxycarbonyl, or diphenylmethoxycarbonyl which is optionally substituted, for example as mentioned, for example benzhydryloxycarbonyl.

A protected 2-amino group can be, for example, in the form of an acylamino, triarylmethylamino, etherified mercapto-amino, 1-acyl-2-lower alkylideneamino or silylamino group, which can be split easily, or in the form of an azido group.

In a corresponding acylamino group, and in a N-acyl-lower alkylsulphonylamino group, acyl is preferably the acyl radical of a carbonic acid half-ester, such as lower alkoxycarbonyl, especially tert.-lower alkoxycarbonyl, for example tert.-butoxycarbonyl, polycycloalkoxycarbonyl, for example adamantyloxycarbonyl, aryl-methoxycarbonyl, wherein aryl preferably represents one or two phenyl radicals which are optionally monosubstituted or polysubstituted, for example by lower alkyl, especially tert.-lower alkyl, for example tert.-butyl, lower alkoxy, such as methoxy, hydroxyl, halogen, for example chlorine, and/or nitro, such as benzyloxycarbonyl which is optionally substituted, for example as mentioned above, for example 4-nitrobenzyloxycarbonyl, or diphenylmethoxycarbonyl which is substituted, for example as mentioned above, for example benzhydryloxycarbonyl or di-(4-methoxyphenyl)-methoxycarbonyl, or 2-halogeno-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl, or acylmethoxycarbonyl, especially aroyl-methoxycarbonyl, wherein the aroyl group preferably represents benzoyl which is optionally substituted, for example by halogen, such as bromine, for example phenacyloxycarbonyl. Acyl in an acyl-amino group or in a N-acyl-lower alkylsulphonylamino group can also represent the corresponding radical of an organic sulphonic acid; such a radical is, in particular, arylsulphonyl, wherein aryl denotes a phenyl radical which is optionally substituted, for example by lower alkyl, such as methyl, halogen, such as bromine,

or nitro, for example 4-methylphenylsulphonyl.

In a triarylmethylamino group, the aryl radicals are, in particular, optionally substituted phenyl radicals; a corresponding group is, above all, trityl.

An etherified mercapto group in an amino group protected by such a radical is, above all, arylthio or aryl lower alkylthio, wherein aryl is, in particular, phenyl which is optionally substituted, for example by lower alkyl, such as methyl or tert.-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or nitro. A corresponding amino protective group is, for example, 4-nitrophenylthio.

In a 1-acyl-2-lower alkylidene radical which can be used as an amino protective group, acyl is preferably the corresponding radical of a lower alkanecarboxylic acid, of a benzoic acid which is optionally substituted, for example by lower alkyl, such as methyl or tert.-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or nitro, or of a carbonic acid half-ester, such as of a carbonic acid lower alkyl half-ester. Corresponding protective groups are, above all, 1-lower alkanoyl-2-propylidene, for example 1-acetyl-2-propylidene, or 1-lower alkoxycarbonyl-2-propylidene, for example 1-ethoxycarbonyl-2-propylidene.

A silylamino group is, above all, an organic silylamino group wherein the silicon atom preferably has lower alkyl, especially methyl, and also lower alkoxy, for example methoxy, and/or halogen, for example chlorine, as substituents. Corresponding silyl groups are, above all, tri-lower alkyl-silyl, especially trimethylsilyl, and also dimethyl-tert.-butyl-silyl, lower alkoxy-lower alkyl-halogeno-silyl, for example methoxy-methyl-chloro-silyl, or di-lower alkyl-halogeno-silyl, for example dimethyl-chloro-silyl. Silyl protective groups, especially those which contain a halogen atom as a substituent, can at the same time protect the amino group in two different molecules of the starting material; that is to say in groups of this type the halogen atom has been replaced by the amino group of a further molecule of the starting material.

The 2-amino group in the starting material II can also be protected in a protonised form; possible anions are, above all, those of strong inorganic acids, such as of hydrogen halide acids, for example the chlorine or bromine anion.

Preferred amino protective groups are the acyl radicals of carbonic acid half-esters, especially tert.-lower alkoxycarbonyl, or benzyloxycarbonyl or diphenylmethoxycarbonyl, which are optionally substituted, for example as indicated or 2-halogeno-lower alkoxycarbonyl.

The starting material II is preferably in the indicated 3-hydroxy-3-cephem form but can also be employed in the corresponding tautomeric cepham-3-one form.

- 5 The conversion of the hydroxyl group in a starting material of the formula II into lower alkoxy R can be effected by etherification with a lower alkyl radical in a manner which is in itself known. Thus, the starting material
- 10 can be reacted, for example, with a diazo-lower alkane, for example diazomethane, diazoethane or diazo-n-butane. Such a reagent is used in the presence of a suitable inert solvent, such as an aliphatic or
- 15 aromatic hydrocarbon which is optionally substituted, for example which contains halogen, such as chlorine, or of a solvent mixture and, depending on the diazo reagent, with cooling, at room temperature
- 20 or with slight warming, and also, if necessary, in a closed vessel and/or under an inert gas atmosphere, for example a nitrogen atmosphere. It can optionally also be manufactured in situ.
- 25 Furthermore, a starting material II can be converted into a compound I, wherein R represents lower alkoxy, by treatment with a reactive ester of a lower alkanol. Suitable esters are, above all, those with strong
- 30 inorganic or organic acids, such as mineral acids, for example hydrogen halide acids, such as hydrochloric acid, hydrobromic acid or hydriodic acid, and also sulphuric acid or strong organic sulphonic acids, such
- 35 as lower alkanesulphonic acids which are optionally substituted, for example by halogen, such as fluorine, or halogenosulphonic acids or aromatic sulphonic acids, such as, for example, benzene-
- 40 sulphonic acids which are optionally substituted, for example by lower alkyl, such as methyl, halogen, such as bromine, and/or nitro, for example methanesulphonic acid, fluorosulphonic acid, trifluoromethane-
- 45 sulphonic acid or p-toluenesulphonic acid. These reagents, and especially di-lower alkyl sulphates, such as dimethyl sulphate, or optionally halogen-substituted methane-
- 50 sulphonic acid lower alkyl esters, for example methyl trifluoromethanesulphonate, and halogenosulphonic acid lower alkyl esters, for example methyl
- 55 fluorosulphonate, are customarily used in the presence of a solvent, such as an aliphatic, cycloaliphatic or aromatic hydrocarbon which is optionally substituted, for example by halogen, such as chlorine, for
- 60 example methylene chloride, an ether, such as dioxane or tetrahydrofuran, or a lower alkanol, such as methanol, or of a solvent mixture. For such reactions, suitable
- 65 condensing agents, such as alkali metal carbonates or bicarbonates, for example sodium carbonate or bicarbonate or potassium carbonate or bicarbonate

(usually together with a sulphate), or organic bases, such as tri-lower alkylamines, preferably sterically hindered tri-lower alkylamines, for example N,N-diisopropyl-N-ethylamine (usually together with lower alkyl halogenosulphates or optionally halogen-substituted methanesulphonic acid lower alkyl esters) are preferably used and the reaction is carried out with cooling, at room temperature or with

75 warming, for example at temperatures of about -20°C to about 50°C and, if necessary, in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

The conversion of a starting material II into a compound I, wherein R represents lower alkoxy, can also be carried out by treatment with a compound which contains two or three lower alkoxy groups on the same carbon atom of aliphatic character, that is to say with a corresponding acetal or ortho-ester, in the presence of an acid agent. Thus, for example, *gem*-lower alkoxy-lower alkanes, such as 2,2-dimethoxypropane, can be used as etherifying agents, in the presence of a strong organic sulphonic acid, such as p-toluenesulphonic acid, and of a suitable solvent, such as a lower alkanol, for example methanol, or a di-lower alkyl sulphoxide or lower alkylene sulphoxide, for example dimethylsulphoxide, or orthoformic acid tri-lower alkyl esters, for example triethyl orthoformate, can be used as etherifying agents, in the presence of a strong acid, such as a mineral acid, for example sulphuric acid, or a strong organic sulphonic acid, such as p-toluenesulphonic acid, and of a suitable solvent, such as a lower alkanol, for

80 example ethanol, or an ether, for example dioxane.

Compounds I, wherein R denotes lower alkoxy, can also be obtained when starting materials II are reacted with tri-lower alkyl-oxonium salts, and also di-lower alkoxy-carbenium salts or di-lower alkylhalonium salts, wherein halonium is, in particular, bromonium, and in particular corresponding salts with complex, fluorine-containing acids, such as the corresponding tetrafluoroborates, hexafluorophosphates or hexafluoroantimonates, or hexachloroantimonates. Such reagents are, for example, trimethyloxonium hexafluoroantimonate, hexachloroantimonate, hexafluorophosphate or tetrafluoborate or triethyloxonium hexafluoroantimonate, hexachloroantimonate, hexafluorophosphate or tetrafluoborate, di-methoxy-carbenium hexafluorophosphate or dimethylbromonium hexafluoroantimonate. These etherifying agents are preferably used in an inert solvent, such as an ether or a halogenated hydrocarbon, for example

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diethyl ether, tetrahydrofuran or methylene chloride, or in a mixture thereof, if necessary in the presence of a base, such as an organic base, for example a tri-lower alkylamine, preferably a sterically hindered tri-lower alkylamine, for example N,N-diisopropyl-N-ethylamine, and with cooling, at room temperature or with slight warming, for example at about -20°C to about 50°C, if necessary in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

Etherification of the enol hydroxyl group in a starting material II can also be produced by treatment with a 1-lower alkyl-triazine compound substituted in the 3-position, in which the substituent on the nitrogen atom in the 3-position denotes an organic radical bonded via a carbon atom, preferably a carbocyclic aryl radical, such as an optionally substituted phenyl radical, for example lower alkylphenyl, such as 4-methyl-phenyl. Triazine compounds of this type are 3-aryl-1-lower alkyl-triazines, for example 3-(4-methyl-phenyl)-1-methyl-triazene. These reagents are customarily used in the presence of inert solvents, such as optionally halogenated hydrocarbons or ethers, for example benzene, or solvent mixtures, and with cooling, at room temperature and, preferably, at elevated temperature, for example at about 20°C to about 100°C, if necessary in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

Replacement of the hydroxyl group in a starting material II by halogen can be carried out in diverse ways, usually by treatment with a halogenating agent, that is to say a fluorinating, chlorinating or brominating agent.

Compounds I, wherein Hal denotes fluorine, chlorine or bromine, can be manufactured, for example, by treating a starting material II with a phosphorus reagent which replaces enol hydroxyl groups by halogen, and subsequently splitting off the protective groups which are present.

Examples of phosphorus reagents of this type are dihalogeno-triorganyl-phosphoranes, trihalogeno-diorganyl-phosphoranes or a mixture consisting of a triorganyl-phosphine and a carbon tetrahalide.

In these reagents halogen is fluorine, chlorine or bromine. In the carbon tetrahalide, halogen is preferably chlorine or bromine. The organyl radicals in the phosphoranes and phosphines represent organic radicals with up to 18 carbon atoms and can be identical or different.

Organyl radicals are, in particular, hydrocarbon radicals which have up to 18, in particular up to 12 and preferably up to 6, carbon atoms and are optionally

substituted, for example by tertiary amino groups, or bonded to polymers, such as lower alkyl radicals, for example methyl, ethyl or propyl, di-lower alkylamino-lower alkyl radicals, for example 3-dimethylaminopropyl, carbocyclic radicals, such as phenyl which is optionally substituted as indicated, and also phenyl substituted by polymers, for example by polystyrene cross-linked with divinylbenzene, or phenyl substituted by di-lower alkylamino-lower alkyl, for example dimethylaminomethyl. In the case of phenyl substituted by polymers there is usually only one radical present on a given phosphorus atom.

Further organyl radicals are secondary amino radicals, such as di-lower alkylamino, above all dimethylamino.

Representative examples of the said phosphoranes are dihalogeno-triphenyl-phosphoranes or trihalogeno-diphenyl-phosphoranes, such as diphenyl-triphenyl-, trifluoro-diphenyl-, dichloro-triphenyl-, trichloro-diphenyl-, dibromo-triphenyl- and tribromo-diphenyl-phosphorane, wherein one of the phenyl groups can be linked to a polymer, such as a polystyrene crosslinked with divinylbenzene, or can be substituted by dimethylaminomethyl.

Representative examples of the said phosphines are triethyl-, methyl-propyl-phenyl-, bis-(3-dimethylaminopropyl)-phenyl-, tris-(dimethylamino)-, bis-(dimethylamino)-phenyl- and especially triphenyl-phosphine, wherein one of the phenyl groups can be linked to a polymer, such as a polystyrene cross-linked with divinylbenzene.

Examples of carbon tetrahalides are carbon tetrabromide and especially carbon tetrachloride.

The reaction with the halogenating phosphorus reagents takes place in a manner which is in itself known in an inert, aprotic, preferably polar solvent, such as a chlorinated hydrocarbon, for example methylene chloride, chloroform, carbon tetrachloride or 1,2-dichloroethane, a nitrile, such as acetonitrile or benzonitrile, or a N,N-disubstituted carboxylic acid amide, such as dimethylformamide or N,N-dimethylacetamide, or mixtures thereof, and, depending on the reactivity of the reagent employed, with cooling or warming, that is to say at temperatures between about -60°C and the reflux temperature of the solvent used, and optionally in an inert gas atmosphere, such as a nitrogen atmosphere. When tri-lower alkyl-phosphines or tris-(di-lower alkylamine)-phosphines and carbon tetrachloride or carbon tetrabromide are used, cooling to about -60° to -20°C is generally necessary.

The halogenating phosphoranes mentioned can also be formed *in situ*, for

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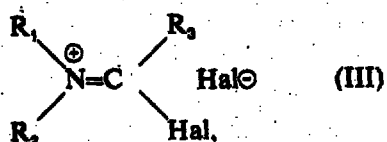
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example by reacting the said phosphines with the desired carbon tetrahalide, in which case other halogenating phosphorus compounds can also be formed in addition to the dihalogeno-triorganyl phosphorane, or by treating the phosphines with halogen, for example chlorine, or by reacting triorganyl-phosphine oxides with a dihalogeno-carbonyl, such as phosgene, or trihalogeno-silane, such as trichlorosilane.

When the halogenating reaction is carried out with said phosphoranes, a weak base, such as pyridine or a *N,N*-di-lower alkyl-aniline, such as *N,N*-dimethylaniline, can be added to the reaction medium in order to take up the hydrogen halide formed.

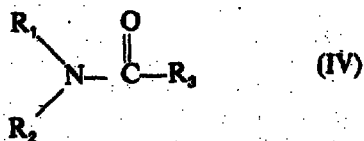
In a preferred embodiment, a starting material II, in one of the inert aprotic solvents mentioned, such as methylene chloride, is treated, at room temperature, that is to say about 20–25°C, with the carbon tetrahalide, preferably in excess, and then with triphenylphosphine, in amounts of about 1.2 to 2 equivalents of the starting material, and the reaction mixture is left to stand, or stirred, at the same temperature until the halogenation is complete.

Compounds I, wherein Hal denotes chlorine or bromine, can be obtained, for example, by treating the starting material II with a corresponding *N,N*-disubstituted halogeno-iminium halide compound, especially of the formula



In the formula III, R_1 and R_2 represent organic radicals, for example aliphatic radicals, above all lower alkyl and especially methyl, and R_3 in particular represents hydrogen but can also be an organic radical, for example an aliphatic radical, such as lower alkyl, especially methyl, whilst Hal is chlorine or bromine.

The above reagent is usually manufactured *in situ* by treating a suitable *N,N*-disubstituted amide of the formula



wherein R_1 , R_2 and R_3 have the above-mentioned meanings, in particular a corresponding *N,N*-disubstituted formamide and above all dimethylformamide, with one of the chlorinating or brominating agents customarily used. The latter are suitable

carbonic acid halides, for example phosgene or carbonyl dibromide, carboxylic acid halides, for example oxalyl chloride or oxalyl bromide, sulphuric acid halides, for example thionyl chloride or thionyl bromide, or phosphoric acid chlorides, for example phosphorus trichloride, phosphorus oxychloride, phosphorus tribromide or phosphorus oxybromide, and also phosphorus pentachloride. Particularly preferred chlorinating and brominating agents are phosphorus trichloride and phosphorus tribromide.

The above reaction is usually carried out in the presence of a solvent or diluent and an amide of the formula IV which is also suitable as a solvent, in particular dimethylformamide, which preferably is in the anhydrous form, can customarily be used as such a solvent or diluent. In addition to the amide, which customarily is dimethylformamide, and also dimethylacetamide, and is usually present in excess, and thus also serves as the solvent, it is also possible correspondingly to use ether-like solvents, for example tetrahydrofuran or dioxane, halogenated hydrocarbons, for example methylene chloride, or sulphoxides, for example dimethylsulphoxide.

The above chlorinating and brominating agents are customarily used in amounts which correspond to two equivalents of the 3-hydroxy-3-cephem starting material II. The reaction can, for example, be carried out by adding the chlorinating or brominating agent to a solution of the 3-hydroxy-3-cephem starting material II in the amide of the formula IV, especially in dimethylformamide. In this case this solution is kept at a temperature of about 0°C to about 15°C, after which the reaction mixture is left to stand for several hours at room temperature. The reaction is initially exothermic; the reaction vessel therefore has to be so cooled that the temperature can be kept below about 25°C during this reaction phase. The reaction mixture is then left to stand at about room temperature for the remainder of the reaction period and the course of the reaction can be followed by thin layer chromatography.

The chlorination or bromination can also be carried out by first mixing the chlorinating or brominating agent with the amide of the formula IV, especially dimethylformamide, and thus forming the halogeno-iminium halide of the formula III and then reacting the latter with a solution of the 3-hydroxy-3-cephem starting material II in the amide, especially in dimethylformamide, to which an additional solvent can also be added, or in another solvent, for example tetrahydrofuran.

If necessary, the reaction is carried out in an inert gas atmosphere.

The conversion of the 3-hydroxyl group into fluorine can be effected, for example, by treating the starting material II with a reagent of the formula F_2S-Am , wherein Am represents a disubstituted amino group; such reagents have been described, inter alia, by Markovsky et al., Synthesis, Volume 1973, page 787. The amino group contains as substituents preferably two monovalent hydrocarbon radicals which are optionally substituted and above all aliphatic or also aromatic, or one divalent, optionally substituted hydrocarbon radical which is preferably aliphatic. Monovalent aliphatic hydrocarbon radicals are, above all, lower alkyl, for example methyl, ethyl, n-propyl, isopropyl or straight-chain or branched butyl, whilst a corresponding aromatic hydrocarbon radical is preferably phenyl which is optionally substituted, for example by lower alkyl, such as methyl, lower alkoxy, such as methoxy, and/or halogen, for example chlorine. In a divalent aliphatic hydrocarbon radical, carbon atoms can optionally be replaced by hetero-atoms, such as an oxygen atom or an optionally substituted nitrogen atom; divalent radicals of this type are lower alkylene, for example 1,4-butylene or 1,5-pentylene, oxa-lower alkylene, for example 3-oxa-1,5-pentylene, or optionally N-lower alkyl-substituted aza-lower alkylene, for example 3-methyl-3-aza-1,5-pentylene. The group Am therefore above all represents di-lower alkylamino, for example dimethylamino, diethylamino, ethyl-methyl-amino, methyl-propyl-amino, di-n-propyl-amino or diisopropylamino, lower alkyl-phenyl-amino, for example methyl-phenyl-amino or ethyl-phenyl-amino, lower alkylene-amino, for example pyrrolidino or piperidino, oxa-lower alkyleneamino, for example morpholino, or optionally aza-lower alkyl-substituted aza-lower alkyleneamino, for example 4-methyl-piperazino.

The above reaction is preferably carried out in the presence of a suitable inert solvent, in which case, for example, optionally substituted carbocyclic hydrocarbons, for example aliphatic hydrocarbons, such as cyclopentane, cyclohexane, cycloheptane or decahydro-naphthalene, or aromatic carbocyclic hydrocarbons, such as benzene, toluene or xylenes, which can also be halogenated in the nucleus, such as chlorobenzene, dichlorobenzenes or bromobenzene, and in particular saturated aliphatic hydrocarbons, such as pentanes, hexanes, heptanes and octanes, or corresponding halogenated, and in particular chlorinated, hydrocarbons, such as chloroform, 1,1- or 1,2-dichloroethane, 1,1-, 1,2- or 1,3-dichloropropane and above all methylene chloride, are used.

Further solvents which can also be used are

aliphatic and, in particular, cyclic ethers, such as diethyl ether, diisopropyl ether, ethylene glycol dimethyl ether, tetrahydrofuran and, above all, dioxane, as well as nitrogen-containing aromatic heterocyclic compounds, such as pyridine and its homologues or quinoline. Optionally, an excess of the fluorinating agent can be used as the solvent and/or several of the said solvents can be combined with one another. If necessary, the reaction is carried out with cooling or warming, for example in a temperature range of about $-20^{\circ}C$ to about $80^{\circ}C$, and preferably of about $0^{\circ}C$ to about $30^{\circ}C$, and/or under an inert gas atmosphere.

A fluorine atom can also be introduced when a starting material II in which the hydroxyl group is in the form of an organic sulphonyloxy group, that is to say a 7 β -[D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetylaminol-3-sulphonyloxy-3-cephem-4-carboxylic acid (IIa), wherein the carboxyl group is in a protected form and the amino group is preferably in a protected form and the sulphonyloxy group represents an organic sulphonyloxy group, is reacted with an organic fluoride in the presence of a crown ether and, if necessary and desired, the additional process steps are carried out.

An organic sulphonyloxy group is, above all, lower alkylsulphonyloxy, especially methylsulphonyloxy, but can also be arylsulphonyloxy, wherein aryl is preferably phenyl which is optionally substituted, for example by lower alkyl, such as methyl, halogen, for example bromine, or nitro, for example 4-methyl-phenylsulphonyloxy.

An inorganic fluoride is, above all, a metal fluoride and, in particular, an alkali metal fluoride, for example sodium fluoride, or a heavy metal fluoride, for example silver fluoride, is used.

The coronene ethers which are used conjointly with the inorganic fluoride are optionally substituted 18-coronene-6-ethers, such as dicyclohexyl-18-coronene-6-ether.

The reaction is carried out in the presence of an inert solvent, especially a nitrile, for example acetonitrile or propionitrile, or a nitro-lower alkane, for example nitromethane or nitroethane, under essentially anhydrous conditions and, if necessary, with cooling, for example in a temperature range of about $-20^{\circ}C$ to about $25^{\circ}C$, and preferably at about room temperature, and/or in an inert gas atmosphere.

The 3-sulphonyloxy-3-cephem starting material (IIa) can also be formed *in situ*, since any 7 β -[D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetylaminol-3-sulphonyloxy-2-cephem-4-carboxylic acid (IIb) which may be present together with the starting material IIa and

wherein the carboxyl group is in a protected form and the amino group is preferably in a protected form and the sulphonyloxy group represents an organic sulphonyloxy group, is converted, under the reaction conditions, into the corresponding 3-sulphonyloxy-3-cephem starting material IIa and enters as such into the reaction with the fluorinating agent.

The starting material II can be manufactured, for example, by acylating the amino group in a 7 β -amino-3-hydroxy-3-cephem-4-carboxylic acid (V), wherein the carboxyl group and the 3-hydroxyl group are in a protected form and the carboxyl group is in particular in an esterified form and the 3-hydroxyl group is in particular in a silylated form, with a D-2-amino-(2-lower alkylsulphonylamino-phenyl)-acetyl radical. The acylation can be carried out, for example, by the methods described below and the 2-amino group in the acylating agent is preferably in a protected form and the lower alkylsulphonylamino group is optionally in a N-acylated form. The hydroxyl group of the enol grouping can be converted into a sulphonyloxy group, for example by treatment with an organic sulphonic acid halide, for example an organic sulphonic acid chloride, in the presence of a tertiary amine, such as triethylamine, or of dimethylformamide and propylene oxide.

The new compounds can also be obtained when the 7 β -amino group in a 7 β -amino-3-R-3-cephem-4-carboxylic acid (VI), wherein the carboxyl group is optionally in a protected form and the 7 β -amino group is optionally in a reactive protected form, that is to say in a form which permits acylation, is acylated with a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetyl radical and, if necessary or desired, the additional measures are carried out.

In a starting material VI, the carboxyl group can preferably be protected in an esterified form, for example as described above and above all in the form of a silyl ester, such as a trimethylsilyl ester (which usually is prepared immediately prior to the acylating reaction, by treatment with a corresponding silylating agent, for example trimethylchlorosilane or bis-(trimethylsilyl)-acetamide). However the carboxylic acid starting material VI can also be employed in the form of a salt, for example in the form of an ammonium salt, such as in the form of a triethylammonium salt, or in a protected form, which is obtainable by reacting the carboxylic acid starting material VI with a suitable organic phosphorus halide compound, such as with a lower alkyl- or lower alkoxy-phosphorus dihalide, such as methyl-phosphorus dichloride, ethyl-phosphorus dibromide or

methoxy-phosphorus dichloride. A 7 β -amino group in a reactive protected form is, for example, a 7 β -amino group protected by a silyl radical, such as one of the corresponding radicals mentioned above.

Further groups which can protect the 7 β -amino group in a reactive form are the carbonyl group (O=C=), and also 1-halogeno- or 1-alkoxy-methylene groups, which are optionally substituted in the 1-position. In such methylene groups, halogen is bromine or, in particular, chlorine and alkoxy is, in particular, optionally substituted lower alkoxy, such as ethoxy, propoxy, butoxy or, preferably, methoxy. The other substituent in the 1-position of such a methylene group is hydrogen or any organic radical which has less steric hindrance, for example optionally substituted lower alkyl, such as methyl, 4-amino-4-carboxybutyl, wherein the amino group and the carboxyl group can be protected, benzyl, phenoxymethyl and thienylmethyl or also furylmethyl, such as 2-thienylmethyl or 2-furylmethyl.

The acylation of the free 7 β -amino group, or of the reactive protected 7 β -amino group, in the starting material VI is carried out in a manner which is in itself known. Acylating agents which can be used are a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetic acid (VII) or a reactive derivative thereof and the 2-amino group can usually be present in a protected form, inter alia also in a protonised or masked form, for example also as an azido group, and the lower alkylsulphonylamino group can optionally be substituted on the nitrogen by an acyl group.

If the free acid VII having a protected 2-amino group and an optionally N-acylated lower alkylsulphonylamino group is employed for the acylation, suitable condensing agents, such as carbodiimides, for example N,N'-diethyl-, N,N'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexyl- or N-ethyl-N'-3-dimethylaminopropyl-carbodiimide, suitable carbonyl compounds, for example carbonyldiimidazole, or isoazolinium salts, for example N-ethyl-5-phenyl-isoxazolinium 3'-sulphonate and N-tert.-butyl-5-methyl-isoxazolinium perchlorate, or a suitable acylamino compound, for example 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline are customarily used. The condensation reaction is preferably carried out in an anhydrous reaction medium, for example in methylene chloride, dimethylformamide or acetonitrile.

Further suitable condensing agents for the acylation of the 7 β -amino group by a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetic acid, which can also be used in the form of its esters, for example the

lower alkyl esters, such as the methyl or ether ester, wherein the 2-amino group can be in a protected form and the lower alkylsulphonylamino group can be in a N-acylated form, are the enzymes, which catalyse the acylation, of suitable micro-organisms, for example of *Pseudomonas melanogenum* ATCC 17,808, or of numerous other known acylating strains, such as *Xanthomonas*, *Acetobacter*, *Achromobacter*, *Beneckea hyperoptica*, *Micrococcus urea*, *Mycobacterium smegmatis* or *Nocardia gluberula*. The enzymatic acylation is carried out in a manner which is in itself known, in the presence of the said micro-organisms, either in an aqueous nutrient medium which contains the known nutrients necessary for growth of the strain used, or in a buffer solution, for example an acetate buffer containing sodium chloride, under aerobic conditions at temperatures between about 20 and about 50°, and at a pH value of 5 to 9, and preferably 6.5 to 7.

A reactive derivative of the said acid VII, which usually has a protected amino group and an optionally N-acylated lower alkylsulphonylamino group, is, above all, an anhydride thereof, including, and preferably, a mixed anhydride. Mixed anhydrides are, for example, those with inorganic acids, especially with hydrogen halide acids, that is to say the corresponding acid halides, for example the acid chloride or acid bromide, and also the anhydride with hydrazoic acid, that is to say the corresponding acid azide, or with a phosphorus-containing acid, for example phosphoric acid or phosphorous acid, with a sulphur-containing acid, for example sulphuric acid, or with a halide, such as the chloride, of the dimethyl-immoniomethyl half-ester of sulphurous acid, or with hydrocyanic acid. Other mixed anhydrides are, for example, those with organic acids, such as organic carboxylic acids, such as with lower alkanecarboxylic acids which are optionally substituted, for example by halogen, such as fluorine or chlorine, for example pivalic acid or trichloroacetic acid, or with half-esters, especially lower alkyl half-esters, of carbonic acid, such as the ethyl or isobutyl half-ester, or with a halide, such as the chloride, of the N,N-dimethyliminomethyl half-ester of carbonic acid, or with organic, and especially aliphatic or aromatic, sulphonic acids, for example p-toluenesulphonic acid.

Further acid derivatives which are suitable for reaction with the amino group in the starting material VI are activated esters of the said acid VII, which usually have a protected amino group, such as esters with vinylogous alcohols (that is to say enols), such as vinylogous lower alkenols, or aryl esters, such as phenyl esters

which are preferably substituted, for example by nitro or halogen, such as chlorine, for example pentachlorophenyl, 4-nitrophenyl or 2,4-dinitrophenyl esters, hetero-aromatic esters, such as benzotriazole esters, or diacylimino-esters, such as succinylimino- or phthalylimino-esters.

The acylation with an acid derivative, such as an anhydride, and especially with an acid halide, can be carried out in the presence of an acid-binding agent, for example an organic base, such as an organic amine, for example a tertiary amine, such as a tri-lower alkylamine, for example triethylamine, a N,N-di-lower alkyl-aniline, for example N,N-dimethylaniline, or a base of the pyridine type, for example pyridine, or an inorganic base, for example an alkali metal hydroxide, carbonate or bicarbonate or alkaline earth metal hydroxide, carbonate or bicarbonate, for example sodium hydroxide, carbonate or bicarbonate, potassium hydroxide, carbonate or bicarbonate or calcium hydroxide, carbonate or bicarbonate, or an oxirane, for example a lower 1,2-alkylene oxide, such as ethylene oxide or 1,2-propylene oxide.

The above acylation can be carried out in an aqueous or, preferably, non-aqueous solvent or solvent mixture, for example in a carboxylic acid amide, such as N,N-di-lower alkylamide, for example dimethylformamide, a halogenated hydrocarbon, for example methylene chloride, carbon tetrachloride or chlorobenzene, a ketone, for example acetone, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or mixtures thereof, and, if necessary, at a lowered or elevated temperature, for example at about 20° to about +100°C, and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

If the 7 β -amino group in the starting material VI has been protected by a radical which permits acylation, this radical is split off during the acylation, or when the reaction product is worked up, for example by hydrolysis, optionally in the presence of a base, such as triethylamine.

The starting materials VI are known and can be manufactured, for example, by splitting the acylamino grouping in 7 β -acylamino-3-R-3-cephem-4-carboxylic acid compounds wherein acyl denotes a radical which differs from a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetyl radical, for example phenylacetyl or phenoxyacetyl, in a manner which is in itself known, for example by treatment with phosphorus pentachloride in the presence of pyridine, followed by methanol and, if desired, water.

Starting materials VI in which the 7 β -amino group is protected in a reactive form

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which permits acylation are also known or can be manufactured analogously to known methods, optionally in situ. A silyl group is introduced by treating the free 7 β -amino group with a corresponding silylating agent, for example trimethyl-chlorosilane or bis-(trimethylsilyl)-acetamide. A carbonyl group can be introduced by treating the free 7 β -amino group with phosgene in the presence of a base, such as a tertiary amine, for example triethylamine. Starting materials VI in which the amino group is protected by a 1-halogenomethylene group which is optionally substituted in the 1-position are obtained by treating a 7 β -acylamino-3-R-3-cephem-4-carboxylic acid (IX), wherein acyl represents an acyl radical which differs from a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetyl (in which amino is optionally protected), for example an optionally substituted lower alkanoyl radical, such as formyl, acetyl, 5-amino-5-carboxy-valeryl, wherein the maino group and the carboxyl group can be protected, phenylacetyl, phenoxyacetyl, thienylacetyl or furylacetyl, and carboxyl and/or functional groups present in the acyl radical are optionally in a protected form, with a phosphorus pentahalide, especially phosphorus pentachloride, in the presence of a base, such as pyridine. The resulting 1-halogeno-methyleneimino compound either can be acylated direct or can be converted by treatment with an alcohol, such as methanol, into the corresponding 1-alkoxymethylene compound, which is optionally substituted in the 1-position, and this compound is also usually acylated without being isolated.

The new compounds I can also be obtained when a 7 β -(D-2-amino-2-(lower alkylsulphonylamino - phenyl) - acetyl-amino) - 3 - R - 2 - cephem - 4 β - carboxylic acid (VIII), wherein 2-amino and/or carboxyl can optionally be in a protected form and/or lower alkylsulphonylamino can optionally be in a N-acylated form, is isomerised and, if necessary or desired, the additional measures are carried out.

The amino and/or carboxyl group in a starting material can be in a protected form, for example as indicated and amino can preferably be in an acylated form and carboxyl can usually be in an esterified form.

The isomerisation can be carried out in a manner which is in itself known.

Thus, it is possible to isomerise a 2-cephem compound VIII by treating it with a basic agent and to isolate the corresponding 3-cephem compound from an equilibrium mixture of the 2- and 3-cephem compounds which may be obtained.

Suitable isomerising agents are, for example, organic nitrogen-containing bases,

such as tertiary heterocyclic bases of aromatic character and above all tertiary aliphatic, aza-cycloaliphatic or araliphatic bases, especially N,N,N-tri-lower alkylamines, for example trimethylamine, triethylamine or N,N-diisopropyl-N-ethylamine, or mixtures of such bases, such as a mixture of a base of the pyridine type, for example pyridine, and a N,N,N-tri-lower alkylamine, for example pyridine and triethylamine. Furthermore, inorganic or organic salts of bases, especially of medium-strength to strong bases, with weak acids, such as alkali metal salts or ammonium salts of lower alkanecarboxylic acids, for example sodium acetate, triethylammonium acetate or N-methyl-piperidine acetate, and also other analogous bases or mixtures of such basic agents, can also be used.

The above isomerisation with basic agents can be carried out, for example, in the presence of a derivative of a carboxylic acid which is suitable for forming a mixed anhydride, such as a carboxylic acid anhydride or carboxylic acid halide, for example with pyridine in the presence of acetic anhydride. The reaction is preferably carried out in an anhydrous medium, in the presence or absence of a solvent, it being possible for bases which are used as reactants and are liquid under the reaction conditions at the same time also to serve as the solvent, and, if necessary, with cooling or heating, preferably in a temperature range of about -30°C to about +100°C, in an inert gas atmosphere, for example a nitrogen atmosphere, and/or in a closed vessel.

The 3-cephem compounds which are thus obtainable can be separated off, in a manner which is in itself known, from any 2-cephem compounds VIII which may still be present, for example by adsorption chromatography and/or crystallisation.

The isomerisation of 2-cephem compounds VIII can also be carried out by oxidising the latter in the 1-position, whereupon rearrangement of the 2-cephem compound into a 3-cephem compound takes place, and, if desired, separating a mixture of isomers, which is obtainable, of the 1-oxides of 3-cephem compounds and reducing the 1-oxides, which are thus obtainable, of the corresponding 3-cephem compounds.

Suitable oxidising agents which can be used for the oxidation of 2-cephem compounds VIII in the 1-position are suitable inorganic or organic per-acids or mixtures of hydrogen peroxide and acids, especially organic carboxylic acids which have a dissociation constant of at least 10⁻⁴. Suitable inorganic per-acids are periodic acid and persulphuric acid. Organic per-

acids are corresponding percarboxylic acids and persulphonic acids, which can be added as such or can be formed *in situ* by using at least one equivalent of hydrogen peroxide and of a carboxylic acid. It is appropriate to use a large excess of the carboxylic acid if, for example, acetic acid is used as the solvent. Suitable peracids are, for example, performic acid, peracetic acid, pertrifluoroacetic acid, permaleic acid, perbenzoic acid, mono-perphthalic acid or p-toluene-persulphonic acid. The oxidation can also be carried out using hydrogen peroxide with catalytic amounts of an acid which has a dissociation constant of at least 10^{-3} , such as acetic acid, perchloric acid or trifluoroacetic acid.

The above oxidation is carried out in a manner which is in itself known, if necessary in the presence of catalysts, and under mild conditions, for example at temperatures of from about -50°C to about $+100^{\circ}\text{C}$ and preferably from about -10°C to about $+40^{\circ}\text{C}$.

The oxidation of 2-cephem compounds to the 1-oxides of the corresponding 3-cephem compounds can also be carried out by treatment with organic hypohalite compounds, such as lower alkyl hypochlorites, for example tert-butyl hypochlorite, which are used in the presence of inert solvents, such as optionally halogenated hydrocarbons, for example methylene chloride, and at temperatures of from about -10°C to about $+30^{\circ}\text{C}$, with periodate compounds, such as alkali metal periodates, for example potassium periodate, which are preferably used as in an aqueous medium at a pH value of about 6 and at temperatures of from about -10°C to about $+30^{\circ}\text{C}$, with iodobenzene dichloride, which is used in an aqueous medium preferably in the presence of an organic base, for example pyridine, and with cooling, for example at temperatures of from about -20°C to about 0°C , or with any other oxidising agent which is suitable for converting a thio grouping into a sulfoxide grouping.

A mixture, which may be obtained, of the α - and β -1-oxide isomers can be separated, for example by chromatography.

The reduction of the 1-oxides of 3-cephem compounds can be carried out in a manner which is in itself known, by treatment with a reducing agent, if necessary in the presence of an activating agent. Reducing agents which can be used are: catalytically activated hydrogen; reducing tin, iron, copper or manganese cations, which are used in the form of corresponding compounds or complexes of an inorganic or organic nature, for example as tin-II chloride, copper-I chloride or manganese-II chloride, or as complexes, for

example with ethylenediaminetetraacetic acid or nitrilotriacetic acid; reducing dithionite, iodide or ferrocyanide anions, which are used in the form of corresponding inorganic or organic salts, such as an alkali metal dithionite, iodide or ferrocyanide, or in the form of the corresponding acids; reducing trivalent inorganic or organic phosphorus compounds, such as phosphines, and also esters, amides and halides of phosphinous, phosphonous or phosphorus acid, and also the phosphorus-sulphur compounds which correspond to these phosphorus-oxygen compounds, wherein organic radicals above all represent lower alkyl or phenyl, for example triphenylphosphine, methyl diphenylphosphinite, diphenylchlorophosphine, dimethyl benzenephosphonite, trimethyl phosphite, phosphorus trichloride or phosphorus tribromide and the like; reducing halogenosilane compounds which contain at least one hydrogen atom bonded to the silicon atom and which, in addition to halogen, for example chlorine, can also contain organic radicals, such as lower alkyl or phenyl, such as chlorosilane, di- or trichlorosilane, diphenylchlorosilane, dimethylchlorosilane and the like; reducing quaternary chloromethyleneiminium halides, wherein the iminium group is substituted by one bivalent organic radical or two monovalent organic radicals, such as lower alkylene or lower alkyl, such as N-chloromethylene - N,N - diethyliminium chloride or N-chloromethylene-pyrrolidinium chloride; and complex metal hydrides, such as sodium borohydride, for example in the presence of suitable activating agents, such as cobalt-II chloride; and also borane dichloride.

Activating agents which may be mentioned and are used together with those of the abovementioned reducing agents which do not themselves display Lewis acid properties, that is to say which above all are employed together with the dithionite, iodide or ferrocyanide reducing agents and the trivalent phosphorus reducing agents which do not contain halogen, or in the case of catalytic reduction, are, in particular, organic carboxylic acid halides and sulphonc acid halides, and also sulphur halides, phosphorus halides or silicon halides which have a second order hydrolysis constant equal to, or greater than, that of benzoyl chloride, for example phosgene, oxalyl chloride, acetyl chloride, 4-toluenesulphonyl chloride, methanesulphonyl chloride, thionyl chloride, phosphorus oxychloride, phosphorus trichloride, dimethylchlorosilane or trichlorosilane, and also suitable acid anhydrides, such as trifluoroacetic anhydride, or cyclic sultones, such as ethanesultone, 1,3-propanesultone,

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1,4-butanedisulfone or 1,3-hexanedisulfone.

The reduction is preferably carried out in the presence of solvents or mixtures thereof and the choice of solvent is determined above all by the solubility of the starting materials and the choice of the reducing agent; solvents used are thus, for example, lower alkanecarboxylic acids or esters thereof, in the case of catalytic reduction, and, for example, optionally substituted, such as halogenated or nitrated, aliphatic, cycloaliphatic, aromatic or araliphatic hydrocarbons, for example methylene chloride, lower alkane carboxylic acid esters or nitriles, for example ethyl acetate or acetonitrile, or amides of inorganic or organic acids, for example dimethylformamide or hexamethylphosphoric acid amide, or ethers, for example diethyl ether, tetrahydrofuran or dioxane, and ketones, for example acetone, and the like and these solvents preferably do not contain any water. The reaction is usually carried out at temperatures of from about -20°C to about 100°C , it being possible to carry out the reaction at lower temperatures when highly reactive activating agents are used.

The starting materials VIII can be manufactured in a manner which is in itself known, for example when a 7β -acylamino-3-R-3-cephem-4-carboxylic acid (IX), wherein acyl represents an acyl radical which can be split off and which differs from D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetyl (which optionally has protected 2-amino and N-acetylated lower alkylsulphonylamino), and carboxyl and/or functional groups present in the acyl radical are optionally in a protected form, is isomerized to the corresponding 2-cephem compound (for example by treatment with a suitable base) and, in this compound, the acyl radical is split off, for example by treatment with phosphorus pentachloride in the presence of pyridine, followed by methanol and, optionally, water. The free amino group is then acylated with a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetyl radical (which preferably has a protected 2-amino group and/or an optionally N-acetylated lower alkylsulphonylamino group) by treatment with a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetic acid (VII), wherein 2-amino is preferably in a protected form and/or lower alkylsulphonylamino is optionally in a N-acetylated form, or with a reactive derivative, especially in anhydride, and preferably a mixed anhydride, thereof, such as a corresponding acid chloride or anhydride with a formic acid lower alkyl ester.

The starting materials VIII, wherein R represents lower alkoxy and wherein carboxyl and 2-amino are preferably in a protected form and lower alkylsulphonylamino

is optionally in a N-acetylated form, can also be formed by the basic cyclisation reaction, which is described in the text which follows, of a 2-[3-[D-amino-2-(lower alkylsulphonylamino-phenyl)-acetylaminol]-4-R₀-thio-2-oxo-1-azetidiny]-3-crotonic acid (X), wherein the carboxyl group and the 2-amino group are preferably in a protected form and the lower alkylsulphonylamino group is optionally in a N-acetylated form.

The new compounds I, wherein R represents lower alkoxy, can also be obtained when a 2-[3-[D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetylaminol]-4-R₀-thio-2-oxo-1-azetidiny]-3-R-crotonic acid (X), wherein the carbonyl group is in a protected form or in the form of a halogenocarbonyl group, for example a chlorocarbonyl group, the 2-amino group is optionally in a protected form and the lower alkylsulphonylamino group is optionally in a N-acetylated form, R represents lower alkoxy and R₀ represents a leaving group, is cyclised by treatment with a base, and, if necessary, or desired, the additional measures are carried out.

In a starting material X, the lower alkoxy group R can be in the trans-position (crotonic acid configuration) or in the cis-position (isocrotonic acid configuration) relative to the carbonyl group.

In a starting material X, in which the carboxyl group and the amino group can be protected in a manner which is in itself known, for example as described above, and the lower alkylsulphonylamino group can optionally be N-acetylated, a leaving group R₀ is, for example, a $-\text{S}-\text{R}_0^{\text{a}}$ group, a $-\text{SO}_2-\text{R}_0^{\text{a}}$ group, which is bonded by the sulphur atom to the thio sulphur, or a $-\text{S}-\text{SO}_2-\text{R}_0^{\text{a}}$ group.

In the group $-\text{S}-\text{R}_0^{\text{a}}$, R₀^a is an optionally substituted monocyclic or bicyclic heterocyclic radical of aromatic character, which contains at least one ring nitrogen atom and optionally a further ring heteroatom, such as oxygen or sulphur, and which is bonded to the thio sulphur by one of its ring carbon atoms, which is bonded to a ring nitrogen atom by means of a double bond. Such radicals can optionally be substituted, for example by lower alkyl, such as methyl or ethyl, lower alkoxy, such as methoxy or ethoxy, halogen, such as fluorine or chlorine, or aryl, such as phenyl.

Such radicals R₀^a are, for example, monocyclic five-membered thiadiazacyclic, thiatriazacyclic, oxadiazacyclic or oxatriazacyclic radicals of aromatic character, but especially monocyclic five-membered diazacyclic, oxazacyclic and thiazacyclic radicals of aromatic character, or, above all, the corresponding benzodiazacyclic, benzoxazacyclic or

benzthiazacyclic radicals, wherein the heterocyclic part is five-membered and is of aromatic character, it being possible, in such radicals, for a ring nitrogen atom which can be substituted to be optionally substituted, for example by lower alkyl, such as methyl. Examples of such groups are 1-methyl-2-imidazolyl, 2-thiazolyl, 1,3,4-thiadiazol-2-yl, 1,3,4,5-thiadiazol-2-yl, 2-oxazolyl, 1,3,4-oxadiazol-2-yl, 1,3,4,5-oxatriazol-2-yl, 2-quinolinyl, 1-methyl-2-benzimidazolyl, 2-benzoxazolyl and, in particular, 2-benzthiazolyl.

A R_5^b group can also represent the acyl radical of an organic carboxylic acid or thiocarboxylic acid and be an optionally substituted, aliphatic, cycloaliphatic, araliphatic, aromatic or heterocyclic acyl or thioacyl radical. Such radicals are, inter alia, lower alkanoyl, for example acetyl or propionyl, lower thioalkanoyl, for example thioacetyl or thiopropionyl, cycloalkylcarbonyl, for example cyclohexylcarbonyl, cycloalkylthiocarbonyl, for example cyclohexylthiocarbonyl, benzoyl, thiobenzoyl, naphthoyl, naphthylthiocarbonyl, pyridoyl, for example 2-, 3- or 4-pyridoyl, thenoyl, for example 2- or 3-thenoyl, furoyl, for example 2- or 3-furoyl, or pyridylthiocarbonyl, for example 2-, 3- or 4-pyridylthiocarbonyl, or corresponding substituted acyl or thioacyl groups, for example acyl or thioacyl groups which are monosubstituted or polysubstituted by lower alkyl, such as methyl, halogen, such as fluorine or chlorine, lower alkoxy, such as methoxy, aryl, such as phenyl, or aryloxy, such as phenoxy.

In the groups

$-\text{SO}_2-\text{R}_5^b$ and $-\text{S}-\text{SO}_2-\text{R}_5^b$,

R_5^b is an optionally substituted, especially aliphatic, cycloaliphatic, araliphatic or aromatic hydrocarbon radical. Suitable groups R_5^b are, for example, optionally substituted, such as lower alkoxy-, for example methoxy-, halogen-, for example fluorine-, chlorine- or bromine-, aryl-, for example phenyl-, or aryloxy-, for example phenoxy-, monosubstituted or poly-substituted alkyl, especially lower alkyl, such as methyl, ethyl or butyl, alkenyl, such as lower alkenyl, for example allyl or butenyl, cycloalkyl, such as cyclopentyl or cyclohexyl, or naphthyl or, especially, phenyl, which are optionally monosubstituted or polysubstituted, for example by lower alkyl, for example methyl, lower alkoxy, for example methoxy, halogen, for example fluorine, chlorine or bromine, aryl, for example phenyl, aryloxy, for example phenoxy, or nitro, such as phenyl, 2-, 3- or, preferably, 4-tolyl, 2-, 3- or, preferably, 4-methoxyphenyl, 2-, 3- or 4-chlorophenyl, 4-biphenyl, 4-phenoxy-

phenyl, 4-nitrophenyl or 1- or 2-naphthyl.

Suitable bases for the cyclisation reaction are, in particular, strong organic or inorganic bases. Bases to be singled out are, in particular, bicyclic amidines, such as corresponding diazabicycloalkenes, for example 1,5-diazabicyclo[4.3.0]non-5-ene or 1,5-diazabicyclo[5.4.0]undec-5-ene, and also substituted guanidines, for example guanidines polysubstituted by lower alkyl, such as methyl, such as tetramethylguanidine, and also metal bases, such as alkali metal hydrides, amides or alcoholates, especially lower alkanolates, for example the hydrides, amides or alcoholates, especially lower alkanolates, of lithium, sodium or potassium, for example sodium hydride, lithium di-lower alkylamides, such as lithium diisopropylamide, or potassium lower alkanolates, such as potassium tert-butylate. Starting materials X, wherein the carboxyl group is in the form of a halogenocarbonyl group, for example a chlorocarbonyl group, can also be cyclised by treatment with a tertiary organic nitrogen base, for example a tri-lower alkylamine, such as triethylamine, and in the presence of an alcohol, such as a suitable lower alkanol, for example tert.-butanol, it is possible to obtain the corresponding ester of a compound I.

The reaction according to the invention is carried out in the presence of a suitable inert solvent, for example in an optionally halogenated, for example chlorinated, aliphatic, cycloaliphatic or aromatic hydrocarbon, such as hexane, cyclohexane, benzene, toluene or methylene chloride, an ether, such as di-lower alkyl ether, for example diethyl ether, a di-lower alkoxy-lower alkane, such as dimethoxyethane, or a cyclic ether, such as dioxane or tetrahydrofuran, or also a lower alkanol, for example methanol, ethanol or tert.-butanol, or in a mixture thereof, at room temperature or, if necessary, with slight warming, for example up to about 50°C, and, if desired, in an inert gas atmosphere, such as a nitrogen atmosphere.

When a starting material X, wherein R_5 denotes a $-\text{S}-\text{R}_5^b$ group, for example the 2-benzthiazolylthio radical, is treated with one of the said bases, for example with 1,5-diazabicyclo[5.4.0]undec-5-ene, it is possible to increase the yield by adding a sulphinic acid of the formula $\text{H}-\text{SO}_2-\text{R}_5^b$, for example p-toluenesulphinic acid.

In the cyclisation reaction according to the invention it is possible, depending on the starting material and the reaction conditions, to obtain a single 3-cephem compound or a mixture thereof with the corresponding 2-cephem compound. Resulting mixtures can be separated in a manner which is in itself known with the aid

of separation procedures, for example by adsorption and fractional elution, including chromatography (column, paper or plate chromatography) using suitable adsorbents, such as silica gel or aluminium oxide, and eluants, and also by fractional crystallization, solvent partition and the like.

The starting materials X can be obtained, for example, when a 6-acylamino-2,2-dimethyl-penam-3-carboxylic acid XI, wherein acyl represents a D-2-amino-2-(lower alkylsulphonylamino)-acetyl radical, in which the 2-amino group is preferably in a protected form and the lower alkylsulphonylamino group can be N-acylated, or any other removable acyl radical of an organic carboxylic acid, in which case any functional groups which may be present in such a radical are preferably in a protected form, and wherein the carboxyl group is in a protected form, is converted, in a manner which is in itself known, for example by treatment with a percarboxylic acid, such as 3-chloroperbenzoic acid, into the corresponding 1-oxide. A 2-(3-acylamino-4-R₂-thio-2-oxo-1-azetidiny)-3-methyl-3-butenic acid XVI, and wherein R₂ represents a S-R₁, -SO₂-R₁ or -S-SO₂-R₁ radical is obtained from the above 1-oxide by reaction with a mercaptan of the formula HS-R₁ (XII), with a sulphinic acid of the formula H-SO₂-R₁ (XIII) or with a corresponding cyanide of the formula N≡C-SO₂-R₁ (XIV), the latter preferably being employed in the presence of a quaternary ammonium halide, or with a thiosulphonic acid of the formula HS-SO₂-R₁ (XV). Compounds XVI, wherein R₁ denotes a -SO₂-R₁ or -S-SO₂-R₁ radical, can also be obtained with a compound XVI, wherein R₁ represents a R₁ radical, is reacted with a corresponding heavy metal sulphinic or heavy metal thiosulphinate, wherein the preferred heavy metals are, for example, monovalent or divalent cations of copper, mercury, silver or tin. These heavy metal salt reagents can optionally be formed *in situ* from the corresponding sulphinic or thiosulphonic acids, or readily soluble salts thereof, by reaction with a suitable heavy metal salt, such as copper-II sulphate, mercury-II diacetate, silver nitrate or tin-II chloride.

In a 3-butenic acid compound XVI, wherein the carboxyl group is in a protected form, the terminal vinylene grouping is converted by oxidation, preferably by treatment with ozone, into the corresponding ozonide and this is decomposed, at the same time or subsequently, by reaction with a suitable reducing agent, such as an alkali metal bisulphite, for example sodium bisulphite, a di-lower alkyl sulphide, for example dimethyl sulphide, a phosphine, for example

triphenylphosphine, or tetracyanoethylene. In this way 2-(3-acylamino-4-R₂-thio-2-oxo-1-azetidiny)-3-hydroxy-crotonic acid (XVII), wherein the carboxyl group is in a protected form and R₂ has the above-mentioned meaning, is obtained. The hydroxy group can now be etherified in a manner which is in itself known, for example as described above, for example by treatment with a diazo-lower alkane, a suitable reactive ester of a lower alcohol, such as a corresponding sulphate, halogenosulphate or sulphonate, with a tri-lower alkyl-oxonium, di-lower alkylcarbenium or di-lower alkylhalonium salt, such as the hexafluoroantimonate, hexafluorophosphate or tetrafluoborate, or with a 1-lower alkyl-triazine compound substituted in the 3-position, such as a 1-lower alkyl-triazine compound substituted in the 3-position by 4-methyl-phenyl, and converted into the desired lower alkoxy group.

If necessary, it is possible at any suitable stage of the manufacture of a starting material X to split off an acyl group which differs from D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetyl, for example by treatment with phosphorus pentachloride in the presence of pyridine, followed by methanol and, optionally, water, and to acylate the free amino group of an intermediate product, which is thus obtainable, with a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetyl radical, wherein 2-amino is preferably in a protected form and lower alkylsulphonylamino is optionally in a N-acylated form, by treatment with the corresponding acid or a reactive derivative, such as an anhydride, preferably a mixed anhydride, for example the chloride, thereof. Furthermore, it is possible, at the suitable stages, to convert a radical R₁ into another radical R₂ and/or to convert a group which is present in the free form or a protected form into a protected form or the free form, or into another protected form.

The new compounds I can also be obtained when a 7β - [D - 2 - amino - 2-(aminophenyl) - acetylaminol - 3 - R - 3-cephem - 4 - carboxylic acid (XVIII), wherein the 2-amino group is in a protected form, the carboxyl group is optionally in a protected form and the amino group on the phenyl ring is optionally in a reactive protected form, that is to say in a form which permits sulphonylation, for example the acylated form, is treated with a lower alkanesulphonic acid or a reactive functional derivative thereof and, if necessary or desired, the additional measures are carried out.

In a starting material XVIII, the carboxyl group can be protected, preferably in an esterified form, for example as described

above, and above all in the form of a silyl ester, such as a trimethylsilyl ester (which usually is manufactured immediately prior to the acylation reaction by treatment with a corresponding silylating agent, for example trimethylchlorosilane or bis-(trimethylsilyl)-acetamide). The carboxylic acid starting material XVIII can, however, also be employed in the form of a salt, for example in the form of an ammonium salt, such as in the form of a triethyl-ammonium salt, or in a protected form, which is obtainable by reacting the carboxylic acid starting material XVIII with a suitable organic phosphoric halide compound, such as with a lower alkyl- or lower alkoxy-phosphorus dihalide, such as methyl-phosphorus dichloride, ethyl-phosphorus dibromide or methoxy-phosphorus dichloride. An amino group, on the phenyl ring, which is in a reactive protected form is, for example, an amino group protected by a silyl radical, such as one of the corresponding radicals mentioned above, or also one of the abovementioned acylated amino groups, for example the tert-butoxyamino group.

The sulphonylation of the free amino group, or the reactive protected amino group, in the starting material XVIII is carried out in a manner which is in itself known. Sulphonylating agents which can be used are lower alkyl-sulphonic acids or reactive derivatives thereof.

If a free lower alkylsulphonic acid is employed for the sulphonylation, suitable condensing agents, such as carbodiimides, for example N,N'-diethyl-, N,N'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexyl- or N-ethyl - N' - 3 - diethylaminopropyl - carbodiimide, suitable carbonyl compounds, for example carbonyldiimidazole, or isoxazolinium salts, for example N-ethyl-5-phenyl-isoxazolinium 3'-sulphonate and N-tert.butyl-5-methyl-isoxazolinium perchlorate, or a suitable acylamino compound, for example 2-ethoxy-1-ethoxy-carbonyl-1,2-dihydroquinoline, are customarily used. The condensation reaction is preferably carried out in an anhydrous reaction medium, for example in methylene chloride, dimethylformamide or acetonitrile.

A functional derivative of a lower alkyl-sulphonic acid is, above all, an anhydride thereof, including, and preferably, a mixed anhydride. Mixed anhydrides are, for example, those with inorganic acids, especially with hydrogen halide acids, that is to say the corresponding sulphonic acid halides, for example the sulphonic acid chloride or sulphonic acid bromide, and also the anhydride with hydrazoic acid, that is to say the corresponding acid azide, with a phosphorus-containing acid, for example phosphoric acid or phosphorus acid, with a

sulphur-containing acid, for example sulphuric acid, or with hydrocyanic acid. Further mixed anhydrides are, for example, those with organic acids, such as organic carboxylic acids, such as with lower alkane-carboxylic acids which are optionally substituted, for example by halogen, such as fluorine or chlorine, for example pivalic acid or trichloroacetic acid, or with half-esters, especially lower alkyl half-esters, of carbonic acid, such as the ethyl or isobutyl half-ester of carbonic acid, or with organic, especially aliphatic or aromatic, sulphonic acids, for example p-toluenesulphonic acid.

Further sulphonic acid derivatives which are suitable for reaction with the amino group in a starting material XVIII are activated esters of lower alkylsulphonic acids, which usually have a protected amino group, such as esters with vinylogous alcohols (that is to say enols), such as vinylogous lower alkenols, or aryl esters, such as phenyl esters, which are preferably substituted, for example by nitro or halogen, such as chlorine, for example pentachlorophenyl, 4-nitrophenyl or 2,4-dinitrophenyl esters, hetero-aromatic esters, such as benzotriazole esters, or diacylimino-esters, such as succinylimino- or phthalylimino-esters.

The sulphonylation with a sulphonic acid derivative, such as with an anhydride and especially with a sulphonic acid halide, can be carried out in the presence of an acid-binding agent, for example an organic base, such as an organic amine, for example a tertiary amine, such as a tri-lower alkylamine, for example triethylamine, a N,N-di-lower alkyl-aniline, for example N,N-dimethyl-aniline, or a base of the pyridine type, for example pyridine, an inorganic base, for example an alkali metal hydroxide, carbonate or bicarbonate or alkaline earth metal hydroxide, carbonate or bicarbonate, for example sodium hydroxide, carbonate or bicarbonate, potassium hydroxide, carbonate or bicarbonate or calcium hydroxide, carbonate or bicarbonate, or an oxirane, for example a lower 1,2-alkylene oxide, such as ethylene oxide or 1,2-propylene oxide.

The above sulphonylation can be carried out in an aqueous or, preferably, non-aqueous solvent or solvent mixture, for example in a carboxylic acid amide, such as a N,N-di-lower alkylamide, for example dimethylformamide, a halogenated hydrocarbon, for example methylene chloride, carbon tetrachloride or chlorobenzene, a ketone, for example acetone, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or in mixtures thereof, and, if necessary, at a lowered or elevated temperature, for example at about 0° to about 100°C, and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

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The starting materials (XVIII) can be obtained when the 7 β -amino group in a 7 β -amino-3-R-3-cephem-4-carboxylic acid (VI), wherein the carboxyl group is optionally in a protected form and the 7 β -amino group is optionally in a reactive protected form, that is to say in a form which permits acylation, is acylated with a D-2-amino-2-(Am-phenyl)-acetyl radical, wherein Am denotes a protected or masked amino group which can be converted into a free amino group and wherein the 2-amino group is protected, and, in a resulting 7 β -(2-amino-2-(Am-phenyl)-acetyl-amino)-3-R-3-cephem-4-carboxylic acid, wherein the 2-amino group is in a protected form and the carboxyl group is optionally in a protected form, the group Am is optionally converted into a free amino group.

A group Am is, for example, a protected amino group which differs from the protected 2-amino group in the way in which it is converted into a free amino group and which can be converted selectively into a free amino group, that is to say without simultaneously liberating the 2-amino group. Thus, for example, the 2-amino group can be protected by a tert.-butoxycarbonyl group and Am can denote a 2,2,2-trifluoroacetoxycarbonylamino group, and in this case the latter can be split into a free amino group using zinc and acetic acid, whilst the 2-tert.-butoxycarbonylamino group remains intact under these conditions. Further such pairs of amino protective groups, and the methods for their selective splitting, can be taken from the description of the additional measures which is given further below. Masked amino groups Am are, for example, the azido group and, in particular, the nitro group.

The acylation of the 7 β -amino-3-R-3-cephem-4-carboxylic acid VI, wherein the functional groups are protected as indicated, is carried out in a manner which is in itself known with D-2-amino-2-(Am-phenyl)-acetic acid, wherein the amino groups are, as indicated, in a protected or masked form, or with a reactive functional derivative thereof, for example an anhydride, such as a corresponding acid chloride, as has been indicated above for the acylation of protected compounds VI with protected D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetic acids VII, or their reactive functional derivatives.

The choice of the carboxyl protective group and of the 2-amino protective group in the starting material VI depends, as indicated above, on the protected or masked amino group Am which is to be used. The conversion of these groups Am in a resulting acylated compound XVIII into a free amino group is carried out in a manner which is in itself known, as indicated further

below for the conversion of protected and masked amino groups. A nitro group Am can, analogously to an azido group, be converted into a free amino group by reduction.

In the compounds obtainable according to the invention, protected carboxyl and/or amino groups and/or N-acylated lower alkylsulphonylamino groups are optionally liberated at the same time in a manner which is in itself known, such as by means of solvolysis, including hydrolysis, alcoholysis or acidolysis, or by means of reduction, including hydrogenolysis or chemical reduction.

Thus, for example, a tert.-lower alkoxy-carbonyl, polycycloalkoxycarbonyl or diphenylmethoxycarbonyl group can be converted into a free carboxyl group by treatment with a suitable acid agent, such as formic acid or trifluoroacetic acid, optionally with the addition of a nucleophilic compound, such as phenol or anisole. An optionally substituted benzyloxy-carbonyl group can, for example, be liberated by means of hydrogenolysis by treatment with hydrogen in the presence of a hydrogenation catalyst, such as a palladium catalyst. Furthermore, certain substituted benzyloxy-carbonyl groups, such as 4-nitrobenzyloxy-carbonyl, can also be converted into a free carboxyl group by means of chemical reduction, for example by treatment with an alkali metal dithionite, for example sodium dithionite, or with a reducing metal, for example zinc, or with a metal salt, such as a chromium-II salt, for example chromium-II chloride, usually in the presence of a hydrogen donor, which, together with the metal, is able to produce nascent hydrogen, such as an acid, above all acetic acid, and also formic acid, or an alcohol, in which case water is preferably added. By means of treatment with a reducing metal or metal salt, as described above, it is also possible to convert a 2-halogeno-lower alkoxy-carbonyl group (optionally after converting a 2-bromo-lower alkoxy-carbonyl group into a 2-iodo-lower alkoxy-carbonyl group) or an acylmethoxycarbonyl group into a free carboxyl group, and an arylmethoxycarbonyl group can also be split by treatment with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate or sodium iodide. A carboxyl group protected, for example, by silylation can be liberated in the customary manner, for example by treatment with water or an alcohol. Analogously, a carboxyl group protected by reaction with an organic phosphorus halide compound can also be liberated by hydrolysis or alcoholysis.

A protected amino group is liberated in a manner which is in itself known and which

differs depending on the nature of the protective group, for example by means of solvolysis or reduction. A 2-halogeno-lower alkoxy-carbonylamino group (optionally after converting a 2-bromo-lower alkoxy-carbonyl group into a 2-iodo-lower alkoxy-carbonyl group), an acylmethoxycarbonylamino group or, for example, a 4-nitro-benzyloxycarbonylamino group can be liberated, for example, by treatment with a suitable chemical reducing agent, such as zinc in the presence of aqueous acetic acid, an aroylmethoxycarbonylamino group can also be liberated by treatment with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate, and a 4-nitro-benzyloxycarbonylamino group can also be liberated by treatment with an alkali metal dithionite, for example sodium dithionite, a diphenylmethoxycarbonylamino, tert.-lower alkoxy-carbonylamino or polycycloalkoxy-carbonylamino group can be liberated by treatment with, for example, formic acid or trifluoroacetic acid, an optionally substituted benzyloxycarbonylamino group can be liberated, for example, by means of hydrogenolysis by treatment with hydrogen in the presence of a hydrogenation catalyst, such as a palladium catalyst, an arylthioamino or aryl-lower alkylthioamino group can be liberated, for example, by treatment with a nucleophilic reagent, such as sulphurous acid, an arylsulphonylamino group can be liberated, for example, by means of electrolytic reduction, a 1-acyl-2-lower alkylideneamino group or a triarylmethyl group can be liberated, for example, by treatment with an aqueous mineral acid and an amino group protected by an organic silyl group can be liberated, for example, by means of hydrolysis or alcoholysis.

An amino group protected in the form of an azido group is converted into a free amino group in a manner which is in itself known, by reduction, for example by catalytic hydrogenation with hydrogen and a hydrogenation catalyst, such as platinum oxide, palladium or Raney nickel, or by means of zinc and an acid, such as acetic acid. The catalytic hydrogenation is preferably carried out in an inert solvent, such as a halogenated hydrocarbon, for example methylene chloride, or also in water or a mixture of water and an organic solvent, such as an alcohol or dioxane, at about 20 to 25°, or also at a lowered or elevated temperature.

A N-acylated lower alkylsulphonylamino group is also converted into a lower alkylsulphonylamino group in a manner which is in itself known, for example by solvolysis or reduction. The methods which can be used to split off these N-acyl groups are the same as those indicated for splitting off acyl

groups, for example 2-halogeno-lower alkoxy-carbonyl, acylmethoxycarbonyl, 4-nitrobenzyloxycarbonyl, aroylmethoxycarbonyl, diphenylmethoxycarbonyl, tert.-lower alkoxy-carbonyl, polycycloalkoxy-carbonyl, benzyloxycarbonyl or arylsulphonyl, from corresponding acylamino groups.

Salts of the new compounds I can be manufactured in a manner which is in itself known. Thus, salts can be formed, for example, by treatment with metal compounds, such as alkali metal salts of suitable carboxylic acids, for example the sodium salt of α -ethyl-caproic acid, or with ammonia or a suitable organic amine, preferably using stoichiometric amounts or only a small excess of the salt-forming agent. Acid addition salts are obtained in the customary manner, for example by treatment with an acid or a suitable anion exchange reagent. Inner salts can be formed, for example, by neutralising, for example, salts, such as acid addition salts, to the isoelectric point, for example with weak bases, or by treatment with liquid ion exchangers.

Resulting salts can be converted into the free compounds in the customary manner, metal salts and ammonium salts, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

The process also comprises those embodiments according to which the starting materials are obtained in situ.

Preferably, the starting materials used and the reaction conditions chosen are such that the compounds mentioned initially as being particularly preferred are obtained.

The new compounds of the present invention can, for example, be used for the manufacture of pharmaceutical formulations which contain an effective amount of the active substance together with, or mixed with, inorganic or organic, solid or liquid, pharmaceutically usable excipients which are suitable for enteral or parenteral administration. Thus, tablets or gelatine capsules are used which contain the active compound together with diluents, for example lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol; tablets also contain binders, for example magnesium aluminium silicate, starches, such as maize starch, wheat starch, rice starch or arrowroot, gelatine, tragacanth, methylcellulose, sodium carboxymethyl-cellulose and/or polyvinylpyrrolidone and, if desired, disintegrating agents, for example starches, agar, alginic acid or a salt thereof, such as

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sodium alginate, and/or effervescent mixtures, or adsorbents, dyestuffs, flavourings and sweeteners. Furthermore, the new pharmacologically active compounds can be used in the form of injectable formulations, for example formulations which can be administered intravenously, or of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions and these can, for example, be manufactured before use from lyophilised formulations which contain the active compound on its own or together with an excipient, for example mannitol. The pharmaceutical formulations can be sterilised and/or contain auxiliaries, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilising agents, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical formulations which can, if desired, contain further pharmacologically valuable substances, are manufactured in a manner which is in itself known, for example by means of conventional mixing, granulating, dragée-making, dissolving or lyophilising processes, and contain from about 0.1% to 100%, and especially from about 1% to about 50%, of the active substance and lyophilisates contain up to 100% of the active substance. The individual dose for a warm-blooded animal about 70 kg in weight is between 0.1 and 0.75 g and the daily dose is between 0.2 and 1.0 g.

In the context of the present description, the organic radicals described as "lower" contain, unless expressly defined, up to 7, and preferably up to 4, carbon atoms.

The examples which follow serve to illustrate the invention; temperatures are given in degrees centigrade.

Example 1.

a) 1.04 ml of bis-(trimethylsilyl)-acetamide are added to a suspension of 0.764 g of finely powdered 7 β -amino-3-methoxy-3-cephem-4-carboxyl acid hydrochloride, which contains one mole of dioxane, in 10 ml of absolute methylene chloride, under an argon atmosphere and at room temperature (the addition is effected in the course of about 10 minutes) and the mixture is stirred for 45 minutes.

0.34 ml of isobutyl chloroformate is added to a solution, which has been cooled to -15°, of 0.896 g of D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetic acid and 0.29 ml of 4 - methyl - morpholine in 10 ml of absolute methylene chloride, under an argon atmosphere, and the mixture is allowed to react for a further 15 minutes. The silylated starting material described above is added dropwise, at -10°, to the mixed anhydride which is thus obtainable

and the reaction mixture is stirred for 15 minutes at -10°, for 15 minutes at 0° and for 15 minutes at room temperature. It is then diluted with 100 ml of ethyl acetate and washed three times with a saturated aqueous solution of sodium chloride. The aqueous phases are again extracted with ethyl acetate and the combined organic solutions are dried over magnesium sulphate and freed from solvent under reduced pressure. The residue is purified over silica gel using a 1:1 mixture of methylene chloride and ethyl acetate as the eluant. 7 β - [D - 2 - tert. - Butoxycarbonylamino - 2 - (3 - methylsulphonylamino-phenyl) - acetylamino] - 3 - methoxy - 3-cephem - 4 - carboxylic acid, which according to thin layer chromatography is a single compound, is obtained as an amorphous product; thin layer chromatogram (silica gel; identification with ninhydrin): Rf=0.63 (system: sec.-butanol/acetic acid/water, 67:10:23), ultraviolet absorption spectrum (in 95% strength aqueous ethanol): λ_{max} =273 nm (ϵ =7,100); infrared absorption spectrum (in methylene chloride): characteristic bands at 3,580, 2,930, 1,765, 1,685, 1,605, 1,485 and 1,160.

The same compound can also be obtained as follows:

ai) 7.52 ml of bis-(trimethylsilyl)-acetamide are added to a suspension of 6.22 g (27 mmols) of finely powdered 7 β -amino-3-methoxy-3-cephem-4-carboxylic acid in 120 ml of absolute methylene chloride, under an argon atmosphere and at room temperature, (the addition is effected in the course of about 10 minutes) and the mixture is stirred for 45 minutes.

3.93 ml of isobutyl chloroformate are added to a solution, which has been cooled to -15°, of 10.33 g (30 mmols) of D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino-phenyl) - acetic acid and 3.33 ml of 4 - methyl - morpholine in 180 ml of absolute acetonitrile, under an argon atmosphere, and the mixture is allowed to react for a further 25 minutes. The silylated starting material described above is added dropwise, at -15°, to the mixed anhydride which is thus obtainable and the reaction mixture is stirred for 2 hours at 0° and for 30 minutes at room temperature. The solvent is then removed in a rotary evaporator and the residue is taken up in 400 ml of ethyl acetate and washed three times with a saturated aqueous solution of sodium chloride. The aqueous phases are again extracted with ethyl acetate. The combined organic solutions are dried over magnesium sulphate and freed from solvent under reduced pressure. The residue is purified over silica gel using a 1:1 mixture of methylene chloride and ethyl acetate as the eluant. 7 β - [D - 2 - tert. - Butoxycar-

bonylamino - 2 - (3 - methylsulphonylamino-phenyl) - acetamino] - 3 - methoxy - 3-cephem - 4 - carboxylic acid, which according to thin layer chromatography in a single compound, is obtained as an amorphous product which, when crystallised from 1:3 methylene chloride/diethyl ether, has a melting point of 140° (decomposition). The physicochemical data are identical to those of Example 1a).

10 aii) 1.23 ml of N,O - bis - (trimethylsilyl)-acetamide are added to a suspension of 891 mg of 7 - amino - 3 - methoxy - cephem - 4 - carboxylic acid in 10 ml of absolute methylene chloride and the mixture is stirred for 1 hour at 23° (solution A).

15 0.58 ml of isobutyl chloroformate is added to a solution of 1.58 g of D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetic acid and 0.52 ml of N - methylmorpholine in 20 ml of acetonitrile, at -10° to -15°, and the mixture is stirred at this temperature for ½ hour (solution B).

25 Solution A is added rapidly, under nitrogen, to solution B, which has been cooled to -25°C, and the mixture is then stirred for 1½ hours at 0°.

30 The batch is stirred into 100 ml of a 1/3 M phosphate buffer which has a pH of 7 and the mixture is freed from organic solvents in vacuo. The residual aqueous solution is washed with ethyl acetate in order to remove the neutral constituents. 35 The aqueous phase is covered with a layer of further ethyl acetate, acidified to pH 2 with 85% strength phosphoric acid, cooled and saturated with sodium chloride. Phase separation and subsequent extraction with ethyl acetate gives an extract which, when dried over sodium sulphate and evaporated, gives 7β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino-phenyl) acetamino] - 3 - methoxy - 3-cephem - 4 - carboxylic acid, which in a thin layer chromatogram is a single compound, in the form of a pale beige foam. The compound can be crystallised according to Example 1 ai).

50 The starting material can be obtained as follows:

55 b) 35 ml of dimethyldichlorosilane are added to a suspension of 1.17 g of 7β-phenoxyacetyl amino - 3 - methoxy - 3-cephem - 4 - carboxylic acid and 1.45 ml of N,N - dimethylaniline in 5.5 ml of absolute methylene chloride, under a nitrogen atmosphere and at 20°, and the mixture is then stirred for 30 minutes at the same temperature. The clear solution is cooled to -20°, 0.8 g of phosphorus pentachloride is added and the mixture is stirred for 30 minutes. At the same temperature, a mixture, which has been precooled to -20°, of 0.45 ml of N,N-dimethylaniline and 0.45

ml of n-butanol is added in the course of 2 to 3 minutes and 10 ml of n-butanol, which has been precooled to -20°, are then added rapidly and the mixture is then stirred for 20 minutes at -20° and for 10 minutes without cooling. 0.2 ml of water is added at about -10°, the mixture is stirred in an ice bath (about 0°) for about 10 minutes, 5.5 ml of dioxane are then added and, after stirring for a further 10 minutes at 0°, about 2.25 ml of tri-n-butylamine are added in portions until samples diluted with water assume a constant pH value of 3.5. After stirring for 1 hour at 0°, the precipitate is filtered off, washed with dioxane and recrystallised from a mixture of water and dioxane. The hydrochloride of 7β-amino-3-methoxy-3-cephem-4-carboxylic acid, which is thus obtainable, contains one mole of dioxane and has a melting point of above 300°; thin layer chromatogram: Rf 0.17 (silica gel; system n-butanol/carbon tetrachloride/methanol/formic acid/water, 30:40:20:5:5).

Example 2.

a) In a manner analogous to Example 1a), treatment of the mixed anhydride, obtained from 0.448 g of D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetic acid and 0.17 ml of isobutyl chloroformate in the presence of 0.14 ml of 4-methylmorpholine and 5 ml of methylene chloride at -15°, with trimethylsilyl 7β - amino - 3 - chloro - 3 - cephem - 4 - carboxylate, obtained from 0.24 g of 7β-amino - 3 - chloro - 3 - cephem - 4 - carboxylic acid and 0.5 ml of bis - (trimethylsilyl) - acetamide in 10 ml of methylene chloride, gives, by the process described above, 7β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino-phenyl) - acetamino] - 3 - chloro - 3 - cephem - 4 - carboxylic acid.

ai) In a manner analogous to Example 1ai), treatment of the mixed anhydride, obtained from 1.55 g (4.5 mmols) of D - 2 - tert.-butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetic acid and 0.6 ml of isobutyl chloroformate in the presence of 0.5 ml of 4-methylmorpholine and 25 ml of acetonitrile at -15°, with trimethylsilyl 7β - amino - 3 - chloro - 3 - cephem - 4 - carboxylate, obtained from 0.88 g (3.75 mmols) of 7β - amino - 3 - chloro - 4 - carboxylic acid and 1.05 ml of bis-(trimethylsilyl)-acetamide in 20 ml of methylene chloride, gives, by the process described above, 7β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino-phenyl) - acetamino] - 3 - chloro - 3-cephem - 4 - carboxylic acid; thin layer chromatogram (silica gel; identification with ninhydrin): Rf ~0.58 (system: sec.-butanol/acetic acid/water, 67:10:23), IR spectrum (in methylene chloride): characteristic bands

at 3,390, 2,930, 1,775, 1,685, 1,485 and 1,160 cm^{-1} .

The starting material can be obtained as follows:

- 5 b) 1.59 g (4 mmols) of diphenylmethyl 7 β -amino-3-chloro-3-cephem-4-carboxylate are dissolved in 5 ml of trifluoroacetic acid at 0° and the solution is stirred for 15 minutes. The clear, pale yellow solution is diluted with 20 ml of toluene and then freed from excess trifluoroacetic acid and toluene under reduced pressure. The residue is dissolved in about 20 ml of water/ethyl acetate (1:1), the organic phase is separated off and the acid aqueous phase is brought to a pH of 3.0 with 20% strength triethylamine in methanol. The pale yellow precipitate is filtered off, washed with ethyl acetate and diethyl ether and dried under a high vacuum. 320 mg of 7 β -amino-3-chloro-3-cephem-4-carboxylic acid are isolated as a pale yellow amorphous powder; thin layer chromatogram: R_f =0.08 (silica gel, n-butanol/acetic acid/water, 67:10:23).

Example 3.

- 25 1.18 ml (9 mmols) of isobutyl chloroformate are added to a solution, which has been cooled to -15°, of 3.1 g (9 mmols) of D-2-tert.-butoxycarbonylamino-2-(3-methylsulphonylamino-phenyl)-acetic acid and 1.0 ml of 4-methylmorpholine in 50 ml of absolute acetonitrile, under an argon atmosphere and with the exclusion of moisture. After 30 minutes, 3.0 g (7.5 mmols) of diphenylmethyl 7 β -amino-3-chloro-3-cephem-4-carboxylate, dissolved in 50 ml of absolute methylene chloride, are added, at -15°, to the mixed anhydride thus obtained. The reaction mixture is stirred for 1½ hours at 0° and for 1½ hours at room temperature. The solvents are then removed in a rotary evaporator. The residue is dissolved in 500 ml of ethyl acetate and washed three times with a saturated aqueous solution of sodium chloride. The organic phase is dried over magnesium sulphate and freed from solvent under reduced pressure. The crude product is purified over 40 times the amount of silica gel using 1:1 methylene chloride/ethyl acetate as the eluant. Diphenylmethyl 7 β -[D-2-tert.-butoxycarbonylamino-2-(3-methylsulphonylamino-phenyl)-acetylamino]-3-chloro-3-cephem-4-carboxylate, which according to thin layer chromatography is a single compound and which has a melting point of 184—187° (from acetone/ether/petroleum ether, 1:2:2) is obtained; thin layer chromatogram (silica gel; identification with ninhydrin): R_f ~0.52 (system: toluene/ethyl acetate, 1:1). IR spectrum (in methylene chloride): characteristic bands at 3,420, 1,790, 1,725, 1,700, 1,620 and 1,158 cm^{-1} .

Example 4.

In a manner analogous to Example 3, treatment of the mixed anhydride, obtained from 1.05 g (4.5 mmols) of D-2-tert.-butoxycarbonylamino-2-(3-methylsulphonylamino-phenyl)-acetic acid and 0.6 ml of isobutyl chloroformate in the presence of 0.5 ml of N-methylmorpholine in 25 ml of acetonitrile at -15°, with 1.49 g (3.75 mmols) of diphenylmethyl 7 β -amino-3-methoxy-4-carboxylate, dissolved in 25 ml of methylene chloride, gives, by the process described above, diphenylmethyl 7 β -[D-2-tert.-butoxycarbonylamino-2-(3-methylsulphonylamino-phenyl)-acetylamino]-3-methoxy-3-cephem-4-carboxylate: melting point 127—130°; thin layer chromatogram: R_f ~0.21 (silica gel; toluene/acetone, 3:1); IR spectrum (in methylene chloride): characteristic bands at 3,440, 1,787, 1,725, 1,705, 1,342 and 1,162 cm^{-1} .

Example 5.

a) 0.31 ml of (4.22 mmols) of thionyl chloride and then 1.5 g (2.11 mmols) of diphenylmethyl 7 β -[D-2-tert.-butoxycarbonylamino-2-(3-methylsulphonylamino-phenyl)-acetylamino]-3-hydroxy-3-cephem-4-carboxylate, dissolved in 6 ml of dimethylformamide, are added carefully dropwise, with the exclusion of moisture and under an argon atmosphere, to 6 ml of dimethylformamide, which has been cooled to 0°. The reaction mixture is brought to room temperature, stirred for a further 4 hours, then diluted with methylene chloride and washed twice with ice water and twice with a saturated aqueous solution of sodium chloride. The organic phase is dried (MgSO_4) and freed from solvent under reduced pressure. The residue, which is a yellow oil, is purified over 30 times the amount of silica gel using 4:1 toluene/ethyl acetate as the eluant and diphenylmethyl 7 β -[D-2-tert.-butoxycarbonylamino-2-(3-methylsulphonylamino-phenyl)-acetylamino]-3-chloro-3-cephem-4-carboxylate is obtained; the physicochemical data of this product are identical to those of the product obtained according to Example 3.

The starting material can be prepared as follows:

b) 1.04 ml (4.16 mmols) of bis-trimethylsilyl-acetamide are added to a solution of 2.17 g (4.16 mmols) of diphenylmethyl 7 β -amino-3-hydroxy-3-cephem-4-carboxylate in 25 ml of freshly distilled methylene chloride. The reaction mixture is stirred for 45 minutes at room temperature, under an argon atmosphere.

0.8 ml of isobutyl chloroformate is added to a solution which has been cooled to -15°, of 2.0 g (5.8 mmols) of D-2-tert.-

butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetic acid and 0.65 ml of N-methyl-morpholine in 24 ml of absolute methylene chloride, with the exclusion of moisture and under an argon atmosphere, and the mixture is allowed to react for a further 20 minutes at -15° . The silylated starting material, which has been described above and has been cooled to -10° , is added dropwise to the mixed anhydride thus obtained and the reaction mixture is then stirred for $\frac{1}{2}$ hour at -10° and for $\frac{1}{2}$ hour at 0° . The reaction solution is then diluted with 100 ml of ethyl acetate and washed three times with a saturated aqueous solution of sodium chloride. After drying the organic phase (MgSO_4), the solvent is removed in a rotary evaporator. The oily residue is purified over 70 g of silica gel using a 4:1 mixture of toluene/ethyl acetate as the eluant. Diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - hydroxy - 3 - cephem - 4 - carboxylate, which according to thin layer chromatography is a single compound, is obtained as an amorphous product; thin layer chromatogram: $R_f \sim 0.18$ (silica gel; ethyl acetate); IR spectrum (in methylene chloride): characteristic bands at 3,380, 1,775, 1,685, 1,605, 1,485 and $1,160 \text{ cm}^{-1}$.

Example 6.

850 mg (1.2 mmols) of diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - hydroxy - 3 - cephem - 4 - carboxylate are dissolved in a mixture of 1 ml of carbon tetrachloride and 20 ml of methylene chloride, 520 mg (2.0 mmols) of triphenylphosphine are added at room temperature and the mixture is left to stand for 24 hours. The reaction mixture is diluted with 50 ml of methylene chloride and washed three times with a saturated solution of sodium chloride. The organic phase is dried (MgSO_4) and freed from solvent in a rotary evaporator. The residue, which is a yellow oil, is purified over 30 times the amount of silica gel using 1:1 toluene/ethyl acetate as the eluant and, after crystallization from methylene chloride/ether, diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - chloro - 3 - cephem - 4 - carboxylate which has a melting point of $126-129^{\circ}$ is obtained.

Example 7.

a) 0.12 ml (0.508 mmol) of bis-trimethylsilyl-acetamide is added to a solution of 400 mg (0.462 mmol) of diphenylmethyl 2 - [4 - (p - toluenesulphonylthio) - 3 - [D - 2 - tert. - butoxycarbonylamino - 2 - 3 - methylsul-

phonylamino - phenyl) - acetylamino] - 2 - oxoazetidin - 1 - yl] - 3 - hydroxycrotonate in 3 ml of 1,2-dimethoxyethane, under a nitrogen atmosphere, and the mixture is stirred for one hour at room temperature. The solution is evaporated completely and the oily residue is dried for one hour under a high vacuum. The silylated crude product is taken up in 3 ml of dried 1,2-dimethoxyethane and, after the solution has been cooled to 0°C , 0.075 ml (0.508 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene is added. After a reaction time of 6 hours at 0°C under a nitrogen atmosphere, 0.3 ml of acetic acid is added and the mixture is diluted with methylene chloride. The methylene chloride solution is washed successively with dilute sulphuric acid, water and dilute bicarbonate solution. The aqueous phases are extracted with methylene chloride and the combined organic phases are dried with sodium sulphate, concentrated in vacuo and dried under a high vacuum. Crude diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - hydroxy - 3 - cephem - 4 - carboxylate is obtained.

b) An excess of an ethereal solution of diazomethane is added, at 0°C , to a solution of the crude product in chloroform and the mixture is left to stand for 5 minutes at 0°C . It is then concentrated completely and the oily residue is chromatographed on silica gel thick layer plates (toluene/ethyl acetate, 3:1). Diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - methoxy - 3 - cephem - 4 - carboxylate is obtained; R_f value ~ 0.21 (silica gel; toluene/acetone, 3:1); melting point, $127-130^{\circ}\text{C}$ (from ether/petroleum ether, 1:1); IR spectrum (in CH_2Cl_2): 3,430, 1,787, 1,720, 1,705, 1,492 and $1,160 \text{ cm}^{-1}$.

Example 8.

A solution of 709 mg (1 mmol) of diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - hydroxy - 3 - cephem - 4 - carboxylate and 200 mg of 1-methyl - 3 - (4 - methylphenyl) - triazene in 50 ml of benzene is boiled under reflux for 2 hours. After cooling, the mixture is evaporated under reduced pressure and the residue is purified over 30 times the amount of silica gel using toluene/ethyl acetate 3:1 as the eluant. Diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - methoxy - 3 - cephem - 4 - carboxylate is obtained; ultra-violet absorption spectrum (in ethanol): $\lambda_{\text{max}} = 265 \text{ nm}$ ($\epsilon = 6,900$); infra-red absorption spectrum (in

methylene chloride); characteristics bands at 3,420, 1,787, 1,720, 1,705, 1,492 and 1,160 cm^{-1} .

Example 9.

5 1.0 ml of dimethyl sulphate and 50 mg of anhydrous potassium carbonate are added to a mixture of 230 mg (0.325 mmol) of crude diphenylmethyl 7 β - [D - α - tert.-butoxycarbonylamino - α - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3-hydroxy - 3 - cephem - 4 - carboxylate and 20 ml of acetone and the reaction mixture is stirred for 16 hours at room temperature, under a nitrogen atmosphere. The reaction mixture is evaporated under reduced pressure, the residue is taken up in methylene chloride and the solution is washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and evaporated under reduced pressure. The residue is purified by preparative layer chromatography (silica gel). The two zones which are visible under ultra-violet light ($\lambda=254 \text{ m}\mu$) are isolated. Diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 2 - cephem - 4 α - carboxylate, which has a Rf of ~ 0.28 (silica gel; system: toluene/acetone, 3:1) and diphenylmethyl 7 β - (D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylate, which has a Rf of ~ 0.22 (silica gel; system: toluene/acetone, 3:1) and a melting point of 127—131° (from ether/petroleum ether, 1:1) are obtained.

Example 10.

40 0.12 ml of diisopropyl-ethylamine and 0.192 g of trimethyloxonium tetrafluoroborate are added to a solution, which has been cooled to -10° , of 709 mg (1 mmol) of crude diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - hydroxy - 3 - cephem - 4 - carboxylate in 30 ml of absolute methylene chloride and the mixture is stirred for 30 minutes at -10° under a nitrogen atmosphere; during this time the oxonium salt gradually dissolves. The reaction mixture is poured onto a mixture of ice and a saturated aqueous solution of sodium chloride; the aqueous mixture is extracted with twice 100 ml of methylene chloride and the organic phase is separated off, dried over sodium sulphate and evaporated under reduced pressure. The residue is purified by means of preparative layer chromatography (silica gel; system: toluene/ethylacetate. The zone which is visible under ultra-violet light ($\lambda=254 \text{ m}\mu$) and which according to thin layer chromatography consists of a single compound is

isolated and stirred with 20 ml of diethyl ether; after stirring for 16 hours, diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylate is obtained in a finely crystalline form; melting point 128—131°; thin layer chromatogram (silica gel, developing with ninhydrin) Rf ~ 0.20 (toluene/acetone, 3:1).

Example 11.

a) 0.045 ml of diisopropyl-ethylamine and 0.03 ml of methyl trifluoromethanesulphonate are added to a solution of 115 mg (0.16 mmol) of crude diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - hydroxy - 3 - cephem - 4 - carboxylate in 5 ml of methylene chloride and the mixture is stirred for 30 minutes under a nitrogen atmosphere and at room temperature. The reaction mixture is worked up by the process described in Example 10) and the product is purified by means of preparative layer chromatography, whereupon diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylate which has a melting point of 127—129° is obtained.

b) Methyl fluorosulphonate can be used as the methylating agent, in place of methyl trifluoromethanesulphonate.

Example 12.

a) A solution of 223 mg (0.254 mmol) of diphenylmethyl 2 - [4 - (p - toluenesulphonylthio) - 3 - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 2 - oxo - azetidin-1 - yl] - 3 - methoxy - crotonate in 2 ml of dimethylformamide and 57 μl (0.38 mmol) of 1,5 - diazabicyclo[5.4.0]undec-5-ene are stirred for 30 minutes at room temperature, ethyl acetate is then added and the mixture is washed with water and 2 N hydrochloric acid until it gives an acid reaction and with a saturated aqueous solution of sodium chloride until it gives a neutral reaction. The organic phase is dried over sodium sulphate and evaporated in vacuo. The residue is chromatographed on silica gel thick layer plates using 4:1 toluene/acetone as the running agent. This gives diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 2 - cephem - 4 α - carboxylate; thin layer chromatogram (silica gel; toluene/acetone, 3:1); Rf value ~ 0.28 ; IR spectrum (in methylene chloride): characteristic bands at 3,400, 1,780, 1,730, 1,700, 1,620, 1,490, 1,335 and 1,160 cm^{-1} ; and diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino-

2 - (3 - methylsulphonylamino - phenyl)-
acetylaminol - 3 - methoxy - 3 - cephem - 4-
carboxylate, which has a melting point of
127—132°C (decomposition); thin layer
chromatogram: Rf value: ~0.22 (silica gel;
toluene/acetone, 3:1); UV spectrum (in
ethanol) $\lambda_{\text{max}}=265$ nm ($\epsilon=7,000$); IR spec-
trum (in methylene chloride): 3,420 (broad);
1,785, 1,725, 1,705, 1,492, 1,340 and 1,160
 cm^{-1} .

The starting material can be prepared as
follows:

b) 16.5 ml (0.12 mol) of isobutyl chloro-
formate are added to a solution, which
has been cooled to -15°C , of 41.33 g (0.12
mol) of D - 2 - tert. - butoxycarbonylamino-
2 - (3 - methylsulphonylamino - phenyl)-
acetic acid and 16.7 ml (0.12 mol) of tri-
ethylamine in 300 ml of tetrahydrofurane
and the mixture is stirred for 30 minutes
at -10°C . A solution of 21.6 g (0.10 mmol)
of 6 - amino - penicillanic acid and 15.4 ml
(0.11 mmol) of triethylamine in 300 ml of
2:1 tetrahydrofurane/water is then added.
The reaction mixture is stirred for 1 hour
at 0°C and for 2 hours at room temperature,
during which time the pH value is kept con-
stant at about 6.9 by adding triethylamine.
The pH of the reaction mixture is adjusted
to 2.0 with phosphoric acid, at 5°C , and
the mixture is saturated with sodium
chloride and extracted with three times 500
ml of ethyl acetate and the organic phase
is washed with a saturated aqueous solution
of sodium chloride, dried over sodium sul-
phate and evaporated. The crude 6 β - [D - 2 -
tert. - butoxycarbonylamino - 2 - (3 - methyl-
sulphonylamino - phenyl) - acetyl-
amino] - 2,2 - dimethyl - penam - 4 α - car-
boxylic acid which is obtained in the form
of a pale yellow foam has a Rf value, in the
thin layer chromatogram, of 0.60. (Silica
gel; ethyl acetate/n-butanol/pyridine/acetic
acid/water, 42:21:21:6:10).

c) 21.6 ml (0.25 mol) of 30% strength
hydrogen peroxide are added to a solution
of 67.84 g of crude 6 β - [D - 2 - tert. - butoxy-
carbonylamino - 2 - (3 - methylsulphonyl-
amino - phenyl) - acetylaminol - 2,2 - di-
methyl - penam - 4 α - carboxylic acid in
100 ml of glacial acetic acid in the course
of 10 minutes and the mixture is stirred for
2.5 hours at room temperature. The re-
action mixture is then poured into 2 litres
of ice water and 6 β - [D - α - tert. - butoxy-
carbonylamino - α - (3 - methylsulphonyl-
amino - phenyl) - acetylaminol - 2,2 - di-
methyl - penam - 4 α - carboxylic acid 1-
oxide, which is obtained in the form of a
voluminous precipitate, is filtered off,
washed well with water and dried in vacuo.
Further amounts of crude 6 β - [D - 2 - tert.-
butoxycarbonylamino - 2 - (3 - methylsul-
phonylamino - phenyl) - acetylaminol - 2,2-
dimethyl - penam - 4 α - carboxylic acid 1-

oxide can be obtained by extracting the
filtrate with ethyl acetate. Thin layer
chromatogram (silica gel: ethylacetate/n-
butanol/pyridine/acetic acid/water 42:21:
21:6:10) Rf value ~0.30.

d) A solution of 32.9 g (0.18 mol) of
diphenyldiazomethane in 130 ml of dioxane
is added to a mixture of 87 g (approx-
imately 0.12 mol) of crude 6 β - [D - 2 - tert.-
butoxycarbonylamino - 2 - (3 - methylsul-
phonylamino - phenyl) - acetylaminol - 2,2-
dimethyl - penam - 4 α - carboxylic acid 1-
oxide in 380 ml of dioxane and the mixture
is stirred for 2.5 hours at room temperature.
After adding 5 ml of glacial acetic acid, the
mixture is evaporated in vacuo. The residue
is digested with petroleum ether, the petro-
leum ether extract is discarded and the
residue, that is to say the 1-oxide of di-
phenylmethyl 6 β - [D - 2 - tert. - butoxy-
carbonylamino - 2 - (3 - methylsulphonyl-
amino - phenyl) - acetylaminol - 2,2 - di-
methyl - penam - 4 α - carboxylate, is iso-
lated as an amorphous powder; IR spectrum
(methylene chloride): characteristic bands
at 3,450, 3,430, 1,798, 1,750, 1,725, 1,697,
1,510, 1,390 and 1,155 cm^{-1} ; thin layer
chromatogram: Rf value ~0.22, (silica gel;
toluene/ethyl acetate, 3:1).

e) A mixture of 12.8 g (17.7 mmols) of
the 1-oxide of diphenylmethyl 6 β - [D - 2 -
tert. - butoxycarbonylamino - 2 - (3 - methyl-
sulphonylamino - phenyl) - acetylaminol]-
2,2 - dimethyl - penam - 4 α - carboxylate
and 3.26 g (19.5 mmols) of mercaptobenz-
thiazole in 170 ml of toluene is boiled for
3 hours in a reflux apparatus which has
a water separator and is then evaporated.
The residue is chromatographed over silica
gel using 3:1 toluene/ethyl acetate as the
eluant and gives amorphous diphenylmethyl
2 - [4 - (benzthiazol - 2 - yldithio) - 3 - [2-
tert. - butoxycarbonylamino - 2 - (3 - methyl-
sulphonylamino - phenyl) - acetylaminol] - 2-
oxoazetidin - 1 - yl] - 3 - methylenebutyrate;
thin layer chromatogram: Rf value ~0.38
(silica gel; toluene/ethyl acetate, 3:1).

f) 0.868 g (3.46 mmols) of silver toluene-
sulphinate is added, at 0°C , to a solution
of 2.62 g (3.0 mmols) of diphenylmethyl
2 - [4 - (benzthiazol - 2 - yldithio) - 3 - [2-
tert. - butoxycarbonylamino - 2 - (3 - methyl-
sulphonylamino - phenyl) - acetylaminol] - 2-
oxoazetidin - 1 - yl] - 3 - methylene-
butyrate in 30 ml of 9:1 acetone/water and the mix-
ture is stirred for 1 hour in an ice bath. The
precipitate which has separated out is fil-
tered off. The filtrate is taken up in toluene
and extracted by shaking with a saturated
aqueous solution of sodium chloride. The
organic phase is dried over sodium sulphate
and, after evaporation, gives amorphous
diphenylmethyl 2 - [4 - (p - toluenesul-
phonylthio) - 3 - [2 - tert. - butoxycarbonyl-
amino - 2 - (3 - methylsulphonylamino-

22

phenyl) - acetylamino] - 2 - oxoazetidin - 1 - yl] - 3 - methylene - butyrate; thin layer chromatogram: Rf value ~0.33 (silica gel; toluene/ethyl acetate, 3:1); IR spectrum (methylene chloride): characteristic bands at 3,440, 3,430, 1,785, 1,752, 1,722, 1,620, 1,510, 1,390 and 1,160 cm^{-1} .

g) A stream of ozone/oxygen (0.5 mmol of ozone per minute) is passed into a solution, which has been cooled to -70°C , of 2.59 g (3.0 mmols) of diphenylmethyl 2 - [4 - (p - toluenesulphonylthio) - 3 - [2 - tert - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 2 - oxoazetidin - 1 - yl] - 3 - methylene - butyrate in 230 ml of methylene chloride for 7 minutes. After adding 1 ml of dimethyl sulphide, the solution is stirred for a further 1 hour without cooling and then evaporated in vacuo. The residue, that is to say diphenylmethyl 2 - [4 - (p - toluenesulphonylthio) - 3 - [2 - tert - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 2 - oxoazetidin - 1 - yl] - 3 - hydroxy - crotonate, is obtained as an amorphous powder; IR spectrum (methylene chloride): characteristic bands at 3,430, 1,785, 1,720, 1,680, 1,665 (shoulder), 1,620, 1,385 and 1,160 cm^{-1} ; thin layer chromatogram: Rf value ~0.56 (silica gel; toluene/ethyl acetate, 1:1).

h) A solution of 6.06 g (0.7 mmol) of diphenylmethyl 2 - [4 - (p - toluenesulphonylthio) - 3 - [2 - tert - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 2 - oxoazetidin - 1 - yl] - 3 - hydroxy - crotonate in 20 ml of 1:1 methylene chloride/methanol is stirred with an excess of an ethereal solution of diazomethane for 15 minutes at 0°C and the mixture is then evaporated in vacuo. Preparative layer chromatography of the residue on silica gel using 1:1 toluene/ethyl acetate as the running agent and elution of the zone visible in UV light gives diphenylmethyl 2 - [4 - (p - toluenesulphonylthio) - 3 - [2 - tert - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 2 - oxoazetidin - 1 - yl] - 3 - methoxy - crotonate; thin layer chromatogram: Rf value ~0.32 (silica gel; toluene/ethyl acetate, 1:1).

Example 13.

A solution of 0.20 g of 3 - chloro - perbenzoic acid in 5 ml of methylene chloride is added to a solution, which has been cooled to 0°C , of 0.723 g (1 mmol) of diphenylmethyl 7 β - [D - 2 - tert - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - methoxy - 2 - cephem - 4 α - carboxylate in 25 ml of methylene chloride. The mixture is stirred for 30 minutes at 0°C , 50 ml of methylene chloride are added and the mixture is

washed successively with 25 ml of a saturated aqueous solution of sodium bicarbonate and 25 ml of a saturated aqueous solution of sodium chloride. The organic phase is dried over sodium sulphate and evaporated under reduced pressure. The crude product is chromatographed over 30 times the amount of silica gel, using 4:1 toluene/acetone as the eluant, and the 1-oxide of diphenylmethyl 7 β - [D - 2 - tert - butoxycarbonylamino - 2 - [3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - methoxy - 3 - cephem - 4 - carboxylate is thus obtained in an amorphous form; thin layer chromatogram: Rf ~0.15 (silica gel; toluene/acetone, 3:1; developing with iodine vapour); infra-red absorption spectrum (in methylene chloride): characteristic bands at 3,420, 1,780, 1,700, 1,490, 1,333, 1,160 and 1,050 cm^{-1} .

Example 14.

2.80 g of phosphorus trichloride are added to a solution, which has been cooled to -10°C , of 1.48 g (2 mmols) of the 1-oxide of diphenylmethyl 7 β - [D - 2 - tert - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - methoxy - 3 - cephem - 4 - carboxylate in 30 ml of dimethylformamide, with the exclusion of air. After it has been left to stand for 15 minutes, the reaction mixture is poured out onto a mixture of ice and an aqueous solution of dipotassium hydrogen phosphate; the aqueous mixture is extracted with twice 100 ml of ethyl acetate. The organic extract is washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and evaporated. The residue is chromatographed on silica gel; elution with 3:1 toluene/acetone gives amorphous diphenylmethyl 7 β - [D - 2 - tert - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 - methoxy - 3 - cephem - 4 - carboxylate, which according to thin layer chromatography is the pure substance, Rf ~0.22 (silica gel; toluene/acetone, 3:1; developing with iodine vapour); ultra-violet absorption spectrum (in ethanol): λ_{max} = 265 nm (ϵ = 6,950); infra-red absorption spectrum (in methylene chloride): characteristic bands at 3,420, 1,780, 1,725, 1,700, 1,335 and 1,160 cm^{-1} .

Example 15.

a) 1.4 ml of bis - (trimethylsilyl) - acetamide are added to a suspension of 2.4 g (5 mmols) of 7 β - [D - 2 - tert - butoxycarbonylamino - 2 - (3 - aminophenyl) - acetylamino] - 3 - methoxy - 3 - cephem - 4 - carboxylic acid in 20 ml of absolute methylene chloride, under nitrogen and with the exclusion of moisture, and the mixture is stirred for 45 minutes at room

34

temperature. The clear, pale yellow solution is cooled to 0°C and, whilst stirring, 1.2 ml of absolute pyridine and then 0.63 g (5.5 mmols) of methylsulphonyl chloride dissolved in 10 ml of absolute methylene chloride are added. After 1 hour at 0°C and 4 hours at room temperature, 2 ml of methanol are added to the reaction mixture and the latter is freed from solvent in a rotary evaporator. The oily residue is taken up in 20 ml of water, the pH is adjusted to 2.0 with 2 N - hydrochloric acid and the aqueous phase is extracted with twice 50 ml of ethyl acetate. The combined organic phases are dried (MgSO₄) and concentrated in a rotary evaporator. The residue is purified over silica gel using a 1:1 mixture of methylene chloride and ethyl acetate as the eluant. This gives 7β-[D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid, which according to thin layer chromatography is a single compound and which, when recrystallised from 1:3 methylene chloride/diethyl ether, melts at 140° with decomposition. Thin layer chromatogram (silica gel; identification with ninhydrin): Rf~0.63 (system: sec.-butanol/acetic acid/water, 67:10:23).

The starting material can be prepared as follows:

b) 3.8 ml of bis-(trimethylsilyl)-acetamide are added to a suspension of 3.11 g (13.5 mmols) of finely powdered 7β - amino - 3 - methoxy - 3 - cephem - 4 - carboxylic acid in 60 ml of absolute methylene chloride, under an argon atmosphere and at room temperature, (the addition is effected in the course of about 10 minutes) and the mixture is stirred for 45 minutes.

1.97 ml of isobutyl chloroformate are added to a solution, which has been cooled to -15°, of 4.44 g (15 mmols) of D - 2 - tert. - butoxycarbonylamino - 2 - (3 - nitrophenyl) - acetic acid and 1.67 ml of 4-methyl-morpholine in 90 ml of absolute acetonitrile, under an argon atmosphere, and the mixture is allowed to react for a further 25 minutes. The silylated starting material described above is added dropwise, at -15°, to the mixed anhydride which is thus obtainable and the reaction mixture is stirred for 2 hours at 0° and for 30 minutes at room temperature. The solvent is then removed in a rotary evaporator and the residue is taken up in 200 ml of ethyl acetate and washed three times with a saturated aqueous solution of sodium chloride. The aqueous phases are again extracted with ethyl acetate. The combined organic solutions are dried over magnesium sulphate and freed from solvent under reduced pressure. The residue is purified over silica gel using a 1:1 mixture of methylene chloride

and ethyl acetate as the eluant. This gives 7β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - nitrophenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid, which according to thin layer chromatography is a single compound, as an amorphous product; thin layer chromatogram (silica gel; identification with ninhydrin): Rf~0.52 (system: sec.-butanol/acetic acid/water, 67:10:23), infra-red absorption spectrum (in methylene chloride): characteristic bands at 3,400, 1,785, 1,710, 1,535 and 1,355 cm⁻¹.

c) 1.17 g (2 mmols) of 7β - [D - 2 - tert.-butoxycarbonylamino - 2 - (3 - nitrophenyl)-acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid, dissolved in 30 ml of ethyl acetate, are hydrogenated at room temperature and under normal pressure in the presence of 200 mg of 5% strength palladium-on-charcoal until 3 equivalents of hydrogen have been taken up. The catalyst is filtered off and washed with a little ethyl acetate. The solvent is stripped off under reduced pressure. The resulting crude product, that is to say 7β - [D - 2 - tert.-butoxycarbonylamino - 2 - (3 - amino-phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid, is used direct for the sulphonylation.

Example 16.

a) 482 mg (1 mmol) of 7β - [D - 2 - azido - 2 - (3 - methylsulphonylamino - phenyl)-acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid, dissolved in 32 ml of 3:1 methanol/chloroform, are hydrogenated in the presence of 120 mg of platinum oxide at room temperature and under normal pressure (reaction time: 2 hours). The solution is diluted with 5 ml of water and the pH is adjusted to 2 with 1 ml of 1 N hydrochloric acid. After filtering, the pH of the aqueous phase is adjusted to 5.2 with a 20% strength solution of triethylamine in methanol. The solution is concentrated to about half its volume, 12 ml of acetone are added and the mixture is left to stand for 16 hours at about -18°. The precipitate which has formed is filtered off, washed with acetone and diethyl ether and dried. In this way 7β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid is obtained in the form of the inner salt, as the monohydrate, which decomposes above 170°; thin layer chromatogram (silica gel; identification with ninhydrin): Rf~0.20 (system: sec.-butanol/acetic acid/water, 67:10:23); ultra-violet absorption spectrum (in 0.1 N aqueous hydrochloric acid): λ_{max}= 272 nm (ε=7200).

The starting material can be prepared as follows:

b) 0.75 ml of bis-(trimethylsilyl)-acetamide

is added to a suspension of 0.622 g (2.7 mmols) of finely powdered 7 β - amino - 3-methoxy - 3 - cephem - 4 - carboxylic acid in 12 ml of absolute methylene chloride, under an argon atmosphere and at room temperature (the addition is effected in the course of about 10 minutes) and the mixture is stirred for 45 minutes.

0.4 ml of isobutyl chloroformate is added to a solution, which has been cooled to -15°, of 0.81 g (3.0 mmols) of D - 2 - azido - 2 - (3 - methylsulphonylamino - phenyl) - acetic acid and 0.33 ml of 4-methylmorpholine in 18 ml of absolute acetonitrile, under an argon atmosphere, and the mixture is allowed to react for a further 25 minutes. The silylated starting material described above is added dropwise, at -15°, to the mixed anhydride which is thus obtainable and the reaction mixture is stirred for 2 hours at 0° and for 30 minutes at room temperature. The solvent is then removed in a rotary evaporator and the residue is taken up in 400 ml of ethyl acetate and washed three times with a saturated aqueous solution of sodium chloride. The aqueous phases are again extracted with ethyl acetate. The combined organic solutions are dried over magnesium sulphate and freed from solvent under reduced pressure. The residue is purified over silica gel using a 1:1 mixture of methylene chloride and ethyl acetate as the eluant. 7 β - [D - 2 - Azido - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol] - 3 - methoxy - 3 - cephem - 4 - carboxylic acid, which according to thin layer chromatography is a single compound, is obtained as an amorphous product, which is employed direct in the next synthesis step.

Example 17.

A mixture of 1.45 g (2 mmols) of diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol] - 3 - methoxy - 2 - cephem - 4 α - carboxylate and 0.2 ml of diisopropyl ethylamine in 30 ml of methyl chloride is left to stand for 6 hours at room temperature. After removing the solvent, the resulting mixture of starting material and diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - 3 - methoxy - 3 - cephem - 4 - carboxylate] is chromatographed over silica gel using 3:1 toluene/acetone as the eluant. Diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - 3 - methoxy - 3 - cephem - 4 - carboxylate] is isolated therefrom in a crystalline form; melting point 128—130°C; thin layer chromatogram (silica gel, de-

veloping with iodine vapour): Rf~0.22 (toluene/acetone, 3:1).

Example 18.

12.5 mmols of solid phosphorus pentachloride are added, at -20°, to a solution of 10 mmols of diphenylmethyl 7 β - (2-phenoxyacetylaminol) - 3 - methoxy - 3 - cephem - 4 - carboxylate and 25 mmols of N,N-dimethylaniline in 50 ml of absolute methylene chloride and the mixture is then stirred for 30 minutes at -20°. A cold mixture of 0.2 mol of methanol and 12 mmols of N,N-dimethylaniline is then added at this temperature and the mixture is then stirred for 2 hours at 0°. 60 mmols of N-methylmorpholine and a solution of the mixed anhydride prepared by stirring a mixture of 15 mmols of D - 2 - (tert. - butoxycarbonylamino) - 2 - (3 - methylsulphonylamino - phenyl) - acetic acid, 14 mmols of isobutyl chloroformate and 16 mmols of N-methylmorpholine in 50 ml of methylene chloride for 30 minutes at 0° are added at 0° and the mixture is stirred for 1 hour at 0°. 100 ml of H₂O are added, the mixture is shaken, the phases are separated and the organic phase is washed with a phosphate buffer with a pH of 2 and with a phosphate buffer with a pH of 6. Drying the extract with sodium sulphate and evaporating gives diphenylmethyl 7 β - [D - 2 - tert. - butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol] - 3 - methoxy - 3 - cephem - 4 - carboxylate, which is dissolved in 20 ml of trifluoroacetic acid and 1 ml of anisole. After standing for 10 minutes at room temperature, the solution is evaporated, the residue is taken up in methanol and 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol] - 3 - methoxy - 3 - cephem - 4 - carboxylic acid is precipitated by carefully adding diethylamine (until the isoelectric point is reached).

Example 19.

a) *Pseudomonas melanogenum* ATCC 17,808 is cultured, as a submersed culture, for 55 hours at 28° in a medium containing 0.7% of acetone, 0.5% of meat extract, 0.5% of yeast extract, 0.5% of sodium L-glutamate and 0.3% of sodium chloride. The cells are centrifuged off, washed with 0.8 per cent strength sodium chloride solution and suspended in a 0.1 normal acetate buffer which has a pH of 6.5. 1 g of 7 β - amino - 3 - methoxy - 3 - cephem - 4 - carboxylic acid and 3 g of the hydrochloride of methyl D - 2 - (3 - methylsulphonylamino - phenyl) - glycinate are added to 100 ml of this suspension (containing about 6 g of moist cells) and the mixture is stirred for 2 hours at 35°. The mixture is centri-

fuged and the clarified filtrate is introduced into a column of Amberlite (Registered Trade Mark) XAD-2. After washing the column with water, 7 β -[D-2-amino-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-3-cephem-4-carboxylic acid is eluted with increasing proportions of methanol in water.

- 10 b) The hydrochloride of methyl D-2-(3-methylsulphonylamino-phenyl)-glycinate is obtained from D-2-(3-methylsulphonylamino-phenyl)-glycine by esterification with methanol in the presence of dry hydrogen chloride.

- 15 The protective groups can be split off from the resulting compounds as follows:

Example 20.

- 20 a) A mixture of 0.557 g of 7 β -[D-2-tert.-butoxycarbonylamino]-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-3-cephem-4-carboxylic acid, 2.5 ml of pre-cooled trifluoroacetic acid and 2.5 ml of methylene chloride is stirred for 30 minutes at 0° under an argon atmosphere and 25 ml of a 1:1 mixture of petroleum ether and diethyl ether is then added at 0°. The beige precipitate is filtered off, washed with a little diethyl ether and dried under reduced pressure.
- 30 The trifluoroacetic acid salt of 7 β -[D-2-amino-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-3-cephem-4-carboxylic acid, which is thus obtained, is dissolved in 5 ml of water, the solution is extracted with twice 3 ml of ethyl acetate and the pH value of the acid aqueous phase (pH 1.8) is adjusted to 5.2 by dropwise addition of a 2 N aqueous solution of sodium hydroxide. The solution is concentrated to about half its volume, 12 ml of acetone are added and the mixture is left to stand for 16 hours at about -18°. The precipitate which has formed is filtered off, washed with acetone and diethyl ether and dried. In this way 7 β -[D-2-amino-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-3-cephem-4-carboxylic acid is obtained in the form of the inner salt, as the monohydrate, which decomposes above 170°; thin layer chromatogram (silica gel; identification with ninhydrin): Rf~0.22 (system: sec.-butanol/acetic acid/water, 67:10:23); ultra-violet absorption spectrum (in 0.1 N aqueous hydrochloric acid): $\lambda_{\max}$ =272 nm (ϵ =7000).

The same compound can also be obtained as follows:

- 60 ai) 40 ml of pre-cooled trifluoroacetic acid are added to a solution, which has been cooled to 0°, of 8.0 g (14.4 mmols) of 7 β -[D-2-tert.-butoxycarbonylamino]-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-3-cephem-4-

carboxylic acid in 40 ml of absolute methylene chloride, the mixture is stirred for 25 minutes at 0° under an argon atmosphere and 500 ml of a 1:1 mixture of petroleum ether and diethyl ether are then added at 0°. The beige precipitate is filtered off, washed with a little diethyl ether and dried under reduced pressure. The trifluoroacetic acid salt of 7 β -[D-2-amino-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-3-cephem-4-carboxylic acid, which is thus obtained, is dissolved in 70 ml of ice water and the solution is extracted with three times 30 ml of ethyl acetate. The pH value of the acid aqueous phase (pH~2.0) is adjusted to 5.2 by the dropwise addition of a 20% strength solution of triethylamine in methanol and 160 ml of isopropanol are added at 0°. The precipitate which has formed is recrystallised from 2:1 isopropanol/water, filtered off, washed with a little isopropanol and dried. Since the crystals still contain a small amount of organic solvent, even after drying, they are digested for a further ½ hour in 50% strength aqueous solution at 40°, the solution is cooled to 0°, filtered and the product is again dried at room temperature under a high vacuum. In this way 7 β -[D-2-amino-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-3-cephem-4-carboxylic acid is obtained in the form of the inner salt which is also in the form of a monohydrate; melting point above 174° (with decomposition).

100 aii) A solution of 300 mg (0.54 mmol) of 7 β -[D-2-tert.-butoxycarbonylamino]-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-3-cephem-4-carboxylic acid in 3 ml of formic acid is stirred for 3 hours at room temperature under argon and then cooled to 0° and subsequently 30 ml of 1:1 diethyl ether/petroleum ether are added. The formic acid salt of 7 β -[D-2-amino-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-3-cephem-4-carboxylic acid, which has precipitated, is dissolved in 3 ml of ice water and the solution is extracted with three times 1.5 ml of ethyl acetate and freed from water and from excess formic acid in a rotary evaporator. The residue is taken up in water twice more, using 3 ml in each case, and the solution is concentrated to dryness and, from the residue, the monohydrate of 7 β -[D-2-amino-2-(3-methylsulphonylamino-phenyl)-acetylaminol]-3-methoxy-4-carboxylic acid can be isolated direct in the form of pale yellow crystals which have a melting point of 173—175° (decomposition); thin layer chromatogram (silica gel; developing with ninhydrin): Rf~0.21 (system: sec.-butanol/acetic acid/water, 67:10:23); UV spectrum (in 0.1 N aqueous

hydrochloric acid): $\lambda_{\max}=272$ nm ($\epsilon=7,100$).
 aiii) A solution of 2.2 g of 7 β - [D - 2 - tert.-
 butoxycarbonylamino - 2 - (3 - methylsulphonylamino - phenyl) - acetylamino] - 3 -
 methoxy - 3 - cephem - 4 - carboxylic acid
 in 22 ml of 99% strength formic acid is left
 to stand for 1½ hours at 23° and is then
 evaporated in vacuo. The resulting resin is
 digested successively with 25 ml of ether,
 25 ml of acetonitrile and 25 ml of 95:5
 acetonitrile/H₂O. 7 β - [D - 2 - Amino - 2 - (3 -
 methylsulphonylamino - phenyl) - acetyl-
 amino] - 3 - methoxy - 3 - cephem - 4 - car-
 boxylic acid is obtained as a pale beige
 powder. After recrystallisation from 1:2
 water/isopropanol, the monohydrate has the
 following characteristics: $[\alpha]_D^{25}=+143^{\circ}\pm 1^{\circ}$
 c=1, 0.1 N HCl, UV absorption in 0.1 N
 HCl: $\lambda_{\max}=272$ nm ($\epsilon=7,300$).

Example 21.

a) In a manner analogous to Example 20a,
 the amino group in 7 β - [D - 2 - tert.-
 butoxycarbonylamino - 2 - (3 - methylsul-
 phonylamino - phenyl) - acetylamino] - 3 -
 chloro - 3 - cephem - 4 - carboxylic acid
 can be liberated by reaction with trifluoro-
 acetic acid and the resulting trifluoroacetic
 acid salt of 7 β - [D - 2 - amino - 2 - (3 -
 methylsulphonylamino - phenyl) - acetyl-
 amino] - 3 - chloro - 3 - cephem - 4 - car-
 boxylic acid can be converted, by treating
 it with an aqueous solution of sodium
 hydroxide until the isoelectric point is
 reached, to the inner salt of 7 β - [D - 2 -
 amino - 2 - (3 - methylsulphonylamino -
 phenyl) - acetylamino] - 3 - chloro - 3 -
 cephem - 4 - carboxylic acid.

ai) In a manner analogous to Example 20 ai),
 the amino group of 7 β - [D - 2 - tert.-
 butoxycarbonylamino - 2 - (3 - methylsul-
 phonylamino - phenyl) - acetylamino] - 3 -
 chloro - 3 - cephem - 4 - carboxylic acid
 can be liberated by reaction with trifluoro-
 acetic acid and the resulting trifluoroacetic
 acid salt of 7 β - [D - 2 - amino - 2 - (3 -
 methylsulphonylamino - phenyl) - acetyl-
 amino] - 3 - chloro - 3 - cephem - 4 - car-
 boxylic acid can be converted, by treating
 it with a 20% strength solution of triethyl-
 amine in methanol until the isoelectric
 point is reached, to the inner salt of 7 β - [D -
 2 - amino - 2 - (3 - methylsulphonylamino -
 phenyl) - acetylamino] - 3 - chloro - 3 - cep-
 hem - 4 - carboxylic acid; melting point
 above 165° (decomposition); thin layer
 chromatogram (silica gel, developing with
 ninhydrin): Rf~0.17 (system: sec.-butanol/
 acetic acid/water, 67:10:23); UV spectrum
 (0.1 N hydrochloric acid): $\lambda_{\max}=267$ nm
 ($\epsilon=7,600$).

aii) In a manner analogous to Example 20
 aii), the amino group in 7 β - [D - 2 - tert.-
 butoxycarbonylamino - 2 - (3 - methylsul-
 phonylamino - phenyl) - acetylamino] - 3 -

chloro - 3 - cephem - 4 - carboxylic acid can
 be liberated by reaction with formic acid.
 7 β - [D - 2 - Amino - 2 - (3 - methylsulphonyl-
 amino - phenyl) - acetylamino] - 3 - chloro-
 cephem - 4 - carboxylic acid is obtained
 as fine crystals which have the same
 physical characteristics as those indicated
 under ai).

Example 22.

A solution of 2.18 g (3 mmols) of di-
 phenylmethyl 7 β - [D - 2 - tert. - butoxy-
 carbonylamino - 2 - (3 - methylsulphonyl-
 amino - phenyl) - 3 - chloro - 3 - cephem-
 4 - carboxylate, 1.8 ml of anisole and 9.6 ml
 of trifluoroacetic acid in 20 ml of methylene
 chloride is stirred for 30 minutes at 0° and
 200 ml of 1:1 ether/petroleum ether are then
 added. The trifluoroacetic acid salt is dis-
 solved in 10 ml of ice water and the solution
 is extracted with twice 4 ml of ethyl
 acetate. The pH of the aqueous phase
 is adjusted to 5.0 with a 20% strength
 solution of triethylamine in methanol and
 after 24 ml of isopropanol have been added
 a colourless precipitate forms. After filter-
 ing, washing with a little isopropanol and
 drying under reduced pressure, colourless
 crystals of 7 β - [D - 2 - amino - 2 - (3 -
 methylsulphonylamino - phenyl) - acetyl-
 amino] - 3 - chloro - 3 - cephem - 4 - car-
 boxylic acid are obtained; melting point
 above 165° (decomposition); thin layer
 chromatogram (silica gel, developing with
 ninhydrin): Rf~0.17 (system: sec.-butanol/
 acetic acid/water, 67:10:23); IR spectrum
 (in Nujol): characteristic bands at 3,500,
 3,220, 1,780, 1,685, 1,340 and 1,155 cm⁻¹.

Example 23.

a) In a manner analogous to Example
 22 it is possible, by treating 1.08 g (1.5
 mmols) of diphenylmethyl 7 β - [D - 2 - tert.-
 butoxycarbonylamino - 2 - (3 - methylsul-
 phonylamino - phenyl) - acetylamino] - 3 -
 methoxy - 3 - cephem - 4 - carboxylate
 with 4.5 ml of trifluoroacetic acid and 0.8
 ml of anisole in 10 ml of methylene
 chloride, to liberate the amino group and
 the protected 4-carboxyl group and to con-
 vert the resulting trifluoroacetic acid salt,
 by treating it with a 20% strength solution
 of triethylamine in methanol until the iso-
 electric point is reached, into the inner
 salt of 7 β - [D - 2 - amino - 2 - (3 - methyl-
 sulphonylamino - phenyl) - 3 - methoxy - 3 -
 cephem - 4 - carboxylic acid; melting point
 above 172° (decomposition).

ai) A mixture of 10.12 g (14 mmols) of
 diphenylmethyl 7 β - [D - 2 - tert. - butoxy-
 carbonylamino - 2 - (3 - methylsulphonyl-
 amino - phenyl) - acetylamino] - 3 - methoxy-
 3 - cephem - 4 - carboxylate, 8.6 ml of
 anisole and 145 ml of trifluoroacetic acid
 is stirred for 15 minutes at 0°C, 400 ml of



pre-cooled toluene are then added and the mixture is evaporated under reduced pressure. The residue is dried under a high vacuum and digested with diethyl ether and the product is filtered off. In this way the trifluoroacetate of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid is obtained in a pulverulent form and this is dissolved in 70 ml of water. The solution is washed with three times 25 ml of ethyl acetate and the pH value is adjusted to about 5.6 with a 20% strength solution of triethylamine in methanol and, after 160 ml of isopropanol have been added, a colourless precipitate forms. The mixture is stirred for one hour in an ice bath. The colourless precipitate is filtered off, washed with isopropanol and diethyl ether and dried under reduced pressure. Since the crystals still contain a little isopropanol and diethyl ether, even after drying, they are digested for a further $\frac{1}{2}$ hour in 50% strength aqueous solution at 40°C; the solution is cooled to 0° and filtered and the product is again dried. In this way 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetamidol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid, as an inner salt, which is also in the form of a monohydrate, is obtained in the form of a microcrystalline powder; melting point above 175°C (with decomposition); $[\alpha]_D^{20} = +144^\circ$ (c=1.035 in 0.1 N hydrochloric acid); thin layer chromatogram (silica gel; developing with ninhydrin): Rf~0.19 (system: sec.-butanol/acetic acid/water, 67:10:23); ultra-violet absorption spectrum (in 0.1 N aqueous hydrochloric acid): $\lambda_{max} = 272$ nm ($\epsilon = 7,300$); infra-red absorption spectrum (in mineral oil): characteristic bands at, inter alia, 3,500, 3,180, 1,760, 1,692, 1,608, 1,150 and 978 cm⁻¹.

Example 24.

A suspension of 4.75 g of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid in 50 ml of water and 2 ml of alcohol is slowly brought into solution, at a pH value of less than 7.6, using a total of about 5 ml of 2 N sodium hydroxide solution, whilst stirring and regulating the pH. On lyophilisation, the solution, which has been freed from a small amount of residual solids by filtration, gives 4.9 g of sodium 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylate.

Example 25.

Dry ampoules or phials containing 0.5 g of the inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetyl-

aminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid are manufactured as follows:

Composition (for 1 ampoule or phial)

Inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid	0.5 g	70
Mannitol	0.05 g	

A sterile aqueous solution of the inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid and of mannitol is subjected to freeze-drying under aseptic conditions in 5 ml ampoules or 5 ml phials and the ampoules or phials are sealed and checked.

Example 26.

Capsules containing 0.25 g of the inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid are manufactured as follows:

Composition (for 4,000 capsules):

Inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid	250,000 g	90
maize starch	50,000 g	
polyvinylpyrrolidone	15,000 g	
magnesium stearate	5,000 g	
ethanol	q.s.	

The inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid and the maize starch are mixed and the mixture is moistened with a solution of the polyvinylpyrrolidone in 50 g of ethanol. The moist mass is pressed through a sieve with a mesh width of 3 mm and dried at 45°. The dry granules are forced through a sieve with a mesh width of 1 mm and mixed with 5 g of magnesium stearate. The mixture is filled, in portions of 0.320 g, into size 0 push-fit capsules.

WHAT WE CLAIM IS:—

1. Process for the manufacture of a 7 β - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetylaminol - 3 - R - cephem - 4 - carboxylic acid (I), in which R denotes lower alkoxy or halogen with an atomic number of up to 35, and its salts, wherein the hydroxyl group in a 7 β - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetylaminol - 3 - hydroxy - 3 - cephem - 4 - carboxylic acid (II), in which

pre-cooled toluene are then added and the mixture is evaporated under reduced pressure. The residue is dried under a high vacuum and digested with diethyl ether and the product is filtered off. In this way the trifluoroacetate of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid is obtained in a pulverulent form and this is dissolved in 70 ml of water. The solution is washed with three times 25 ml of ethyl acetate and the pH value is adjusted to about 5.6 with a 20% strength solution of triethylamine in methanol and, after 160 ml of isopropanol have been added, a colourless precipitate forms. The mixture is stirred for one hour in an ice bath. The colourless precipitate is filtered off, washed with isopropanol and diethyl ether and dried under reduced pressure. Since the crystals still contain a little isopropanol and diethyl ether, even after drying, they are digested for a further $\frac{1}{2}$ hour in 50% strength aqueous solution at 40°C; the solution is cooled to 0° and filtered and the product is again dried. In this way 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetamidol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid, as an inner salt, which is also in the form of a monohydrate, is obtained in the form of a microcrystalline powder; melting point above 175°C (with decomposition); $[\alpha]_D^{20} = +144^\circ$ (c=1.035 in 0.1 N hydrochloric acid); thin layer chromatogram (silica gel; developing with ninhydrin): R_f~0.19 (system: sec.-butanol/acetic acid/water, 67:10:23); ultra-violet absorption spectrum (in 0.1 N aqueous hydrochloric acid): $\lambda_{max} = 272$ nm ($\epsilon = 7,300$); infra-red absorption spectrum (in mineral oil): characteristic bands at, inter alia, 3,500, 3,180, 1,760, 1,692, 1,608, 1,150 and 978 cm⁻¹.

Example 24.

A suspension of 4.75 g of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid in 50 ml of water and 2 ml of alcohol is slowly brought into solution, at a pH value of less than 7.6, using a total of about 5 ml of 2 N sodium hydroxide solution, whilst stirring and regulating the pH. On lyophilisation, the solution, which has been freed from a small amount of residual solids by filtration, gives 4.9 g of sodium 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylate.

Example 25.

Dry ampoules or phials containing 0.5 g of the inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetyl-

aminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid are manufactured as follows: 65

Composition (for 1 ampoule or phial)
Inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid 0.5 g 70
Mannitol 0.05 g

A sterile aqueous solution of the inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid and of mannitol is subjected to freeze-drying under aseptic conditions in 5 ml ampoules or 5 ml phials and the ampoules or phials are sealed and checked. 75

Example 26.

Capsules containing 0.25 g of the inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid are manufactured as follows: 80

Composition (for 4,000 capsules):
Inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid 250,000 g 90
maize starch 50,000 g
polyvinylpyrrolidone 15,000 g
magnesium stearate 5,000 g
ethanol q.s.

The inner salt of 7 β - [D - 2 - amino - 2 - (3 - methylsulphonylamino - phenyl) - acetylaminol - 3 - methoxy - 3 - cephem - 4 - carboxylic acid and the maize starch are mixed and the mixture is moistened with a solution of the polyvinylpyrrolidone in 50 g of ethanol. The moist mass is pressed through a sieve with a mesh width of 3 mm and dried at 45°. The dry granules are forced through a sieve with a mesh width of 1 mm and mixed with 5 g of magnesium stearate. The mixture is filled, in portions of 0.320 g, into size 0 push-fit capsules. 100

WHAT WE CLAIM IS:—

1. Process for the manufacture of a 7 β - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetylaminol - 3 - R - cephem - 4 - carboxylic acid (I), in which R denotes lower alkoxy or halogen with an atomic number of up to 35, and its salts, wherein the hydroxyl group in a 7 β - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetylaminol - 3 - hydroxy - 3 - cephem - 4 - carboxylic acid (II), in which 110 115

the carboxyl group is in a protected form, the 2-amino group is optionally in a protected form and the lower alkylsulphonyl-amino group is optionally in a N-acylated form, is converted into the radical R, or wherein the 7 β -amino group in a 7 β -amino-3 - R - cephem - 4 - carboxylic acid (VI), in which the carboxyl group is optionally in a protected form and the 7 β -amino group is optionally in a reactive protected form, that is to say in a form which permits acylation, is acylated with a D-2-amino-(lower alkylsulphonylamino - phenyl) - acetyl radical, or wherein a 7 β [D - 2 - amino - 2 - lower alkylsulphonylamino - phenyl] - acetylaminol - 3 - R - 2 - cephem - 4 - ξ - carboxylic acid (VIII), in which 2-amino and/or carboxyl can optionally be in a protected form and/or lower alkylsulphonylamino can optionally be in a N-acylated form, is isomerised, or wherein a 2 - [3 - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetylaminol] - 4 - R_o - thio - 2 - oxo - 1 - azetidinyll] - 3 - R - crotonic acid (X), in which the carboxyl group is in a protected form or in the form of a halogenocarbonyl group, the 2-amino group is optionally in a protected form and the lower alkylsulphonylamino group is optionally in a N-acylated form, R represents lower alkoxy and R_o represents a leaving group, is cyclised by treatment with a base, and, if necessary, in a resulting compound a protected 2-amino group and/or a N-acylated lower alkylsulphonylamino group are converted into the free amino group and into the lower alkylsulphonylamino group respectively, and/or the protected carboxyl group is converted into a free carboxyl group, and, if desired, a resulting salt is converted into the free compound or into another salt and/or a free compound is converted into a salt.

2. Process for the manufacture of a 7 β - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetylaminol] - 3 - R - 3 - cephem - carboxylic acid (I), in which R denotes lower alkoxy or halogen with an atomic number of up to 35, or salts thereof, wherein the hydroxyl group in a 7 β - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetylaminol] - 3 - hydroxy - 3 - cephem - 4 - carboxylic acid (II), in which the carboxyl group is in a protected form and the 2-amino group is optionally in a protected form, is converted into the radical R, or the 7 β -amino group in a 7 β - amino - 3 - R - 3 - cephem - 4 - carboxylic acid (VI), in which the carboxyl group is optionally in a protected form and the 7 β -amino group is optionally in a reactive protected form, is acylated with a D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetyl radical, or a 7 β - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetyl

aminol] - 3 - R - 2 - cephem - 4 - ξ - carboxylic acid (VIII), in which 2-amino and/or carboxyl are optionally in a protected form, is isomerised, or a 2 - [3 - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetylaminol] - 4 - R_o - thio - 2 - oxo - 1 - azetidinyll] - 3 - R - crotonic acid (X), in which the carboxyl group is in a protected form or in the form of a halogenocarbonyl group and the 2-amino group is optionally in a protected form, R represents lower alkoxy and R_o represents a leaving group, is cyclised by treatment with a base and, if necessary, in a resulting compound the protected 2-amino group is converted into the free 2-amino group and/or the protected carboxyl group is converted into the free carboxyl group, and, if desired, a resulting salt is converted into the free compound or into another salt and/or a free compound is converted into a salt.

3. Process according to Claim 1, wherein the hydroxyl group in a starting material II is converted into a lower alkoxy group R by treatment with a diazo-lower alkane, with a reactive ester of a lower alkanol, with a compound which contains two or three lower alkoxy groups on the same carbon atom of aliphatic character, that is to say with a corresponding acetal or ortho-ester, with a tri-lower alkyloxonium salt, a di-lower alkoxy-carbenium salt or a di-lower alkylhalonium salt or with a 1-lower alkyl-triazine compound which is substituted in the 3-position.

4. Process according to Claim 2, wherein the hydroxyl group in the starting material II is converted into a lower alkoxy group R by treatment with a diazo-lower alkane, with a reactive ester of a lower alkanol, with a compound which contains two or three lower alkoxy groups on the same carbon atom of aliphatic character, that is to say with a corresponding acetal or ortho-ester, with a tri-lower alkyloxonium salt, a di-lower alkoxy-carbenium salt or a di-lower alkyl-halonium salt or with a 1-lower alkyl-triazene compound which is substituted in the 3-position.

5. Process according to Claim 1, wherein the hydroxyl group in a starting material II is converted into halogen by treatment with a phosphorus reagent which replaces enolhydroxyl groups by halogen.

6. Process according to Claim 1, wherein the hydroxyl group in the starting material II is converted into chlorine or bromine by treatment with a corresponding N,N-disubstituted halogeno-iminium halide compound, in which halogen denotes chlorine or bromine.

7. Process according to Claim 2, wherein the hydroxyl group in the starting material II is converted into chlorine or bromine by treatment with a corresponding N,N-



40

disubstituted halogeno-iminium halide compound, in which halogen denotes chlorine or bromine.

8. Process according to Claim 1, wherein the hydroxyl group in the starting material II is converted into fluorine by treatment with a reagent of the formula F_2S-Am , in which Am represents a disubstituted amino group.

10 9. Process according to Claim 2, wherein the hydroxyl group in the starting material II is converted into fluorine by treatment with a reagent of the formula F_2S-Am , in which Am represents a disubstituted amino group.

15 10. Process according to Claim 1, wherein, in the starting material II, in which the hydroxyl group is in the form of an organic sulphonyloxy group, the hydroxyl group is converted into fluorine by treatment with an inorganic fluoride in the presence of a crown ether.

20 11. Process according to Claim 2, wherein, in the starting material II, in which the hydroxyl group is in the form of an organic sulphonyloxy group, the hydroxyl group is converted into fluoride by treatment with an inorganic fluoride in the presence of a crown ether.

30 12. Process according to Claim 1, wherein the 7β -amino group in a starting material VI is acylated by treatment with a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetic acid (VII), in which the 2-amino group can be in a protected or masked form and the lower alkylsulphonylamino group can optionally be substituted on the nitrogen by an acyl group, or with a reactive derivative thereof.

35 13. Process according to Claim 2, wherein the 7β -amino group in a starting material VI is acylated by treatment with a D-2-amino-2-(lower alkylsulphonylamino-phenyl)-acetic acid (VII), in which the 2-amino group is optionally in a protected form, or with a reactive derivative thereof.

40 14. Process according to Claim 1, wherein a 2-cephem starting material VIII is isomerised by treatment with a basic agent and isolating the corresponding 3-cephem compound from an equilibrium mixture of the 2- and 3-cephem compounds which may be obtained.

45 15. Process according to Claim 2, wherein a 2-cephem starting material VIII is isomerised by treatment with a basic agent and isolating the corresponding 3-cephem compound from an equilibrium mixture of the 2- and 3-cephem compounds which may be obtained.

50 16. Process according to Claim 1, wherein a 2-cephem starting material VIII is isomerised by oxidising it in the 1-position, optionally separating a mixture of isomers, which is obtainable, of the 1-oxides of 3-

cephem compounds and reducing the obtainable 1-oxide of the corresponding 3-cephem compound.

17. Process according to Claim 2, wherein a 2-cephem starting material VIII is isomerised by oxidising it in the 1-position, optionally separating a mixture of isomers, which is obtainable, of the 1-oxides of 3-cephem compounds and reducing the obtainable 1-oxide of the corresponding 3-cephem compound.

18. Process according to Claim 1, wherein a starting material X, in which a leaving group R_2 represents a $-S-R_2^1$ group, a $-SO_2-R_2^1$ group, which is bonded by the sulphur atom to the thio sulphur, or a $-S-SO_2-R_2^1$ group, in which R_2^1 is an optionally substituted monocyclic or bicyclic heterocyclic radical of aromatic character, which contains at least one ring nitrogen atom and optionally a further ring hetero-atom and which is bonded to the thiosulphur by one of its ring carbon atoms, which is bonded to a ring nitrogen atom by means of a double bond, or represents the acyl radical of an organic carboxylic or thiocarboxylic acid, and in which R_2^1 represents an optionally substituted hydrocarbon radical, is cyclised by treatment with a strong organic or inorganic base.

19. Process according to Claim 2, wherein a starting material X, in which a leaving group R_2 represents a $-S-R_2^1$ group, a $-SO_2-R_2^1$ group, which is bonded by the sulphur atom to the thiosulphur, or a $-S-SO_2-R_2^1$ group, in which R_2^1 is an optionally substituted monocyclic or bicyclic heterocyclic radical of aromatic character, which contains at least one ring nitrogen atom and optionally a further ring hetero-atom and which is bonded to the thiosulphur by one of its ring carbon atoms, which is bonded to a ring nitrogen atom by means of a double bond, or represents the acyl radical of an organic carboxylic or thiocarboxylic acid, and in which R_2^1 represents an optionally substituted hydrocarbon radical, is cyclised by treatment with a strong organic or inorganic base.

20. Process according to one of Claims 1, 3, 5, 6, 8, 10, 12, 14, 16 and 18, wherein, in a compound obtained according to the process, a protected 2-amino group and/or a N-acylated lower alkylsulphonylamino group are converted, by solvolysis or reduction, into the free 2-amino group and into the lower alkylsulphonylamino group respectively, and/or a protected carboxyl group is converted, by solvolysis or reduction and optionally at the same time, into a free carboxyl group.

21. Process according to one of Claims 2, 4, 7, 9, 11, 13, 15, 17 and 19, wherein, in a compound obtainable according to the

- process, a protected carboxyl group and/or 2-amino group are liberated optionally at the same time.
22. Process according to one of Claims 1, 3, 5, 6, 8, 10, 12, 14, 16, 18 and 20, wherein the starting materials are obtained *in situ*.
23. Process according to one of Claims 2, 4, 7, 9, 11, 13, 15, 17, 19 and 21, wherein the starting materials are obtained *in situ*.
24. Process according to one of Claims 1, 3, 5, 6, 8, 10, 12, 14, 16, 18, 20 and 22, wherein starting materials are used in the form of derivatives or formed during the reaction.
25. Process according to one of Claims 2, 4, 7, 9, 11, 13, 15, 17, 19, 21 and 23, wherein starting materials are used in the form of derivatives or formed during the reaction.
26. Process according to one of Claims 1, 3, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24, wherein a compound I according to Claim 1, or a salt thereof, in which lower alkylsulphonylamino is in the 3-position of the phenyl radical, is manufactured.
27. Process according to one of Claims 2, 4, 7, 9, 11, 13, 15, 17, 19, 21, 23 and 25, wherein a compound I according to Claim 1, or a salt thereof, in which lower alkylsulphonylamino is in the 3-position of the phenyl radical, is manufactured.
28. Process according to one of Claims 1, 3, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24, wherein a 7 β - [D - 2 - amino - 2 - (3-methylsulphonylamino - phenyl) - acetyl-amino] - 3 - R' - 3 - cephem - 4 - carboxylic acid, in which R' denotes methoxy or chlorine, or a salt thereof, is manufactured.
29. Process according to one of Claims 2, 4, 7, 9, 11, 13, 15, 17, 19, 21, 23 and 25, wherein a 7 β - [D - 2 - amino - 2 - (3-methylsulphonylamino - phenyl) - acetyl-amino] - 3 - R' - 3 - cephem - 4 - carboxylic acid, in which R' denotes methoxy or chlorine, or a salt thereof, is manufactured.
30. The process described in Examples 1ai), 1aii), 2ai), 3, 4, 5a), 6, 7b), 8—11, 12a), 13, 14, 15a), 16—18, 19a), 20ai), 20aii), 20aiii), 21ai), 21aii) and 22—24.
31. The process described in Examples 1a), 2a), 20a) and 21a).
32. The compounds I, when obtained according to the process of Claims 1, 3, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.
33. The compounds I, when obtained according to the process of Claims 2, 4, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29 and 31.
34. Protected derivatives of compounds I, when obtained according to the process of Examples 1ai), 1aii), 2ai), 3, 4, 5a), 6, 7b), 8—11, 12a), 13, 14, 15a), 16—18, 19a), 20ai), 20aii), 20aiii), 21ai), 21aii) and 22—24.
35. Protected derivatives of compounds I, when obtained according to the process of Examples 1a), 2a), 20a) and 21a).
36. A 7 β - [D - 2 - amino - 2 - (lower alkylsulphonylamino - phenyl) - acetyl-amino] - 3 - R - 3 - cephem - 4 - carboxylic acid (I), in which R denotes lower alkoxy or halogen with an atomic number of up to 35.
37. A compound of Claim 36, in which lower alkylsulphonylamino is in the 3-position of the phenyl radical.
38. A 7 β - [D - 2 - amino - 2 - (3-methylsulphonylamino - phenyl) - acetyl-amino] - 3 - R' - 3 - cephem - 4 - carboxylic acid, in which R' represents methoxy or chlorine.
39. 7 β - [D - 2 - Amino - 2 - (3-methylsulphonylamino - phenyl) - acetyl-amino] - 3-methoxy - 3 - cephem - 4 - carboxylic acid.
40. 7 β - [D - 2 - Amino - 2 - (3-methylsulphonylamino - phenyl) - acetyl-amino] - 3-chloro - 3 - cephem - 4 - carboxylic acid.
41. Salts of the compounds of Claims 36—40.
42. Pharmaceutically usable salts of the compounds of Claims 36—40.
43. A pharmaceutical preparation comprising a compound as claimed in any one of claims 36—40 and 42 in admixture or conjunction with a pharmaceutically suitable carrier.
44. Method of treating infectious diseases in non-human animals, wherein the compounds of Claims 36—40 and 42, optionally in the form of pharmaceutical formulations, are used.
45. The compounds I and protected derivatives thereof described in Examples 20 and 21.
46. The compounds I and protected derivatives thereof described in Examples 1—19 and 22—24.

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