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# PATENT SPECIFICATION

964449

NO DRAWINGS

964449

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International Classification:—C 07 d (C 07 f)

C2 A

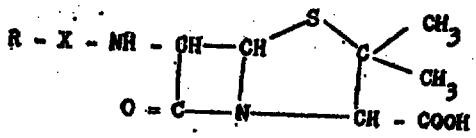
## COMPLETE SPECIFICATION

## Derivatives of 6-Amino Penicillanic Acid

We, CHEMIE GRÜNENTHAL G.M.B.H., of Stolberg im Rheinland, Germany, a Body Corporate organised under the laws of Germany, 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:—

The present invention relates to derivatives of amino acids of the general formula

I



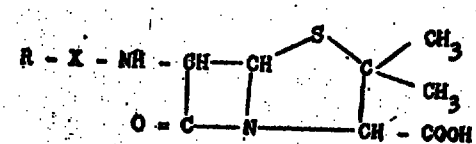
in which R represents an alkyl radical which may be substituted or may be interrupted by hetero atoms, or a cycloaliphatic, aromatic, heterocyclic or araliphatic radical, which may be substituted, X represents a —CO— or —$SO_2$— group, and salts thereof.

The present invention also relates to a process for the manufacture of the compounds of formula I. The starting material for this process is 6-amino penicillanic acid, which was prepared for the first time by Sakaguchi and Murao (J.Agric.Chem. Soc. Japan *23* (1950) 411) by enzymatic hydrolysis of ~~penicillin~~. Some years later this work was repeated with the aim of using 6-amino penicillanic acid for the ~~production~~ of penicillins or penicillin-like compounds. Owing to the fact that 6-amino penicillanic acid is soluble only in solvents containing water it was necessary hitherto to use such solvents for the acylation. According to this the acylating agents (for instance halides or anhydrides of carboxylic acids) are destroyed at least partially before the acylation starts. The separation from the penicillins of the acids formed in this way is very difficult.

penicillin production

The first step of the process of the present invention consists in transforming 6-amino penicillanic acid into compounds which are soluble in solvents free of water and which can be acylated in such solvents. The present invention therefore provides a process for the preparation of compounds of the general formula

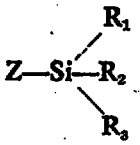
I



in which R represents an alkyl radical, which may be substituted or may be interrupted by hetero atoms, or a cycloaliphatic, aromatic, heterocyclic or araliphatic radical, which may be substituted, X represents a —CO— or —$SO_2$— group wherein 6-amino-penicillanic acid or a salt of 6-aminopenicillanic acid is reacted with a compound of the formula

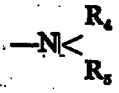
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II



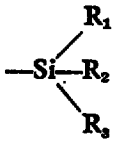
in which $R_1$, $R_2$ and $R_3$ which may be the same or different, represent alkyl, aralkyl, cycloalkyl or aryl radicals and Z represents a halogen atom or the radical

III



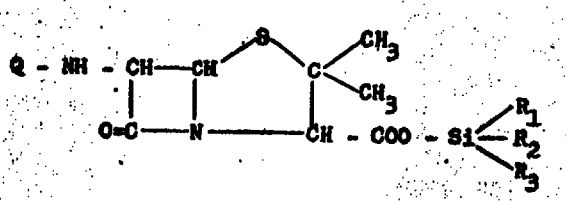
in which $R_4$ and $R_5$, which may be the same or different represent hydrogen atoms, lower alkyl radicals or the group

IV

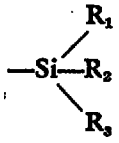


and, if Z represents a halogen atom, the reaction takes place in the presence of a compound or compounds able to fix hydrogen halides, to give a compound of the formula

V



in which Q represents a hydrogen atom or the radical



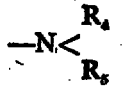
in which $R_1$, $R_2$ and $R_3$ have the meanings given above, or a mixture of such compounds which is or are reacted with an acid of the formula

VI

$$R—Y$$

wherein R has the meaning given above and Y represents a —COOH or $—SO_3H$ group or with an anhydride or halide of such an acid, preferably in the presence of a compound able to fix water or acids, followed by hydrolysis or alcoholysis to give a compound of the formula I.

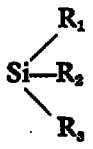
If Z in formula II is a halogen atom the reaction between that compound and 6-amino penicillanic acid or a salt thereof preferably takes place with heating in a non-aqueous solvent, such as an aliphatic or low boiling aromatic hydrocarbon or a cyclic ether such as tetrahydrofuran or dioxan. If Z represents a



group then, instead of an inert solvent, an excess of the compound of formula II can be used. It is possible to perform this embodiment of the invention in the presence of an ammonium salt as catalyst or in the presence of a compound of Formula II in which Z represents a halogen atoms.

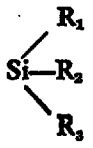
Compounds that can fix hydrogen halides that can conveniently be used according to the invention include ammonia, amines, alkali metal carbonates or alkaline earth metal carbonates.

If an excess of the compound of formula II is used one obtains a mixture of compounds of formula V. The relative amounts of the compound of formula V in which Q is a hydrogen atom to those in which it is a

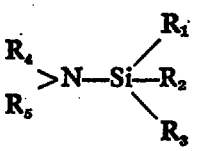


group is enlarged by increasing the excess of the compound of formula II. This fact, however, plays no role in realising the present invention because both compounds of formula V are reacted in the following acylation in the same manner and therefore, in any case, in the end of the total process compounds of formula I are obtained.

Naturally the compounds of formula V in which Q is a



group may also be made by preparing from 6-amino penicillanic acid at first a compound of formula V in which Q is a hydrogen atom which is then transformed by reaction with a compound of formula



The compounds of formula V are especially sensitive to moisture. If in their preparation the compounds of formula II, were not used in excess the reaction mixture is (if necessary after filtering) used in the following acylation without isolating the compounds of formula V. If, however, the compounds of formula V are to be isolated or if in their preparation the compounds of formula II were used in excess, it is possible (if necessary after filtering) to free the solution from the solvent, preferably in vacuum under a stream of an inert gas such as nitrogen or hydrogen or others.

The preparation of the compounds of formula I from those of formula V preferably takes place in the presence of a compound which is able to split off water or to fix acids, for instance a carbodiimide, an amine or a hydroxide or carbonate of an alkali metal or an alkaline earth metal and the compounds of formula I are liberated by hydrolysis or alcoholysis and transformed into salts if desired, by treatment with inorganic or organic bases.

The acylation may be carried out for instance, by using hydrocarbons or cyclic ethers as solvents owing to the fact that the compounds of formula V are soluble in solvents free of water or hydroxy groups. By this fact it becomes possible to use such functional derivatives of the acids of formula VI which in the presence of solvents containing hydroxy groups hydrolyse or would react in another manner with the solvent. The process of the invention therefore has the advantage that it is not necessary to use the acylating agent in excess and that it is possible to obtain the compounds of formula I in a relatively pure state.

The hydrolysis or alcoholysis, of the products obtained by acylating the compounds of Formula V to give the compounds of formula I is preferably made by adding water or a lower aliphatic alcohol or by adding a phenol to the reaction mixture. The reagent which causes the splitting off the silyl radicals may be added in one portion; it is, how-

ever, also possible to bring a gas carrying water or alcohol vapours (for instance moist air) into contact with the reaction mixture.

The following Examples serve to illustrate the invention.

EXAMPLE 1:

2.5 g. of potassium 6-amino penicillanate are treated with stirring in 50 ml of absolute benzene with 1.1 g. of trimethylchlorosilane. While further being stirred the mixture is refluxed for 5 hours. After cooling the reaction mixture is filtered and the filtrate which contains trimethylsilyl 6-amino penicillanate is used either for further reactions or is freed from benzene at reduced pressure in a dry stream of nitrogen, whereby the product is obtained in a nearly quantitative yield as a thick oil. On treating with a small amount of petrol ether and standing for some time the product solidifies. This solid turns on heating to a red-brown colour at about 175° C. and decomposes totally with foaming at about 220—225° C.

EXAMPLE 2:

2.2 g. 6-amino penicillanic acid are suspended in 50 ml. of absolute benzene and then under stirring 2.4 g. of triethylamine followed by 2.4 g. of trimethylchlorosilane are added. The mixture is refluxed for 5 hours with stirring, then cooled and filtered whereby a solution of trimethylsilyl N-trimethylsilyl 6-amino penicillanate is obtained. The oil remaining on distilling off the benzene solidifies upon standing for some time. On heating the product slowly decomposes until at about 225° C. complete decomposition has been effected.

EXAMPLE 3:

The process is the same as in Example 2, however, instead of the trimethylamine 2.5 g. of N-ethylpiperidine are used.

EXAMPLE 4:

To 2.2 g. of 6-amino penicillanic acid 50 ml. of absolute toluene and then 2.4 g. of trimethylchlorosilane are added. The mixture is stirred and boiled under reflux for 5 hours while a stream of dry ammonia is bubbled in. After this time the boiling solution is treated with a vigorous stream of dry nitrogen until the ammonium chloride formed in the reaction is removed from the solution. (The ammonium chloride sublimes into the reflux condenser). The remaining solution contains trimethylsilyl N-trimethylsilyl 6-amino penicillanate which may be isolated by distilling off the toluene in a vacuum in a stream of nitrogen.

EXAMPLE 5:

A suspension of 21.6 g. of 6-amino penicillanic acid in 50 ml. of hexamethyldisilazane is, after addition of 0.5 g. of ammonium sulphate, heated for 4—5 hours at 80° C. During this time the mixture is stirred and treated with a stream of dry nitrogen. Then the excess of hexamethyldisilazane is distilled off in a vacuum, the residue is dissolved in warm petrol ether and the solution thus obtained is filtered. On cooling trimethylsilyl 6-amino penicillanate crystallises from the filtrate. The mother liquor on evaporating yields an oil which solidifies after some time and consists of trimethylsilyl N-trimethylsilyl 6-amino penicillanate.

EXAMPLE 6:

A suspension of 21.6 g. of 6-amino penicillanic acid in 50 ml of hexamethyldisilazane is stirred and treated with a stream of dry nitrogen and heated under a reflux condenser for 4—5 hours at 80° C. and then for 30 minutes at 120° C. The reaction mixture is freed in a vacuum from the excess of hexamethyldisilazane whereby a viscous oil is obtained which is a mixture of trimethylsilyl 6-amino penicillanate and trimethylsilyl N-trimethylsilyl 6-amino penicillanate. This mixture is dissolved in such a quantity of dry tetrahydrofuran that the volume of the solution amounts to 100 ml.

EXAMPLE 7:

15 ml. of the solution obtained in example 6 (containing 3.24 g. of 6-amino penicillanic acid) are mixed with 1.82 g. of trimethylamine and chilled. At a temperature below 5° C. a solution of 3.28 g. of α-phenylisobutyryl chloride in 10 ml. of tetrahydrofuran is added dropwise with stirring. After standing for 3 hours the mixture is added to 250 ml. of butyl acetate and after cooling to 0—5° C. 2 ml. of isopropanol are added. After 45 minutes the mixture is filtered and the filtrate is treated with a solution of

potassium α-ethyl hexanoate in butyl acetate until pH 6.5 is reached. By adding ether, filtering and washing the solids thus obtained with butyl acetate, acetone and ether potassium N-(α-phenylisobutyryl)-6-amino penicillanate is isolated in a yield of 67% of the theoretical yield. On heating the product decomposes at 195—200° C. By the same process, by using phenoxyisobutyryl chloride, α-acetoxypropionyl chloride or 1-phenoxycyclopentane-1-carboxylic acid chloride, respectively, potassium salts of the appropriate N-acylated 6-amino penicillanic acid derivatives are obtained.

EXAMPLE 8:

20 ml. of the solution obtained in example 6 are chilled to 0° C. and mixed with 2.2 g. of triethylamine. With stirring a solution of 4 g. of 2,5-dimethoxy benzoyl chloride in 20 ml. of tetrahydrofuran is added dropwise. After 30 minutes a mixture of 10 ml. of tetrahydrofuran and 2 ml. ethanol is added with stirring and after a further 15 minutes the reaction mixture is filtered. The filtrate is neutralised with alcoholic potassium hydroxide solution and then added with stirring to 300 ml. of ether. Thus potassium N-(2¹,5¹-dimethoxybenzoyl)-6-amino penicillanate is obtained in a yield of 67% of the theoretical one. The product decomposes at 200—205° C.

EXAMPLE 9:

A solution of 6 g. tri-(bromomethyl) acetic acid in 20 ml. of dry tetrahydrofuran is treated with 1.52 g. of triethylamine followed by 1.56 g. of ethyl chloroformate and filtered. The solution thus obtained containing the mixed anhydride is added to 15 ml. of the solution obtained in Example 6. After standing for 2 hours the mixture is added to 250 ml. of butyl acetate and after cooling to 0.5° C. 2 ml. of 95% ethyl alcohol are added. After 15 minutes the mixture is filtered and the filtrate worked up as described in example 7. Thereby a yield of 57% of the theoretical one of potassium N-(tri-(bromomethyl)-acetyl)-6-amino penicillanate is obtained. On heating the product turns to a brown colour at about 200° C. and decomposes at 210—212° C. In the same manner, however, by using N-(α-phenoxypropionyl)-glycine and N-acetyl-β-alanine, respectively, the potassium salts of the appropriate N-acylated 6-amino penicillanic acid derivatives were obtained.

EXAMPLE 10:

10 ml. of the solution obtained in example 6 are mixed with 10 ml. of tetrahydrofuran and 1.1 g. of triethylamine. This mixture is treated below 5° C. dropwise with stirring with a solution of 2.62 g. of α-phenoxypropionyl chloride in 10 ml. of tetrahydrofuran. After being stirred for 30 minutes the mixture is added with stirring to 300 ml. of ice water. After 10 minutes the mixture is filtered, the filtrate is chilled and 200 ml. of butyl acetate are added. After acidifying to pH 2 and shaking, the aqueous layer is separated and again extracted with butyl acetate several times. The organic layers are combined, extracted with water, then dried with anhydrous sodium sulphate and filtered. The filtrate is treated with the solution of potassium α-ethyl hexanoate in butyl acetate until pH 6.5 is reached and then ether is added. The solid formed is filtered off and washed with butyl acetate, acetone and ether successively. Thereby potassium N-(α-phenoxypropionyl)-6-amino penicillanate is obtained in a yield of 92% of the theoretical yield. The product decomposes at about 229—234° C.

EXAMPLE 11:

15 ml. of the solution obtained in example 6 are mixed with 1.6 g. of triethylamine and chilled to 5° C. Under stirring a solution of 2.84 g. of benzene sulphonyl chloride is added dropwise in 10 ml. of tetrahydrofuran. After 1 hour the mixture is treated with 2 ml. of methanol and after stirring for 30 minutes filtered. The filtrate is neutralised with N-ethyl piperidine, ether is added and the mixture is cooled. Thus the N-ethyl piperidine salt of 6-benzene sulphonamido penicillanic acid is obtained in a yield of 72% of the theoretical one. Melting point 165—167° C.

EXAMPLE 12:

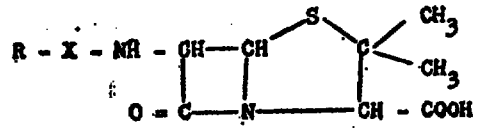
A mixture of 100 ml. of absolute benzene, 2.1 g. of 6-amino penicillanic acid and 0.89 g. of hexamethyldisilazane is refluxed until the evolution of ammonia is finished. The solution thus obtained is mixed with a solution of 2.7 g. of the mixed anhydride of phenoxy acetic acid and ethyl carbonate (obtained from phenoxy acetic acid and ethyl chloroformate in the presence of triethylamine) in 40 ml. of absolute benzene. The reaction mixture is stirred for some hours and then added with vigorous stirring to a solu-

tion of 5 g. of sodium hydrogen carbonate in 200 ml. of water. After thorough mixing the organic layer is separated. To the aqueous layer 50 ml. of butyl acetate are added and then the mixture is acidified to pH 1—2. After shaking the organic layer is separated, the aqueous layer is re-extracted twice with butyl acetate. The organic extracts are combined, dried with anhydrous sodium sulphate, filtered and the filtrate is neutralised with a solution of potassium α-hexyl hexanoate in butanol. Thereby potassium N-phenoxyacetyl 6-amino penicillanate is obtained in a yield of 92% of the theoretical one. The product decomposes at 258—262° C.

WHAT WE CLAIM IS:—

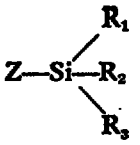
1. A process for the preparation of compounds of the general formula

I



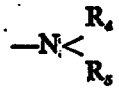
in which R represents an alkyl radical, which may be substituted or may be interrupted by hetero atoms, or a cycloaliphatic, aromatic, heterocyclic or araliphatic radical, which may be substituted, X represents a —CO— or —$SO_2$— group wherein 6-aminopenicillanic acid or a salt of 6-aminopenicillanic acid is reacted with a compound of the formula

II



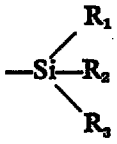
in which $R_1$, $R_2$ and $R_3$, which may be the same or different represent alkyl, aralkyl, cycloalkyl or aryl radicals and Z represents a halogen atom or the radical

III



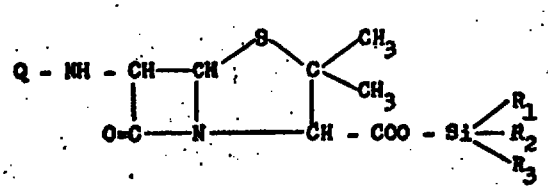
in which $R_4$ and $R_5$, which may be the same or different represent hydrogen atoms, lower alkyl radicals or the group

IV



and, if Z represents a halogen atom, the reaction takes place in the presence of a compound or compounds able to fix hydrogen halides, to give a compound of the formula

V



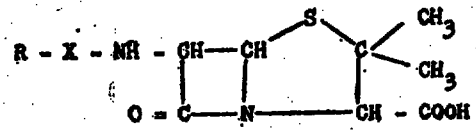
in which Q represents a hydrogen atom or the radical

tion of 5 g. of sodium hydrogen carbonate in 200 ml. of water. After thorough mixing the organic layer is separated. To the aqueous layer 50 ml. of butyl acetate are added and then the mixture is acidified to pH 1—2. After shaking the organic layer is separated, the aqueous layer is re-extracted twice with butyl acetate. The organic extracts are combined, dried with anhydrous sodium sulphate, filtered and the filtrate is neutralised with a solution of potassium α-hexyl hexanoate in butanol. Thereby potassium N-phenoxyacetyl 6-amino penicillanate is obtained in a yield of 92% of the theoretical one. The product decomposes at 258—262° C.

WHAT WE CLAIM IS:—

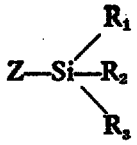
1. A process for the preparation of compounds of the general formula

I



in which R represents an alkyl radical, which may be substituted or may be interrupted by hetero atoms, or a cycloaliphatic, aromatic, heterocyclic or araliphatic radical, which may be substituted, X represents a —CO— or —$SO_2$— group wherein 6-aminopenicillanic acid or a salt of 6-aminopenicillanic acid is reacted with a compound of the formula

II



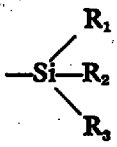
in which $R_1$, $R_2$ and $R_3$, which may be the same or different represent alkyl, aralkyl, cycloalkyl or aryl radicals and Z represents a halogen atom or the radical

III



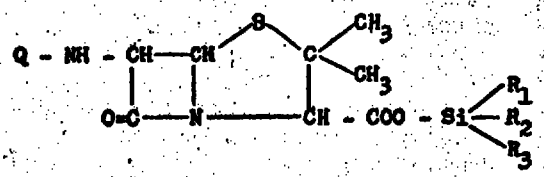
in which $R_4$ and $R_5$, which may be the same or different represent hydrogen atoms, lower alkyl radicals or the group

IV



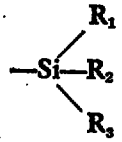
and, if Z represents a halogen atom, the reaction takes place in the presence of a compound or compounds able to fix hydrogen halides, to give a compound of the formula

V



in which Q represents a hydrogen atom or the radical

* C L M S *



in which $R_1$, $R_2$ and $R_3$ have the meanings given above, or a mixture of such compounds which is or are reacted with an acid of the formula

R—Y

wherein R has the meaning given above and Y represents a —COOH or —$SO_3H$ group or with an anhydride or halide of such an acid, preferably in the presence of a compound able to fix water or acids, followed by hydrolysis or alcoholysis to give a compound of the formula I.

2. A process as claimed in claim 1 wherein the compound of formula I is further reacted with an organic or inorganic base so as to convert it into a salt.

3. A process as claimed in claim 1, wherein the process is carried out without isolating the compound or compounds of formula V.

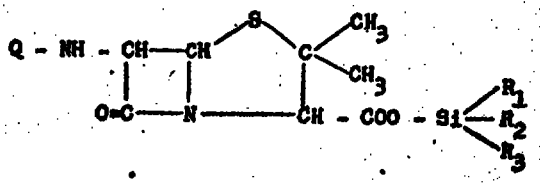
4. A process as claimed in claim 1, wherein 6-amino penicillanic acid is heated with an excess of the compound of formula II, in which Z represents an



radical, possibly in the presence of an ammonium salt, preferably ammonium sulphate, or the compound of formula II in which Z represents a halogen atom.

5. A process as claimed in claims 1 to 3 characterised in using inert solvents, preferably aliphatic or low-boiling aromatic hydrocarbons or cyclic ethers.

6. Compounds of the formula

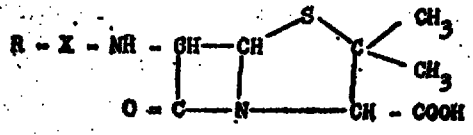


wherein Q, $R_1$, $R_2$ and $R_3$ have the meanings given above.

7. Trimethylsilyl 6-amino penicillanate.

8. Trimethylsilyl N-trimethyl-silyl-6-amino penicillanate.

9. Compounds of the formula I



whenever produced by the process claimed in any one of claims 1 to 5.

ELKINGTON & FIFE,
Chartered Patent Agents,
High Holborn House,
52—54 High Holborn,
London, W.C.1.

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