

PATENT SPECIFICATION

NO DRAWINGS

1.189.022



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COMPLETE SPECIFICATION

Process for Preparation of 6-Amino-Penicillanic Acid and Salts thereof

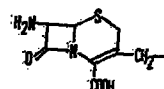
We, KONINKLIJKE NEDERLANDSCHE GIST-EN SPIRITUSFABRIEK N.V., a Dutch limited liability company, having a place of business at Delft, the Netherlands, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to a process for the preparation of 6-amino-penicillanic acid, or a salt thereof, by removal of the acyl radical from a 6 - acylamino - penicillanic acid, or salt.

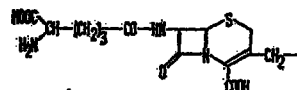
In Nature (Vol. 195, 1962, pg. 1000) it is disclosed that the alkaline hydrolysis of penicillins results in the formation of the corresponding penicilloic acids. With certain penicillins, the alkaline hydrolysis may also split off the side chain and, under certain conditions, up to 1% of these penicillins may be converted into 6 - amino - penicillanic acid. For example, storage of a 1% solution of phenoxymethylpenicillanic acid in a 0.05 molar phosphate buffer solution of pH 8.5 at 70° C. results in a 0.5% yield of 6 - amino - penicillanic acid. Benzyl-penicillin treated in the same way results in a yield of less than 0.03% 6-aminopenicillanic acid.

Up to the present, 6-aminopenicillanic acid has been prepared by microbiological methods on a technical scale but these methods suffer certain disadvantages since infection may occur with penicillinase-forming substances which break the penicillin down into penicilloic acids. Therefore, continuous, commercial production thereof is not yet feasible.

Specification No. 1,041,985 describes and claims a process for the manufacture of 7 - amino - cephalosporanic acid or a derivative thereof with a free amino group of the formula I



or an ester thereof, in which R represents an esterified hydroxyl group or in which R and the —OH group of the 4-carboxyl group are replaced by a lactone oxygen atom —O—, wherein cephalosporin C or a derivative thereof of the formula II



whose amino and carboxyl groups are blocked and in which H has the meaning given above or in which R and the —OH group of the 4-carboxyl group are replaced by a lactone oxygen atom —O—, is treated with an agent forming an imide halide, the imide halide is converted into the corresponding iminoether and the latter is hydrolysed with water in the presence of an acidic or basic substance at a pH value of at most 10 and, if desired, the group blocking the 4-carboxyl group is split off by hydrogenolysis or acid hydrolysis.

We have attempted to apply the process described in Specification No. 1,041,985 to 6-aminopenicillanic acid and have found that little or no product is obtained. It is known that the low stability of the penicillins is due to the β -lactam bond which is present in the penicillin ring system, the bond is easily cleaved under both acidic and basic conditions. We believe that cleavage of the β -lactam bond precludes the direct application of the process described in Specification No.

[Price 5s. 0d.]

1,041,985 to the analogous production of 6-amino - penicillanic acid—the β -lactam bond in the latter acid being sufficiently less stable than the corresponding bond in the 7-aminocephalosporanic acid to be unable to withstand the necessary reaction conditions.

We have now found that the cleavage of the β -lactam bond may be avoided so that 6-aminopenicillanic acid, or a salt thereof, may be prepared from a 6-acylaminopenicillanic acid, or salt, in a high yield. According to the present invention, therefore, we provide a process for the preparation of 6-aminopenicillanic acid or a salt thereof, which comprises esterifying the 4-carboxylic acid group of a 6-acylaminopenicillanic acid or a salt thereof, reacting the ester to form an imino bond on the 6-amido nitrogen atom, reacting the resulting compound to introduce an —OR group on the imino carbon atom, wherein R is an alkyl group of from 1 to 12 carbon atoms or an aralkyl group of from 7 to 14 carbon atoms, to form an imino ether, and splitting the imino bond of the imino ether and reforming the free 4-carboxylic acid, or a salt thereof; and in which process the reaction conditions used to split the imino ether and to reform the free 4-carboxylic acid, or salt, are sufficiently mild so as not to rupture the β -lactam bond of the product.

An N-substituted imino ether may be formed in several different ways. In J. Chem. Soc., Vol. 83, Pg. 321, (1903), a method is described for their preparation from an imino chloride by treating the latter with sodium ethanolate. Under the influence of hydrolysis, an ester and a primary amine are formed from the imino ether. An N-substituted imino chloride can be prepared according to Ber., Vol. 28, pg. 2367, (1895), from an N-mono-substituted amide with PCl_5 . An N-substituted imino ether can also be prepared directly by reacting an N-monosubstituted amide with dimethyl sulphate, (Ber., Vol. 98, pg. 2757, (1965)). In this case an N-mono-substituted imidium acid methyl ester methyl sulphate is formed, which can be converted with an acid binding agent (such as a tertiary amine) into an N-substituted imino ether. It is also possible to treat an N-substituted amide with a trialkyl oxonium salt such as trialkyl oxonium fluoroborate (Ber., Vol. 89, pg. 2063, (1956)). In this case, an N-substituted imidium acid alkyl ester fluoroborate is formed which can be converted with an acid binding agent into an N-substituted imino ether. Any of these processes can be used to form the imino derivative of the 6-acylaminopenicillanic acids or salts after the free 4-carboxylic acid group has been protected by esterification.

The process of this invention leaves the β -lactam bond of the penicillanic acid intact because a very mild hydrolysis or alcoholysis will suffice for the splitting of the imino bond.

In order to enable very mild hydrolysis or alcoholysis conditions to be used (i.e. conditions which leave the β -lactam bond intact), it is preferable to use an ester that can be readily hydrolyzed. Preferably a silyl ester of 6-acylaminopenicillanic acid is used in which a silicon atom is bound to an oxygen atom of the 4-carboxylic acid group. The silyl ester may be prepared from any suitable silylating agent.

Preferably the trimethylsilyl ester, the dimethylsilyl diester and the monosilyltriester are prepared. The trimethylsilyl ester can be prepared by treating a salt of a 6-acylaminopenicillanic acid with trimethylchlorosilane in an anhydrous medium. The silyl ester decomposes readily upon the addition of alcohol or water without the necessity of using acid or basic catalysts; it is thus capable of being split to form the free 4-carboxylic acid without the β -lactam bond rupturing.

It is also possible to start with aralkyl esters such as the benzyl or the benzhydryl ester. These can be split to form the 4-carboxylic acid by hydrogenolysis.

Any penicillin can be used as the starting material; in practice penicillins are used which can be obtained by microbiological processes. Examples are the alkali metal salts of 6-acylaminopenicillanic acids where the acyl radical is derived from aliphatic carboxylic acids such as acetic acid, propionic acid, Δ^2 -pentenyl carboxylic acid and n-heptylcarboxylic acid; aralkyl carboxylic acids, such as p-hydroxyphenylacetic acid and phenylacetic acid; and aryloxyalkyl carboxylic acids such as phenoxyacetic acid.

After esterification of the 6-acylaminopenicillanic acid or salt, the esters are then reacted with an agent to form an imino bond on the 6-amido nitrogen atom. Preferably an imino halide is formed. A suitable agent for preparing an imino halide is an acid halide in the presence of an acid binding agent such as a tertiary amine, e.g. pyridine or triethylamine. Examples of suitable acid halides are phosphorus pentachloride, phosgene, phosphorous oxychloride, oxalyl chloride and p-toluene sulfonic acid chloride. Phosphorus pentachloride and phosphorus oxychloride are preferred.

In the formation of the imino halide, the optimum duration of the reaction with the halogenating agent is dependent upon both the agent and the reaction temperature. Preferably a small excess of acid chloride is used. Phosphorus pentachloride reacts very rapidly, so that a lower temperature (for instance 0°C .) is used. Phosphorous oxychloride reacts more slowly, so that the reaction is preferably carried out at a higher temperature (for instance 20 to 27°C .)

Furthermore, the quantity of solvent used affects the duration of the reaction; with a greater concentration of the reaction components, the reaction proceeds more rapidly. The

type of solvent is also important; the temperature being equal, the reaction proceeds more slowly in chloroform than in methylene chloride or dichloroethane. It is preferable to operate with somewhat less than the stoichiometric quantity of the acid binding agent. Thus one may take from 3.8 to 3.95 mols of the tertiary base to 1 mol. of PCl_5 .

- The resulting imino compounds are then treated to introduce an $-\text{OR}$ grouping, in which R is an alkyl group of 1 to 12 carbon atoms or an aralkyl group of 7 to 14 carbon atoms, onto the imino carbon atom. This is preferably effected by reacting an imino halide with a corresponding alcohol, preferably an alcohol containing from 1 to 5 carbon atoms. The advantage of using a silyl ester in this reaction is that the silyl ester decomposes when the alcohol is added to the reaction mixture. The corresponding free 4-carboxylic acid containing the imino ether group is therefore formed without the β -lactam bond breaking. The reaction of the alcohol with the imino halide is preferably effected in the presence of an acid binding agent, such as a tertiary amine, preferably pyridine.

- Examples of suitable alcohols for reaction with the imino halide are aliphatic alcohols containing from 1 to 12 carbon atoms, preferably 1 to 5 carbon atoms, such as methanol, ethanol, propanol, isopropyl alcohol, amyl alcohol and butyl alcohol, and aralkyl alcohols such as benzyl alcohol and 2-phenyl-ethanol-1.

- To obtain as high a yield of 6-aminopenicillanic acid as possible in the reaction with the alcohol, the reaction temperature and the reaction time will vary depending upon the specific alcohol used. If a higher molecular weight alcohol is used (e.g. one containing from 6 to 12 carbon atoms), under comparable circumstances a slightly longer reaction time is required than with a lower molecular weight alcohol (e.g. one containing up to 5 carbon atoms). With a higher molecular weight alcohol, a higher reaction temperature can be applied or the quantity of the acid binding agent can be reduced.

- When the imino ether has been formed, the imino bond must finally be split, e.g. by mild hydrolysis or alcoholysis, especially if an excess of alcohol is used and hydrogen ions are present, for instance by the use of less acid binding agent than is theoretically necessary to bind the acid liberated. When a benzyl ester is used, hydrogenolysis may be applied to obtain 6-aminopenicillanic acid.

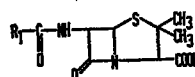
- It is not essential that the iminoether be formed in two stages from the 6-iminopenicillanic acid ester (e.g. via the imine halide). It is possible to introduce the imino ether bond in one stage, for instance see Example X hereinafter.

- The separation of the 6-aminopenicillanic acid from the reaction mixture is effected by

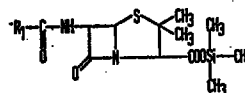
bringing the reaction mixture to, or in the vicinity of, the isoelectric point, in consequence of which crystallization takes place. The 6-aminopenicillanic acid obtained according to the present process is general is 96 to 99% pure, so that recrystallization is not necessary. It will, of course, be appreciated that at the isoelectric point the acid exists in solution as a zwitterion and crystallises as an inner salt. Crystallisation from solutions at a lower pH value results in acid addition salts.

A typical reaction scheme is illustrated in Table I.

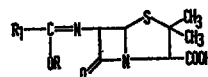
Table I



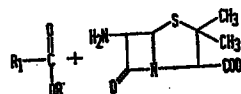
pyridine
trimethylchlorosilane.



1. PCl_5 , pyridine
2. ROH, pyridine



H^+ , H_2O , mild



in which R is an alkyl group containing from 1 to 12 carbon atoms or an aralkyl group containing from 7 to 14 carbon atoms and R_1 is an aliphatic, aralkyl or aryloxyalkyl group.

EXAMPLE I

In a three-necked flask equipped with a stirrer, a dropping funnel, a thermometer, and a calcium chloride tube, 14 g of technical grade penicillin V acid were dissolved in 140 ml of dry, alcohol-free chloroform, and 6.4 ml of triethylamine and 6 ml of trimethylchlorosilane were added. The temperature rose to about 30°C . After 15 minutes, 19 ml of pyridine were added and after cooling to -10°C , a solution of 12.5 g of PCl_5 in 260 ml of anhydrous, alcohol-free chloroform was added dropwise over a period about 7 minutes. Cooling was required to prevent the temperature of the mixture rising above 0°C . After 45 minutes' stirring at about 0°C (-1° to $+2^\circ\text{C}$), the mixture was cooled again to -10°C and then 130 ml of absolute methanol were added dropwise over a period of 5 minutes in such a way that the temperature did not rise above 0°C .

After a reaction time of 120 minutes, 40 ml of distilled water were added to the reaction mixture and the pH was brought to 2.0 with the aid of 6 *N* ammonium hydroxide. After 3 hours' standing at about 5° C, the pH was adjusted to 4.0 again, with the aid of 6 *N* ammonium hydroxide. The next morning, the crystallized 6-aminopenicillanic acid was separated from the mixture, which had been stored in the ice-box. The crystals were washed with 60% and 100% methanol and dried, to obtain 3.64 g of 6-aminopenicillanic acid, (a yield of 42.1%). According to a microbiological estimation, the mother liquor still contained 4.9% of 6-aminopenicillanic acid.

EXAMPLE II

14.88 g of the potassium salt of penicillin G, suspended in 140 ml of chloroform, were converted with 6.9 ml of trimethylchlorosilane into the trimethylsilyl ester, (reaction time 92 minutes at 23 to 25° C). 13.6 ml of pyridine were then added and the mixture was cooled to -10° C. 9 g of PCl₅ in 185 ml of chloroform were added over a period of about 1 1/2 minutes and the temperature rose to 0° C. After 33 minutes stirring at 0° C, and cooling to -11° C, 100 ml of absolute methanol were added over a period of about 4 minutes during which the temperature rose again to 0° C. After a reaction time of 159 minutes at this temperature, the mixture was added to 40 ml of distilled water and the pH was adjusted immediately to 4.0 by means of 6 *N* NaOH. After 20 hours' storage at about 5° C, the precipitate was separated from the mother liquor, washed with cold 60% and 100% methanol and dried to obtain 4.52 g of 6-aminopenicillanic acid (yield 52.2%) having a pale yellow color. According to an estimate, the mother liquor still contained 6.2% of 6-aminopenicillanic acid. According to a biological assay, the purity of the precipitate was 97.5% and according to a chemical analysis, 98.3%. The IR spectrum, and the R_F values obtained in chromatography, corresponded to those of authentic 6-aminopenicillanic acid.

EXAMPLE III

29.76 g of the potassium salt of penicillin G were converted, in 50 ml of pure chloroform to which 9.2 ml of pyridine had been added, with 14 ml of trimethylchlorosilane into the trimethylsilyl ester. After cooling the solution to -30° C, a solution of 18 g of PCl₅ in 150 ml of pure chloroform was added over about 1 minute, during which the temperature rose to -1° C. With continued stirring, the reaction mixture was maintained for 20 minutes at a temperature of 0° C. and then cooled to -20° C. A mixture of 150 ml of absolute ethanol and 18.4 ml of pyridine was then added (two thirds of the quan-

tity over a period of 3 minutes, the remainder over a period of 1 hour) while the temperature was maintained at about 0° C. After another 20 minutes stirring at 0° C, the reaction mixture was added with stirring to a solution of 33 g of sodium acetate trihydrate in 100 ml of water. The pH of the mixture was adjusted from 3.8 to 3.95 with 6 *N* NaOH. After 19 hours standing at about 5° C, the precipitate was drawn off, washed and dried to obtain 7.28 g of 6-aminopenicillanic acid (yield 42.1%). According to analysis, the mother liquor still contained 5.9% of 6-aminopenicillanic acid and 1.4% of penicillin G.

EXAMPLE IV

14.88 g of the potassium salt of penicillin G, suspended in 140 ml of pure chloroform, was converted with 6.4 ml of trimethylchlorosilane into the trimethylsilyl ester, cover a period of 75 minutes at 23 to 25° C). After this, 13.2 ml of pyridine were added, the mixture was cooled to -18° C, and over a period of 3 minutes a solution of 9 g of PCl₅ in 185 ml of pure chloroform was added dropwise, during which the temperature rose to -3° C.

After 32 minutes stirring at 0° C. and cooling again to -23° C, 100 ml of *n*-propanol were added. After a reaction time of 197 minutes at 0° C and another 128 minutes at 7 to 9° C, 21 ml of water were added and the pH was adjusted to 3.95. After 6 hours standing at 4° C, the 6-aminopenicillanic acid was separated from the mother liquor, washed and dried to obtain 2.58 g of 6-aminopenicillanic acid, (yield 29.8%). After working-up, the mother liquor was still found to contain 4.9% of 6-aminopenicillanic acid and 0.6% of benzylpenicillin.

EXAMPLE V

The trimethylsilyl ester of benzylpenicillin was prepared from 14.88 g of the potassium salt of benzylpenicillinate and 6.4 ml of trimethylchlorosilane in 140 ml of pure chloroform (to which 13.2 ml of pyridine had been added). After cooling to -18° C, 9 g of PCl₅ in 185 ml of pure chloroform were added, in consequence of which the temperature rose to almost 0° C. After a reaction time of 32 minutes at 0° C, the mixture was cooled again (to -20° C), upon which 100 ml of *n*-butanol was added. The mixture was stirred for 140 minutes at 0° C, for 85 minutes at 5° C and for 73 minutes at 15 to 20° C. After this, 21 ml of distilled water were added with continual stirring and the pH was adjusted to 3.95. After 4 hours' standing at 4° C, the precipitate was separated from the mother liquor, washed and dried to obtain 2.89 g of 6-aminopenicillanic acid (yield 33.5%). The mother liquor still contained 4.4% of 6-aminopenicillanic acid and 0.7 g of benzylpenicillin.

EXAMPLE VI

Using the procedure of Example V, the trimethylsilyl ester of penicillin G was reacted with PCl_5 . This time, however, the cooled reaction mixture was reacted further with 125 ml of amyl alcohol instead of *n*-butanol. This reaction was carried out first at 0°C (for 148 minutes), then at $+5^\circ\text{C}$ (for 63 minutes), and finally at $+10$ to 15°C (for 95 minutes). The product obtained was 2.78 g of 6-aminopenicillanic acid (yield 32.2%). The mother liquor still contained 5.4% of 6-aminopenicillanic acid.

EXAMPLE VII

A suspension of 14.88 g of the potassium salt of benzylpenicillin in 50 ml of pure methylene chloride was converted, in the presence of 6.8 ml of pyridine, with 6.4 ml of trimethylchlorosilane into the trimethylsilyl ester. The solution was cooled to -25°C and a solution of 9 g of PCl_5 in 100 ml of pure methylene chloride was added to the ester, all at once. The temperature rose to -3°C . The reaction mixture was then stirred for a period of 12 minutes at 0°C and subsequently cooled to -30°C . At this temperature, a mixture of 6.8 g of pyridine and 100 ml of methanol was added during which the temperature rose to 0°C . After 125 minutes, 40 ml of distilled water were added and the pH was adjusted to 4.0. After standing for 24 hours at 5°C , the crystallized 6-aminopenicillanic acid was vacuum filtered, washed and dried, to obtain 3.48 g of 6-aminopenicillanic acid (yield 40.3%). The mother liquor still contained 3.3% of 6-aminopenicillanic acid.

EXAMPLE VIII

A solution of 4.25 g of benzylpenicillin benzyl ester in 35 ml of pure chloroform was cooled to -20°C . 3.4 ml of pyridine and a solution of 2.25 g of phosphorus pentachloride in 45 ml of chloroform was added thereto. The mixture was stirred for 120 minutes at 0°C and cooled again to -20°C . 20 ml of methanol were then added, the temperature rose and the mixture was stirred further at 0°C . After 2 hours, 10 ml of water were added and the pH was adjusted to 2.7. The aqueous layer was separated from the chloroform layer and the latter was washed with 5 ml of water. The aqueous layers were subsequently extracted three times with 5 ml portions of ethyl acetate. The extracted aqueous layer was adjusted to pH 8.3 and extracted three times with 10 ml of ethyl acetate. The collected ethyl acetate extracts were dried over Na_2SO_4 and by means of thin-layer chromatography using a butanol-acetic acid-water system and spraying with iodine azide, 6-aminopenicillanic acid benzyl ester was shown to be present. 10 ml of methanol and 1 ml of acetic acid were then added to

one half of the ethyl acetate solution. The mixture was subsequently hydrogenated using a Pd-C (10%) catalyst and, after hydrogenation, the solution was found to contain 6-aminopenicillanic acid together with non-converted benzyl ester.

EXAMPLE IX

7.44 g of the potassium salt of penicillin G were suspended in 25 ml of pure methylene chloride and 1.6 ml of pyridine and 6.4 ml of trimethylchlorosilane were added to the suspension. After cooling to 20°C , 1.9 ml of phosphorus oxychloride in 25 ml of pure methylene chloride were added dropwise to the trimethylsilyl ester formed and the temperature was brought to room temperature (about 26°C). At this temperature, the mixture was stirred for 3 $\frac{3}{4}$ hours. It was then cooled to -20°C and with continued stirring, first 25 ml of methanol and subsequently a mixture of 25 ml of methanol and 4.0 ml of pyridine were added. After 115 minutes stirring at 0°C , 20 ml of distilled water were added and the pH of the mixture was adjusted to 7.3. The layers were separated and the methylene chloride layer was further extracted with 5 ml of distilled water. According to a microbiological estimation, the aqueous layers thus obtained contained 6-aminopenicillanic acid.

EXAMPLE X

7.45 g of potassium benzylpenicillinate were suspended in 80 ml of dry, alcohol-free chloroform and, with stirring 2.6 ml of trimethylchlorosilane were added to the suspension whilst nitrogen gas was passed over the reaction mixture. After 30 minutes stirring at room temperature, during which a solution was formed, 2 g of triethyloxonium tetrafluoroborate in 17 ml of chloroform were added. After a further 2 $\frac{1}{2}$ hours stirring at room temperature, 40 ml of pyridine were added. 13.5 ml of the reaction mixture was subsequently evaporated to dryness under a pressure of 25 cm Hg and at a temperature of 30°C . The residue was taken up in 200 ml of dioxane. 120 ml of 5% phosphoric acid were then added dropwise. After standing for 3 $\frac{1}{2}$ hours at room temperature, 6-aminopenicillanic acid was shown to be present in the mixture by chromatography. A microbiological test also indicated the presence of 6-aminopenicillanic acid.

EXAMPLE XI

29.8 g of the potassium salt of benzyl penicillin (technical grade, 1579 U/mg) were suspended in 300 ml of technical chloroform. Then, in succession, 32 ml of quino-line and 14.5 ml of dimethyldichlorosilane were added to the suspension; the temperature rose from 20.5°C to 26°C . After stirring for about 40 minutes, the suspension

was cooled to -25°C and at this temperature 18 g of PCl_5 were added. After a reaction period of 3 hours, 200 ml of n-propanol were added quickly (over about 4 minutes) under vigorous stirring but in such a way that the temperature did not rise about -20°C . After a reaction period of 2 hours, the reaction mixture was added to 175 ml of water whilst stirring and the pH was adjusted to 4.0 by means of ammonium bicarbonate. After standing for 12 hours at 4°C , the 6-aminopenicillanic acid was separated from the mother liquor and washed with 65 ml of 50% cold methanol and 70 ml of acetone. After drying, 13.85 g of 6-aminopenicillanic acid was obtained having a content of 2702 U/mg (yield 80.1%).

WHAT WE CLAIM IS:—

1. A process for the preparation of 6-aminopenicillanic acid or a salt thereof, which comprises esterifying the 4-carboxylic acid group of a 6-acylaminopenicillanic acid or a salt thereof, reacting the ester to form an imino bond on the 6-amido nitrogen atom, reacting the resulting compound to introduce an —OR group on the imino carbon atom, wherein R is an alkyl group of from 1 to 12 carbon atoms or an aralkyl group of from 7 to 14 carbon atoms, to form an imino ether, and splitting the imino bond of the imino ether and reforming the free 4-carboxylic acid, or a salt thereof; and in which process the reaction conditions used to split the imino ether and to reform the free 4-carboxylic acid, or salt, are sufficiently mild so as not to rupture the β -lactam bond of the product.
2. A process according to claim 1, in which the 4-carboxylic acid ester is a silyl ester.
3. A process according to claim 2, in which the silyl ester is a trimethylsilyl ester.
4. A process according to any of claims 1 to 3, in which the 6-acylaminopenicillanic acid is benzylpenicillin.

5. A process according to any of claims 1 to 3, in which the 6-acylaminopenicillanic acid is phenoxymethylpenicillin.

6. A process according to any of claims 1 to 5, in which the esterified 6-acylaminopenicillanic acid, or salt, is reacted with an acid halide to form the corresponding imino halide.

7. A process according to claim 6, in which the reaction with the acid halide is effected in the presence of an acid binding agent.

8. A process according to claim 6 or 7, in which the acid halide is phosphorus pentachloride.

9. A process according to claim 6 or 7, in which the acid halide is phosphorus oxychloride.

10. A process according to any of claims 6 to 9, in which the imino halide is reacted with an alcohol to form the imino ether.

11. A process according to claim 10, in which the alcohol is an aliphatic alcohol containing from 1 to 5 carbon atoms.

12. A process according to claim 10 or 11, in which the reaction with the alcohol is effected in the presence of pyridine.

13. A process according to any of claims 1 to 12, in which the imino bond of the imino ether is split by hydrolysis.

14. A process according to claim 1 for the preparation of 6-aminopenicillanic acid, or a salt thereof, substantially as hereindescribed with especial reference to any of the Examples.

15. 6-aminopenicillanic acid, or a salt thereof, whenever prepared by the process according to any of claims 1 to 14.

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A. A. Thornton

was cooled to -25°C and at this temperature 18 g of PCl_5 were added. After a reaction period of 3 hours, 200 ml of n-propanol were added quickly (over about 4 minutes) under vigorous stirring but in such a way that the temperature did not rise about -20°C . After a reaction period of 2 hours, the reaction mixture was added to 175 ml of water whilst stirring and the pH was adjusted to 4.0 by means of ammonium bicarbonate. After standing for 12 hours at 4°C , the 6-aminopenicillanic acid was separated from the mother liquor and washed with 65 ml of 50% cold methanol and 70 ml of acetone. After drying, 13.85 g of 6-aminopenicillanic acid was obtained having a content of 2702 U/mg (yield 80.1%).

WHAT WE CLAIM IS:—

1. A process for the preparation of 6-aminopenicillanic acid or a salt thereof, which comprises esterifying the 4-carboxylic acid group of a 6-acylaminopenicillanic acid or a salt thereof, reacting the ester to form an imino bond on the 6-amido nitrogen atom, reacting the resulting compound to introduce an —OR group on the imino carbon atom, wherein R is an alkyl group of from 1 to 12 carbon atoms or an aralkyl group of from 7 to 14 carbon atoms, to form an imino ether, and splitting the imino bond of the imino ether and reforming the free 4-carboxylic acid, or a salt thereof; and in which process the reaction conditions used to split the imino ether and to reform the free 4-carboxylic acid, or salt, are sufficiently mild so as not to rupture the β -lactam bond of the product.
2. A process according to claim 1, in which the 4-carboxylic acid ester is a silyl ester.
3. A process according to claim 2, in which the silyl ester is a trimethylsilyl ester.
4. A process according to any of claims 1 to 3, in which the 6-acylaminopenicillanic acid is benzylpenicillin.

5. A process according to any of claims 1 to 3, in which the 6-acylaminopenicillanic acid is phenoxymethylpenicillin.

6. A process according to any of claims 1 to 5, in which the esterified 6-acylaminopenicillanic acid, or salt, is reacted with an acid halide to form the corresponding imino halide.

7. A process according to claim 6, in which the reaction with the acid halide is effected in the presence of an acid binding agent.

8. A process according to claim 6 or 7, in which the acid halide is phosphorus pentachloride.

9. A process according to claim 6 or 7, in which the acid halide is phosphorus oxychloride.

10. A process according to any of claims 6 to 9, in which the imino halide is reacted with an alcohol to form the imino ether.

11. A process according to claim 10, in which the alcohol is an aliphatic alcohol containing from 1 to 5 carbon atoms.

12. A process according to claim 10 or 11, in which the reaction with the alcohol is effected in the presence of pyridine.

13. A process according to any of claims 1 to 12, in which the imino bond of the imino ether is split by hydrolysis.

14. A process according to claim 1 for the preparation of 6-aminopenicillanic acid, or a salt thereof, substantially as hereindescribed with especial reference to any of the Examples.

15. 6-aminopenicillanic acid, or a salt thereof, whenever prepared by the process according to any of claims 1 to 14.

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