

PATENT SPECIFICATION

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NO DRAWINGS

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(54) PROCESS FOR THE PREPARATION OF
6-AMINOPENICILLANIC ACID

(71) We, KONINKLIJKE NEDERLANDSCHE GIST- EN SPIRITUSFABRIEK N.V., a Dutch limited liability company, having its 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:—

This invention relates to a process for the preparation of 6-aminopenicillanic acid and is an improvement in or modification of the invention described and claimed in our earlier Specification No. 1,189,022.

Specification No. 1,189,022 describes and claims 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. It is preferred that the 4-carboxylic acid ester is a silyl ester such as the trimethylsilyl ester. Typically the imino bond is introduced into the molecule on the 6-amido nitrogen atom by reacting the 4-carboxylic acid ester with an acid halide, such as phosphorus pentachloride, to form the corresponding imino halide. The imino halide may then be reacted with, say, an alcohol to form the imino ether.

The reaction temperature and reaction time for the process claimed in our earlier specification are very important for a good yield.

The reaction with the acid chloride as well as that with the alcohol are carried out at temperatures of about 0°C. Before carrying out each of the successive steps of the reaction the reaction mixture is cooled to lower temperatures (varying from -10° to -30°C) to ensure that the temperature will not rise too much when adding the reaction components. After the addition of the next reaction component, the temperature again rises to around 0° and the bulk of the reaction takes place at this temperature. This process leads to yields of about 52%.

We have now found that considerable higher yields, amounting to 90% or more, can be obtained by carrying out the reaction of the imino halide with the alcohol to form the imino ether at very much lower temperatures and according to the present invention, therefore, we provide a process for the preparation of 6-aminopenicillanic acid or a salt thereof as claimed in claim 2 of Specification No. 1,189,022, in which the silyl ester of the 6-acylaminopenicillanic acid is reacted with a substance capable of forming an imino halide on the 6-amido nitrogen atom and in which the imino halide is reacted with an alcohol to form the imino ether at a temperature not exceeding -20°C. Preferably the reaction with the alcohol is carried out at from -40°C. to -60°C.

In order that the invention may be more fully understood the following Example is given by way of illustration only. From the Example, and the accompanying Table, it will be seen that the reaction time is also important for optimum yields.

EXAMPLE.

30 g of the crude potassium salt of penicillin G (1565 I.U./mg) were suspended in 125 ml of dichloromethane in a round bottomed flask with three necks. 8 ml of dimethyl dichloro silane and 21 ml of N,N-dimethylaniline were added while stirring vigorously, during which addition the temperature rose

to approximately +30°C. The mixture was kept at +25°C for half an hour and was then cooled to about -52°C, after which 18 g of phosphorus pentachloride (PCl₅) were added. The temperature again rose slightly. The mixture was kept at -40°C for two hours and was then cooled to a temperature 20° below that at which it was intended to carry out the reaction with the alcohol. 4 ml of dimethylaniline and 125 ml of n.butanol were then added within a minute.

When -60°C was chosen as the reaction temperature it was necessary to precool the butanol to -50°C before adding it to the reaction mixture. At -10° and -20°C, the reaction with butanol proceeds very rapidly. It was therefore necessary to ensure that the temperature did not rise above these values due to addition of the reagents. Depending upon the reaction temperature, 50 ml samples were removed from the reaction mixture at different times and these were mixed with 20

ml of water while stirring. These mixtures were adjusted to pH 4.0 by the addition of 8.5 ml of 6 N ammonia followed by the addition of ammonium bicarbonate.

The precipitated 6-aminopenicillanic acid was collected by suction filtration and washed with a mixture of acetone and water (1:1) and then with acetone. The results of the reaction with butanol at different temperatures are shown in Table I.

TABLE I
Yields after reaction times (in minutes)

Reaction temperatures	2	3½	5	7½	10	15	20	30	45	60
-10°C	73.8	80.0	81.7 ±0.4	79.8 ±0.45	78.8 ±0.45	75.7	71.5	—	—	—
-20°C	—	—	83.0	—	85.1	86.5 ±0.3	85.0 ±0.2	83.4 ±0.3	81.7	80.2
-30°C	—	—	—	—	—	86.3	—	88.4	88.2	87.6
-40°C	—	—	—	—	—	—	—	87.7 ±0.4	—	90.5 ±0.3
-50°C	—	—	—	—	—	—	—	—	—	81.6
-60°C	—	—	—	—	—	—	—	—	—	—

TABLE I (Continued)

Yields after reaction times (in minutes)

Reaction temperatures	90	120	150	180	210	240	270	300	330	360	390
-10°C	—	—	—	—	—	—	—	—	—	—	—
-20°C	—	—	—	—	—	—	—	—	—	—	—
-30°C	85.9	—	—	—	—	—	—	—	—	—	—
-40°C	90.6 ±0.2	89.8 ±0.3	89.6 ±0.2	— —	— —	— —	— —	— —	— —	— —	— —
-50°C	88.0	90.6	90.3	89.9	—	—	—	—	—	—	—
-60°C	—	—	—	81.0	83.9	86.9	89.3 ±0.3	89.9 ±0.2	90.5	91.2	90.9

TABLE I.

- These figures show that only a slight increase of the optimal yield can be obtained below -40°C at the cost of a considerable prolongation of the reaction time. The yield at -30°C is approximately 2% lower than that obtained at -40°C, and is lowered by another 2% at -20°C.
- 10 The yield is further decreased by about 5% at -10°C. At 0°C the best obtainable yield is lowered by another 7%. At temperatures between 0°C and -20°C there is a very marked decrease in the yield if a slightly shorter or longer time than the optimal reaction time is used. This is very clearly shown in the accompanying diagram 1 in which the
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data of Table I have been plotted. Moreover the time for obtaining the optimal yield at these temperatures is too short for practical purposes.

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The influence of temperature on the reaction of the 6-acylaminopenicillanic acid silyl ester with PCl₅ is less important than on the reaction of the imino halide with the alcohol. The yield at -10° is only about 2% lower than that -40°C as is shown in Table II below. In the experiments shown in this Table, the reaction temperatures in the PCl₅ reaction step are -10°C and -40°C. The optimal reaction time values are 90 minutes in both cases. The reaction with butanol was carried out at -40°C in both cases.

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TABLE II

% yield after reaction with butanol at -40°C ; reaction time in minutes

Reaction temperature of the PCl_5 -step	30	60	90	120	150
-10°C	86.2	88.6	88.6	87.9	87.6
-40°C	87.7	99.5	90.6	89.8	89.6

WHAT WE CLAIM IS:—

1. A process for the preparation of 6-aminopenicillanic acid or a salt thereof as claimed in claim 2 of Specification No. 1,189,022, in which the silyl ester of the 6-acylaminopenicillanic acid is reacted with a substance capable of forming an imino halide on the 6-amido nitrogen atom and in which the imino halide is reacted with an alcohol to form the imino ether at a temperature not exceeding -20°C .
2. A process according to claim 1, in which the imino halide is reacted with the alcohol

at a temperature of from -40°C . to -60°C . 15

3. A process for the preparation of 6-aminopenicillanic acid or a salt thereof substantially as herein described in the Example.

4. 6-aminopenicillanic acid or a salt thereof when prepared by the process claimed in any of claims 1 to 3. 20

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