(12) UK Patent Application (19) GB (11) 2 070 009 A

(21) Application No 8105382
(22) Date of filing 20 Feb 1981
(30) Priority data
(31) 488783
(32) 20 Feb 1980
(33) Spain (ES)
(43) Application published
3 Sep 1981
(51) INT CL³
C07D 501/04
(52) Domestic classification
C2C 1314 214 220 22Y 256 25Y 30Y 321 32Y 342 34Y 351 352 365 366 367 36Y 628 650 662 AB KE
(56) Documents cited
None
(58) Field of search
C2C
(71) Applicant
Gema S.A.,
Balmes 348, Barcelona,
Spain
(72) Inventors
Antonio Luis Palomo Coll,
Jose Diago Meseguer,
Asuncion Esteve Bianchini,
Esteve Sans Pitarch
(74) Agent
Reddie & Grose,
16 Theobalds Road,
London, WC1X 8PL

(54) A Process for the Preparation of 7-(D(—)-Alpha-amino-p-hydroxyphenyl-acetamido)-desacetoxycephalosporanic Acid

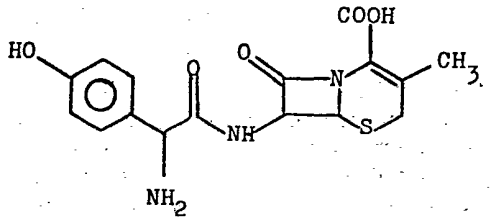
(57) There is described a process for the preparation of 7-(D(—)-alpha-amino-p-hydroxyphenylacetamido)-desacetoxy-cephalosporanic acid in which a D(—)-p-hydroxy-N-(1-alkoxy-carbonyl-2-propenyl)-alpha-aminophenylacetic acid salt is reacted with trimethylsilyl-2-oxazolidinone. The resulting reaction product is reacted in turn with an acyl chloride or an alkyl chloroformate to give a mixed anhydride which is reacted with 7-aminodesacetoxycephalosporanic acid silylated with trimethylsilyl-2-oxazolidinone, dissolved in an anhydrous organic solvent, and the blocking groups are removed.

GB 2 070 009 A

SPECIFICATION

A Process for the Preparation of 7-(D(—)-alpha-amino-P-hydroxyphenyl-acetamido)desacetoxycephalosporanic Acid

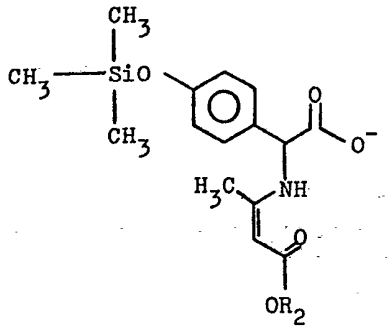
The present invention relates to a process for the preparation of 7-(D(—)-alpha-amino-p-hydroxyphenylacetamido)desacetoxycephalosporanic acid having the structurel formula:



(I)

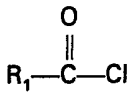
which is otherwise known as p-hydroxycephalexin or cephadroxyl and is of interest in human and verterinary medicine.

The invention provides a process for the preparation of p-hydroxycephalexin (cephadroxyl), which comprises reacting a D(—)-p-hydroxy-N-(1-alkoxycarbonyl-2-propenyl)-alpha-aminophenylacetic acid salt with trimethylsilyl-2-oxazolidinone (TMSO) to give a compound having the general formula:



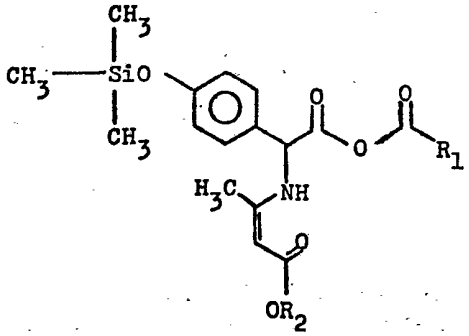
(II)

where R_2 is a C_1 to C_4 alkyl group;
reacting this compound with a compound of the general formula:



(III)

where R_1 is a methoxy, ethyoxy, phenyl or C_4 to C_9 alkyl group, preferably, an acyl chloride or an alkyl chloroformate, to give a mixed anhydride having the following general formula:



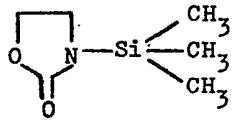
(IV)

reacting the mixed anhydride of formula IV with a solution of silylated 7-aminodesacetoxycephalosporanic acid (7-ADCA) in an anhydrous organic solvent; and removing the blocking groups to give p-hydroxycephalexin (cephadroxyl).

(IV)+silylated 7-ADCA
↓ unblocking and precipitation
p-HYDROXYCEPHALEXIN (I)

In the process the most important features may be summarised as follows:

1) Selective silylation of the D(—)-2-p-hydroxyphenylglycine phenol group with the amino group blocked as enamine, as disclosed in Spanish Patent 459,494. For this purpose, trimethylsilyl-2-oxozolidinone (TMSO) having the formula:

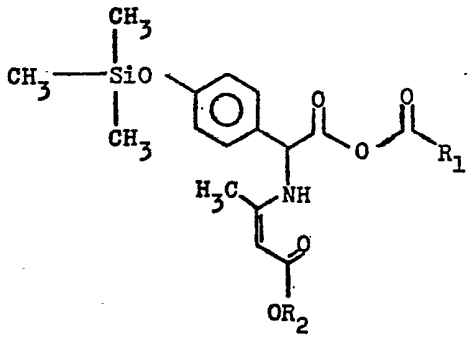


(V)

a reactant disclosed in Spanish Patent 411,867, is considered to be most appropriate.

The blocking of the phenol group inhibits competitive reactions in which the —OH group is inevitably involved, both in the mixed anhydride formation step and in the later acylation step. With silyation, not only the yield but also the quality of the finished product is increased.

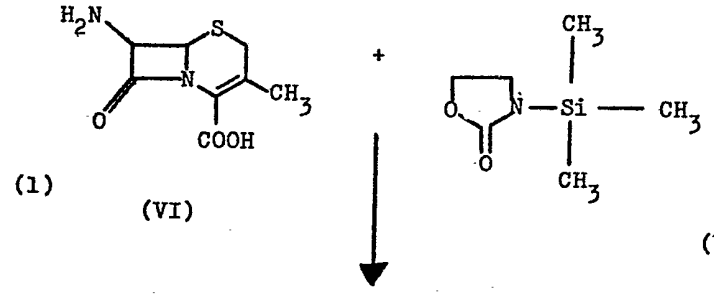
2) Reaction of the D(—)-p-trimethylsiloxyphenylglycine salt, having the amino group blocked as enamine, with an acyl chloride or alkyl chloroformate to give the mixed anhydride:



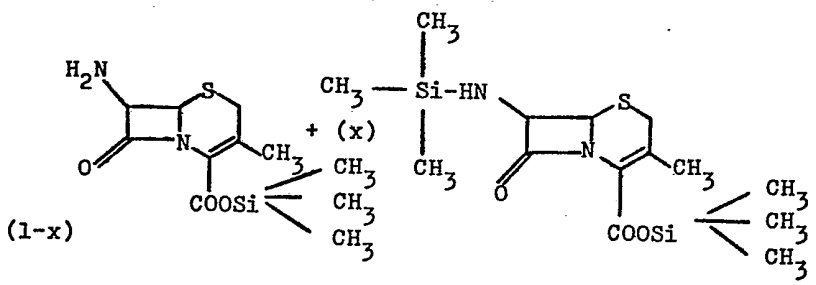
(IV)

in which R_1 may be: —OCH_2CH_3, —OCH_3, phenyl or C_4—C_9 alkyl groups and R_2 is C_1 to C_4 alkyl.

3) Silylation of 7-aminodesacetoxycephalosporanic acid (7-ADCA) of formula VI with TMSO of formula V in an anhydrous organic solvent.



(I) (VI) (V)



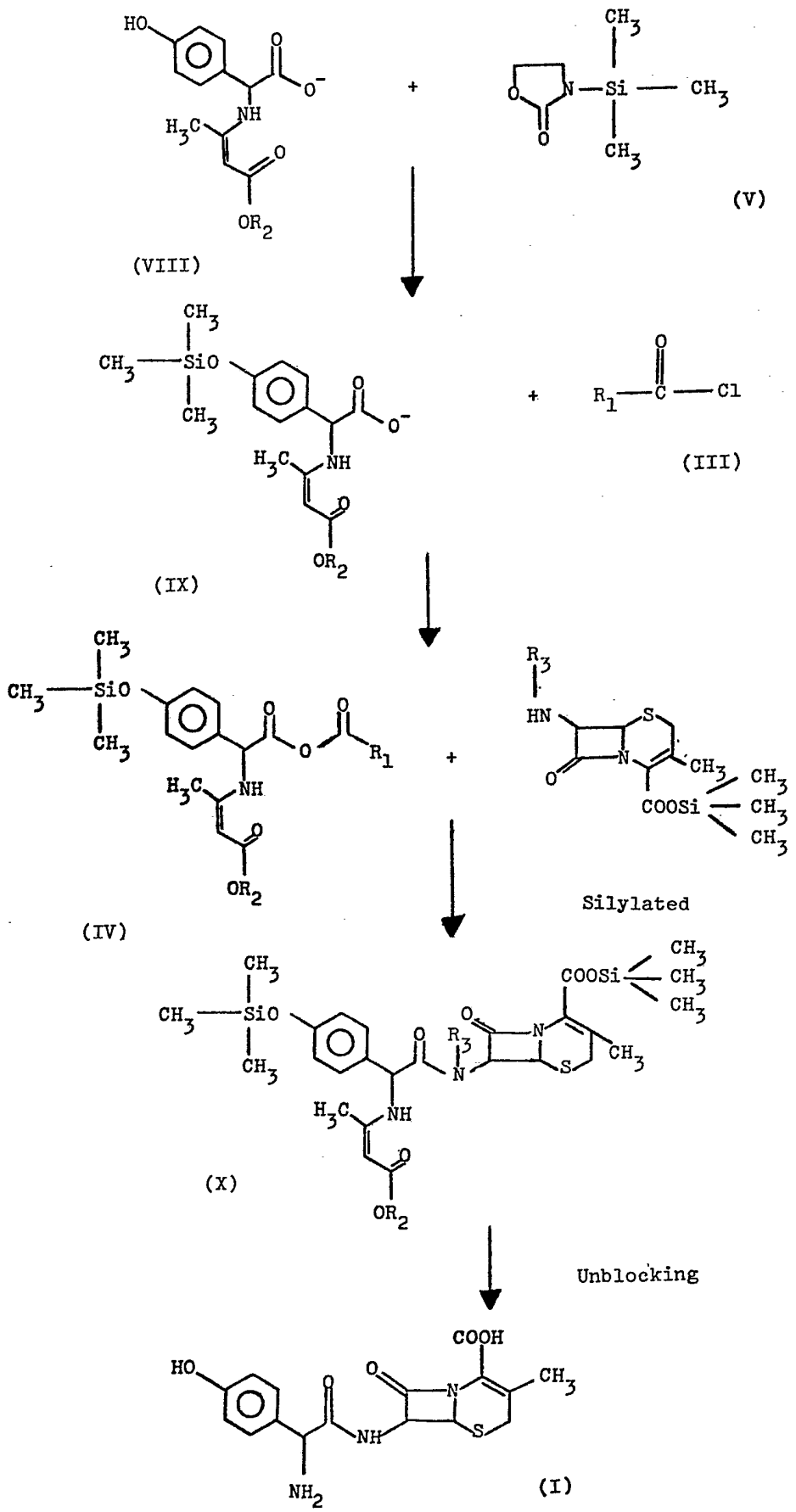
(I-x) (VII)

4) Reaction of the mixed anhydride of formula IV with the solution of silylated 7-ADCA which, after the unblocking and precipitation step, leads to the formation of p-hydroxycephalexin (cephadroxyl).

The importance of carrying out all the reactions in anhydrous organic solvent lies in the inhibition of the beta-lactam ring degradation processes, particularly promoted in aqueous media and above all under basic conditions ("Cephalosporins and Penicillins" E. H. Flynn, Academic Press Inc., New York, 1972, page 105 et seq.).

The process of the invention leads to the preparation of p-hydroxycephalexin, with excellent yield and quality.

Graphically illustrated, the new process for the preparation of p-hydroxycephalexin proceeds according to the following scheme:



in which R_1 and R_2 are as hereinbefore defined and R_3 is hydrogen or a trimethylsilyl group.

The following Examples illustrate the invention.

Example 1

7(D(—)-alpha-amino-p-hydroxyphenylacetamido)desacetoxycephalosporanic Acid

Trimethylsilyl-2-oxazolidinone (3.2 ml, 2.082 cmoles) was added to a suspension of D(—)-p-hydroxy-N-(1-methoxycarbonyl-2-propenyl)alpha-aminophenylacetic acid potassium salt (6.31 g, 2.082 cmoles) in acetonitrile (50 ml). There was obtained a fluid suspension which was stirred for 40 minutes. It was chilled to —20°C and pivaloyl chloride (2.64 ml, 2.134 cmoles) was added. An immediate fluidification was observed, giving a cream coloured fluid suspension which was stirred for 30 minutes at —10°C.

A solution of 7-aminodesacetoxycephalosporanic acid (3.6 g, 1.69 cmoles), acetonitrile (50 ml) and trimethylsilyl-2-oxazolidinone (11.3 ml, 7.38 cmoles) was prepared refluxing for 10 minutes. The resultant ochre coloured solution was cooled to room temperature and added the above suspension chilled to —15°C over a period of 30 minutes. A cream coloured suspension, which was stirred for 2 hours at —10°C, was obtained.

Thereafter methanol (25 ml) was added and the mixture was stirred for 10 minutes at 0/—5°C. It was filtered through a filter aid to remove the unreacted KCl and 7-ADCA. The filter was washed with acetonitrile and the filtrates were chilled to 0°C, and water was added (25 ml). The ochre coloured solution was adjusted to pH 2 with hydrochloric acid and was stirred for 20 minutes at 0—5°C. The pH was raised to 5.5 with the addition of triethylamine (TEA) at room temperature. There was obtained a suspension which was stirred for 90 minutes at room temperature. It was filtered, washed with acetonitrile (40 ml) and dried, to give the compound p-hydroxycephalexin.

Example 2

Following Example 1, but replacing the pivaloyl chloride with benzoyl chloride (2.48 ml, 2.134 cmoles), p-hydroxycephalexin was prepared.

Example 3

Following Example 1, but replacing the D(—)-p-hydroxy-N-(1-methoxycarbonyl-2-propenyl)-alpha-aminophenylacetic acid potassium salt with D(—)-p-hydroxy-N-(1-ethoxycarbonyl-2-propenyl)-alpha-aminophenylacetic acid potassium salt (6.602 g, 2.082 cmoles), p-hydroxycephalexin was obtained.

Example 4

Following Example 1, but replacing the pivaloyl cloride with ethyl chloroformate (2.03 ml, 2.134 cmoles), p-hydroxycephalexin was prepared.

Example 5

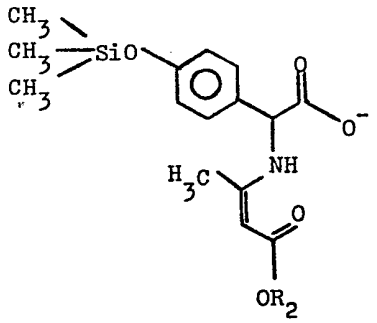
Example 1, was followed but the solution of 7-aminodesacetoxy-cephalosporanic acid was formed by adding trimethylsilyl-2-oxazolidinone (6.46 ml, 4.225 cmoles) to a suspension of 7-aminodesacetoxycephalosporanic acid (3.6 g, 1.69 cmoles) in acetonitrile (50 ml) and was refluxed for 45 minutes. p-Hydroxycephalexin was obtained.

Example 6

Following Example 1, but replacing the pivaloyl chloride with methyl chloroformate (1.65 ml, 2.134 cmoles), p-hydroxycephalexin was obtained.

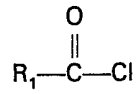
Claims

1. A process for the preparation of 7-(D(—)- alpha-amino-p-hydroxyphenylacetamido)desacetoxycephalosporanic acid, wherein D(—)-p-hydroxy-N-(1-alkoxycarbonyl-2-propenyl)-alpha-aminophenylacetic acid salt is reacted with trimethylsilyl-2-oxazolinone (TMSO) to give a compound of the following general formula:



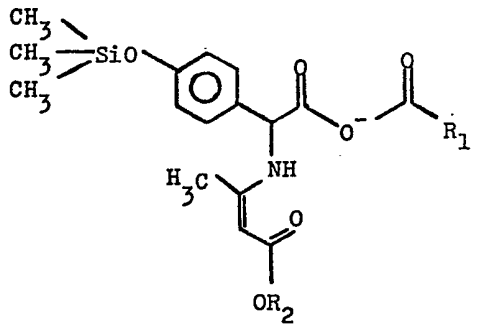
(IX)

which is then reacted with a compound of the general formula:



(III)

to give a mixed anhydride of the general formula:



(IV)

in which R_1 may be methoxy, ethoxy, phenyl or a C_4—C_9 aliphatic chain and R_2 is a C_1 to C_4 alkyl with mixed anhydride is reacted with a solution of 7-aminodesacetoxycephalosporanic acid (7-ADCA) obtained by silylation, in an anhydrous organic solvent, with trimethylsilyl-2-oxazolidinone and removing the blocking groups.

2. A process according to claim 1, wherein the compound of the general formula III is an acyl chloride.

3. A process according to claim 2, wherein the acyl chloride is pivaloyl chloride or benzoyl chloride.

4. A process according to claim 1, wherein the compound of the general formula III is an alkyl chloroformate.

5. A process according to claim 4, wherein the alkyl chloroformate is ethyl chloroformate or methyl chloroformate.

6. A process according to any one of claims 1 to 5, wherein R_2 is a methyl or ethyl group.

7. A process according to claim 1, conducted substantially as described in any one of the Examples.

8. 7-(D(—)-alpha-amino-p-hydroxyphenyl-acetamido)desacetoxycephalosporanic acid whenever produced by a process according to any one of claims 1 to 7.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.