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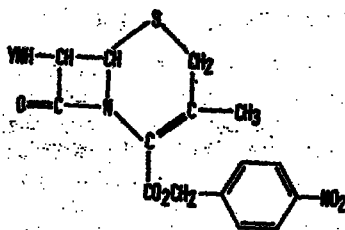
(54) NEW CEPHALOSPORINS USEFUL AS INTERMEDIATES IN MAKING CEPHALEXIN AND IMPROVED PROCESS FOR THE SYNTHESIS OF CEPHALEXIN

(71) We, ELI LILLY AND COMPANY, a Corporation organised under the laws of the State of Indiana, United States of America, of 307 East McCarty Street, City of Indianapolis, State of Indiana, United States of America, 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 concerns new cephalosporin compounds and their preparation, useful as intermediates in making cephalexin, (3-methyl-7-(2-amino-2-phenylacetamido)- Δ^3 -cephen-4-carboxylic acid), and an improved process for the synthesis of cephalexin.

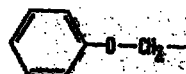
We have now discovered that the use of the *p*-nitrobenzyl ester of a penicillin sulphoxide in the synthesis of cephalexin and certain new intermediate cephalosporin compounds by the ring expansion of the penicillin sulfoxide by heating under acidic conditions, followed by side chain cleavage and acylation with phenylglycine where necessary, and removal of the *p*-nitrobenzyl group and side chain amino protecting group results in increased yields and greater ease of handling and processability of the intermediates. The *p*-nitrobenzyl ester function confers on the several intermediate products a strong tendency to crystallize, thus enhancing isolation ease, product purity, and yields. In addition, this ester group is stable to acid so that no undesirable side products arise during the ring expansion or side chain cleavage steps due to partial de-esterification. Removal of the *p*-nitrobenzyl group to yield cephalexin is readily accomplished by reduction in acidic media, a clean, mild reaction free of degradation and Δ^2 isomerization hazards.

More particularly, this invention provides as novel compounds, useful in the synthesis of cephalexin, compounds having the formula

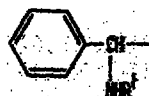


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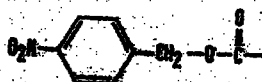
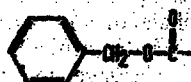
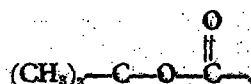
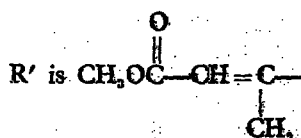
wherein Y is hydrogen or $\text{R}-\text{C}(=\text{O})-$ in which R is



or



in which

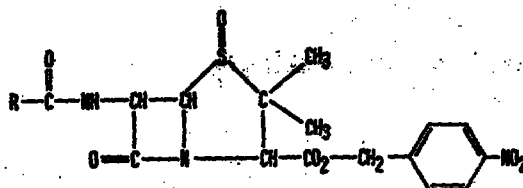


hydrogen, or
hydrogen *p*-toluene sulfonate.

All of the novel compounds of the invention are *p*-nitrobenzyl esters of cephalosporin compounds and are useful intermediates in the preparation of cephalixin from penicillins. The *p*-nitrobenzyl ester group confers unique properties on these compounds, including a tendency to crystallize, is stable under the conditions encountered in the process, but is easily removed by hydrogenation or chemical reduction under acid conditions.

These esters are the ester of 7-aminodesacetoxycephalosporinic acid and those esters obtained from rearrangement of the corresponding esters of the sulfoxides of penicillin G, penicillin V, and ampicillin when a side-chain amino group is present, it may be protected by the enamine obtained by reaction with methyl acetoacetate, the *t*-butoxycarbonyl group, or the *p*-nitrobenzyloxycarbonyl group. In addition, this amino group may be present as the *p*-toluenesulfonic acid salt or the free amine.

This invention also provides a process for the synthesis of a cephalosporin from a penicillin sulfoxide ester, which comprises heating a penicillin sulfoxide ester having the formula

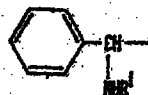


wherein R is as defined in Formula I except that R' is not hydrogen or hydrogen *p*-toluenesulphonate under acidic conditions to effect conversion thereof to the corresponding desacetoxycephalosporin ester.

The resulting desacetoxycephalosporin ester compounds are those of formula (I)

5 above in which Y is $\text{R}-\text{C}(=\text{O})-$ and R and R' have the same meaning as in formula (II) above. The compound of formula (I) where Y is hydrogen, i.e. the corresponding 7-aminodesacetoxycephalosporanic acid ester would normally be obtained by cleavage of the amido group from the side chain of compounds of formula (I) where R is benzyl or phenoxyethyl. Acylation of the 7-amino group with phenylglycine having its amino group protected yields a correspondingly protected 7-phenylglycylamidodes-
10 acetoxycephalosporanic acid ester. Removal of the amino protecting group for the phenylglycine and replacement by hydrogen or hydrogen *p*-toluenesulfonate results in a compound of formula (I) in which R' is hydrogen or hydrogen *p*-toluenesulfonate. If the *p*-nitrobenzyl ester group is also removed, cephalixin is obtained.

15 When the starting penicillin sulfoxide ester has the formula (II) in which R is



20 the novel intermediate compounds of formula (I) in which R' is hydrogen or hydrogen *p*-toluenesulfonate, are obtained by removing the amino protecting group following the ring expansion of the penicillin sulfoxide. If the *p*-nitrobenzyl ester group is also removed, cephalixin is obtained.

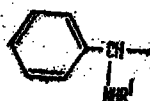
25 Although in formula (II) above, R can be any of the previously defined substituents which are sufficiently stable to permit the desired ring expansion yet can be cleaved from the resulting cephalosporin to yield the 7-amino product, from a practical standpoint the use of a sulfoxide in which R is benzyl or phenoxyethyl is preferred, since these are the side chains present in penicillin G and penicillin V.

30 The penicillin sulfoxide ester of formula (II) can be prepared in any suitable manner, e.g. by the oxidation of the penicillin free acid as described in United States Patent 3,197,466 followed by esterification of the sulfoxide by treatment with a *p*-nitrobenzyl halide or the ester of the penicillin may first be prepared and the penicillin ester then oxidized to the sulfoxide.

35 As the first step in the process of this invention for the synthesis of intermediate cephalosporins and of cephalixin, this penicillin sulfoxide ester is heated under acid conditions at a temperature between about 75° and 175°C., e.g. using the technique of United States Patent 3,275,626. This treatment results in expansion of the penicillin nucleus to yield a cephalosporin compound having the formula (I). This type of compound is known as a desacetoxy cephalosporin since it is substituted in the 3-position with a methyl group rather than an acetoxymethyl group as is found in cephalosporin C.

40 In the preferred embodiment, where R is benzyl or phenoxyethyl, the desacetoxy cephalosporin from the first step of the process is then subjected to side chain cleavage to yield the 7-amino compound having the formula (I) in which Y is hydrogen. This is the *p*-nitrobenzyl ester of 7-aminodesacetoxycephalosporanic acid. This side chain cleavage step may be accomplished by any suitable procedure, e.g. such as are described in United States Patents 3,188,311, 3,207,755 and 3,234,223, British Patent 1,119,806 and Dutch Patent 6,513,095.

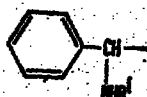
45 In the next step of this embodiment of the process, the free amino group is acylated with phenylglycine having its amino group protected to yield a compound of formula (I) in which Y is



50 and wherein R' has the meaning given to it in formula (II). This acylation is accomplished using well-known acylation procedures wherein the phenylglycine is activated

by a carbodiimide or is used in the form of an acid chloride or bromide or mixed anhydride such as the isobutyl or sec-butyl mixed anhydride. It is to be understood that the amino group of the phenylglycine is protected during the acylation reaction with a commonly-used amino protecting group such as *t*-butoxycarbonyl, benzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, or the enamine formed with methyl acetoacetate.

All that remains to obtain cephalixin is the replacement of the amine and carbonyl blocking groups by hydrogen. The procedure used to remove the amine blocking group will depend upon the group employed, and, for example, may be accomplished by acid hydrolysis or hydrogenolysis. This step of the process may be used to obtain compounds of formula (I) in which Y is

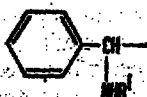


and wherein R' is hydrogen or hydrogen *p*-toluenesulfonate.

The removal of the *p*-nitrobenzyl group is readily accomplished by reduction in an acidic medium. This same treatment will remove certain amine blocking groups such as the enamine groups and will therefore serve to remove both blocking groups. The reduction may be accomplished chemically, such as by the use of zinc and hydrochloric acid, or by catalytic hydrogenation using catalysts such as palladium, platinum, or the oxides thereof.

Although the reaction mechanism is not fully understood, it appears that a partial reduction of the *p*-nitrobenzyl group occurs, leading to an acid-labile intermediate. This intermediate readily cleaves in the presence of an acid to give the cephalosporin free acid.

In a further embodiment of the process of this invention, if the penicillin sulfoxide ester starting material contains the phenylglycyl side chain, i.e. formula (II) in which R is



it is rearranged in the first step to the *p*-nitrobenzyl ester of cephalixin. It is understood that the amino group of the phenylglycyl side chain is protected during the rearrangement of the penicillin nucleus to the cephalosporin nucleus. Since this rearrangement involves acid conditions the preferred amino protecting group is the *p*-nitrobenzyloxycarbonyl group, which is acid stable. Both the *p*-nitrobenzyloxycarbonyl group and the *p*-nitrobenzyl ester group are replaced by hydrogen reduction and treatment with an acid to yield cephalixin. Therefore, it is possible to go from the penicillin sulfoxide ester to cephalixin without side chain cleavage and reacylation.

The present invention will be further illustrated by the following examples. The *p*-nitrobenzyl ester of penicillin V 1-oxide used as a starting material in Example 1 was prepared as follows:

A solution of 37.0 g. of penicillin V 1-oxide, 15.0 ml. of trimethylamine, and 22.0 g. of *p*-nitrobenzyl bromide in 300 ml. of acetone is stirred for 4 hours at room temperature. A crystalline solid begins to precipitate during the first hour, and the mixture becomes quite thick during the reaction period. The mixture is treated with 600 ml. of water, stirred for one-half hour, and the solid collected and washed with water and ether. After drying, the colorless crystals weigh 47 g., m.p. 186° to 196°C. The product is shown to be one component by thin layer chromatography, and its structure and purity are established by nuclear magnetic resonance spectroscopy.

p-Nitrobenzyl chloride reacts similarly to provide the desired ester if promoted by the addition of a small amount of potassium iodide. Dimethylformamide or dimethylacetamide provides a better solvent medium than acetone in this case. Esterification may be accomplished with *p*-nitrobenzyl alcohol via the phosgene procedure.

EXAMPLE 1

A solution of 10.0 g. of the *p*-nitrobenzyl ester of penicillin V 1-oxide obtained as described above, 1.0 g. of *p*-toluenesulfonic acid monohydrate, 10.0 ml. of acetic anhydride and 400 ml. of dimethylacetamide is warmed on a steam bath for 16 hours.

The amber-colored solution is concentrated on the steam bath *in vacuo* and the residual syrup is triturated with 150 ml. of methanol causing almost immediate crystallization of the product. After chilling for several hours the tan crystals are collected, washed with methanol and dried. The crude product weighs 6.25 g., m.p. 172° to 180°C. Recrystallization from acetonitrile gives pure *p*-nitrobenzyl 3-methyl-7-phenoxyacetamido- Δ^3 -cephem-4-carboxylate as fine, colorless needles, m.p. 191° to 193°C. Purity and structure are determined by thin layer chromatography and nuclear magnetic resonance spectroscopy.

EXAMPLE 2

A mixture of 4.84 g. of the product from Example 1 and 3.80 g. of *p*-toluenesulfonic acid monohydrate in 100 ml. of methanol is heated under reflux for 5 hours. After cooling, unreacted starting material is recovered by filtration (1.15 g.). The mother liquor is concentrated to about 50 ml. under reduced pressure and then treated with ether to induce crystallization. After chilling, the waxy, somewhat unstable *p*-toluenesulfonic acid salt of *p*-nitrobenzyl 3-methyl-7-amino- Δ^3 -cephem-4-carboxylate is collected and dried. This product weighs 2.57 g. and has a m.p. of 100° to 105°C. The identity of the product is established by thin-layer chromatography and conversion to the free base, m.p. 174° to 176°C., and to the hydrochloride, m.p. (dec.) 197° to 200°C.

EXAMPLE 3

A suspension of 30.0 g. of sodium N-(2-methoxycarbonyl-1-methylvinylamino)-D- α -phenylglycine in 500 ml. of dry acetonitrile is cooled to -10°C. and treated with stirring with 1.0 ml. of N-methylmorpholine and then with 11.0 ml. of ethyl chloroformate. This mixture is stirred for 30 minutes and 38.7 g. of the hydrochloride from Example 2 is added followed by 14.0 ml. of triethylamine dropwise over a ten-minute period. The mixture is stirred for one and one-half hours at -10°C., 1500 ml. of water is added rapidly dropwise, and stirring is continued for another one-half hour. The white solid which has precipitated is collected, washed with water and dried. The crude *p*-nitrobenzyl 3-methyl-7-[2-(2-methoxycarbonyl-1-methylvinylamino)-2-D-phenylacetamido]- Δ^3 -cephem-4-carboxylate weighs 58.0 g., m.p. 158°-162°C. Recrystallization from warm methanol raises the m.p. to 188° to 190°C. The product is shown to be one component material by thin-layer chromatography and the structure is confirmed by nuclear magnetic resonance spectroscopy.

EXAMPLE 4

The procedure of Example 3 is repeated using 6.0 g. of the sodium salt of phenylglycine blocked with the *t*-butoxycarbonyl group, 0.1 ml. of N-methylmorpholine, 100 ml. of acetonitrile, 2.20 ml. of ethyl chloroformate, 7.74 g. of the product from Example 2, and 2.8 ml. of triethylamine. There is obtained 10.1 g. of crude product, *p*-nitrobenzyl-3-methyl-7-[2-(*t*-butoxycarboxamide)-2-D-phenylacetamido]- Δ^3 -cephem-4-carboxylate, m.p. 120° to 126°C. Recrystallization from acetonitrile raises the m.p. to 130° to 132°C.

EXAMPLE 5

The product from Example 3 is subjected to hydrogenation under acidic conditions to remove both the enamine blocking group and the *p*-nitrobenzyl group. A Parr hydrogenation vessel is charged with 5.8 g. of the product from Example 3, 2.0 g. of 5 percent palladium on alumina, 30 ml. of 1.0 N hydrochloric acid, and 70 ml. of methanol. The mixture is agitated on a shaker for one-half hour and then hydrogenated under 50 psi. hydrogen pressure. After hydrogen uptake is complete the mixture is filtered and most of the methanol is removed under reduced pressure. The aqueous mixture is adjusted to pH 8 with concentrated ammonium hydroxide and extracted with several portions of ethyl acetate. The pH of the aqueous fraction is then adjusted to 4.5 with aqueous hydrochloric acid and crystallization is induced by the addition of 3 to 4 volumes of acetonitrile. The pure cephalixin is obtained as a slightly off-white crystalline solid which weighs 2.30 g. Purity and structure are confirmed by nuclear magnetic resonance spectroscopy.

EXAMPLE 6

The *p*-nitrobenzyl group is removed from the product from Example 4 by hydrogenation. The hydrogenation vessel is charged with 5.8 g. of the doubly-blocked cephalixin from Example 4, 2.0 g. of 5 percent palladium on alumina, 25 ml. of 3A ethanol (see, for instance, Handbook of Chemistry, 9th Ed., McGraw-Hill p 181), and 75 ml. of methanol. This mixture is hydrogenated on a Parr apparatus under 50 psi.

(13)

hydrogen pressure. After the hydrogen uptake is complete the mixture is filtered and the catalyst washed with methanol. The combined filtrate and washings are concentrated *in vacuo*. The yellow residual syrup is dissolved in 150 ml. of ethyl acetate and extracted with 100 ml. of saturated sodium bicarbonate solution. The aqueous extract is stirred with 150 ml. of ethyl acetate while the pH is adjusted to about 1.5 with concentrated hydrochloric acid. The ethyl acetate layer is separated and the aqueous layer extracted with another portion of ethyl acetate. The combined ethyl acetate extract is dried over magnesium sulfate and concentrated under reduced pressure to about 50 ml. volume. The solution is filtered, diluted with 200 ml. of isopropyl ether, and then treated to turbidity with benzene. After chilling for several hours the colorless solid is collected and dried. The *t*-butyloxycarbonyl blocked cephalixin weighs 2.60 g. The structure and purity are confirmed by nuclear magnetic resonance spectroscopy.

When the amino group of the phenylglycine is protected by the enamine blocking group, the blocking group is readily removed following the acylation step by treatment with *p*-toluenesulfonic acid monohydrate. The product obtained is the *p*-nitrobenzyl ester of cephalixin, *p*-toluenesulfonic acid salt. This is illustrated by the following example.

EXAMPLE 7

A stirred mixture of 30.0 g. of sodium *N*-(2-methoxycarbonyl-1-methylvinyl-amino)-*D*- α -phenylglycine and 500 ml. of acetonitrile is chilled to -15°C . and treated with 9.0 ml. of methyl chloroformate followed by 0.5 ml. of *N*-methylmorpholine. After 15 minutes, 38.7 g. of the hydrochloride from Example 2 is added followed by 14.0 ml. of triethylamine in 40 ml. of acetonitrile dropwise during 30 minutes. The reaction mixture is stirred for another 2 hours allowing the temperature to gradually increase to about 20°C . To the reaction mixture is added 25 g. of *p*-toluenesulfonic acid and stirring is continued for about 2 hours. The colorless crystalline precipitate of *p*-nitrobenzyl 3-methyl-7-phenylglycylamido- Δ^5 -cephem-4-carboxylate *p*-toluenesulfonic acid salt is collected and dried. The yield was 62.0 g., m.p. 211° – 216°C . (dec.). The product is sufficiently pure for conversion to cephalixin without further treatment.

EXAMPLE 8

A mixture of 6.54 g. of the product from Example 7, 50 ml. of acetonitrile, 10 ml. of water, and 200 mg. of platinum oxide is hydrogenated under 50 psi. hydrogen. Workup of the reaction mixture as described in Example 5 yields 2.81 g. of cephalixin.

EXAMPLE 9

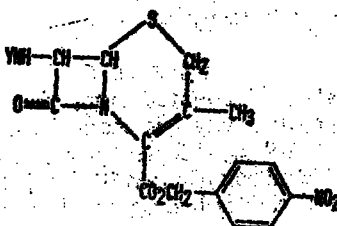
A mixture of 6.54 g. of the product from Example 7, 50 ml. of acetonitrile, 10 ml. of water, and 1.3 g. of zinc is stirred for 2 to 3 hours while maintaining pH 1 by periodic addition of concentrated hydrochloric acid. The reaction mixture is filtered and the pH adjusted to about 4.5 to precipitate 1.90 g. of cephalixin.

EXAMPLE 10

Ampicillin 1-oxide wherein the side-chain amino group is protected by the *p*-nitrobenzyloxycarbonyl group is converted to the *p*-nitrobenzyl ester by the standard procedure described earlier with reference to the ester of penicillin V 1-oxide. This ester is treated with *p*-toluenesulfonic acid monohydrate, acetic anhydride, and dimethylacetamide as described in Example 1 to yield the *p*-nitrobenzyl ester of cephalixin wherein the side-chain amino group is protected by the *p*-nitrobenzyloxycarbonyl group. This doubly-blocked cephalixin is hydrogenated under 50 psi. hydrogen over a 5 percent palladium on alumina catalyst in the presence of hydrochloric acid following the procedure of Example 5. Workup of the reaction mixture as described in Example 5 yields cephalixin.

WHAT WE CLAIM IS:—

1. A compound having the formula



hydrogen pressure. After the hydrogen uptake is complete the mixture is filtered and the catalyst washed with methanol. The combined filtrate and washings are concentrated *in vacuo*. The yellow residual syrup is dissolved in 150 ml. of ethyl acetate and extracted with 100 ml. of saturated sodium bicarbonate solution. The aqueous extract is stirred with 150 ml. of ethyl acetate while the pH is adjusted to about 1.5 with concentrated hydrochloric acid. The ethyl acetate layer is separated and the aqueous layer extracted with another portion of ethyl acetate. The combined ethyl acetate extract is dried over magnesium sulfate and concentrated under reduced pressure to about 50 ml. volume. The solution is filtered, diluted with 200 ml. of isopropyl ether, and then treated to turbidity with benzene. After chilling for several hours the colorless solid is collected and dried. The *t*-butyloxycarbonyl blocked cephalixin weighs 2.60 g. The structure and purity are confirmed by nuclear magnetic resonance spectroscopy.

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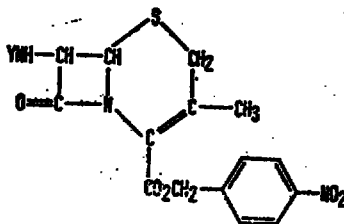
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WHAT WE CLAIM IS:—

1. A compound having the formula

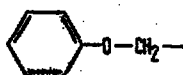
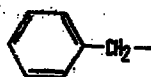




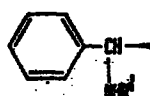
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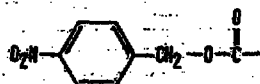
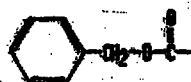
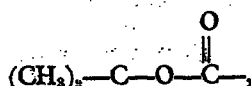
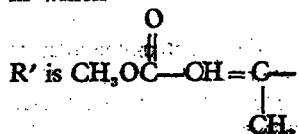
wherein Y is hydrogen or $\text{R}-\text{C}(=\text{O})-$ in which R is



or

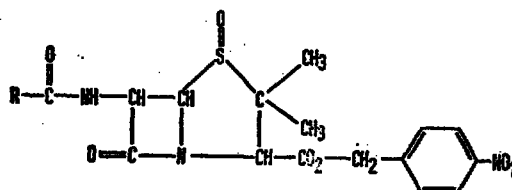


in which



hydrogen, or
hydrogen *p*-toluenesulfonate.

2. A process for the synthesis of a cephalosporin from a penicillin sulfoxide ester, which comprises heating a penicillin sulfoxide ester having the formula



wherein R is as defined in Claim 1 except that R' is not hydrogen or hydrogen *p*-toluenesulphonate, under acidic conditions to effect conversion thereof to the corresponding desacetoxycephalosporin ester.

3. A process according to claim 2, wherein the penicillin sulfoxide ester employed has the indicated formula wherein R is benzyl or phenoxyethyl, and the 7-phenylacetamido or 7-phenoxyacetamido group of the resulting desacetoxycephalosporin ester is cleaved to give the corresponding 7-aminodesacetoxycephalosporanic acid ester.

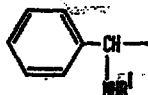
4. A process according to claim 3, wherein the 7-amino group of the resulting acid ester is acylated with phenylglycine having its amino group protected, to give a correspondingly protected 7-phenylglycylamidodesacetoxycephalosporanic acid ester.

5. A process according to claim 4, wherein the amino protecting group for the phenylglycine is removed from the resulting acid ester and replaced by hydrogen or hydrogen *p*-toluenesulfonate.

6. A process according to claim 4, wherein both the amino protecting group for the phenylglycine and the *p*-nitrobenzyl ester group are replaced by hydrogen to yield cephalixin.

5 7. A process according to claim 2, wherein the penicillin sulfoxide ester employed is of the indicated formula in which

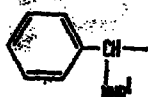
R is



in which the amino protecting group R', which has the same meaning as in claim 2, is removed from the resulting desacetoxycephalosporin ester and replaced by hydrogen or hydrogen *p*-toluenesulfonate.

10 8. A process according to claim 2, wherein the penicillin sulfoxide ester employed is of the indicated formula in which

R is



in which R' has the same meaning as in claim 2, and both the *p*-nitrobenzyl ester group and the R' group are replaced by hydrogen to yield cephalixin.

15 9. A process for preparing a cephalosporin as defined in claim 1, substantially as herein described with particular reference to the specific examples.

10. A process for preparing cephalixin substantially as herein described with particular reference to the specific examples.

20 11. Cephalosporin compounds as defined in Claim 1 when prepared by the process of any of claims 2 to 5, 7 or 9.

12. Cephalixin when prepared by the process of claim 6, 8, or 10.

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