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PATENT SPECIFICATION (11) 1 570 095

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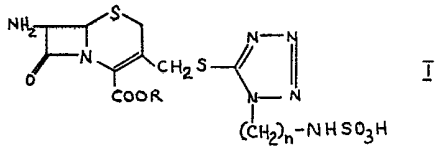
(72) Inventor DAVID ALAN BERGES

(54) 7-AMINOCEPHALOSPORIN INTERMEDIATES

(71) We, SMITHKLINE CORPORATION, of 1500 Spring Garden Street, Philadelphia, Pennsylvania 19101, United States of America, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the 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 relates to cephalosporin compounds which are useful as intermediates in preparing other cephalosporin compounds which have antibacterial activity and are described and claimed in our copending Application 44441/76 (Serial No. 1570093).

According to the present invention there are provided compounds of the formula

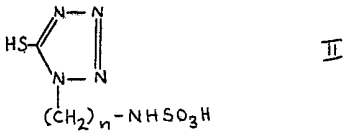


I

where *n* is an integer from two to five; and R is hydrogen or a protective ester-forming group.

Examples of suitable ester-forming groups R are *t*-butyl, benzhydryl, trichloroethyl, benzyl, benzyloxymethyl, *p*-nitrophenyl, *p*-methoxyphenyl, *p*-methoxybenzyl and *p*-nitrobenzyl groups. The ester-forming groups R can be introduced and removed by known methods.

The 7 - amino - 3 - sulfaminoalkyltetrazolylthiomethyl cephalosporin compounds of formula I can be prepared by reacting 7-formamidocephalosporanic acid, prepared by reaction of 7 - amino - cephalosporanic acid with formic acid and acetic anhydride, and a tetrazole-thiol of formula



II

(where *n* is as defined above) or a salt thereof, followed by treatment with an acid, such as hydrochloric acid, to remove the formyl group from the product.

The tetrazole-thiols of formula II are described and claimed in our copending Application 19786/79 (Serial 1570094).

The invention also includes salts of the compounds of formula I, for example with alkali metals such as sodium or potassium, alkaline earth metals, such as calcium, or the ammonium cation.

The following Example illustrates the invention but is not to be construed as limiting the scope thereof. The temperatures are in degrees Centigrade (°C).

EXAMPLE

7 - Amino - 3 - [1 - (2 - sulfaminoethyl)-tetrazol - 5 - ylthiomethyl] - 3 - cephem - 4 - carboxylic acid

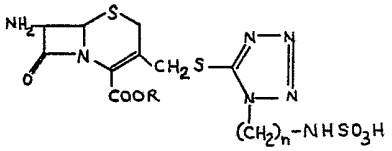
To a mixture of 97 g (200 ml, 2.1 mol) of formic acid, distilled from anhydrous copper sulfate, and 37.5 ml (0.4 mol) of acetic acid anhydride were added 25.0 g (0.1

mol) of 7-aminocephalosporanic acid. The mixture was stirred at ambient temperature for 0.5 hour, then evaporated to dryness. The residue was dissolved in ethyl acetate, and the ethyl acetate solution was filtered and evaporated to dryness to give a residue which was recrystallized from ether-petroleum ether to give 7-formamidocephalosporanic acid.

A mixture of 1.0 g (3.3 mol) of 7-formamidocephalosporanic acid and 0.7 g (2.6 mol) of 1 - (2 - sulfaminoethyl)-tretrazole - 5 - thiol disodium salt in 15 ml of water is stirred at 65—70° for 3 hours while maintaining the pH at 7.0. The mixture is cooled, acidified to pH 1.0 with hydrochloric acid and extracted with ethyl acetate. The extract is filtered, and the filtrate is evaporated to dryness to give a residue which is dissolved in methanol. The methanol solution is filtered and ether is added to precipitate the title compound which is collected by filtration.

WHAT WE CLAIM IS:—

1. A compound of the formula:



I

where *n* is an integer from two to five; and R is hydrogen or a protective ester-forming group.

2. A compound according to claim 1, where R is benzhydryl, *t*-butyl, trichloroethyl, benzyl, benzyloxymethyl, *p*-nitrophenyl, *p*-methoxyphenyl, *p*-methoxybenzyl or *p*-nitrobenzyl.

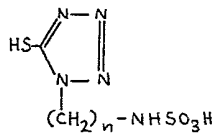
3. A compound according to claim 2, where *n* is two.

4. 7 - Amino - 3 - [1 - (2 - sulfaminoethyl)tetrazol - 5 - ylthiomethyl] - 3 - cephem - 4 - carboxylic acid.

5. A compound according to any of the preceding claims in the form of a salt thereof.

6. A compound as claimed in claim 1, as herein specifically described in the Example.

7. A process for preparing a compound according to claim 1 which comprises reacting 7-aminocephalosporanic acid with formic and acetic anhydride to produce 7-formamidocephalosporanic acid and reacting the 7-formamidocephalosporanic acid with a tetrazole-thiol of formula



II

(where *n* is as defined in claim 1) or a salt thereof, followed by treatment with an acid to remove the formyl group from the product.

8. A process for preparing a compound of claim 1, substantially as described in the Example.

9. A compound according to claim 1, whenever prepared by a process according to any of claims 7 and 8.

G. H. HARGREAVES,
Chartered Patent Agent.

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