

PATENT SPECIFICATION

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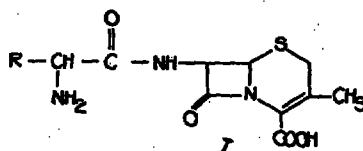
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 GRANATEK

(54) DERIVATIVES OF ALPHA-AMINOCEPHALOSPORINS

(71) We, BRISTOL-MYERS COMPANY, a Corporation organised under the laws of the State of Delaware, United States of America, of 345 Park Avenue, New York, New York, 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 new synthetic compounds of value as antibacterial agents, as nutritional supplements in animal feeds, as agents for the treatment of mastitis in cattle and as therapeutic agents in poultry and animals, including man, in the treatment of infectious diseases caused by Gram-positive and Gram-negative bacteria. More particularly, this invention relates to derivatives of certain α -aminocephalosporins, said derivatives being prepared by reaction of the α -aminocephalosporin with certain aldehydes and ketones.

The starting materials in the present invention are α -aminocephalosporins having the general formula



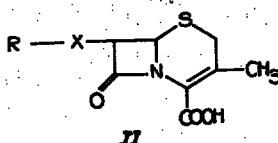
wherein R is



in which R¹, R² and R³ are hydrogen, halo, hydroxy, (lower)alkyl, nitro, amino (lower)alkanoyl, trifluoromethyl, (lower)alkoxy or (lower)alkylmercapto. These starting material cephalosporins are described for example in U.K. Patents 1,174,335 and 1,240,687 and in U.S. Patent 3,352,858.

It was an object of the present invention to provide novel cephalosporin derivatives which would possess potent antibacterial activity against a wide spectrum of Gram-positive and Gram-negative bacteria. It was an additional object of this invention to provide novel derivatives of the above-described α -aminocephalosporins which would be substantially superior in aqueous stability to the cephalosporins *per se*.

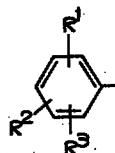
The objects of the present invention have been achieved by providing a process for the preparation of compounds of the general formula



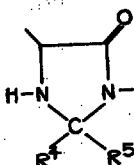
wherein R is



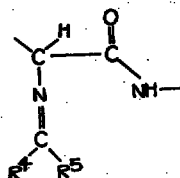
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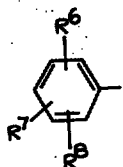
in which R¹, R² and R³ are hydrogen, halo, hydroxy, (lower)alkyl, nitro, amino, (lower)alkanoyl, trifluoromethyl, (lower)alkoxy or (lower)alkylmercapto; and X is



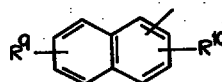
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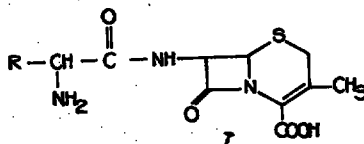
in which either (a) R⁴ is hydrogen and R⁵ is C₂-C₆ alkyl or $\overline{A}$ wherein $\overline{A}$ represents an aromatic radical of the formula



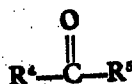
or



in which R⁶, R⁷, R⁸, R⁹ and R¹⁰ are hydrogen, nitro, di(lower)alkylamino, (lower)-alkanoylamino, (lower)alkanoyloxy, (lower)alkyl, (lower)alkoxy, sulfamyl, halo, trifluoromethyl, (lower)alkylthio, (lower)alkylsulfonyl, carbo(lower)alkoxy, benzyl, phenethyl, cyclopentyl, cyclohexyl or cycloheptyl; or (b) R⁴ and R⁵ when taken together with the carbon atom to which they are attached represent cycloalkylidene having 4 to 7 carbon atoms inclusive; and nontoxic pharmaceutically acceptable salts thereof; which process comprises reacting a cephalosporin of the formula



wherein R is as defined above, or a salt thereof, with a carbonyl compound having the formula



wherein R⁴ and R⁵ are as defined above.

The term "(lower)alkyl" as used herein means both straight and branched chain aliphatic hydrocarbon radicals having from 1 to 6 carbon atoms. Similarly, where the term "(lower)" is used as part of the description of another group, e.g. (lower)alkoxy,

it refers to the alkyl portion of such group which is therefore as described above in connection with (lower)alkyl.

The nontoxic pharmaceutically acceptable salts of the compounds of formula II include, for example, (1) nontoxic pharmaceutically acceptable salts of the acidic carboxylic acid group such as the sodium, potassium, calcium, aluminum and ammonium salts and nontoxic substituted ammonium salts such as salts of tri(lower)alkylamines, procaine, dibenzylamine, N-benzyl-beta-phenethylamine, 1-phenamine, N,N'-dibenzylethylenediamine, dehydroabietylamine, N,N'-bis-dehydroabietyleneethylenediamine, N-(lower) alkylpiperidines, such as N-ethylpiperidine, and other amines which have been used to form salts of benzylpenicillin; and (2) nontoxic pharmaceutically acceptable acid addition salts (i.e. salts of the basic nitrogen) such as (a) the mineral acid addition salts such as the hydrochloride, hydrobromide, hydroiodide, sulfate, sulfamate, sulfonate, and phosphate, and (b) the organic acid addition salts such as the maleate, acetate, citrate, tartrate, oxalate, succinate, benzoate, fumarate, malate, mandelate, ascorbate, β -naphthalene sulfonate, and p-toluenesulfonate. Also included are the easily hydrolyzed esters or amides of acid the carboxylic group which may be converted to the free form by chemical or enzymatic hydrolysis.

Preferred embodiments of the present invention include the reaction products of the α -aminocephalosporins of formula I wherein R is unsubstituted phenyl, p-hydroxyphenyl or 3-chloro-4-hydroxyphenyl with aldehydes selected from benzaldehyde, p-tolualdehyde, o-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, p-anisaldehyde, p-nitrobenzaldehyde, naphthaldehyde, valeraldehyde and isovaleraldehyde and ketones selected from cyclohexanone and cyclopentanone. Particularly preferred embodiments include the alkali metal salts (especially of sodium and potassium) of the above-mentioned α -aminocephalosporin reaction products.

The α -carbon atom of the cephalosporin starting material bearing the free amino group is an asymmetric carbon atom and therefore, the compounds of the present invention can exist in two optically active isomeric forms (the D- and L-diastereoisomers), as well as in a mixture of the two optically active forms. The most preferred compounds are those of the D-configuration.

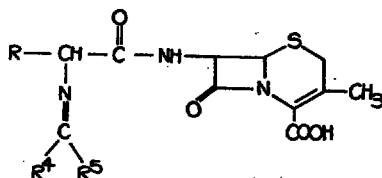
In preparing the compounds of formula II, the proportions of the cephalosporin and carbonyl compound are not critical. Thus, some reaction will occur regardless of the proportions of reactants. It is preferred, however, in order to obtain maximum yields, to use a molar excess of the carbonyl compound. The pH of the reaction mixture desirably should be from about 5 to about 9 and preferably on the alkaline side.

The temperature during the reaction is not critical. The reaction will proceed satisfactorily at room temperature and may be hastened by heating.

After the cephalosporin has reacted with the carbonyl compound, the resultant compound may be recovered by the methods conventionally used with similar compounds, e.g. precipitation, lyophilization, flash evaporation, etc.

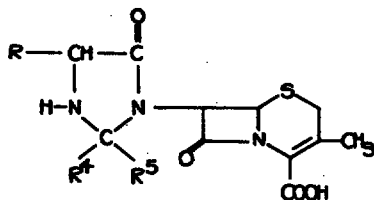
The cephalosporin derivatives of the present invention have been found to be substantially more stable in aqueous solution than the cephalosporins from which they are derived. The compounds prepared by this invention have also been found to possess potent antibacterial activity against a wide variety of both Gram-positive and Gram-negative bacteria.

The cephalosporin-carbonyl adducts of the present invention have been found to have either the Schiff base structure



III

or the cyclic structure



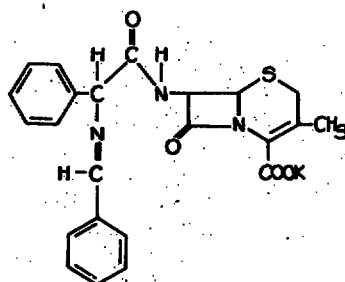
IV

wherein R, R⁴ and R⁵ are all as defined above. The particular structure of any given compound is believed to depend on the structure of the starting materials and/or the reaction conditions, e.g. solvents, etc. used in preparing the adduct. Compounds of both the Schiff base and cyclic structure are included within the scope of the present invention.

The invention also provides pharmaceutical compositions containing the cephalosporin-carbonyl adducts prepared as described above together with an inert pharmaceutically acceptable carrier.

The following examples will serve to illustrate the present invention without limiting it thereto.

Example 1.

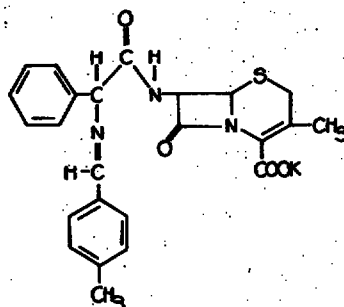


The dimethylformamide solvate of cephalixin [cephalexin (DMF)₂] (1.8 g.) was slurried in 40 ml. n-butanol and dissolved by adding 1.6 ml. triethylamine. After addition of 0.386 ml. benzaldehyde and 0.2 ml. water, the system was allowed to react at 50–60°C for 30–45 minutes. Potassium ethyl hexanoate (0.58 g.) was added and went into solution. A small amount of crystalline material precipitated and the system was allowed to gradually cool. Some additional solids precipitated but appeared to be amorphous. The original crystals slowly dissolved and the system was subjected to an ice-water bath for 45 minutes after which the product crystallised and was recovered by filtration, washed with 20 ml. of methylene chloride and dried under vacuum. The dried product the Schiff base benzaldehyde adduct of potassium cephalixin, weighed 0.675 g. and appeared as white crystalline granules; m.p. 157°C. (dec.). The IR and NMR spectra were consistent for the Schiff base structure shown above.

Elemental Analysis Calculated for Monohydrate: C, 56.00; H, 4.66; N, 8.51.
Found: C, 55.36; H, 4.69; N, 8.52.
Moisture (Karl Fischer) = 5.61%

This compound was found to inhibit *D. pneumoniae* at a concentration of 0.8 mcg./ml., *Str. pyogenes* at 0.8 mcg./ml., *Sal. enteritidis* at 4 mcg./ml. and *E. coli* Juhl at 8 mcg./ml.

Example 2.



A mixture of 0.388 g. potassium cephalixin, 0.13 ml. p-tolualdehyde and 15.0 ml. methylene chloride was slurried in a closed 50 ml. erlenmeyer flask. After stirring for about 6 hours, complete dissolution had not taken place since potassium cephalixin is

only partially soluble in the reaction mixture. The system was kept at room temperature for another 15 hours to enable all of the potassium cephalixin to react. On reaction the latter goes into solution whereas the product simultaneously precipitates out. The latter was recovered by filtration and dried under vacuum. The dried product weighed 380 mg.; m.p. $>165^{\circ}\text{C}$ (dec.). The IR and NMR are consistent for the Schiff base form of the p-tolualdehyde adduct of potassium cephalixin.

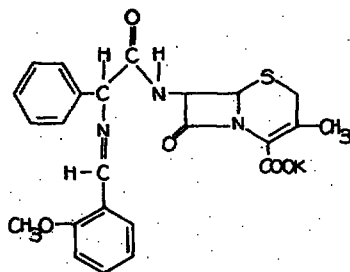
Analysis Calculated for Monohydrate: C, 57.0; H, 5.54; N, 8.30.

Found: C, 52.14; H, 4.53; N, 8.83.

Moisture (Karl Fischer) = 12.01%.

This compound was found to inhibit *D. pneumoniae* at a concentration of 0.3 mcg./ml., *Str. pyogenes* at 0.3 mcg./ml., *S. aureus* BX1633—2 at 4 mcg./ml., *Sal enteritidis* at 4 mcg./ml. and *K. pneumoniae* at 8 mcg./ml.

Example 3.



A mixture of 0.406 g. potassium cephalixin monohydrate, 0.15 ml. o-methoxybenzaldehyde and 15 ml. methylene chloride was slurried for about 4 hours. Dissolution did not occur after this time (see Example 2) but the system became more viscous. The product was recovered by filtration, washed with methylene chloride and dried under vacuum. The dried product, the Schiff base o-methoxybenzaldehyde adduct of potassium cephalixin appeared very pale yellow and crystalline and weighed 300 mg.; m.p. $>130^{\circ}\text{C}$ (dec.). The infrared spectrum was consistent for the Schiff base structure shown above.

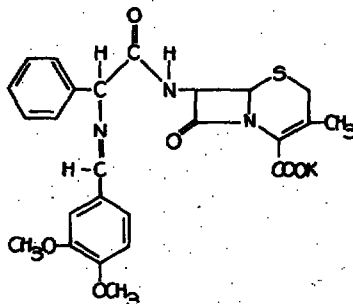
Analysis Calculated for Monohydrate: C, 55.28; H, 4.8; N, 8.05.

Found: C, 53.42; H, 4.72; N, 8.48.

Moisture (Karl Fischer) = 8.63%.

This compound was found to inhibit *D. pneumoniae* at a concentration of 0.16 mcg./ml., *Str. pyogenes* at 0.16 mcg./ml., *S. aureus* Smith at 0.6 mcg./ml., *S. aureus* BX1633—2 at 2 mcg./ml., and *Sal. enteritidis* at 2 mcg./ml.

Example 4.

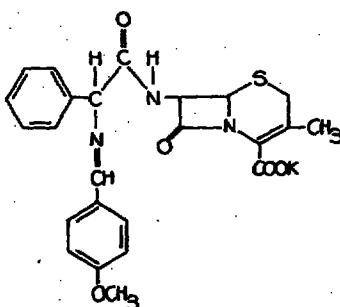


To a mixture of 0.406 g. potassium cephalixin monohydrate and 15 ml. methylene chloride was added with agitation 0.170 g. 3,4-dimethoxybenzaldehyde. Stirring was continued for an additional 3 hours during which the reaction mixture thickened.

After being allowed to stand at 25°C for 16 hours, the system was filtered with suction to recover the product which was dried for 68 hours at 25°C in a vacuum oven. The product, the Schiff base 3,4-dimethoxybenzaldehyde adduct of potassium cephalixin, weighed 0.440 g. and darkened upon heating at 130°C. The infrared spectrum is consistent for the Schiff base structure shown above.

Analysis Calculated for Monohydrate: C, 54.60; H, 4.76; N, 7.64;
Found: C, 51.32; H, 4.64; N, 8.35.
Moisture (Karl Fischer) = 4.76%

Example 5.

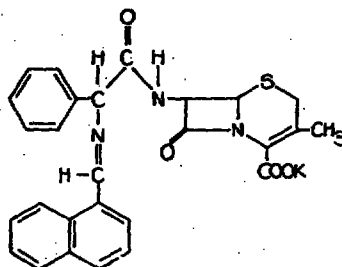


The dimethylformamide solvate of cephalixin [cephalexin (DMF)₂] (1.8 g.) was slurried in 40 ml. n-butanol and dissolved by addition of 1.6 ml. triethylamine and 0.4 ml. water. To this solution was added 0.495 g. p-anisaldehyde and the system was reacted for one hour. Potassium ethyl hexanoate (0.58 g.) was added and crystallization occurred. The crystals were allowed to form over a span of two hours and were collected by suction filtration. The product was dried for 15 hours under vacuum and the dried product weighed 250 mg. and appeared as off-white crystals. The IR and NMR spectra were consistent for the Schiff base form of the p-anisaldehyde adduct of potassium cephalixin.

Analysis Calculated for Monohydrate: C, 54.8; H, 5.33; N, 7.99;
Found: C, 53.98; H, 4.93; N, 7.75.
Moisture (Karl Fischer) = 4.35%

This compound was found to inhibit *D. pneumoniae* at a concentration of 0.16 mcg./ml., *Str. pyogenes* at 0.16 mcg./ml., *S. aureus* Smith at 0.6 mcg./ml., *S. aureus* BX1633-2 at 4 mcg./ml., *E. coli* Juhl at 8 mcg./ml., *K. pneumoniae* at 8 mcg./ml., *Pr. mirabilis* at 8 mcg./ml. and *Sal enteritidis* at 4 mcg./ml.

Example 6.



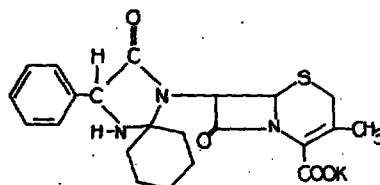
The dimethylformamide solvate of cephalixin [cephalexin (DMF)₂] (1.8 g.) was slurried in 40 ml. n-butanol and dissolved by addition of 1.6 ml. triethylamine. To this solution was added 0.568 ml. of 1-naphthaldehyde and 0.4 ml. water and the system was allowed to stand for 15 minutes. Upon addition of 0.58 g. potassium ethyl hexanoate, a glassy waxlike precipitate starting forming and the system was allowed to stand for 63 hours at 25°C. The product, the Schiff base 1-naphthaldehyde adduct

of potassium cephalixin, was recovered by suction filtration, washed with 60 ml. of fresh butanol and dried in a vacuum oven for 16 hours at 25°C. The dried product weighed 1.15 g. The infrared and nuclear magnetic resonance spectra were consistent with the Schiff base structure shown above.

5 *Analysis Calculated for Monohydrate:* C, 60.00; H, 4.66; N, 7.77.
 Found: C, 58.56; H, 4.44; N, 7.56.
Moisture (Karl Fischer) = 3.52%.

10 This compound was found to inhibit *D. pneumoniae* at a concentration of 0.16 mcg./ml., *Str. pyogenes* at 0.16 mcg./ml., *S. aureus* Smith at 0.6 mcg./ml., *S. aureus* Bx 1633—2 at 2 mcg./ml., *Sal. enteritidis* at 4 mcg./ml., *K. pneumoniae* at 4 mcg./ml. and *Pr. mirabilis* at 4 mcg./ml.

Example 7.

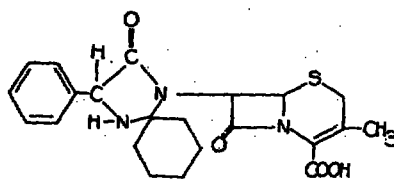


15 Potassium cephalixin monohydrate (0.812 g.) and cyclohexanone (0.2 ml.) were reacted in 5 ml. methanol for 4 hours. Isopropanol (100 ml.) was then added in an attempt to precipitate-out the reaction product. When this failed, the system was flash evaporated and dried under vacuum to yield 0.81 g. of glassy product; m.p. >165°C. (dec.). The IR and N.M.R. spectra were consistent for the cyclic form of the cyclohexanone adduct of potassium cephalixin.

20 *Analysis Calc'd on basis of monohydrate:* C, 54.70; H, 5.59; N, 8.69.
 Found: C, 53.14; H, 5.28; N, 8.75.
Moisture (Karl Fischer) = 5.98%.

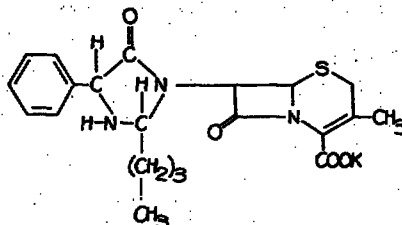
25 This compound was found to inhibit *D. pneumoniae* at a concentration of 0.8 mcg./ml., *Str. pyogenes* at 0.8 mcg./ml., *Sal. enteritidis* at 4 mcg./ml., *S. aureus* Smith at 1.6 mcg./ml. and *Pr. mirabilis* at 8 mcg./ml.

Example 8.



30 The dimethylformamide solvate of cephalixin [cephalexin (DMF)₂] (1.8 g.) was dissolved in 40 ml. water by adding 0.5 ml. triethylamine. Cyclohexanone (0.45 ml.) was added and the solution was stirred for 2 hours. A total of 39 ml. 0.1N HCl was added to bring the solution to pH 3.0 whereupon a white, amorphous precipitate formed. The product, the cyclic form of the cyclohexanone adduct of cephalixin, was recovered by filtration and dried under vacuum to yield 100 mg.; m.p. >165°C. (dec.). The absence of a 1500—1550 cm⁻¹ peak and the presence of strong 2950 and 2870 cm⁻¹ peaks on the IR spectrum are consistent for the cyclic structure shown above.

Example 9.



Potassium cephalosporin (0.388 g.) was slurried in 15 ml. methylene chloride and 0.1 ml. n-valeraldehyde. After stirring in a closed container for about 4 hours, dissolution was completed and the system was allowed to stand at ambient temperature for 12 hours. After filtering, the filtrate was flash evaporated to dryness. Complete drying was accomplished under vacuum to yield 390 mg. of dried product; m.p. 110°C. (dec.). The IR and NMR spectra were consistent for the cyclic form of the valeraldehyde adduct of potassium cephalosporin.

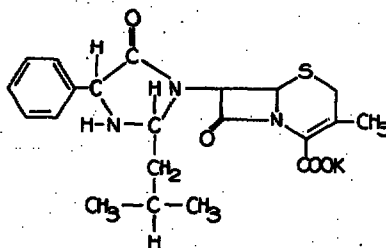
Analysis Calc'd for monohydrate: C, 50.80; H, 5.49; N, 8.87.

Found: C, 51.62; H, 5.26; N, 8.22.

Moisture (Karl Fischer) = 5.40%.

This compound was found to inhibit *D. pneumoniae* at a concentration of 1.3 mcg./ml., *Str. pyogenes* at 1.3 mcg./ml., *S. aureus* Bx 1633—2 at 8 mcg./ml. and *Sal. enteritidis* at 8 mcg./ml.

Example 10.



To a slurry of potassium cephalosporin monohydrate (0.406 g.) and 15 ml. methylene chloride was added 0.10 ml. isovaleraldehyde. The reaction flask was covered with foil and stirring continued for 4 hours. After being allowed to stand overnight at 25°C., a mostly clear solution had formed which was filtered and then dried by flash evaporation. Drying was completed in a vacuum oven at 25°C. for 63 hours. The dried product, the cyclic isovaleraldehyde adduct of potassium cephalosporin, was found to weigh 0.415 g.; m.p. 100°C. (dec.). The IR and NMR spectra were consistent for the cyclic structure shown above.

Analysis: Calc'd: C, 51.60; H, 5.37; N, 8.63.

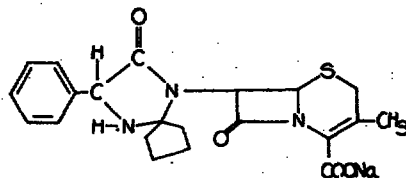
Found: C, 53.75; H, 5.60; N, 8.88.

Moisture (Karl Fischer) = 6.00%.

This compound was found to inhibit *D. pneumoniae* at a concentration of 0.3 mcg./ml., *Str. pyogenes* at 0.3 mcg./ml., *S. aureus* Smith at 1.3 mcg./ml., *S. aureus* Bx 1633—2 at 4 mcg./ml., *K. pneumoniae* at 8 mcg./ml. and *Pr. mirabilis* at 8 mcg./ml.

118

Example 11.

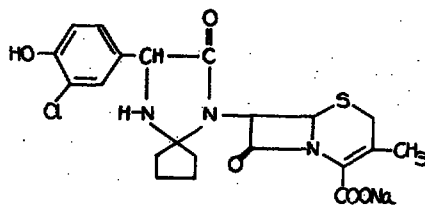


Sodium cephalixin monohydrate (1.16 g.) was dissolved in 6 ml. methanol and 0.3 ml. cyclopentanone was added. After being allowed to stand for 15 to 20 hours at ambient temperature, the solution was filtered and the filtrate flash-evaporated to dryness. Complete drying was accomplished under vacuum to yield 1.15 g. of a yellowish powder which appears to be about 50% crystalline chunks m.p. 160°C. (dec.). The IR and NMR spectra were consistent for the cyclic form of the cyclopentanone adduct of sodium cephalixin.

Analysis Calc'd on basis of monohydrate: C, 53.8; H, 5.33; N, 8.96.
Found: C, 51.36; H, 5.27; N, 9.12.
Moisture (Karl Fischer) = 1.95%.

This compound was found to inhibit *D. pneumoniae* at a concentration of 0.3 mcg./ml., *Str. pyogenes* at 0.3 mcg./ml., *S. aureus* Smith at 1.3 mcg./ml., *S. aureus* Bx 1633—2 at 4 mcg./ml., *Sal. enteritidis* at 4 mcg./ml., *E. coli* Juhl at 8 mcg./ml., *K. pneumoniae* at 8 mcg./ml. and *Pr. mirabilis* at 8 mcg./ml.

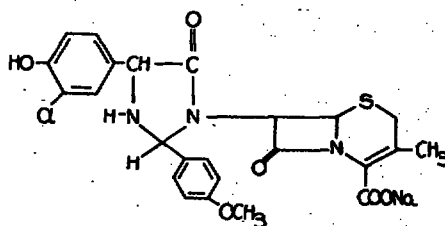
Example 12.



The procedure of Example 9 is repeated except that the potassium cephalixin and n-valeraldehyde used therein are replaced by sodium 3-chloro-4-hydroxycephalexin and cyclopentanone, respectively. There is produced the cyclic form of the cyclopentanone adduct of the sodium salt of 3-chloro-4-hydroxycephalexin; m.p. 90—100°C. (decomp.); purity: 85—90%; specific rotation $[\alpha]_D^{25} = +142^\circ$ (c, 1 in water).

The IR and NMR spectra were consistent with the cyclic structure shown above.

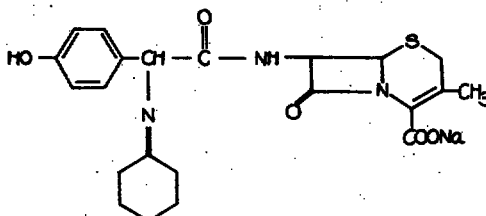
Example 13.



The procedure of Example 12 was repeated except that the cyclopentanone was replaced by cyclohexanone and the sodium 3-chloro-4-hydroxycephalexin by sodium hyde adduct of the sodium salt of 3-chloro-4-hydroxycephalexin; m.p. 170—175°C. (decomp.); purity: 90—95%; specific rotation $[\alpha]_D^{25} = +138^\circ$ (c, 1 in water).

The IR and NMR spectra were consistent for the cyclic structure shown above.

Example 14.



The procedure of Example 12 was repeated except that the cyclopentanone was replaced by cyclohexanone and the sodium 3-chloro-4-hydroxycephalexin by sodium p-hydroxycephalexin. There was obtained in quantitative yield the cyclohexanone adduct of the sodium salt of p-hydroxycephalexin; m.p. 235—240°C. (decomp.); purity 90—95%; specific rotation $[\alpha]_D^{25} = +158$.
(c, 1 in water)

The IR and NMR spectra were consistent with the Schiff base structure shown above.

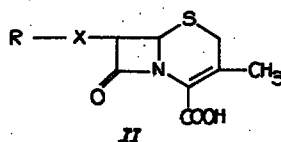
Example 15.

The procedure of Example 12 was repeated except that the cyclopentanone was replaced by p-nitrobenzaldehyde and the sodium 3-chloro-4-hydroxycephalexin by sodium p-hydroxycephalexin. There was obtained in quantitative yield the p-nitrobenzaldehyde adduct of the sodium salt of p-hydroxycephalexin; m.p. 164—166°C. (decomp.); purity: 85—90%; specific rotation $[\alpha]_D^{25} = +70^\circ$.
(c, 1 in water)

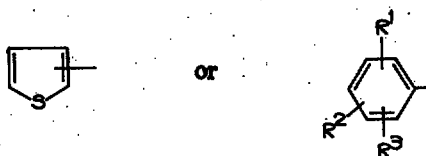
The IR and NMR spectra were consistent with the structure of the sodium salt of the acid having the cyclic structure shown in claim 21.

WHAT WE CLAIM IS:—

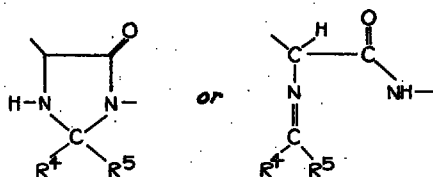
1. A process for the preparation of compounds of the general formula



wherein R is



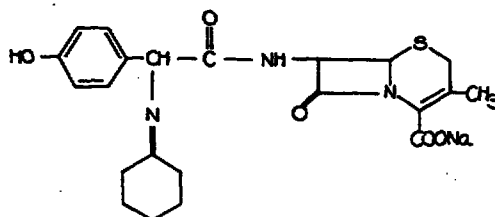
in which R¹, R² and R³ are hydrogen, halo, hydroxy, (lower)alkyl, nitro, amino, (lower)alkanoyl, trifluoromethyl, (lower)alkoxy or (lower)alkylmercapto; and X is



in which either (a) R⁴ is hydrogen and R⁵ is C₂—C₆ alkyl or Ar wherein Ar represents an aromatic radical of the formula



Example 14.



The procedure of Example 12 was repeated except that the cyclopentanone was replaced by cyclohexanone and the sodium 3-chloro-4-hydroxycephalexin by sodium p-hydroxycephalexin. There was obtained in quantitative yield the cyclohexanone adduct of the sodium salt of p-hydroxycephalexin; m.p. 235—240°C. (decomp.); purity 90—95%; specific rotation $[\alpha]_D^{25} = +158$.

(c, 1 in water)

The IR and NMR spectra were consistent with the Schiff base structure shown above.

Example 15.

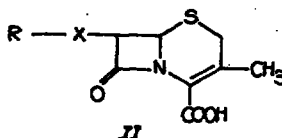
The procedure of Example 12 was repeated except that the cyclopentanone was replaced by p-nitrobenzaldehyde and the sodium 3-chloro-4-hydroxycephalexin by sodium p-hydroxycephalexin. There was obtained in quantitative yield the p-nitrobenzaldehyde adduct of the sodium salt of p-hydroxycephalexin; m.p. 164—166°C. (decomp.); purity: 85—90%; specific rotation $[\alpha]_D^{25} = +70^\circ$.

(c, 1 in water)

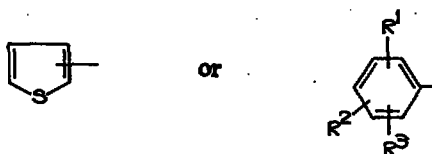
The IR and NMR spectra were consistent with the structure of the sodium salt of the acid having the cyclic structure shown in claim 21.

WHAT WE CLAIM IS:—

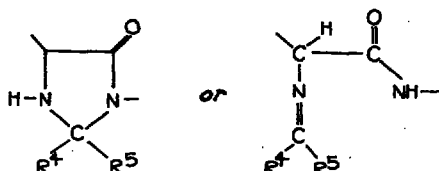
1. A process for the preparation of compounds of the general formula



wherein R is



in which R^1 , R^2 and R^3 are hydrogen, halo, hydroxy, (lower)alkyl, nitro, amino, (lower)alkanoyl, trifluoromethyl, (lower)alkoxy or (lower)alkylmercapto; and X is



in which either (a) R^4 is hydrogen and R^5 is C_2-C_6 alkyl or $\mathcal{A}$ wherein $\mathcal{A}$ represents an aromatic radical of the formula

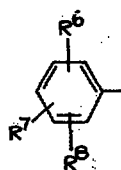
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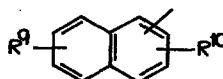
11

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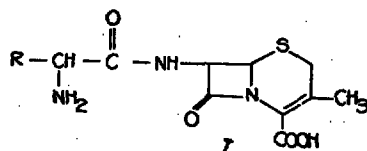
or



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in which R^6 , R^7 , R^8 , R^9 , and R^{10} are hydrogen, nitro, di(lower)alkylamino, (lower)-alkanoylamino, (lower)alkanoyloxy, (lower)alkyl, (lower)alkoxy, sulfamoyl, halo, trifluoromethyl, (lower)alkylthio, (lower)alkylsulfonyl, carbo(lower)alkoxy, benzyl, phenethyl, cyclopentyl, cyclohexyl, or cycloheptyl or (b) R^4 and R^5 when taken together with the carbon atom to which they are attached represent cycloalkylidene having 4 to 7 carbon atoms inclusive; and nontoxic pharmaceutically acceptable salts thereof; which process comprises reacting a cephalosporin of the formula

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wherein R is as defined above, or a salt thereof, with a carbonyl compound having the formula

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wherein R^4 and R^5 are as defined above.

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2. The process of Claim 1 wherein substituent R in the cephalosporin starting material is unsubstituted phenyl, p-hydroxyphenyl or 3-chloro-4-hydroxyphenyl.

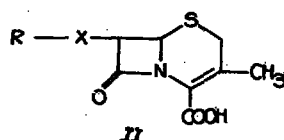
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3. The process of Claim 2 wherein the carbonyl compound is benzaldehyde, p-tolualdehyde, o-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, p-anisaldehyde, 1-naphthaldehyde, cyclohexanone, n-valeraldehyde, iso-valeraldehyde, cyclopentanone or p-nitrobenzaldehyde.

20

4. Compounds of the formula

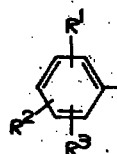
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wherein R is



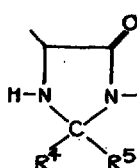
or



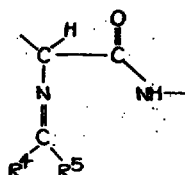
25

in which R^1 , R^2 and R^3 are hydrogen, halo, hydroxy, (lower)alkyl, nitro, amino, (lower)alkanoyl, trifluoromethyl, (lower)alkoxy or (lower)alkylmercapto; and X is

25



or



(2)



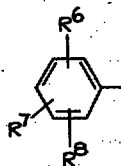
* C L M S *

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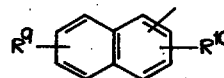
12

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in which either (a) R^4 is hydrogen and R^5 is C_2-C_6 alkyl or $\overline{A}R$ wherein $\overline{A}$ represents an aromatic radical of the formula

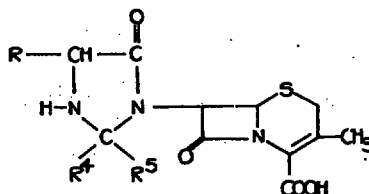


or



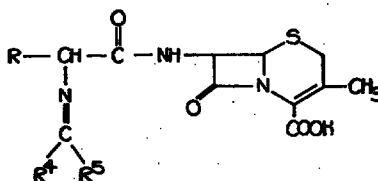
in which R^6 , R^7 , R^8 , R^9 and R^{10} are hydrogen, nitro, di(lower)alkylamino, (lower)-alkanoylamino, (lower)alkanoyloxy, (lower)alkyl, (lower)alkoxy, sulfamyl, halo, trifluoromethyl, (lower)alkylthio, (lower)alkylsulfonyl, carbo(lower)alkoxy, benzyl, phenethyl, cyclopentyl, cyclohexyl, or cycloheptyl or (b) R^4 and R^5 when taken together with the carbon atom to which they are attached represent cycloalkylidene having 4 to 7 carbon atoms inclusive; and nontoxic pharmaceutically acceptable salts thereof.

5. Compounds of the formula



wherein R , R^4 and R^5 are as defined in Claim 4, or nontoxic pharmaceutically acceptable salts thereof.

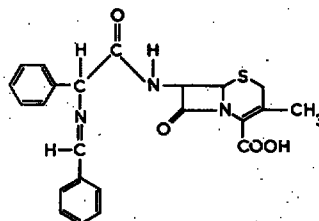
6. Compounds of the formula



wherein R , R^4 and R^5 are as defined in Claim 4, or nontoxic pharmaceutically acceptable salts thereof.

7. The compounds of any of Claims 4-6 wherein R is unsubstituted phenyl, p-hydroxyphenyl or 3-chloro-4-hydroxyphenyl, or nontoxic pharmaceutically acceptable salts thereof.

8. The compound of the formula



and nontoxic pharmaceutically acceptable salts thereof.



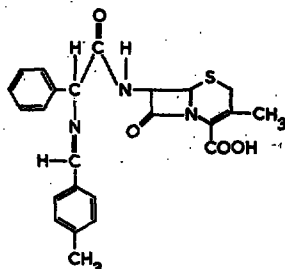
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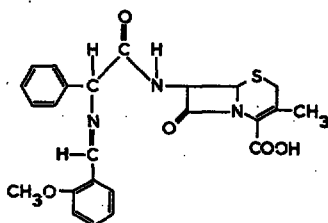
13

9. The compound of the formula



and nontoxic pharmaceutically acceptable salts thereof.

10. The compound of the formula

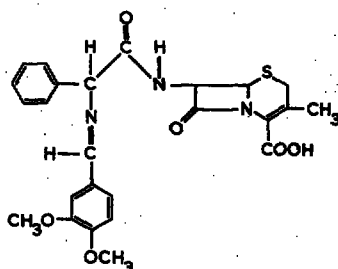


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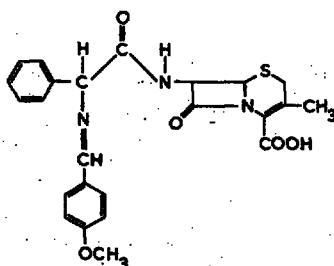
and nontoxic pharmaceutically acceptable salts thereof.

11. The compound of the formula



and nontoxic pharmaceutically acceptable salts thereof.

12. The compound of the formula

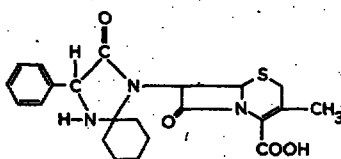


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and nontoxic pharmaceutically acceptable salts thereof.

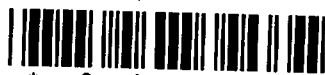
13. The compound of the formula



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and nontoxic pharmaceutically acceptable salts thereof.

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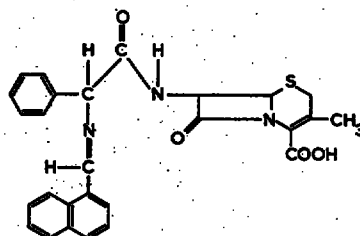
* C L M S *

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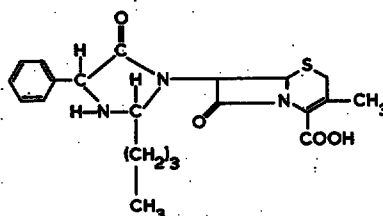
14

14. The compound of the formula



or nontoxic pharmaceutically acceptable salts thereof.

15. The compound of the formula

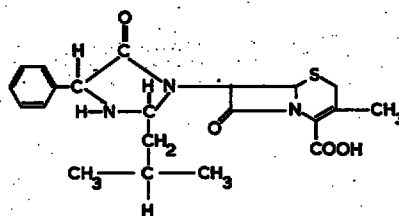


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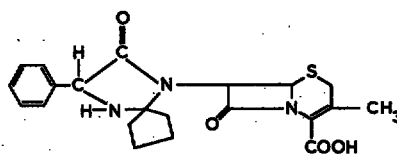
or nontoxic pharmaceutically acceptable salts thereof.

16. The compound of the formula



or nontoxic pharmaceutically acceptable salts thereof.

17. A compound of the formula

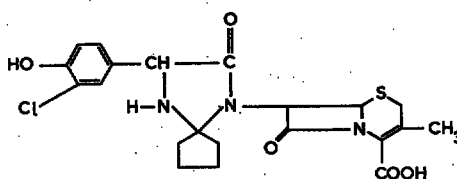


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or nontoxic pharmaceutically acceptable salts thereof.

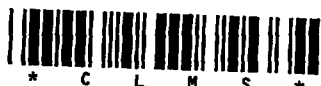
18. The compound of the formula



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or nontoxic pharmaceutically acceptable salts thereof.

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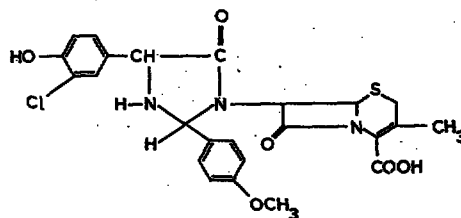
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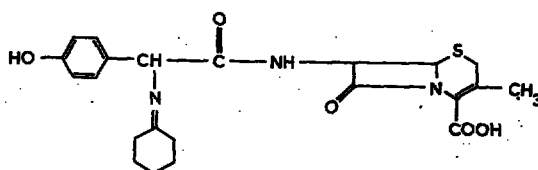
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19. The compound of the formula



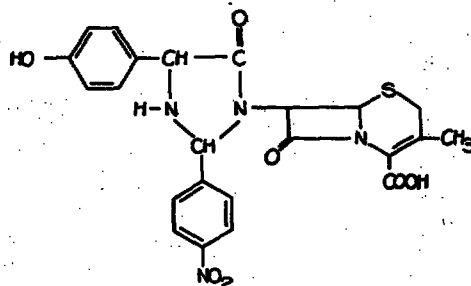
or nontoxic pharmaceutically acceptable salts thereof.

20. The compound of the formula



or nontoxic pharmaceutically acceptable salts thereof.

21. The compound of the formula



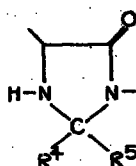
or nontoxic pharmaceutically acceptable salts thereof.

22. The sodium or potassium salts of the compounds of any of Claims 8—21.

23. The compounds of any of Claims 8—22 having the D-configuration.

24. A process according to any of Claims 1 to 3 wherein the cephalosporin of formula (I) is in the D-form.

25. A process according to any of Claims 1 to 3 and 24 wherein R is unsubstituted phenyl
X is



in which (a) R⁴ is hydrogen and R⁵ is C₂—C₆ alkyl or (b) R⁴ and R⁵ when taken together with the carbon atom to which they are attached represent cycloalkylidene having 4 to 7 carbon atoms inclusive.

26. A process according to Claim 25 substantially as herein described in any of Examples 7 to 11.

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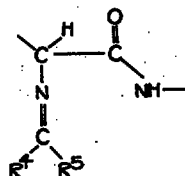
* C L M S *

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27. A process according to any of Claims 1 to 3 and 24 wherein R is unsubstituted phenyl
X is



- 5 in which R⁴ is hydrogen and R⁵ is $\mathcal{R}$. 5
28. A process according to Claim 27 substantially as herein described in any of Examples 1 to 6.
29. A process according to Claim 1, substantially as herein described in any of Examples 12 to 15.
- 10 30. A cephalosporin-carbonyl compound adduct when prepared by the process of Claim 25 or 26. 10
31. A cephalosporin-carbonyl compound adduct when prepared by the process of Claim 27 or 28.
- 15 32. A cephalosporin-carbonyl compound adduct when prepared by the process of Claims 1 to 3, 24, and 29. 15
33. A compound according to Claim 5 wherein R is unsubstituted phenyl, and (a) R⁴ is hydrogen and R⁵ is C₂-C₆ alkyl or (b) R⁴ and R⁵ when taken together with the carbon atom to which they are attached represent cycloalkylidene having 4 to 7 carbon atoms inclusive.
- 20 34. A cephalosporin-carbonyl compound adduct substantially as herein described in any of Examples 7 to 11. 20
35. An adduct according to Claim 33 or 34 when in the D-form.
36. A compound according to Claim 6 wherein R is unsubstituted phenyl, R⁴ is hydrogen, and R⁵ is $\mathcal{R}$.
- 25 37. A cephalosporin-carbonyl compound adduct substantially as herein described in any of Examples 1 to 6. 25
38. An adduct according to Claim 36 or 37 when in the D-form.
39. A cephalosporin-carbonyl compound adduct substantially as herein described in any of Examples 12 to 15.
- 30 40. An adduct according to any of Claims 4 to 7 and 39 when in the D-form. 30
41. A pharmaceutical composition which comprises the compound claimed in any of Claims 30 and 33 to 35 together with an inert pharmaceutically-acceptable carrier.
42. A pharmaceutical composition which comprises the compound claimed in any of Claims 31 and 36 to 38 together with an inert pharmaceutically-acceptable carrier.
- 35 43. A pharmaceutical composition which comprises the compound claimed in any of Claims 32, 39 and 40 together with an inert pharmaceutically-acceptable carrier. 35

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