

[54] CERTAIN CEPHALOSPORANIC ACID DERIVATIVES 3,268,523 8/1966 Raap et al..... 260/243 C

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[57] ABSTRACT

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[52] U.S. Cl..... 260/243 C; 260/239.1; 424/246; 424/271

[51] Int. Cl.²..... C07D 501/22; C07D 501/34

[58] Field of Search 260/243 C

3-[4-Oxo-2-thioxo-3-thiazolidinyl (lower) alkanamido]-1,4-[cyclo-(1'-carboxy)alkylenethio]azetid-2-one derivatives possessing antibacterial activity are produced by the reaction of a 4-oxo-2-thioxo-4-thiazolidinyl-(lower)alkanoic acid derivative and a 6-aminopenicillanic or 7-aminocephalosporanic acid derivative in the presence of a condensing agent, or via an acid halide of the carboxylic acid.

[56] References Cited

UNITED STATES PATENTS

3,218,318 11/1965 Flynn 260/243 C

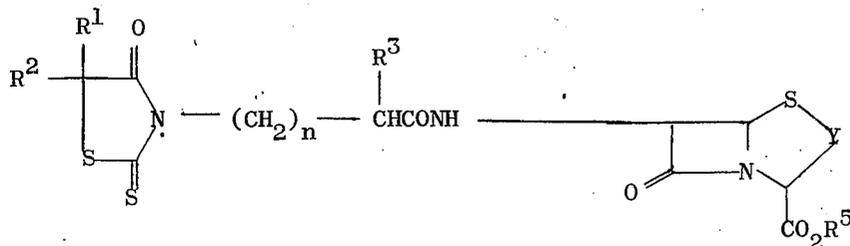
5 Claims, No Drawings

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CERTAIN CEPHALOSPORANIC ACID
DERIVATIVES

DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided a group of azetidin-2-one derivatives which are potent antibacterial agents generically termed 3-[4-oxo-2-thioxo-3-thiazolidinyl-(lower) alkanamido]-1,4-[cyclo-(1'-carboxy)alkylenethio]azetidin-2-ones and the pharmaceutically acceptable salts thereof. These compounds present the structural formula:



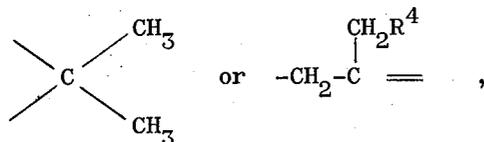
wherein

R¹ is a member selected from the group consisting of —H, alkyl of 1 to 6 carbon atoms, aryl of 6 to 10 carbon atoms, and aralkyl of 7 to 12 carbon atoms;

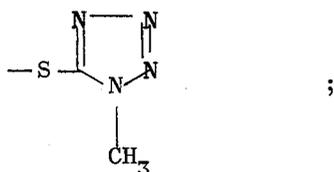
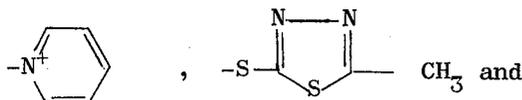
R² is a member selected from the group consisting of —H and alkyl of 1 to 6 carbon atoms;

R³ is a member selected from the group consisting of —H, alkyl of 1 to 6 carbon atoms, monocyclic aryl of 6 to 10 carbon atoms, monocyclic aralkyl of 7 to 10 carbon atoms, —OH, —NH₂ and —CO₂H;

Y is a member selected from the group consisting of



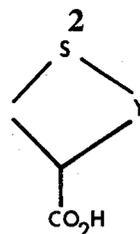
wherein R⁴ is —H, (lower)alkanoyloxy,



R⁵ is a member selected from the group consisting of —H, an alkali metal cation and the ammonium ion; and

n is an integer from 0 to 5, inclusive.

The expression 1,4-[cyclo-(1'-carboxy)alkylenethio], used in the generic name for the compounds of this invention, is intended to embrace the 1-carboxy



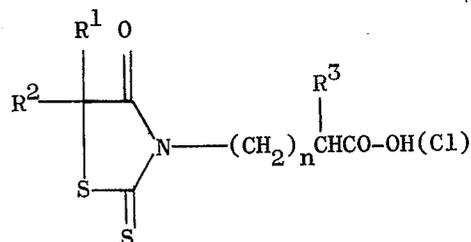
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as it appears in the preceding paragraph. The term (lower)alkyl is used to designate univalent aliphatic, hydrocarbon radicals containing from 1 to 6 carbon atoms, illustrative of which members are methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, n-hexyl

and the like. The term (lower)alkanoyloxy embraces the lower fatty acyloxy moieties such as acetoxy, propanoyloxy, butanoyloxy, amyloxy, hexanoyloxy, and the like. The pharmaceutically acceptable addition salts contemplated, embrace the alkali metal (preferably sodium or potassium) salts and the ammonium salt of the 1'-carboxy group as well as the acid addition salts of the free α -amino group, such as those derived from hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, benzenesulfonic, toluenesulfonic, methylsulfonic, and ethylsulfonic acids, and the like.

The process of this invention, by which the above described compounds are prepared involves reacting the appropriately substituted precursor acid derivative of the formula:



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with an appropriate 6-aminopenicillanic or 7-aminocephalosporanic acid derivative. The reaction proceeds smoothly in an inert organic at a temperature of from about -40° to about $+25^{\circ}\text{C}$. When the free carboxylic acid is employed, the reaction is performed in the presence of a condensing agent such as carbonyl diimidazole; dicyclohexylcarbodiimide; dicyclohexylcarbodiimide in the presence of N-hydroxysuccinimide or 1-hydroxybenzotriazole; isobutylchloroformate; and the like. These and similar condensing agents which are operable in the preparation of the antibacterial agents of this invention are presented in Spencer et al., J. Med. Chem. 9, pp 746-750 (1966); Micetich et al., J. Med. Chem. 15 pp. 333-335 (1972); Klausner et al., Synthesis, pp. 453-463 (1972) and U.S. Pat. No. 3,338,896.

Alternatively, the precursor carboxylic acid derivative may be converted by known means to an acid

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| | |
|---------|---------------------------------|
| BO BR - | <i>Bordetella brochiseptica</i> |
| ES IN - | <i>Escherichia intermedia</i> |
| PR VU - | <i>Proteus vulgaris</i> |
| PR MI - | <i>Proteus mirabilis</i> |
| EN AE - | <i>Enterobacter aerogenes</i> |

EXAMPLE 1

7-[(4-Oxo-2-thioxo-3-thiazolidinyl)acetamido]cephalosporanic acid

A solution of 4-oxo-2-thioxo-3-thiazolidine acetic acid (0.96 g, 0.005 moles) in dry tetrahydrofuran (20 ml) containing triethylamine (0.70 ml) is cooled to -10°C . Isobutyl chloroformate (0.66 ml) is added all at once under nitrogen and the mixture stirred at -10°C . under nitrogen another 10 minutes. A solution of 7-ACA (1.36 g, 0.005 moles) in tetrahydrofuran/water (1:1, 18 ml) containing *N,N*-diisopropylethylamine (0.87 ml) is cooled to 0°C and added rapidly to the above mixture. The temperature of the mixture is maintained at 5°C . for 1 hour and then 20°C . for another hour. The tetrahydrofuran is evaporated in vacuo $< 40^{\circ}\text{C}$. A mixture of water (150 ml) and ethyl acetate (40 ml) is added to the residue, the mixture shaken thoroughly and the organic layer discarded. Ethyl acetate (200 ml) is added to the aqueous layer, the mixture cooled to 5°C . and acidified to pH 2.5 with concentrated hydrochloric acid. The organic layer is separated, the aqueous layer extracted with ethyl acetate (60 ml), the organic layer and extract combined, washed with brine, dried over anhydrous sodium sulfate and evaporated in vacuo $< 40^{\circ}\text{C}$. The gummy residue is crystallized from acetone/benzene to give the title compound, 0.88 g tan solid, m.p. $> 300^{\circ}\text{C}$; λ_{max}^{KBr} 5.55, 5.70, 5.74, 5.83 μ ; NMR has 2.05 and 3.58 ppm singlets.

Elemental Analysis for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_7\text{S}_3 \cdot 0.2\text{C}_6\text{H}_6$:

Calc'd: C, 42.06; H, 3.53; N, 9.09; S, 20.82.

Found: C, 41.90; H, 3.62; N, 9.10; S, 19.72.

| Bacteria | Strain | MIC in $\mu\text{g/ml}$ |
|----------|--------|-------------------------|
| BA SU | 6633 | .122 |
| ST AU | 6538P | .488 |
| ST AU | SMITH | .488 |
| ST AU | CHP | 1.95 |
| ST AU | 53-180 | .976 |
| SA PA | 11737 | 7.81 |
| KL PN | 10031 | 15.6 |
| BO BR | 4617 | 15.6 |
| ES IN | 65-1 | 125 |
| PR VU | 6896 | 125 |
| EN AE | 13048 | 250 |
| HE SP | 9955 | 250 |
| NE CA | 8193 | 62.5 |
| ES CO | 9637 | 62.5 |

The in vivo data for the product of Example 1, in terms of the curative dose (CD_{50}) expressed as the dose in milligrams per mouse via subcutaneous administration is as follows:

| Bacteria | Strain | CD_{50} mg/mouse |
|----------|--------|---------------------------|
| ES CO | 920 | 3.17 |
| KL PN | KL-1 | 1.59 |
| PR MI | 3 | 1.36 |
| PR VU | 347 | 4.31 |

EXAMPLE 2

6-[(4-Oxo-2-thioxo-3-thiazolidinyl)acetamido]penicilanic acid

Using the method described in Example 1 but substituting 6-APA (1.08 g, 0.005 moles) for 7-ACA and triturating the gummy product with diethyl ether gives the title compound, 0.50 g yellow solid, m.p. $160^{\circ}\text{--}170^{\circ}\text{C}$. (decomp.); λ_{max}^{KBr} 5.60 (shoulder), 5.71 and 5.90 μ (shoulder); NMR has 1.46 and 1.60 ppm singlets.

Elemental Analysis for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_5\text{S}_3 \cdot 2\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2$

Calc'd: C, 40.91; H, 4.24; N, 10.40; S, 23.81.

Found: C, 40.89; H, 4.61; N, 10.08; S, 20.98.

| Bacteria | Strain | MIC in $\mu\text{g/ml}$ |
|----------|--------|-------------------------|
| BA SU | 6633 | .976 |
| ST AU | 6538P | .488 |
| ST AU | SMITH | .488 |
| ST AU | CHP | 15.6 |
| ST AU | 53-180 | 125 |
| NE CA | 8193 | 7.81 |
| ES CO | 9637 | 125 |
| SA PA | 11737 | 1.95 |
| PR VU | 6896 | 31.3 |
| HE SP | 9955 | 62.5 |

EXAMPLE 3

7-[(4-Oxo-2-thioxo-3-thiazolidinyl)acetamido]cephalosporanic acid, sodium salt

To a slurry of 7-[(4-oxo-2-thioxo-3-thiazolidinyl)acetamido]cephalosporanic acid (1.0 g, 0.0022 moles) in water (20 ml) is added 1.0 M aqueous sodium hydroxide (2.0 ml, 0.0020 moles) dropwise over 15 minutes. The solution is filtered and freeze-dried to give the title compound, 0.83 g orange solid, m.p. $165^{\circ}\text{--}180^{\circ}\text{C}$ (decomp.), λ_{max}^{KBr} 5.68 and 6.21 μ ; NMR has 2.02 ppm singlet;

Elemental Analysis for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_7\text{S}_3\text{Na} \cdot \text{H}_2\text{O}$

Calc'd: C, 36.43; H, 3.46; N, 8.51; S, 19.45; H_2O , 5.47

Found: C, 36.88; H, 3.33; N, 8.55; S, 18.98; H_2O , 6.16

EXAMPLE 4

3-Methyl-8-oxo-7-[2-(4-oxo-2-thioxo-3-thiazolidinyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Using the method described in Example 1 but substituting 7-ADCA (1.07 g, 0.005 moles) for 7-ACA and triethylamine (0.70 ml.) for *N,N*-diisopropylethylamine and slurrying the product with diethyl ether gives the title compound; 0.15 g tan solid, m.p. $210^{\circ}\text{--}216^{\circ}\text{C}$.; λ_{max}^{KBr} 5.55, 5.72, 5.85 μ ; NMR has 2.04, 4.37 and 4.60 ppm singlets.

Another 0.25 g of product is obtained by filtering off the solid formed after acidification to pH 25 with concentrated hydrochloric acid in the work up.

| Bacteria | Strain | MIC in $\mu\text{g/ml}$ |
|----------|--------|-------------------------|
| BA SU | 6633 | 3.90 |
| ST AU | SMITH | 7.81 |
| ST AU | SMITH | 7.81 |
| ST AU | CHP | 31.3 |
| ST AU | 53-180 | 15.6 |

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| Bacteria | Strain | MIC in $\mu\text{g/ml}$ |
|----------|--------|-------------------------|
| SA PA | 11737 | 125 |
| KL PN | 11737 | 125 |
| KL PN | 10031 | 250 |
| PR VU | 6898 | 250 |

EXAMPLE 5

7-[3-(4-Oxo-2-thioxo-3-thiazolidinyl)propionamido]-cephalosporanic acid

Using the method described in Example 1 but substituting 4-oxo-2-thioxo-3-thiazolidine propionic acid

(1.03 g, 0.005 moles) for 4-oxo-2-thioxo-3-thiazolidine acetic acid and triturating the product with diethyl ether gives the title compound, 1.45 g off-white solid, m.p. 137°-141°C. (decomp.) λ_{max}^{KBr} 5.56, 5.75, 6.03 μ ; NMR has 2.03 ppm singlets

Elemental Analysis for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_7\text{S}_3 \cdot 1/4 \text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$

Calc'd: C, 42.72; H, 4.11; N, 8.79, S, 20.11

Found: C, 42.60; H, 4.24; N, 8.62; S, 18.36

| Bacteria | Strain | MIC in $\mu\text{g/ml}$ |
|----------|--------|-------------------------|
| BA SU | 6633 | .061 |
| ST AU | 6538P | .244 |
| ST AU | SMITH | .122 |
| ST AU | CHP | .976 |
| ST AU | CHP | .976 |
| ST AU | 53-80 | .976 |
| NT CA | 8193 | 31.3 |
| ES CO | 9637 | 15.6 |
| ES IN | 65-1 | 125 |
| SA PA | 11737 | 1.95 |
| EN AE | 13048 | 125 |
| KL PN | 10031 | 7.81 |
| BO BR | 4617 | 31.3 |
| PR VV | 6896 | 7.81 |

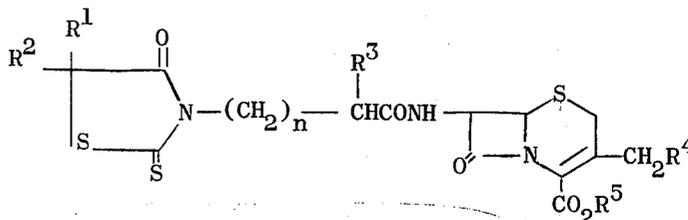
EXAMPLE 6

7-[3-Phenyl-2-(4-oxo-2-thioxo-3-thiazolidinyl)propionamido]cephalosporanic acid

Using the method described in Example 1 but substituting 3-phenyl-2-[4-oxo-2-thioxo-3-thiazolidinyl]propionic acid (1.68 g, 0.005 moles) for 4-oxo-2-thioxo-3-thiazolidine acetic acid gives the title compound as a gum, $\lambda_{max}^{CHCl_3}$ 5.59, (shoulder), 5.78 μ ; NMR has 1.97 and 7.29 ppm singlets.

What is claimed is:

1. A compound of the formula:



in which

R^1 is a member selected from the group consisting of

—H, alkyl of 1 to 6 carbon atoms, aryl of 6 to 10 carbon atoms and aralkyl of 7 to 12 carbon atoms;

R^2 is a member selected from the group consisting of —H and alkyl of 1 to 6 carbon atoms;

R^3 is a member selected from the group consisting of —H and benzyl;

R^4 is a member selected from the group consisting of —H and acetoxy;

R^5 is a member selected from the group consisting of —H, an alkali metal cation and the ammonium cation;

and

n is an integer from 0 to 5, inclusive.

2. A compound of claim 1 which is 7-[(4-oxo-2-thioxo-3-thiazolidinyl)acetamido]cephalosporanic acid, or an alkali metal or the ammonium salt thereof.

3. A compound of claim 1 which is 7-(3-(4-oxo-2-thioxo-3-thiazolidinyl)propionamido)cephalosporanic acid, or an alkali metal or the ammonium salt thereof.

4. A compound of claim 1 which is 3-methyl-8-oxo-7-[2-(4-oxo-2-thioxo-3-thiazolidinyl)acetamido]-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid, or an alkali metal or the ammonium salt thereof.

5. A compound of claim 1 which is 7-[3-phenyl-2-(4-oxo-2-thioxo-3-thiazolidinyl)propionamido]cephalosporanic acid, or an alkali metal salt or the ammonium salt thereof.

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