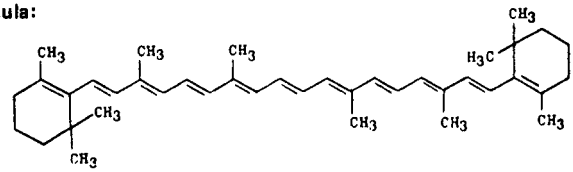
DOT 19 (4) 185 (1983)
I.N. p. 190
Noguchi, J. and Sakota, N.; U.S. Patent 3,135,788; June 2, 1964; assigned to Nihon Zoki Seiyaku Kabushikikaisha (Japan)

β-CAROTENE

Therapeutic Function: As a vitamin A precursor; sunscreen agent

Chemical Name: β-Carotene

Structural Formula:



Chemical Abstracts Registry No.: 7235-40-7

Trade Name	Manufacturer	Country	Year Introduced
Carotaben	Hermal	W. Germany	1975
Solatene	Roche	U.S.	1975
Vitacarotene	Pellestier	Spain	–
Beta-Carotene	Solgar	U.S.	–

Raw Materials

3,8-Dimethyl-3,5,7-decatrien-1,9-diyne
Phenyl Lithium
4-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-methyl-2-buten-1-al
Hydrogen

Manufacturing Process

3.6 g (0.023 mol) of 3,8-dimethyl-3,5,7-decatrien-1,9-diyne were dissolved in 50 ml of absolute ether, and to the solution was added 0.05 mol of ethereal phenyl-lithium solution. The mixture was refluxed for 30 minutes. Then a solution of 11 g (0.05 mol) of 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-methyl-2-buten-1-al in 100 ml of ether was added dropwise, and the reaction mixture was boiled for 2 hours. The reaction mixture was then hydrolyzed with aqueous ammonium acetate solution, and the ethereal layer was separated, dried and concentrated. The residue, i.e., 1,18-di(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,7,12,16-tetramethyl-4,15-dihydroxy-2,7,9,11,16-octadecapentaen-5,13-diyne, was a resinous product (having 1.9 active hydrogen atoms and absorption maxima in the ultraviolet spectrum at 326 and 341 mμ) which was used for the next step without any further purification. The resin was dissolved in 200 ml of methylene chloride, 10 ml of glacial acetic acid were added to the solution, and the mixture was cooled to -40°C in a carbon dioxide atmosphere, while stirring. Then, 9 ml of aqueous hydrobromic acid (60%) were added in one portion, the mixture was stirred at -35°C for 1½ minutes, and subsequently 200 ml of ice water were run into the mixture. After further stirring the mixture for 2 hours at 0°C, the methylene chloride layer was separated, washed with water and sodium bicarbonate solution, dried with Na_2SO_4 and concentrated in vacuo. The residue, i.e., 11,12-11',12'-bisdehydro-β-carotene, was a tough resin or a foamy solid (having no active hydrogen atoms and possessing absorption maxima in the ultraviolet

spectrum at 334 and 408 mμ). This product can be purified by chromatography. The crude product can also be used for the next step without any preliminary purification.

11.4 g of 11,12-11',12'-bisdehydro-β-carotene were dissolved in 100 ml of petroleum ether (boiling range 80° to 100°C), and the solution was hydrogenated under normal conditions after the addition of 0.5 ml of quinoline and 5 g of a lead-poisoned palladium catalyst. After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration and the filtrate was extracted with dilute sulfuric acid to remove the quinoline. By concentrating the solution in the usual manner there was obtained 11,12-11',12'-di-cis-carotene. The product was purified by recrystallization from benzene-alcohol. The purified product melts at 154°C; absorption maxima in the ultraviolet spectrum at 276, 334, 338, 401 and 405 mμ. The isomerization was effected by heating the product for 10 hours at 90° to 100°C in high-boiling petroleum ether in a carbon dioxide atmosphere. The resulting β-carotene melted at 180°C; ultraviolet absorption maxima at 452 and 480 mμ.

Preparation of the intermediates for the above chemical synthesis are also described in U.S. Patent 2,917,539. The other patents cited below describe a fermentation route. U.S. Patent 2,848,508 describes preparation from carrots.

References

Merck Index 1837
PDR pp. 1501, 1734
I.N. p. 136
REM p. 1005
Barnett, H.M., Hartmann, M.L., Mosher, R.C. and Espoy, H.M.; U.S. Patent 2,848,508; August 19, 1958; assigned to Barnett
Isler, O., Montavon, M., Ruegg, R. and Zeller, P.; U.S. Patent 2,917,539; December 15, 1959; assigned to Hoffman-LaRoche, Inc.
Zajic, J.E.; U.S. Patents 2,959,521 and 2,959,522; November 8, 1960; both assigned to Grain Processing Corp.
Miescher, G.M., U.S. Patent 3,001,912; September 26, 1961; assigned to Commercial Solvents Corp.
Zajic, J.E.; U.S. Patent 3,128,236; April 7, 1964; assigned to Grain Processing Corp.

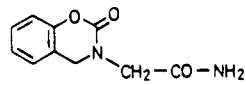
CAROXAZONE

Therapeutic Function: Antidepressant

Chemical Name: 2-Oxo-2H-1,3-benzoxazine-3(4H)-acetamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 18464-39-6

Trade Name	Manufacturer	Country	Year Introduced
Timostenil	Farmitalia	Italy	1975

Raw Materials

Ethyl glycinate HCl	Hydrogen

Salicylic aldehyde
Ammonia

Phosgene

Manufacturing Process

37.9 g of ethyl glycinate hydrochloride were dissolved in 400 cc of ethanol and 33.5 g of salicylic aldehyde were added. It is refluxed for half an hour and cooled. 38 cc of triethylamine and 25 g of Raney nickel are then added whereafter hydrogenation is carried out at room temperature and under atmospheric pressure. After hydrogen adsorption was complete, the mixture was filtered and the alcohol evaporated off. The residue was taken up with acidified water, extracted with ether to eliminate part of the by-products, consisting mainly of o-cresol, then made alkaline with ammonia and extracted with ethyl acetate. The solvent was removed in vacuo and the residue crystallized from ether/petroleum ether. 36.7 g of o-hydroxybenzylaminoacetic acid ethyl ester melting at 47°C are obtained.

20 g of this compound were dissolved in 100 cc of tetrahydrofuran and 100 cc of a 30% solution of phosgene in tetrahydrofuran solution were added. After one night at room temperature, the reaction mixture was dried, taken up with 150 cc of anhydrous pyridine and allowed to stand overnight. The pyridine was then removed in vacuo and the residue dissolved in benzol was washed several times with water and chromatographed over 250 g of alumina. Elution with benzene/petroleum ether yielded 16 g of 4H-3-carboethoxymethyl-1,3-benzoxazine-2-one, melting at 90°-91°C.

5 g of this last compound were dissolved in 120 cc of absolute ethanol and saturated with NH_3 at 0°C. It was allowed to stand overnight whereafter 1.5 g of 4H-3-carboxamidomethyl-1,3-benzoxazine-2-one, melting at 205°C, were obtained. By evaporation from the mother liquors further quantities of the same product were obtained.

References

Merck Index 1842
Kleeman & Engel p. 157
OCDS Vol. 3 p. 191 (1984)
DOT 12 (6) 236 (1976)
I.N. p. 190
Bernardi, L., Coda, S., Pegrassi, L. and Suchowsky, G.K.; U.S. Patent 3,427,313; February 11, 1969; assigned to Societa Farmaceutici Italia (Italy)

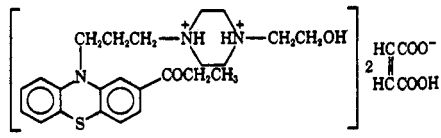
CARPHENAZINE MALEATE

Therapeutic Function: Tranquilizer

Chemical Name: 1-[10-[3-[4-(2-hydroxyethyl)-1-piperazinyl] propyl] 10H-phenothiazin-2-yl]-1-propanone dimaleate

Common Name: Carfenazine maleate

Structural Formula:



Chemical Abstracts Registry No.: 2975-34-0; 2622-30-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Proketazine	Wyeth	U.S.	1962

Raw Materials

2-Propionylphenothiazine
N-(2-hydroxyethyl)-piperazine
Sodium Hydride
Trimethylene chlorobromide

Manufacturing Process

As described in U.S. Patent 3,023,146, in a round-bottomed flask were placed 35 g of 2-propionyl phenothiazine (0.14 mol) 7 g of 50% sodium hydride in mineral oil (0.14 mol), and 240 cc of dimethyl formamide dried over sodium hydride. The resultant solution was stirred at room temperature for 2 hours, and then 88 g (0.56 mol) of trimethylene chlorobromide was added at once.

The mixture was stirred for 2 hours, heated at 60° to 70°C for 1 hour and poured into 2 liters of H_2O. The resulting suspension was extracted with ether, the ether layer separated and the ether removed under vacuum. A gummy mass remained which was dissolved in decalin and the solution was partly distilled to remove excess chlorobromide. After removal of most of the decalin under vacuum, the residue was treated with a large excess of N-(β-hydroxyethyl)-piperazine and heated on a steam bath for 2 hours. This material was extracted with dilute aqueous HCl, this acid layer neutralized with aqueous base and the resulting oil extracted into ether. The ether layer was washed with water until the washings were neutral and dried over anhydrous potassium carbonate. On treatment with maleic acid in ether a yellow solid separated which was recrystallized from isopropanol. This yellow solid had MP 175° to 177°C.

References

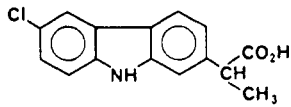
Merck Index 1844
Kleeman & Engel p. 154
OCDS Vol. 1 p. 383 (1977)
I.N. p. 188
REM p. 1086
Tislow, R.F., Bruce, W.F. and Page, J.A.; U.S. Patent 3,023,146; February 27, 1962; assigned to American Home Products Corporation
Sherlock, M.H. and Sperber, N.; U.S. Patent 2,985,654; May 23, 1961; assigned to Schering Corporation

CARPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: 6-Chloro-α-methylcarbazole-2-acetic acid

Structural Formula:



Chemical Abstracts Registry No.: 53716-49-7

Trade Name	Manufacturer	Country	Year Introduced
Imadyl	Roche	Switz.	1981
Imadyl	Roche	W. Germany	1982

Trade Name	Manufacturer	Country	Year Introduced
Imafen	Roche	–	–
Rimadyl	Roche	–	–

Raw Materials

6-Chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester
p-Chloranil
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

A mixture of 34.9 g of 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester (mixture of diastereomers), 350 ml CP xylene and 56.0 g of p-chloranil was stirred and heated under an atmosphere of dry nitrogen. The reaction flask was wrapped in aluminum foil in order to keep out any extraneous light. After the reaction mixture had stirred at reflux temperature for 6 hours, heating and stirring were stopped and the reaction mixture was left overnight at room temperature. The supernatant liquid was decanted through a filter. The residue was triturated with 100 ml of warm benzene and the supernatant liquid was decanted through a filter. This process was repeated three more times. Ether (300 ml) was added to the combined filtrates. The solution was extracted with cold 2N sodium hydroxide (3 x 100 ml), washed by extraction with water until neutral and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the solvent, a residue of 35.5 g remained. Crystallization from 50 ml of methanol gave 14.8 g of 6-chloro-α-methyl-carbazole-2-acetic acid ethyl ester, MP 106°–107.5°C (43.2%).

A stirred mixture of 11 g of 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester, 100 ml ethanol and 100 ml of 3N sodium hydroxide was heated (N_2 atmosphere). After 2 hours at reflux, the reaction mixture was concentrated to dryness under reduced pressure. Water (300 ml) and ice (200 g) were added to the residue and concentrated hydrochloric acid was added until the mixture was strongly acid. The acidic mixture was extracted with ether (3 x 200 ml). The ether extracts were combined, washed by extraction with water (3 x 100 ml) and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the solvent, a yield of 9.8 g (98.2%) was obtained. Crystallization from $CHCl_3$ yielded 6.2 g (62.0%) of 6-chloro-α-methylcarbazole-2-acetic acid, MP 197°–198°C. A second crop of 1.6 g, MP 195°–199°C was obtained from the mother liquors.

References

Merck Index 1846
DFU 2 (1) 15 (1977)
OCDS Vol. 3 p. 169 (1984)
DOT 18 (4) 172 (1982)
I.N. p. 191
Berger, L. and Corraz, A.J.; U.S. Patent 3,896,145; July 22, 1975; assigned to Hoffmann-LaRoche, Inc.

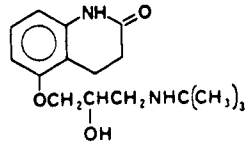
CARTEOLOL

Therapeutic Function: Beta-adrenergic receptor antagonist

Chemical Name: 5-(3-tert-Butylamino-2-hydroxypropoxy)-3,4-dihydrocarbostyril

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 51781-06-7

Trade Name	Manufacturer	Country	Year Introduced
Mikelan	Otsuka	Japan	1981
Endak	Madaus	W. Germany	1982

Raw Materials

5-Hydroxy-3,4-dihydrocarbostyril
Epibromohydrin
t-Butylamine

Manufacturing Process

A mixture of 1.63 g of 5-hydroxy-3,4-dihydrocarbostyril, 2.5 g of epibromohydrin and 2 drops of piperidine was heated at a temperature of 95°C to 100°C for a period of 4 hours with stirring. The reaction mixture was then concentrated to dryness under reduced pressure and the residue was recrystallized from acetone to obtain 1.2 g of 5-(2,3-epoxy)propoxy-3,4-dihydrocarbostyril as a colorless powder having a melting point of 172°C to 173°C.

A mixture of 0.75 g of 5-(2,3-epoxy)propoxy-3,4-dihydrocarbostyril, 1.0 g of tert-butylamine and 25 ml of ethanol was stirred at a temperature of from 50°C to 55°C for a period of 4 hours. Ethanol and unreacted tert-butylamine were distilled off under reduced pressure and the resulting residue was dissolved in acetone.

References

Merck Index 1850
DFU 2 (5) 288 (1977)
Kleeman & Engel p. 158
OCDS Vol. 3 p. 183 (1984)
DOT 18 (10) 551 (1982) & 19 (7) 413 (1983)
I.N. p. 191
Tamura, Y., Nakagawa, K., Yoshizaki, S. and Murakami, N.; U.S. Patent 3,910,924; October 7, 1975; assigned to Otsuka Pharmaceutical Co., Ltd.

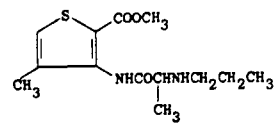
CARTICAINE

Therapeutic Function: Local anesthetic

Chemical Name: 4-Methyl-3-[[1-oxo-2-(propylamino)propyl]amino]-2-thiophene carboxylic acid methyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 23964-58-1; 23964-57-0 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Ultracain	Hoechst	W. Germany	1976
Ultracain	Hoechst	France	1981

Raw Materials

3-Amino-2-carbomethoxy-4-methyl thiophene
Chloropropionyl chloride
n-Propylamine

Manufacturing Process

3-α-Chloropropionylamino-2-carbomethoxy-4-methylthiophene (prepared from 3-amino-2-carbomethoxy-4-methylthiophene and chloropropionyl chloride) was dissolved in toluene and n-propylamine added. The whole mixture was heated to boiling for 6 to 7 hours. After cooling, the propylamine hydrochloride that had formed was removed by washing with water. The toluene phase was dried with sodium sulfate, and then the solvent and excess propylamine were removed by distillation. The oily residue was taken up in ether. The hydrochloride of 3-n-propylamino-α-propionylamino-2-carbomethoxy-4-methylthiophene was obtained by introducing hydrogen chloride gas or by means of methanolic hydrogen chloride. The base boils at 162°C to 167°C under 0.3 mm of mercury pressure and the hydrochloride melts at 177°C to 178°C.

References

Merck Index 1853
Kleeman & Engel p. 158
DOT 12 (4) 132 (1976)
Ruschig, H., Schorr, M., Muschaweck, R. and Rippel, R.; U.S. Patent 3,855,243; December 17, 1974; assigned to Farbwerke Hoechst AG (Germany)

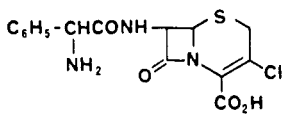
CEFACLOR

Therapeutic Function: Antibiotic

Chemical Name: 7-(D-α-Phenylglycylamido)-3-chloro-3-cephem-4-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53994-73-3

Trade Name	Manufacturer	Country	Year Introduced
Ceclor	Lilly	U.S.	1979
Panoral	Lilly	W. Germany	1979
Distaclor	Dista	U.K.	1979
Ceclor	Lilly	Switz.	1980
Alfatil	Lilly	France	1980
Panacef	Lilly	Italy	1981

Trade Name	Manufacturer	Country	Year Introduced
Kefral	Shionogi	Japan	1982
Kefolor	Lilly	—	—

Raw Materials

p-Nitrobenzyl-7-amino-3-chloro-3-cephem-4-carboxylate HCl
Hydrogen
N,O-Bis-(trimethylsilyl)acetamide
Methyl-3α-carboxybenzylaminocrotonate sodium salt
Methyl chloroformate

Manufacturing Process

Preparation of 7-amino-3-chloro-3-cephem-4-carboxylic acid: To a solution of 750 mg (1.85 mmol) of p-nitrobenzyl 7-amino-3-chloro-3-cephem-4-carboxylate hydrochloride in 20 ml of tetrahydrofuran and 40 ml of methanol was added a suspension of 750 mg of prereduced 5% palladium on carbon catalyst in 20 ml of ethanol and the suspension was hydrogenated under 50 psi of hydrogen at room temperature for 45 minutes. The catalyst was filtered and washed with THF and water. The filtrate and catalyst washes were combined and evaporated to dryness. The residue was dissolved in a water-ethyl acetate mixture and the pH adjusted to pH 3. The insoluble product was filtered and triturated with acetone. The product was then dried to yield 115 mg of 7-amino-3-chloro-3-cephem-4-carboxylic acid.

Preparation of 7-(D-α-phenylglycylamido)-3-chloro-3-cephem-4-carboxylic acid: To a suspension of 280 mg (1.2 mmol) of 7-amino-3-chloro-3-cephem-4-carboxylic acid in 14 ml of acetonitrile was added with stirring at room temperature 0.5 ml of N,O-bis-(trimethylsilyl)acetamide to form the soluble disilylmethyl derivative thereof. The solution was cooled to 0°C and was slowly added to a solution of the mixed anhydride formed by reacting 408 mg (1.5 mmol) of methyl-3-α-carboxybenzylaminocrotonate sodium salt with 161 mg (1.7 mmol) of methyl chloroformate in the presence to 2 drops of N,N-dimethylbenzyl amine in 7 ml of acetonitrile.

The mixture was stirred at ice bath temperature for 2 hours, 1 ml of methanol was added and the mixture was filtered to remove insoluble impurities. Two milliliters of water were added to the filtrate and the pH was adjusted momentarily to pH 1.5, to effect removal of the enamine block, and then to pH 4.5 with triethylamine. After stirring for an additional hour at ice bath temperature the reaction product, 7-(D-α-phenylglycylamido)-3-chloro-3-cephem-4-carboxylic acid (zwitterion) precipitated from the reaction mixture as a crystalline solid. The product was filtered, washed with acetonitrile and dried in vacuo to yield 200 mg.

References

Merck Index 1896
DFU 2 (6) 368 (1977)
Kleeman & Engel p. 160
OCDS Vol. 3 p. 209 (1984)
DOT 15 (7) 311 (1979)
I.N. p. 193
REM p. 1184
Chauvette, R.R.; British Patent 1,461,323; January 13, 1977; assigned to Eli Lilly & Co.
Chauvette, R.R.; U.S. Patent 3,925,372; December 9, 1975; assigned to Eli Lilly & Co.

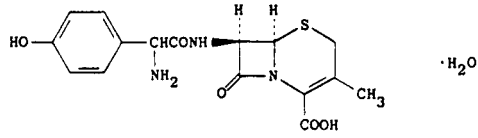
CEFADROXIL

Therapeutic Function: Antibacterial

Chemical Name: 7-[[Amino-(4-hydroxyphenyl)acetyl] amino] -3-methyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0] -oct-2-ene-2-carboxylic acid monohydrate

Common Name: p-Hydroxycephalexine monohydrate

Structural Formula:



Chemical Abstracts Registry No.: 50370-12-2

Trade Name	Manufacturer	Country	Year Introduced
Oracefal	Bristol	France	1977
Duricef	Mead Johnson	U.S.	1978
Ultracef	Bristol	U.S.	1980
Duracef	Ciba Geigy	Switz.	1980
Cephamox	Bristol	W. Germany	1980
Duracef	Bristol	Italy	1980
Sedral	Banyu	Japan	1982
Baxan	Bristol	U.K.	1982
Bidocef	Bristol-Myers	–	–
Cefos	C.T.	Italy	–
Droxicef	Alfa Farm.	Italy	–

Raw Materials

Sodium N-(1-methoxycarbonyl-1-propen-2-yl)-D(-)-α-amino-(4-hydroxyphenyl)acetate
Ethyl chlorocarbonate
7-Amino-3-methyl-3-cephem-4-carboxylic acid

Manufacturing Process

1.8 g of sodium N-(1-methoxycarbonyl-1-propen-2-yl)-D(-)-α-amino-(4-hydroxyphenyl)acetate was suspended in 10 ml of acetone, and one droplet of N-methylmorpholine was added thereto, and the mixture was cooled to -15°C. There was added 0.85 g of ethyl chlorocarbonate thereto, and the mixture was reacted at -13°C to -10°C for 30 minutes, and then the reaction solution was cooled to -20°C.

On the other hand, 1 g of 7-amino-3-methyl-3-cephem-4-carboxylic acid was suspended in 20 ml of methanol, and 1.4 g of triethylamine was added thereto to be dissolved, and 0.4 ml of acetic acid was further added thereto. This solution was cooled to -20°C and the mixed acid anhydride prepared previously was added thereto. After the mixture was reacted at -20°C for 1 hour, the temperature of the reaction mixture was raised to 0°C over a period of 1 hour, and the mixture was reacted for 3 hours at the same temperature.

After the reaction, 1 ml of water was added to the reaction mixture, and the mixture was adjusted to a pH of 1.0 with concentrated hydrochloric acid while being cooled, and then stirred for 30 minutes. The insoluble matters were filtered off, and the filtrate was adjusted to a pH of 5.5 with triethylamine. This solution was concentrated under reduced pressure, and the residue was diluted with 20 ml of acetone to precipitate white crystals. The crystals were collected by filtration and washed with ethanol to obtain 1.46 g of white crystals of 7-[D(-)-α-amino-(4-hydroxyphenyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid having a decomposition point of 197°C.

References

Merck Index 1897

Kleeman & Engel p. 161
PDR pp. 716, 1124
OCDS Vol. 2 p. 440 (1980)
DOT 13 (3) 126 (1977) & 13 (11) 471 (1977)
I.N. p. 194
REM p. 1185
Ishimaru, T. and Kodama, Y.; U.S. Patent 3,864,340; February 4, 1975; assigned to Toyama Chemical Co. Ltd. (Japan)
Crast, L.B. Jr. and Gottstein, W.J.; U.S. Patent 3,985,741; October 12, 1976; assigned to Bristol-Myers Co.

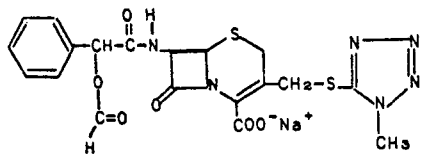
CEFAMANDOLE NAFATE SODIUM SALT

Therapeutic Function: Antibiotic

Chemical Name: Sodium 7-(D-2-formyloxy-2-phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 42540-40-9; 34444-01-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Mandokef	Lilly	W. Germany	1977
Kefadol	Lilly	U.K.	1978
Mandol	Lilly	U.S.	1978
Kefandol	Lilly	France	1978
Mandokef	Lilly	Italy	1981
Cedol	Tiber	Italy	–
Cefam	Magis	Italy	–
Cefman	I.B.P.	Italy	–
Cemado	Farmochimica	Italy	–
Cemandil	S.I.T.	Italy	–
Fado	Errekappa	Italy	–
Lampomandol	A.G.I.P.S.	Italy	–
Mandolsan	San Carlo	Italy	–
Neocefal	Gibipharma	Italy	–

Raw Materials

D(–) mandelic acid
Thionyl chloride
Monotrimethyl silyl acetamide
7-Amino-3-(1-methyl-1H-tetrazol-5-yl-thiomethyl)-3-cephem-4-carboxylic acid
Formic acid
Sodium 2-ethylhexanoate

Manufacturing Process

To 21.6 kg (17.8 ℓ) of 98% formic acid was added 1.14 kg (7.5 mols) of D-(–)-mandelic acid

and the reaction mixture was heated for 4 hours at 70°C with stirring. The excess formic acid was evaporated off in vacuo and the residual syrup was dissolved in 6 ℓ of benzene. The solution was washed twice with 6 ℓ portions of water and was dried over magnesium sulfate. The drying agent was filtered and washed with 1.5 ℓ of benzene, the washes being added to the filtrate. The dried filtrate was evaporated in vacuo to obtain the D-(−)-mandelic acid formate ether as a syrup. The product can be crystallized from cyclohexane to yield material melting at about 55°C to 58°C.

The mandelic acid formate ester obtained as a syrup as described above is stirred for 2 hours with 2.9 kg (~1.75 ℓ) of thionyl chloride at a temperature of about 70°C. The excess thionyl chloride is removed by evaporation and the residual green solution is vacuum distilled. The product, O-formyl mandeloyl chloride, distills over at 127°C to 130°C (15 mm) or at 108°C to 112°C (7 mm).

To 13 ℓ of ethyl acetate were added 85.1 g (2.59 mols) of 7-amino-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid and 1,361 g (10.37 mols) of monotrimethylsilyl acetamide, and the mixture was stirred at 50°C until a clear solution was obtained. The solution was cooled to 20°C and 514 g (2.59 mols) of O-formyl mandeloyl chloride was added at a rate such that the temperature of the reaction solution was maintained between about 20°C to 25°C with ice-cooling.

The reaction mixture was stirred for 1.5 hours at about room temperature after the addition of the mandeloyl chloride was completed. Five liters of water were then added to the reaction mixture and the diluted mixture was stirred for about 10 minutes. The organic layer was separated and was washed twice with water. The combined washes are extracted with 1.5 ℓ of ethyl acetate and the extract is combined with the washed organic layer. The whole was dried over magnesium sulfate, filtered and evaporated in vacuo on a 25°C water bath to yield 1,460 g of product, 7-(D-2-formyloxy-2-phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, as a yellow foam.

The product was dissolved in 5 ℓ of acetone and the solution was mixed with a solution of 430 g (2.59 mols) of sodium 2-ethylhexanoate in 5.4 ℓ of acetone. The combined solutions were seeded and stirred in an ice bath for 1.5 hours. The crystalline precipitate of sodium 7-(D-2-formyloxy-2-phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate was filtered and washed with 5 ℓ of acetone. The crystalline salt was dried overnight in a vacuum oven at 40°C to yield 1,060 g (80%) of product, melting at 182°C to 184°C.

References

Merck Index 1898
DFU 2 (10) 646 (1977)
Kleeman & Engel p. 166
PDR p. 1059
OCDS Vol. 2 p. 441 (1980) & 14 (4) 151 (1978)
DOT 12 (5) 177 (1976)
I.N. p. 196
REM p. 1185
Greene, J.M. and Indelicato, J.M.; U.S. Patent 3,928,592; December 23, 1975; assigned to Eli Lilly & Co.

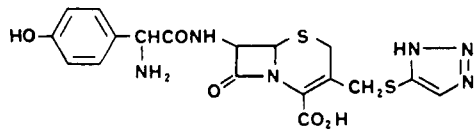
CEFATRIZINE

Therapeutic Function: Antibiotic

Chemical Name: 7-[D-α-Amino-α-(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 51627-14-6

Trade Name	Manufacturer	Country	Year Introduced
Bricef	Bristol-Banyu	Japan	1980
Cepticol	Banyu	Japan	1980
Cefatrix	Ausonia	Italy	1982
Latocef	Dukron	Italy	1982

Raw Materials

7-[D-α-t-Butoxycarbonylamino-α-(p-hydroxyphenyl)acetamido] -3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid
Formic acid

Manufacturing Process

A total 6.5 g (11.55 mmol) of 7-[D-α-t-butoxycarbonylamino-α-(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid was dissolved in 175 ml (98 to 100% formic acid under anhydrous conditions. The mixture was stirred at room temperature for 2.5 hours. Part of the solution, 125 ml, was evaporated under reduced pressure to an amber oil. The oil was then azeotroped 3 times with 70 ml of toluene under reduced pressure. The residue was suspended in an 80:20 H_2O–CH_3OH solution (700 ml) and stirred for 0.5 hour until most of the solid dissolved, then filtered. The filtration was treated with 1.5 g of (Darko) charcoal for about 20 minutes. The charcoal was filtered off through a Celite pad. The solution was then freeze-dried in 9 separate 100 ml round bottom flasks. The freeze-dried material weighed 2.415 g. It was recrystallized in batches of 0.200 g as described above to yield a total of 0.923 g 7-[D-α-amino-α-(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid. NMR was consistent, indicating the presence of 0.33 mol of CH_3OH.

References

Merck Index 1899
DFU 2 (10) 653 (1977)
OCDS Vol. 3 p. 211 (1984)
DOT 12 (5) 183 (1976)
I.N. p. 197
Kaplan, M.A. and Granatek, A.P.; U.S. Patent 3,970,651; July 20, 1976; assigned to Bristol-Myers Co.

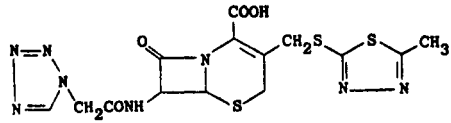
CEFAZOLIN SODIUM

Therapeutic Function: Antibacterial

Chemical Name: (6R-trans)-3-([(5-methyl-1,3,4-thiadiazol-2-yl)thio] methyl)-8-oxo-7-([(1-H-tetrazol-1-yl)acetyl] amino)-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid sodium salt

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 27164-46-1; 25953-19-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cefamedin	Fujisawa	Japan	1971
Kefzol	Lilly	U.S.	1973
Ancef	SKF	U.S.	1973
Totacef	Bristol	Italy	1973
Grammaxin	Boehr./Mann	W. Germany	1974
Kefzol	Lilly	U.K.	1974
Kefzol	Serum Impfinst.	Switz.	1974
Cefacidal	Allard	France	1976
Kefzol	Lilly	France	1976
Acef	Tiber	Italy	–
Areuzolin	Areu	Spain	–
Atirin	Intersint	Italy	–
Biazolina	Panthox & Burck	Italy	–
Bor-Cefazol	Proter	Italy	–
Brizolina	Bristol-Myers	–	–
Caricef	Antibioticos	Spain	–
Cefacene	Centrum	Spain	–
Cefalomicina	Marxer	Argentina	–
Cefamezin	Fujisawa	Japan	–
Cefazina	Chemil	Italy	–
Celmetin	A.L.	Norway	–
Cromezin	Crosara	Italy	–
Elzogram	Lilly	W. Germany	–
Fidesporin	Fides	Spain	–
Firmacel	Firma	Italy	–
Kurgan	Normon	Spain	–
Legemzolina	Legem	Spain	–
Lifezolina	Lifepharma	Spain	–
Liviclina	Sierochimica	Italy	–
Maksipor	Fako	Turkey	–
Neofazol	Rubio	Spain	–
Vifazolin	Vianex	Greece	–
Zolicef	Bristol-Myers	W. Germany	–

Raw Materials

7-Amino-cephalosporanic acid
1-H-Tetrazole-1-acetyl chloride
5-Methyl-1,3,4-thiadiazole-2-thiol
Sodium hydroxide
Sodium bicarbonate

Manufacturing Process

7-Amino-cephalosporanic acid is converted to its sodium salt and acylated with 1H-tetrazole-1-acetyl chloride. The acetoxy group is then displaced by reaction with 5-methyl-1,3-4-thiadiazole-2-thiol in buffer solution. The product acid is converted to the sodium salt by $NaHCO_3$.

References

Merck Index 1901
Kleeman & Engel p. 168

PDR pp. 1058, 1701
OCDS Vol. 3 p. 442 (1984)
DOT 7 (5) 146, 167, 181 (1971)
I.N. p. 197
REM p. 1185
Takano, T., Kurita, M., Nikaido, H., Mera, M., Konishi, N. and Nakagawa, R.; U.S. Patent 3,516,997; June 23, 1970; assigned to Fujisawa Pharmaceutical Co., Ltd., Japan

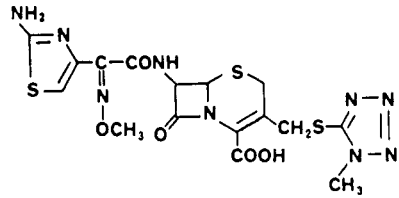
CEFMENOXIME

Therapeutic Function: Antibacterial

Chemical Name: 7β-[α-Methoxyimino-α-(2-aminothiazol-4-yl)acetamido]-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 65085-01-0

Trade Name	Manufacturer	Country	Year Introduced
Tacef	Takeda	W. Germany	1983
Bestcall	Takeda	Japan	1983

Raw Materials

7β-[α-Methoxyimino-α-(2-aminothiazol-4-yl)acetamido] cephalosporanic acid trifluoroacetic acid salt
1-Methyl-5-mercapto-1H-tetrazole

Manufacturing Process

7β-[α-Methoxyimino-α-(2-aminothiazol-4-yl)acetamido] cephalosporanic acid trifluoroacetic acid salt is dissolved in a solution of 272 mg of 1-methyl-5-mercapto-1H-tetrazole, 555 mg of sodium bicarbonate and 68 mg of triethylbenzylammonium bromide in 10 ml of water. The solution is heated at 60°C in nitrogen atmosphere for 6 hours. After cooling, the reaction solution is passed through a column of Amberlite XAD-2 and eluted with water and then with 2.5% ethanol. The procedure yields sodium 7β-[α-methoxyimino-α-(2-aminothiazol-4-yl)acetamido]-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate, MP 174°C to 175°C (decomposition).

References

Merck Index 1902
DFU 5 (3) 146 & (12) 635 (1980) (as SCE-1365)
DOT 19 (6) 335 & (8) 429 (1983)
I.N. p. 198

REM p. 1189
Ochiai, M., Okada, T., Aki, O., Morimoto, A., Kawakita, K. and Matsushita, Y.; U.S. Patent 4,098,888; July 4, 1978; assigned to Takeda Chemical Industries, Ltd.

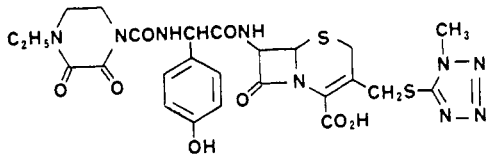
CEFOPERAZONE

Therapeutic Function: Antibiotic

Chemical Name: 7-[D-(-)-α-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-α-(4-hydroxyphenyl)acetamido] -3-[(1-methyl-1 H-tetrazol-5-yl)thiomethyl] -3-cephem-4-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 62893-19-0; 62893-20-3 (Sodium Salt)

Trade Name	Manufacturer	Country	Year Introduced
Cefobid	Pfizer	W. Germany	1981
Cefobine	Pfizer	France	1981
Cefobis	Pfizer	Switz.	1981
Cefoperazin	Pfizer Taito	Japan	1982
Cefobid	Roerig	U.S.	1982

Raw Materials

7-[D-(-)-α-Amino-p-hydroxyphenylacetamido] -3-[5-(1-methyl-1,2,3,4-tetrazolyl)-thiomethyl] -Δ^3-cephem-4-carboxylic acid
4-Ethyl-2,3-dioxo-1-piperazinocarbonyl chloride

Manufacturing Process

To a suspension of 3.0 g of 7-[D-(-)-α-amino-p-hydroxyphenylacetamido] -3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl] -Δ^3-cephem-4-carboxylic acid in 29 ml of water was added 0.95 g of anhydrous potassium carbonate. After the solution was formed, 15 ml of ethyl acetate was added to the solution, and 1.35 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride was added to the resulting solution at 0°C to 5°C over a period of 15 minutes, and then the mixture was reacted at 0°C to 5°C for 30 minutes. After the reaction, an aqueous layer was separated off, 40 ml of ethyl acetate and 10 ml of acetone were added to the aqueous layer, and then the resulting solution was adjusted to a pH of 2.0 by addition of dilute hydrochloric acid. Thereafter, an organic layer was separated off, the organic layer was washed two times with 10 ml of water, dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was dissolved in 10 ml of acetone, and 60 ml of 2-propanol was added to the solution to deposit crystals. The deposited crystals were collected by filtration, washed with 2-propanol, and then dried to obtain 3.27 g of 7-[D-(-)-α-(4-ethyl-2,3-dioxo)-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido] -3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl] -Δ^3-cephem-4-carboxylic acid, yield 80.7%. The product forms crystals, MP 188°C to 190°C (with decomposition).

References

Merck Index 1905

DFU 4 (9) (675) & (12) 911 (1979) (as T-1551)
Kleeman & Engel p. 169
PDR p. 1521
DOT 17 (12) 535 (1981)
I.N. p. 198
REM p. 1185
Saikawa, I., Takano, S., Yoshida, C., Takashima, O., Momonoi, K., Kuroda, S., Komatsu, M., Yasuda, T. and Kodama, Y.; British Patent 1,508,071; April 19, 1978; assigned to Toyama Chemical Co., Ltd. and U.S. Patent 4,110,327; August 29, 1978; also assigned to Toyama Chemical Co., Ltd.

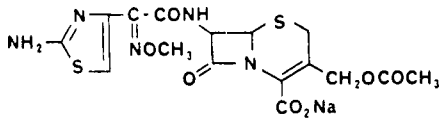
CEFOTAXIME SODIUM

Therapeutic Function: Antibiotic

Chemical Name: Sodium 3-acetoxymethyl-7-[2-(2-amino-4-thiazolyl)-2-methoxyimino]-acetamido-3-cephem-4-carboxylate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 64485-93-4; 63527-52-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Claforan	Hoechst-Roussel	W. Germany	1980
Claforan	Roussel Maestre	Italy	1980
Claforan	Roussel	France	1980
Zariviz	Hoechst	Italy	1980
Claforan	Roussel-Hoechst	Switz.	1981
Claforan	Roussel	U.K.	1981
Cefotax	Roussel	Japan	1981
Claforan	Hoechst	U.S.	1981
Pretor	Hoechst	–	–
Primafen	Hoechst	–	–
Ralopar	Hoechst	–	–
Tolycar	Hoechst	–	–

Raw Materials

Sodium bicarbonate
3-Acetoxymethyl-7-[2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido]-ceph-3-em-4-carboxylic acid (Cefotaxime)

Manufacturing Process

A solution of 8 g of sodium bicarbonate in about 20 ml of ethanol was progressively added to 45.55 g of pure 3-acetoxymethyl-7-[2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido]-ceph-3-eme-4-carboxylic acid in 100 ml of distilled water and another 80 ml of ethanol and 4.5 g of activated carbon were added thereto. The mixture was stirred for 5 minutes and was filtered. The filter was rinsed with ethanol and the filtrate was evaporated to dryness under

reduced pressure. The residue was taken up in 100 ml of ethanol and evaporated to dryness again. The residue was dissolved in 100 ml of methanol and the solution was poured into 2 ℓ of acetone. The mixture was vigorously stirred and was vacuum filtered. The recovered product was rinsed with acetone and then ether and dried under reduced pressure to obtain 43.7 g of a white product which rehydrated in air to obtain a final weight of 45.2 g of sodium 3-acetoxymethyl-7-[2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido] -ceph-3-eme-4-carboxylate.

References

Merck Index 1907
DFU 3 (12) 905 (1978)
Kleeman & Engel p. 171
PDR p. 935
OCDS Vol. 3 p. 216 (1984)
DOT 17 (1) 16 (1981)
I.N. p. 198
REM p. 1186
Heymes, R. and Lutz, A.; U.S. Patent 4,152,432; May 1, 1979; assigned to Roussel Uclaf

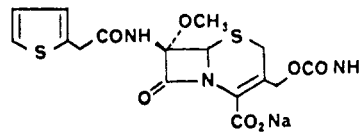
CEFOXITIN SODIUM

Therapeutic Function: Antibiotic

Chemical Name: 3-Carbamoyloxymethyl-7α-methoxy-7β-(2-thienylacetamido)decephalosporanic acid sodium salt

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 33654-30-6; 35607-66-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Mefoxin	Merck Sharp & Dohme	U.S.	1978
Mefoxitin	Sharp/Dohme	W. Germany	1978
Mefoxin	MSD	U.K.	1978
Mefoxitin	MSD	Switz.	1979
Mefoxin	MSD	Italy	1979
Cenomicin	Daiichi-Seiyaku	Japan	1980
Mefoxin	MSD	France	1980
Merkicin	Merck Banyu	Japan	1980
Betacel	Firma	Italy	—
Boncefin	MSD	—	—
Cefaxicina	Cefa	Spain	—
Cefoctin	Teva	Israel	—
Farmoxin	Farm. Carlo Erba	Italy	—

Raw Materials

Benzhydryl 3-carbamyloxymethyl-7α-hydroxy-7β-(2-thienylacetamino)-decephalosporanate

Sodium hydride
Dimethyl sulfate
Trifluoroacetic acid

Manufacturing Process

Benzhydryl 3-carbamoyloxymethyl-7α-hydroxy-7β-(2-thienylacetamido)decephalosporanate, 543 mg, is stirred in 15 ml dry DMSO. Sodium hydride, 24 mg (48 mg of a 50% suspension of NaH in mineral oil, which has been washed with hexane to remove the oil), is added. When hydrogen evolution has ceased, 126 mg dimethyl sulfate is added. The solution is stirred for one hour at room temperature, diluted with 100 ml benzene and washed six times with water; the last wash is made to pH 8, if necessary, by adding sodium bicarbonate. The solution is dried over $MgSO_4$, filtered and evaporated, leaving benzhydryl 3-carbamoyloxymethyl-7β-(2-thienylacetamido)-7α-methoxydecephalosporanate, which may be purified if desired by chromatography on silica gel, eluting with 25:1 chloroform-ethyl acetate.

Other methylating agents may be used in place of methyl sulfate, e.g., an equimolar amount of methyl iodide, bromide or chloride, using the same conditions, or methyl trifluoromethylsulfonate or trimethyloxonium trinitrobenzenesulfonate. The solvent in the latter two reagents is dimethyl ether-HMPA 1:1, using a reaction temperature of -20°C warming later to 25°C. In each instance, the benzhydryl 3-carbamoyloxymethyl-7β-(2-thienylacetamido)-7α-methoxydecephalosporanate is obtained.

Benzhydryl 3-carbamoyloxymethyl-7β-(2-thienylacetamido)-7α-methoxydecephalosporanate (300 mg) in 0.5 ml in anisole and 2.5 ml of trifluoroacetic acid is reacted for 15 minutes at 10°C. The resulting mixture is evaporated at reduced pressure and flushed twice with anisole. The residue is dissolved in methylene chloride and extracted with 5% sodium bicarbonate solution. The aqueous solution is adjusted to pH 1.8 with 5% phosphoric acid and extracted with ethyl acetate. The organic solution is dried and evaporated to yield the pure 3-carbamoyloxymethyl-7α-methoxy-7β-(2-thienylacetamido)decephalosporanic acid, MP 165°C to 167°C. This may then be converted to the sodium salt.

References

Merck Index 1910
DFU 3 (6) 434 (1978)
Kleeman & Engel p. 173
PDR p. 1194
OCDS Vol. 2 pp. 435, 443 (1980)
DOT 14 (2) 545 (1978)
I.N. p. 199
REM p. 1186
Christiansen, B.G. and Firestone, R.A.; U.S. Patent 3,775,410; November 27, 1973; assigned to Merck & Company, Inc.
Hazen, G.C.; U.S. Patent 3,780,033; December 18, 1973; assigned to Merck & Company, Inc.

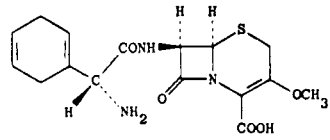
CEFROXADINE

Therapeutic Function: Antibacterial

Chemical Name: 7-[(Amino-1,4-cyclohexadien-1-yl-acetyl)amino]-3-methoxy-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 51762-05-1

Trade Name	Manufacturer	Country	Year Introduced
Oraspor	Ciba Geigy	Switz.	1981
Oraspor	Ciba Geigy	Japan	1982
Oraspor	Ciba Geigy	W. Germany	1983
Oraspor	Ciba Geigy	Italy	1983

Raw Materials

D-α-Amino-α-(1,4-cyclohexadienyl)acetic acid
Phosphorus pentachloride
7β-Amino-3-methoxy-3-cephem-4-carboxylic acid hydrochloride dioxanate
Bis(Trimethylsilyl)acetamide
Propylene oxide
Sodium hydroxide

Manufacturing Process

A suspension of 30.64 g (0.2 mol) of D-α-amino-α-(1,4-cyclohexadienyl)-acetic acid in 600 ml of methylene chloride is cooled under a stream of argon to 6°C, whereupon hydrogen chloride is passed in for about 30 minutes until the mixture is saturated. Phosphorpentachloride (62.4 g, 0.3 mol) is added in two portions. The mixture is stirred for 2 hours at 6°C to 8°C. The colorless precipitate is filtered off under nitrogen and exclusion of moisture, washed with methylene chloride and dried for 18 hours at 0.05 mm Hg at room temperature to give D-α-amino-α-(1,4-cyclohexadienyl)-acetylchloride hydrochloride in form of colorless crystals.

A suspension of 37.3 g (0.1 mol) of 7β-amino-3-methoxy-3-cephem-4-carboxylic acid hydrochloride dioxanate in 500 ml methylene chloride is stirred for 15 minutes at room temperature under an argon atmosphere and treated with 57.2 ml (0.23 mol) of bis-(trimethylsilyl)-acetamide. After 45 minutes the faintly yellow slightly turbid solution is cooled to 0°C and treated within 10 minutes with 31.2 g (0.15 mol) of D-α-amino-α-(1,4-cyclohexadienyl)-acetyl chloride hydrochloride. Thirty minutes thereafter 15 ml (about 0.21 mol) of propylene oxide is added and the mixture is further stirred for 1 hour at 0°C. A cooled mixture of 20 ml of absolute methanol in 200 ml of methylene chloride is added within 30 minutes, after another 30 minutes the precipitate is filtered off under exclusion of moisture, washed with methylene chloride and dried under reduced pressure at room temperature. The obtained hygroscopic crystals of the hydrochloride of 7β-[D-α-(1,4-cyclohexadienyl)-acetylamino]-3-methoxy-3-cephem-4-carboxylic acid are stirred into 200 ml of ice water and the milky solution treated with about 66 ml of cold 2N sodium hydroxide solution until pH 3.5 is reached. The solution is clarified by filtration through diatomaceous earth, washed with ice water, cooled to 0°C and treated with 20 ml of 2N sodium hydroxide solution until pH 5.7 is reached. A second filtration through a glass filter frit results in a clear solution which is treated with acetone (800 ml) at 0°C. The crystals are filtered washed with acetone:water (2:1), acetone and diethyl ether and dried for 20 hours at room temperature and 0.05 mm Hg to give the 7β-[D-α-amino-α-(1,4-cyclohexadienyl)-acetylamino]-3-methoxy-3-cephem-4-carboxylic acid dihydrate.

References

Merck Index 1911
DFU 4 (12) 911 (1979)
OCDS Vol. 3 p. 210 (1984)

DOT 19 (4) 190 (1983)
I.N. p. 200
Scartazzini, R. and Bickel, H.; U.S. Patent 4,073,902; February 14, 1978; assigned to Ciba-Geigy Corp.

CEFSULODIN

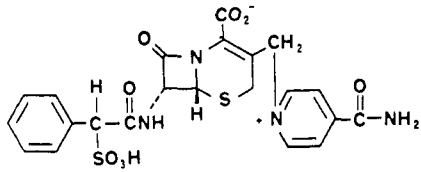
Therapeutic Function: Antibiotic

Common Name: Sulcephalosporin

Chemical Name: 7-(α-Sulfophenylacetamido)-3-(4'-carbamoylpyridinium)methyl-3-cephem-4-carboxylate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 52152-93-9 (Sodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Pseudomonil	Ciba Geigy	W. Germany	1980
Monaspor	Ciba Geigy	Switz.	1980
Pyocefalin	Cassene Takeda	France	1981
Takesulin	Takeda	Japan	1981
Tilmapor	Ciba Geigy	Japan	1981
Monaspor	Ciba Geigy	U.K.	1982
Pseudocef	Grunenthal	W. Germany	–

Raw Materials

7-(α-Sulfophenylacetamido)cephalosporanic acid
Isonicotinamide
Potassium Thiocyanate

Manufacturing Process

0.514 g (4 x 10^{-3} mol) of 7-(α-sulfophenylacetamido)cephalosporanic acid, 0.466 g (3 x 10^{-3} mol) of isonicotinamide and 2.0 g (2.06 x 10^{-3} mol) of potassium thiocyanate were dissolved in 2.5 ml of water. The resulting solution was allowed to stand and heated for 20 hours in a thermostat kept at 50°C and then directly purified by chromatography on an Amberlite XAD-2 column (16 x 880 mm). Subsequently, the fractions containing the cephalosporins were collected and subjected to freeze-drying to obtain 270 g of the title product in the form of a pale yellowish white powder. The product is usually used as the sodium salt.

References

Merck Index 1912
DFU 5 (2) 67 (1980)
OCDS Vol. 3 p. 214 (1984)
DOT 17 (12) 542 (1981)

I.N. p. 200
REM p. 1188
British Patent 1,387,656; March 19, 1975; assigned to Takeda Chemicals Industries, Ltd.

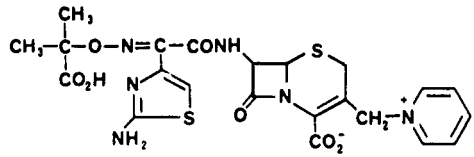
CEFTAZIDIME

Therapeutic Function: Antibiotic

Chemical Name: (6R,7R)-1-[(Z)-2-(2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)-acetamido] -3-(1-pyridiniummethyl)-ceph-3-em-4-carboxylic acid inner salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 72558-82-8

Trade Name	Manufacturer	Country	Year Introduced
Fortum	Glaxo	U.K.	1983

Raw Materials

(Z)-2-(2-t-Butoxycarbonylprop-2-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetic acid
t-Butyl(6R,7R)-3-acetoxymethyl-7-aminoceph-3-em-4-carboxylate
Pyridine

Manufacturing Process

(a) t-Butyl(6R,7R)-3-acetoxymethyl-7-[(Z)-2-(2-t-butoxycarbonylprop-2-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido] ceph-3-em-4-carboxylate: A stirred solution of (Z)-2-(2-t-butoxycarbonylprop-2-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetic acid (572 mg) and t-butyl(6R,7R)-3-acetoxymethyl-7-aminoceph-3-em-4-carboxylate (328 mg) in dimethylformamide (10 ml) was cooled to 0°C, and 1-hydroxybenzotriazole (150 mg) was added, followed by dicyclohexylcarbodiimide (225 mg). The mixture was warmed to room temperature, stirred for 5 hours and allowed to stand overnight. The mixture was filtered, and the white solid washed with a little ether. The filtrate and washings were diluted with water (50 ml) and extracted with ethyl acetate. The organic extracts were combined, washed successively with water, 2 N hydrochloric acid, water, sodium bicarbonate solution, and saturated brine, dried and evaporated. The residue was eluted through a silica column with ether. The product-containing eluate was collected and concentrated to give the title compound (533 mg). A portion was recrystallized from diisopropyl ether, MP 103°C to 113°C (decomp.); $[\alpha]_D^{20}$ +8.5° (conc. 1.0, DMSO).

(b) (6R,7R)-3-Acetoxymethyl-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido] ceph-3-em-4-carboxylic acid: Trifluoroacetic acid (18 ml) was added to a solution of the product of (a) (2.4 g) in anisole (18 ml) at 0°C. The mixture was stirred at room temperature for 2 hours and concentrated. The residue was dissolved in ethyl acetate and extracted with saturated sodium bicarbonate solution. The pH of the aqueous extracts was adjusted to 6, and the solution washed with ethyl acetate. The aqueous phase was acidified to pH 1.5 under ethyl acetate, saturated with sodium chloride, and extracted with ethyl

acetate. The combined organic extracts were washed with saturated brine, dried and evaporated. The residue was dissolved in warm 50% aqueous formic acid (20 ml) and allowed to stand for 2 hours. The mixture was diluted with water (50 ml) and filtered. The filtrate was concentrated. The residue was taken up in water (50 ml), refiltered, and lyophilized to give the title compound (920 mg).

(c) (6R,7R)-7-[(Z)-2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido] -3-(1-pyridiniummethyl)-ceph-3-em-4-carboxylate, monosodium salt: Pyridine (2 ml) and the product of (b) (1.8 g) were added to a stirred solution of sodium iodide (7.12 g) in water (2.2 ml) at 80°C. The solution was stirred at 80°C for 1 hour, cooled, and diluted to 100 ml with water. The pH of the solution was adjusted to 6.0 with 2N sodium hydroxide solution, and this solution was concentrated to remove pyridine. The aqueous residue was diluted to 100 ml with water, methyl isobutyl ketone (2 drops) was added, and the solution was acidified to pH 1 with 2N hydrochloric acid. The mixture was filtered, and the solid was washed with a little water. The filtrate and washings were collected and washed with ethyl acetate, and the pH adjusted to 6.0 with 2N sodium hydroxide solution. The solution was concentrated to 50 ml and applied to a column of 500 g Amberlite XAD-2 resin, using first water and then 20% aqueous ethanol as eluting solvent. The product-containing fractions were concentrated and lyophilized to give the title compound (0.56 g).

References

Merck Index 1913
DFU 6 (10) 612 (1981)
PDR p. 909
OCDS Vol. 3 p. 216 (1984)
DOT 19 (6) 336 (1983)
REM p. 1188
O'Callaghan, C.H., Livermore, D.G.H. and Newall, C.E.; British Patent 2,025,398; January 23, 1980; assigned to Glaxo Group Ltd.

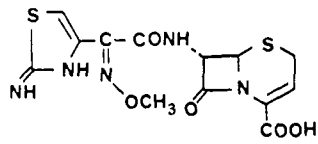
CEFTIZOXIME

Therapeutic Function: Antibacterial

Chemical Name: 7-[2-Methoxyimino-2-(2-amino-1,3-thiazol-4-yl)acetamido]-cephalosporanic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 68401-81-0; 68401-82-1 (Sodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Eposelin	Fujisawa	Japan	1982
Cefizox	SKF	U.S.	1983
Ceftix	Boehr./Mann	W. Germany	1983
Cefizox	Burroughs Wellcome	U.K.	–

Raw Materials

Phosphorus oxychloride
2-Methoxyimino-2-(2-amino-1,3-thiazol-4-yl)acetic acid
Bis(Trimethylsilyl)acetamide
7-Aminocephalosporanic acid

Manufacturing Process

Phosphorus oxychloride (2.0 g) was added at one time at 5°C to 10°C to a suspension of 2-methoxyimino-2-(2-amino-1,3-thiazol-4-yl)acetic acid (syn isomer) (2 g) in dry ethyl acetate (20 ml). After stirring for 20 minutes at 7°C to 10°C, bis(trimethylsilyl)acetamide (0.4 g) was added thereto at the same temperature. After stirring for 10 minutes at 7°C to 10°C, phosphorus oxychloride (2.0 g) was dropwise added thereto at the same temperature. The resulting mixture was stirred for 10 minutes at 7°C to 10°C, and dry dimethylformamide (0.8 g) was dropwise added thereto at the same temperature. The mixture was stirred for 30 minutes at 7°C to 10°C to give a clear solution. On the other hand, trimethylsilylacetamide (7.35 g) was added to a suspension of 7-aminocephalosporanic acid (2.45 g) in dry ethyl acetate (8 ml), after which the mixture was stirred at 40°C to give a clear solution.

To this solution was added at one time the above-obtained ethyl acetate solution at -15°C, and the resulting mixture was stirred for 1 hour at -10°C to -15°C. The reaction mixture was cooled to -30°C, and water (80 ml) was added thereto. The aqueous layer was separated, adjusted to pH 4.5 with sodium bicarbonate and subjected to column chromatography on Diaion HP-20 resin (Mitsubishi Chemical Industries Ltd.) using 25% aqueous solution of isopropyl alcohol as an eluent. The eluate was lyophilized to give 7-[2-methoxyimino-2-(2-amino-1,3-thiazol-4-yl)acetamido] cephalosporanic acid (syn isomer) (1.8 g), MP 227°C (decomp.).

References

Merck Index 1915
DFU 5 (5) 226 (1980)
PDR p. 1704
OCDS Vol. 3 p. 218 (1984)
DOT 19 (3) 133 (1983)
I.N. p. 200
REM p. 1189
Takaya, T., Masugi, T., Takasugi, H. and Kochi, H.; U.S. Patent 4,166,115; assigned to Fujisawa Pharmaceutical Co., Ltd.

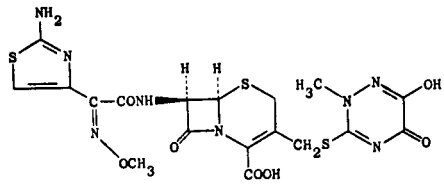
CEFTRIAXONE SODIUM

Therapeutic Function: Antibacterial

Chemical Name: Sodium salt of (6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-8-oxo-3-[[(1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl)thio] methyl]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 75478-69-1; 73384-59-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Rocephin	Roche	Switz.	1982
Rocephin	Roche	W. Germany	1983
Acantex	Roche	–	–

Raw Materials

(6R,7R)-7-[2-[2-(2-Chloroacetamido)-4-thiazolyl]-2-(methoxyimino)acetamido]-8-oxo-3-[[(1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl)thio] methyl]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid
Formic acid

Manufacturing Process

19 g of (6R,7R)-7-[2-[2-(2-chloroacetamido)-4-thiazolyl]-2-(methoxyimino)acetamido]-8-oxo-3-[[(1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl)thio] methyl]-5-thia-1-azabicyclo-[4.2.0] oct-2-ene-2-carboxylic acid are suspended in 150 ml of water together with 9.5 g of thiourea. The pH is adjusted to 6.8 with 5% sodium hydrogen carbonate solution while gassing with nitrogen and stirring, there being obtained a yellow-orange solution. The pH of the solution is held constant at 6.8–7.0 for 6 hours by adding sodium hydrogen carbonate solution by means of an autotitrator. 100% formic acid is added to the orange colored solution until the pH is 3.5. The precipitated material is filtered off under suction and washed with 100 ml of 10% formic acid. This material is denoted as (1). The filtrate is adjusted to pH 2.5 by adding 100% formic acid, whereby additional substance precipitates out. The mixture is held in an ice-bath for 1 hour, the precipitated substance is then filtered off and washed with a small amount of ice-water. This material is denoted as fraction I. The aforementioned orange-brown material (1) is suspended in 250 ml of water. The suspension is adjusted to pH 7 with 2N sodium hydroxide, there being obtained an orange-brown solution. Additional 100% formic acid is added to this solution until the pH is 3.5. The material which thereby precipitates out is filtered off under suction and discarded. The filtrate is adjusted to pH 2.5 with 100% formic acid, whereby additional substance precipitates out. The mixture is held in an ice-bath for 1 hour, the precipitated substance is then filtered off under suction and washed with a small amount of ice-water. This material is denoted as fraction II. Fractions I and II are suspended together in 500 ml of ethanol and evaporated in a rotary evaporator in order to remove water. After adding ether, the mixture is filtered under suction and the precipitate is washed successively with ether and low-boiling petroleum ether. There is thus obtained the title substance in the form of a yellowish solid material which is denoted as A.

The mother liquors and washings of fractions I and II are concentrated from a volume of about 1.7 liters to 250 ml, the pH is adjusted to 2.5 with 100% formic acid and the solution is stored overnight in a refrigerator, whereby further substance crystallizes. This is filtered off under suction and washed with a small amount of water. The residue on the suction filter is azeotropically distilled with ethanol. There is obtained solid, almost colorless title substance which is denoted as B. B is purer than A according to thin-layer chromatography.

In order to obtain pure title substance, the acid B is suspended in 150 ml of methanol and treated while stirring with 10 ml of a 2N solution of the sodium salt of 2-ethylcaproic acid in ethyl acetate. After about 10 minutes, there results a solution which is treated with 100 ml of ethanol. The mixture is extensively concentrated at 40°C in vacuo. The sodium salt precipitates out in amorphous form after adding ethanol. This salt is filtered off under suction, washed successively with ethanol and low-boiling petroleum ether and dried at 40°C in a high vacuum. There is obtained the title substance in the form of an almost colorless amorphous powder.

References

Merck Index 1916
PDR p. 1499

DOT 19 (12) 653 (1983)
I.N. p. 200
REM p. 1189
Montavon, M. and Reiner, R.; British Patent 2,022,090; December 12, 1979; assigned to F. Hoffman-La Roche & Co. A.G. (Switz.)

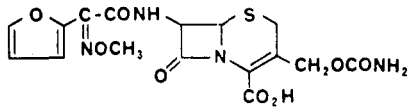
CEFUROXIME

Therapeutic Function: Antibiotic

Chemical Name: (6R,7R-3-Carbamoyloxymethyl-7-[2-(2-furyl)-2-(methoxyimino)acetamido]-ceph-3-em-4-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 55268-75-2; 56238-63-2 (Sodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Ultroxim	Duncan	Italy	1978
Curoxime	Glaxo	Italy	1978
Zinacef	Hoechst	W. Germany	1978
Zinacef	Glaxo	U.K.	1978
Zinacef	Glaxo	Switz.	1978
Ceroxime	Glaxo	France	1980
Zinacef	Glaxo	Japan	1982
Zinacef	Tanabe Seiyaku	Japan	1982
Zinacef	Glaxo	U.S.	1983
Altacel	Pulitzer	Italy	–
Biociclin	Del Saz & Filippini	Italy	–
Bioxima	Italsuisse	Italy	–
Cefamar	Firma	Italy	–
Cefoprim	Esseti	Italy	–
Cefumax	Locatelli	Italy	–
Cefur	Tiber	Italy	–
Cefurex	Sarm	Italy	–
Cefurin	Magis	Italy	–
Cefurox	Glaxo	–	–
Colifossim	Coli	Italy	–
Curocef	Glaxo	–	–
Duxima	Dukron	Italy	–
Furex	Lafare	Italy	–
Gibicef	Gibipharma	Italy	–
Itorex	Ausonia	Italy	–
Kefox	C.T.	Italy	–
Kesint	Proter	Italy	–
Ketocef	Glaxo	–	–
Lamposporin	Von Boch	Italy	–
Medoxin	Medici	Italy	–
Polixima	Sierochimica	Italy	–
Supero	Farmochimica	Italy	–
Ultroxim	Sigmatau	Italy	–

Raw Materials

(6R,7R)-7-Amino-3-carbamoyloxymethylceph-3-em-4-carboxylic acid
Phosphorus pentachloride
2-(Fur-2-yl)-2-methoxyiminoacetic acid
Hydrogen chloride

Manufacturing Process

A stirred mixture of N,N-dimethylacetamide (75 ml), acetonitrile (75 ml), triethylamine (42 ml, 0.3 mol) and (6R,7R)-7-amino-3-carbamoyloxymethylceph-3-em-4-carboxylic acid was immersed in an ice-bath and water (10 ml) was added. The mixture was stirred at 0°C to 2°C for 45 minutes, the solid slowly dissolving to give a yellow solution.

Meanwhile a stirred suspension of phosphorus pentachloride (14.99 g, 0.072 mol) in dry dichloromethane (150 ml) was cooled to 0°C, and N,N-dimethylacetamide (27.5 ml) was added. The resulting solution was recooled to -10°C and 2-fur-2-yl)-2-methoxyiminoacetic acid (syn-isomer) (12.17 g, 0.072 mol) was added. The mixture was stirred at -10°C for 15 minutes and crushed ice (35 g) was added. The mixture was stirred at 0°C for 10 minutes, whereafter the lower dichloromethane phase was added over 10 minutes to the cephalosporin solution prepared above, cooled to -10°C so that the reaction temperature rose steadily to 0°C. The mixture was stirred at 0°C to 2°C for 1 hour, whereafter the cooling bath was removed and the reaction temperature allowed to rise to 20°C over 1 hour. The reaction mixture was then added slowly to 2N hydrochloric acid (100 ml) diluted with cold water (1.15 ℓ) at 5°C. The pH of the two-phase mixture was adjusted to below 2 with 2N hydrochloric acid (10 ml), and the mixture was stirred and recooled to 5°C. The solid which precipitated was filtered, washed with dichloromethane (100 ml) and water (250 ml), and dried in vacuo at 40°C overnight to give the title compound (22.04 g, 86.6%).

References

Merck Index 1917
DFU 3 (4) 266 (1978)
Kleeman & Engel p. 177
PDR p. 922
OCDS Vol. 3 p. 216 (1984)
DOT 12 (5) 189 (1976) & 15 (1) 10 (1979)
I.N. p. 200
REM p. 1187
Cook, M.C., Gregory, G.I. and Bradshaw, J.; U.S. Patent 3,966,717; June 29, 1976; assigned to Glaxo Laboratories, Ltd.
Cook, M.C., Gregory, G.I. and Bradshaw, J.; U.S. Patent 3,974,153; August 10, 1976; assigned to Glaxo Laboratories, Ltd.

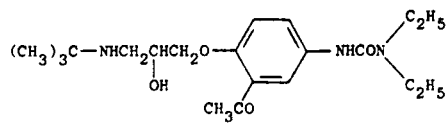
CELIPROLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: N'-[3-Acetyl-4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenyl]-N,N-diethylurea

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 56980-93-9

Trade Name	Manufacturer	Country	Year Introduced
Selectol	Chemie Linz	Austria	1983
Selectol	Chemie Linz	W. Germany	1983

Raw Materials

3-Acetyl-4-hydroxyaniline
Dimethylcarbamoyl chloride
Epichlorohydrin
t-Butylamine

Manufacturing Process

3-Acetyl-4-hydroxyaniline, in solution in pyridine, is reacted with dimethylcarbamoyl chloride at room temperature to give N-(3-acetyl-4-hydroxy)-phenyl-N'-dimethylurea, which after evaporating the pyridine, taking up the residue in chloroform and evaporating the latter, is obtained in a crystalline form. Melting point: 160°–162°C. After reaction of the product in alkaline aqueous solution, with epichlorohydrin, N-[3-acetyl-4-(2',3'-epoxy)-propoxy]-phenyl-N'-dimethylurea (melting point: 98°–102°C) is obtained, and this, in turn, is reacted with excess tert-butylamine in aqueous solution at room temperature to give N-[3-acetyl-4-(3'-tert-butylamino-2'-hydroxy)-propoxy]-phenyl-N'-dimethylurea of melting point: 120°–122°C.

References

Merck Index 1921
DFU 4 (3) 181 (1979)
DOT 18 (12) 632 (1982)
I.N. p. 201
Zolss, G., Pittner, H., Stormann-Menninger-Lerchenthal, H. and Lindner, I.; U.S. Patent 3,983,169; September 28, 1976; assigned to Chemie Linz AG (Austria)

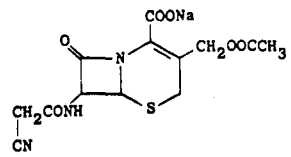
CEPHACETRILE SODIUM

Therapeutic Function: Antibiotic

Chemical Name: 7-(2-cyanoacetamido)-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid acetate monosodium salt

Common Name: Sodium 7-(2-cyanoacetamido)-cephalosporanic acid

Structural Formula:



Chemical Abstracts Registry No.: 23239-41-0; 10206-21-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Celospor	Ciba Geigy	Switz.	1969
Celospor	Ciba	France	1973
Clospor	Gruenenthal	W. Germany	1974
Celospor	Ciba	Italy	1974
Celospor	Ciba	W. Germany	1974
Celtol	Takeda	Japan	1978

Trade Name	Manufacturer	Country	Year Introduced
Celospor	Ciba Geigy	Japan	1978
Flunicef	Alfa Farm.	Italy	–

Raw Materials

7-Amino-cephalosporanic acid
Cyanoacetyl chloride
Sodium hydroxide

Manufacturing Process

13.6 g (0.05 mol) of 7-amino-cephalosporanic acid are taken up in a mixture of 150 ml of methylene chloride and 19.5 ml of tributylamine (0.12 mol) and at 0°C a solution of 8.4 g of cyanoacetylchloride (0.07 mol) in 100 ml of methylene chloride is stirred in. The bath is then stirred for ½ hour at 0°C and for ½ hour at 20°C, the reaction solution is evaporated under vacuum and the residue taken up in 10% aqueous dipotassium hydrogen-phosphate solution. This aqueous phase is washed with ethyl acetate, acidified to pH 2.0 with concentrated hydrochloric acid and extracted with ethyl acetate.

After having been dried over sodium sulfate and evaporated under vacuum, this extract gives as a solid residue 14.7 g of crude 7-cyanoacetylamino-cephalosporanic acid which is purified by chromatography on 30 times its own weight of silica gel. The fractions eluted with chloroform plus acetone (7:3) furnish a product which crystallizes from acetone plus ether in the form of needles melting at 168° to 170°C with decomposition.

5.10 g (15 mmol) of 7-cyanoacetyl-aminocephalosporanic acid are suspended in 102 ml of distilled water and converted into the sodium salt by stirring in dropwise 15 ml of N sodium hydroxide solution.

References

Merck Index 1934
Kleeman & Engel p. 159
DOT 7 (5) 181 (1971) 9 (2) 50 (1973) & 10 (7) 239 (1974)
I.N. p. 193
Bickel, H., Bosshardt, R., Fechtig, B., Schenker, K. and Urech, J.; U.S. Patent 3,483,197; December 9, 1969; assigned to Ciba Corporation

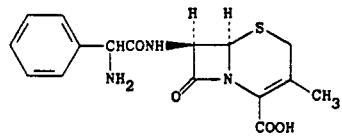
CEPHALEXIN

Therapeutic Function: Antibiotic

Chemical Name: 7-[(Aminophenylacetyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 15686-71-2; 23325-78-2 (Monohydrate)

Trade Name	Manufacturer	Country	Year Introduced
Ceporex	Glaxo	U.K.	1970
Ceprorexine	Glaxo	France	1970
Cepol	Torii	Japan	1970
Keflex	Shionogi	Japan	1970
Keflex	Lilly	U.K.	1970
Keflex	Lilly	U.S.	1971
Ceporex	Glaxo	Italy	1971
Keforal	Lilly	France, Italy	1971
Oracef	Lilly	W. Germany	1971
Keflex	Serum Impfinst	Switz.	1974
Acaxina	Martin Santos	Spain	—
Acinipan	Aldon	Spain	—
Ambal	Medical	Spain	—
Amplicefal	Miluy	Spain	—
Ampligram	Hermes	Spain	—
Ausocef	Ausonia	Italy	—
Basporin	Basileos	Spain	—
Bilatox	Biopharma	Spain	—
Bioporina	Biologia Marina	Spain	—
Brisoral	Bristol-Myers	—	—
Cefabiot Oral	Galepharma Iberica	Spain	—
Cefadina	Antibioticos	Spain	—
Cefadros	Proter	Italy	—
Cefa-Iskia	Iskia	Spain	—
Cefaleh Ina	Alvarez Gomez	Spain	—
Cefalekey	Pereira	Spain	—
Cefalex-Gobens	Normon	Spain	—
Cefalival	Valles Mestre	Spain	—
Cefaloto	Lifepharma	Spain	—
Cefa-Reder	Reder	Spain	—
Cefaxin	Bristol	Italy	—
Cefibacter	Rubio	Spain	—
Ceflon	Mulda	Turkey	—
Ceflor	Coli	Italy	—
Ceforal	Teva	Israel	—
Cepexin	Glaxo	—	—
Cephalomax	Daisan	Japan	—
Cephazal	Hokuriku	Japan	—
Cepol	Torii	Japan	—
Cepoven	Glaxo	Italy	—
CEX	Glaxo	Japan	—
Chemosporal	Erba	Italy	—
Cilicef Oral	Hortel	Spain	—
Ciponium	Nippon Kayaku	Japan	—
Derantel	Nippon Chemiphar	Japan	—
Devaleksin	Deva	Turkey	—
Diabeton	Teknofarma	Italy	—
Erifalecin	Dreikehl	Spain	—
Erocetin	Roemmers	Argentina	—
Esmezin	Sawai	Japan	—
Falecina	Italquimica	Spain	—
Farexin	Lafare	Italy	—
Fergon	Alfar	Spain	—
Garasin	Wakamoto	Japan	—
Grafalex	Graino	Spain	—
Huberlexina	Hubber	Spain	—
Ibilex	I.B.I.	Italy	—
Iwalexin	Iwaki	Japan	—

Trade Name	Manufacturer	Country	Year Introduced
Janocilin	Janovich	Spain	–
Keflex	Shionogi	Japan	–
Kelfison	Davur	Spain	–
Larixin	Toyama	Japan	–
Latoral	Dukron	Italy	–
Lefosporina	Bicsa	Spain	–
Lexibiotico	Llano	Spain	–
Libesporal	Liberman	Spain	–
Llenas Biotic	Llenas	Spain	–
Lorexina	Crosara	Italy	–
Madlexin	Meiji	Japan	–
Maksipor	Fako	Turkey	–
Mamalexin	Showa	Japan	–
Mepilacin	Kanto	Japan	–
Neolexina	Asia	Spain	–
Nilexina	Pental	Spain	–
Ohlexin	Ohta	Japan	–
Oracocin	Tobishi	Japan	–
Oralexine	Novo	Denmark	–
Oroxin	Otsuka	Japan	–
Ortisporina	Turro	Spain	–
Ospexin	Biochemie	Austria	–
Palitrex	Galenira	Yugoslavia	–
Porinabis	Santos	Spain	–
Pracefal	Pradel	Spain	–
Prindex	Hosbon	Spain	–
Pyassan	Chinoin	Hungary	–
Rinesal	Kissei	Japan	–
Rogeridina	Roger	Spain	–
Salitex	Banyu	Japan	–
Sargetina	Sarget	France	–
Sartosona	Sanomed	Spain	–
Sasperos	Schiapparelli	Italy	–
Sayra	Legem	Spain	–
Sefaleksin	Ilsan	Turkey	–
Segoramin	Takata	Japan	–
Sencephalin	Takeda	Japan	–
Septilisin	Bago	Argentina	–
Syncel	Toyo Jozo	Japan	–
Taicelexin	Taiyo	Japan	–
Talinsul	Ester	Spain	–
Testaxina	Bryan	Spain	–
Tokiolexin	Isei	Japan	–
Torlasporin	Torlan	Spain	–
Wasserporina	Wassermann	Spain	–
Xahl	S.S. Seiyaku	Japan	–

Raw Materials

Soidum-D-α-phenylglycine
Methyl acetoacetate
p-Nitrobenzyl-7-aminodesacetoxycephalosporanate
Zinc
Hydrogen chloride

Manufacturing Process

To a 1 liter flask containing dimethylformamide at 0°C, was added 24.8 g sodium N-(2-methoxycarbonyl-1-methylvinyl)-D-α-phenylglycine (prepared from sodium D-α-phenylglycine and methyl acetoacetate). The mixture was cooled to –40°C and methyl chloroformate (7.5

ml) and dimethylbenzylamine (0.26 ml) added. After stirring for 25 minutes, p-nitrobenzyl 7-aminodesacetoxycephalosporanate (32.8 g) in the form of its hydrochloride salt was added, followed by triethylamine (12.1 ml) and dimethylformamide (140 ml) over a period of 20 minutes. The reaction mixture was stirred for 2 hours at -25°C to -35°C, then warmed to 0°C and water (32 ml) added. To the resulant solution, hydrochloric acid (54 ml) was added followed by zinc (21.8 g) in portions over a period of 5 minutes, the temperature being maintained at 5°C to 10°C. Further hydrochloric acid (35 ml) was added and the solution stirred at 15°C to 20°C for 7 hours.

The pH was adjusted to 3.3 with triethylamine and semicarbazide hydrochloride (9.5 g) added. The mixture was brought back to pH 3 with further triethylamine, then stirred for 30 minutes at pH 3. The resultant mixture was adjusted slowly over 4 hours to pH 6.8 by addition of triethylamine, seeding being carried out when pH 4.5 was reached. The precipitated cephalexin was filtered off, washed with dimethylformamide (200 ml) and the cephalexin recovered, yield 75%.

References

Merck Index 1936
Kleeman & Engel p. 161
PDR p. 841
OCDS Vol. 1 p. 417 (1977) & 2 p. 439 (1980)
DOT 5 (1) 29 (1969) & 6 (5) 165 (1970)
I.N. p. 194
REM p. 1189
Davison, M., Frankham, D.B., Spence, T.W.M.; U.S. Patent 3,946,002; March 23, 1976; assigned to Lilly Industries Ltd.

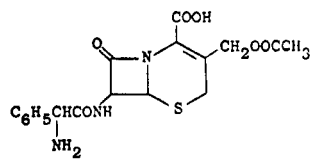
CEPHALOGLYCIN

Therapeutic Function: Antibacterial

Chemical Name: 3-[(acetyloxy)methyl]-7-[(aminophenylacetyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Common Name: 7(D-α-aminophenylacetylamido)-caphalosporanic acid

Structural Formula:



Chemical Abstracts Registry No.: 3577-01-3

Trade Name	Manufacturer	Country	Year Introduced
Kefglycin	Shionogi	Japan	1969
Kafocin	Lilly	U.S.	1970

Raw Materials

D-Phenylglycine
7-Amino-cephalosporanic acid
Isobutyl chloroformate
Carbobenzoxy chloride
Hydrogen

Manufacturing Process

dl-Phenylglycine is resolved in a conventional manner by reaction with cinchonine, fractional crystallization of the resulting diastereoisomers, and acidification to release the phenylglycine enantiomorphs. D-phenylglycine, thus prepared, is reacted with carbobenzoxy chloride in a conventional manner to produce N-carbobenzoxy-D-phenylglycine.

A 0.60 g portion of N-carbobenzoxy-D-phenylglycine is dissolved in 10 ml of dry tetrahydrofuran. The solution is cooled in an ice-salt bath, and to it is added 0.29 ml of triethylamine with stirring over a period of 10 minutes, followed by 0.29 ml of isobutyl chloroformate, after which stirring is continued for 10 minutes at -5°C. During this time, 0.57 g of 7-amino-cephalosporanic acid and 0.29 ml of triethylamine are dissolved in 5 ml of tetrahydrofuran and 5 ml of water, and the solution is centrifuged to remove a dark sludge. The clarified solution is cooled in ice and slowly added to the reaction mixture, and stirring is continued in the ice bath for 0.5 hour, followed by one hour at room temperature.

The reaction product mixture is a homogenous solution having a pH of about 6. It is evaporated under vacuum to a semisolid residue. To the residue are added 35 ml of water and a few drops of triethylamine to raise the pH to 8. The aqueous solution obtained thereby is extracted successively with 50 ml and 35 ml portions of ethyl acetate, the pH being adjusted to 2 at each extraction with hydrochloric acid. The extracts are combined, filtered, dried over sodium sulfate, stripped of solvent, and evaporated under vacuum. The product is 7-(N-carbobenzoxy-D-α-aminophenylacetamido)cephalosporanic acid in the form of a yellow-white amorphous solid weighing 1.10 g.

Of this material 1.0 g is dissolved in 150 ml of warm 95% ethyl alcohol. To the solution is added 1.0 g of 5% palladium on carbon catalyst, and the mixture is hydrogenated at room temperature and atmospheric pressure by bubbling hydrogen into it for 3 hours with stirring. The hydrogenation product is filtered. The solid phase, comprising the catalyst and the desired product, is suspended in ethyl acetate and water and adjusted to pH 2 with hydrochloric acid. The suspension is filtered to remove the catalyst. The aqueous phase is separated from the filtrate, and is evaporated under vacuum to recover the desired product, 7-(D-α-aminophenylacetamido)cephalosporanic acid.

References

Merck Index 1938
Kleeman & Engel p. 163
OCDS Vol. 1 p. 417 (1977)
DOT 6 (5) 169 (1970)
I.N. p. 195
British Patent 1,017,624; January 19, 1966; assigned to Merck & Co., Inc.
British Patent 985,747; March 10, 1965; assigned to Eli Lilly and Company
Wall, W.F., Fatherey, M. and Boothroyd, B.; U.S. Patent 3,422,103; January 14, 1969; assigned to Glaxo Laboratories, Ltd.
Pfeiffer, R.R. and Bottorff, E.M.; U.S. Patent 3,497,505; February 24, 1970; assigned to Eli Lilly & Co.
Jackson, B.G.; U.S. Patent 3,671,449; June 20, 1972; assigned to Eli Lilly & Co.

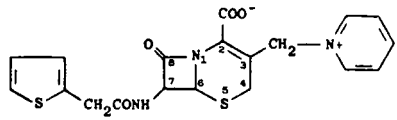
CEPHALORIDINE

Therapeutic Function: Antibacterial

Chemical Name: (6R-trans)-1-[[2-Carboxy-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl] pyridinium hydroxide inner salt

Common Name: Cefaloridin

Structural Formula:



Chemical Abstracts Registry No.: 50-59-9

Trade Name	Manufacturer	Country	Year Introduced
Ceporin	Glaxo	U.K.	1964
Ceporin	Glaxo	Switz.	1965
Cepaloridin	Glaxo	W. Germany	1965
Keflodin	Lilly	France	1967
Loridine	Lilly	U.S.	1968
Ceporin	Glaxo	Italy	1976
Acaporina	Martin Santos	Spain	—
Aliporina	Asla	Spain	—
Ampliceriná	Miluy	Spain	—
Ampligram	Hermes	Spain	—
Basporidina	Basileos	Spain	—
Bioporina	Biologia Marina	Spain	—
Cefabena	Jebena	Spain	—
Cefabiot	Galepharma Iberica	Spain	—
Cefaclox	Sigma Tau	Italy	—
Cefalescord	Callol	Spain	—
Cefalisan	Lifepharma	Spain	—
Cefalobiotic	Wolner	Spain	—
Cefalogobens	Normon	Spain	—
Cefalomiso	Oftalmiso	Spain	—
Cefamusel	De La Cruz	Spain	—
Cefaresan	Alacan	Spain	—
Ceflorin	Glaxo	—	—
Cepalorin	Glaxo	—	—
Ceporan	Glaxo	—	—
Ceporan	Torii	Japan	—
Ceproduc	Glaxo	Italy	—
CER	Glaxo	Japan	—
Cidan-Cef	Cidan	Spain	—
Cilicef	Hortel	Spain	—
Cobalcina	Pradel	Spain	—
Cusisporina	Norte De Espana	Spain	—
Diclocef	Medici	Italy	—
Dinasint	Proter	Italy	—
Eldia	Legem	Spain	—
Endosporol	Cantabria	Spain	—
Enebiotico	Llano	Spain	—
Faredina	Lefare	Italy	—
Filoklin	Lifasa	Spain	—
Floridin	Coli	Italy	—
Gencefal	Morgens	Spain	—
Glaxoridin	Glaxo	—	—
Huberlexina	Hubber	Spain	—
Intrasporin	Torlan	Spain	—
Janosina	Janovich	Spain	—
Keflodin	Shionogi	Japan	—
Kefspor	Lilly	—	—
Kelfison	Davur	Spain	—

Trade Name	Manufacturer	Country	Year Introduced
Latorex	Durron	Italy	–
Lauridin	Crosara	Italy	–
Lexibiotico	Llano	Spain	–
Libesporina	Liberman	Spain	–
Liexina	ICN	–	–
Llenas Biotic	Llenas	Spain	–
Lloncefal	Castillon	Spain	–
Poricefal	Santos	Spain	–
Prinderin	Hosbon	Spain	–
Rogeridina	Roger	Spain	–
Rolexina	Fedal	Spain	–
Sargefal	Sarget	France	–
Sintoridyn	I.S.F.	Italy	–
Sporanicum	Incasa-Wolff	Spain	–
Talinsul	Ester	Spain	–
Tapiola	Guadalupe	Spain	–
Testadina	Bryan	Spain	–
Totalmicina	Emyfar	Spain	–
Wasseridina	Wassermann	Spain	–

Raw Materials

7-Aminocephalosporanic acid
2-Thienylacetyl chloride
Pyridine

Manufacturing Process

7-Aminocephalosporanic acid (5.00 g) which passed through a 100-mesh sieve was suspended in boiling ethyl acetate (200 ml), and 2-thienylacetyl chloride (Cagniant, *Bull. Soc. Chim. France,* 1949, 847) (4.42 g, 1.5 equiv.) was added in ethyl acetate (20 ml). The mixture was boiled under reflux for 40 minutes, cooled, and filtered. Aniline (5.03 ml) was added, and after 1 hour the mixture was extracted with 3% sodium hydrogen carbonate solution (1 x 150 ml, 2 x 100 ml, 1 x 50 ml) and the alkaline extracts washed with ethyl acetate (3 x 100 ml). The aqueous solution was acidified to pH 1.2, and extracted with ethyl acetate (2 x 150 ml). The ethyl acetate extract was washed with water (4 x 40 ml), dried ($MgSO_4$), and concentrated in vacuo to low volume. The crude 7-2'-thienylacetamidocephalosporanic acid (2.5 g) which separated was collected by filtration. Evaporation of the filtrate gave a further 2.68 g (71%) of the product, which was purified by crystallization from ethyl acetate, then aqueous acetone, MP 150°C to 157°C (decomp.).

7-2'-Thienylacetamidocephalosporanic acid (7.0 g) was suspended in water (60 ml) and stirred with pyridine (7 ml) until the acid dissolved. The resulting solution (pH 5.9) was kept at 35°C for 3 days, then filtered and extracted with methylene chloride (4 x 60 ml). The methylene chloride extract was back-extracted with a little water and the total aqueous solutions were then percolated through a column of Dowex 1 x 8 resin, (100 to 200 mesh, 150 g) in the acetate form at pH 4.3. The column was washed with water until the optical rotation of the eluate fell to zero and the eluate (500 ml) was freeze-dried. The residual white solid was dissolved in the minimum volume of methanol and after a few minutes the pyridine derivative crystallized; this is the cephaloridine product.

References

Merck Index 1940
Kleeman & Engel p. 164
OCDS Vol. 1 p. 417 (1977)
DOT 1 (3) 88 (1965)
I.N. p. 195

Arkley, V., Eardley, S. and Long, A.G.; British Patent 1,030,630; May 25, 1966; assigned to Glaxo Laboratories, Ltd.
Higgins, H.M. Jr.; U.S. Patent 3,270,012; August 30, 1966; assigned to Eli Lilly & Co.

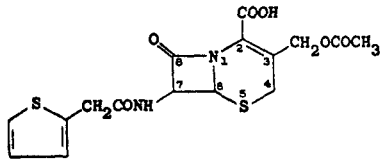
CEPHALOTHIN SODIUM

Therapeutic Function: Antibacterial

Chemical Name: 6R-trans-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-carboxylic acid sodium salt

Common Name: 7-(2-thienylacetamido)cephalosporanic acid

Structural Formula:



(base)

Chemical Abstracts Registry No.: 58-71-9; 153-61-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Keflin	Lilly	U.S.	1964
Cepovenin	Hoechst/Glaxo	W. Germany	1965
Keflin	Lilly	France	1965
Keflin	Serum Impfinst.	Switz.	1965
Keflin	Shionogi	Japan	1966
Keflin	Lilly	Italy	1967
Keflin	Lilly	U.K.	1969
Seffin	Glaxo	U.S.	1983
Averon	Alfar	Spain	—
Averon-I	Alfa Farm.	Italy	—
Cephalotin	Lilly	W. Germany	—
Cephation	Meiji	Japan	—
Ceporacin	Glaxo	—	—
Cepovenin	Hoechst	W. Germany	—
CET	Glaxo	Japan	—
Coaxin	Tobishi	Japan	—
Loccalline	Showa	Japan	—
Lospoven	Hoechst	—	—
Restin	Ono	Japan	—
Sodium Cephalotin	Green Cross	Japan	—
Sucira N	Mohan	Japan	—
Synclotin	Toyo Jozo	Japan	—
Toricelosin	Torii	Japan	—

Raw Materials

2-Thienylacetic acid
7-Aminocephalosporanic acid
Thionyl chloride
Sodium hydroxide

Manufacturing Process

7-(2'-Thienylacetamido)cephalosporanic acid sodium salt may be produced from 2-thienylacetyl chloride, obtainable by treatment of 2-thienylacetic acid [Ernst, *Berichte, 19* (1886)

3281] with thionyl chloride in a conventional manner. The 2-thienylacetyl chloride is then reacted with 7-aminocephalosporanic acid and then converted to the sodium salt using sodium hydroxide.

References

Merck Index 1943
Kleeman & Engel p. 165
PDR pp. 911, 1056
OCDS Vol. 1 pp. 417, 420 (1977)
DOT 2 (2) 44 (1966)
I.N. p. 196
REM p. 1187
British Patent 982,252; February 3, 1965; assigned to Eli Lilly and Company

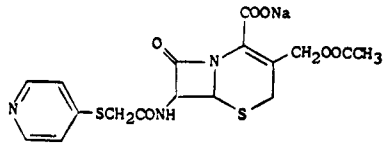
CEPHAPIRIN SODIUM

Therapeutic Function: Antibacterial

Chemical Name: 3-[(acetyloxy)methyl]-8-oxo-7-([(4-pyridinylthio)acetyl]amino)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monosodium salt

Common Name: Sodium 7-(pyrid-4-ylthioacetamido)cephalosporanate

Structural Formula:



Chemical Abstracts Registry No.: 24356-60-3; 21593-23-7 (Acid)

Trade Name	Manufacturer	Country	Year Introduced
Cefadyl	Bristol	U.S.	1974
Bristocef	Bristol	W. Germany	1974
Cephaloject	Bristol	France	1974
Cefatrexyl	Essex	Switz.	1974
Brisporin	Bristol	Italy	1976
Cefatrexyl	Bristol	Japan	1977
Brisfirina	Bristol-Myers	—	—
Cefa-Lak	Bristol	—	—
Cefatrex	Bristol-Myers	—	—
Cefatrexil	Mead-Johnson	—	—
Cefatrexyl	Galenika	Yugoslavia	—
Piricef	C.T.	Italy	—
Today	Bristol-Myers	—	—

Raw Materials

Aminocephalosporanic acid
Sodium bicarbonate
Sodium-3-ethyl hexanoate
Bromoacetyl bromide
2-Mercaptopyrimidine

Manufacturing Process

One route is that described in U.S. Patent 3,422,100 as follows, starting with amino-cephalosporanic acid (ACA): 27.2 g (0.1 mol) of 7-ACA, 33.2 g (0.3 mol) of $NaHCO_3$, 200 ml of water and 100 ml of acetone were mixed together, cooled to 0°C and stirred rapidly while 20.1 g (0.1 mol) of bromoacetyl bromide dissolved in 100 ml of acetone was added in one fast addition. The temperature was kept at 0° to 5°C for ten minutes, then the ice-salt bath was removed and stirring continued for one hour as the temperature approached 25°C. The mixture was concentrated in vacuo at 20°C to one-half volume and 200 ml of water added. Two 400 ml ether extracts were made and discarded. The aqueous solution was covered with 200 ml of ethyl acetate and vigorously stirred and cooled while being acidified to pH 2 with 40% phosphoric acid.

The mixture was filtered, the ethyl acetate layer separated and washed with three 100 ml portions of water, dried over Na_2SO_4, filtered and treated with 30 ml of sodium 2-ethyl-hexanoate in n-butanol (34 ml = 0.1 mol). The oil which settled out was scratched to induce crystallization. After stirring for 20 minutes the product, sodium 7-(α-bromoacetamido)cephalosporanate, was scraped from the sides of the flask and collected. The filter cake was washed with several portions of acetone, air dried, and dried in vacuo over P_2O_5. The yield was 22.5 g and decomposed at 193°C.

A solution of 1.13 g (0.01 mol) of 2-mercaptopyrimidine and 1.06 g (0.01 mol) of sodium carbonate dissolved in 25 ml of water was added dropwise over a period of an hour at room temperature, to a stirred solution of 4.15 g (0.01 mol) of sodium 7-(α-bromoacetamido)-cephalosporanate in 25 ml of water.

Stirring was continued an additional 90 minutes and then 50 ml of ethyl acetate was added. Forty percent H_3PO_4 was added dropwise with vigorous stirring until pH 2.5 to 3 was obtained. The product crystallized immediately and was filtered off, washed several times with water and then three times with 25 ml portions of ethyl acetate, following which it was air dried. The yield was 2.9 g of crystals that decomposed at 167° to 168°C. The IR and NMR spectra were consistent with the desired product, 7-[α-(2-pyrimidinylthio)acetamido]-cephalosporanic acid monohydrate.

An alternate route is that described in U.S. Patent 3,503,967 which uses ACA in the last step.

Another alternative route is that described in U.S. Patent 3,578,661 uses bromomethyl-cephalosporin as one raw material.

However the acid is prepared, the sodium salt may be prepared as described in U.S. Patent 3,503,967: Five liters of methylene chloride were added to a clean dry vessel equipped with stirrer. 7-[α(4-pyridylthio)acetamido] cephalosporanic acid (1,000 g) was added to the vessel, followed by 350 ml of triethylamine. The resultant solution was treated with decolorizing charcoal for 15 minutes and filtered. A solution of sodium-3-ethyl-hexanoate (27.3%) in butanol-methylene chloride was added to the filtrate with stirring. Seven thousand five hundred milliliters of acetone was added. Crystallization occurred while stirring was continued several hours under dry conditions. The crystals were collected by filtration, washed with large volumes of acetone, and then dried in vacuo at 50°C to yield about 950 g of the title compound.

References

Merck Index 1945
Kleeman & Engel p. 167
PDR p. 695
OCDS Vol. 2 p. 441 (1980)
DOT 9 (2) 56 (1973) & 10 (11) 299 (1974)
I.N. p. 197
REM p. 1187

Crast, L.B. Jr.; U.S. Patent 3,422,100; January 14, 1969; assigned to Bristol-Myers Company
Silvestri, H.H. and Johnson, D.A.; U.S. Patent 3,503,967; March 31, 1970; assigned to Bristol-Myers Company
Havranek, R.E. and Crast, L.B. Jr.; U.S. Patent 3,578,661; May 11, 1971; assigned to Bristol-Myers Company

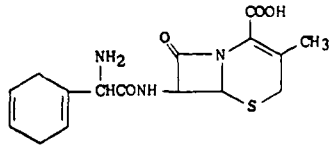
CEPHRADINE

Therapeutic Function: Antibiotic

Chemical Name: 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 38821-53-3

Trade Name	Manufacturer	Country	Year Introduced
Sefril	Squibb	Switz.	–
Eskacef	SKF	U.K.	1972
Velosef	Squibb	U.K.	1972
Sefril	Von Heyden	W. Germany	1973
Velocef	Squibb	Italy	1973
Velosef	Squibb	U.S.	1974
Anspor	SKF	U.S.	1974
Velosef	Squibb	France	1975
Eskacef	SKF	France	1975
Dicefalin	Nippon Squibb	Japan	1978
Cefro	Sankyo	Japan	1978
Lisacef	Lisapharma	Italy	1980
Askacef	SKF	–	–
Cefamid	Gibipharma	Italy	–
Cefosan	San Carlo	Italy	–
Cefradex	Ausonia	Italy	–
Cefrag	Magis	Italy	–
Cefro	Sankyo	Japan	–
Cefrum	San Carlo	Italy	–
Celex	Aristochimica	Italy	–
Cesporan	Errekappa	Italy	–
Citicel	C.T.	Italy	–
Dimacef	Dima	Italy	–
Ecosporina	Ecobi	Italy	–
Eskacef	SKF	Italy	–
Eskacef	SK Dauelsberg	W. Germany	–
Forticef	Godecke	W. Germany	–
Lisacef	Lisapharma	Italy	–

Trade Name	Manufacturer	Country	Year Introduced
Medicef	Medici	Italy	–
Megacef	Beytout	France	–
Noblitina	Juste	Spain	–
Protocef	Ripari-Gero	Italy	–
Samedrin	Savoma	Italy	–

Raw Materials

D-Phenylglycine
Methyl acetoacetate
3-Deacetoxy-7-aminocephalosporanic acid
Lithium
Ammonia

Manufacturing Process

In a first step, D-2-amino-2-(1,4-cyclohexadienyl)acetic acid is obtained as follows. A solution of 11.0 g (72.7 mmol) of D-phenylglycine in 900 ml distilled ammonia (which has been treated with 45 mg lithium after distillation to destroy traces of moisture) is slowly diluted with 370 ml dry tert-butyl alcohol.

Over a period of hours, 1.65 g lithium (3.27 eq) is added in small portions until a permanent blue color is obtained. The blue reaction mixture is then treated with 38 g of triethylamine hydrochloride. The ammonia is allowed to evaporate at room temperature overnight and the residual solvent is evaporated at reduced pressure. The white residue is taken up in a small amount of methanol-water and added to 4 liters of cold 1:1 chloroform-acetone to precipitate the crude product. After 20 minutes stirring the suspension is filtered and the white filter cake dried in vacuo; the filter cake is then pulverized and submitted once more to the precipitation process from 1:1 chloroform-acetone.

The white, crystalline product, 11.8 g, MP 297°C (dec), $[\alpha]_D$ -89.7° (2 N NaOH) is quantitatively obtained but is slightly contaminated with lithium chloride, 0.6% ionic chlorine being found by analysis.

The product of a second step is the methyl acetoacetic ester enamine of N-2-amino-2-(1,4-cyclohexadienyl)acetic acid sodium salt. 306 mg D-2-amino-2-(1,4-cyclohexadienyl)-acetic acid (2.00 mmol) are dissolved by warming in a solution of 108 mg of $NaOCH_3$ (2.00 mmol) in 4.3 ml reagent grade MeOH. 255 mg (0.24 ml, 2.20 mmol) methyl acetoacetate are added and the mixture refluxed for 45 minutes. The MeOH is almost totally stripped off in vacuo. Five milliliters benzene are added and distilled off to a small residual volume. The addition and distillation of benzene is repeated to insure complete removal of the MeOH and water. The product crystallizes out overnight from a small residual volume of benzene. It is filtered off, washed with benzene, and dried in vacuo. Yield 463 mg.

Then 3-deacetoxy-7-aminocephalosporanic acid is condensed with the abovedescribed sodium salt in the presence of triethylamine to give cephradine.

References

Merck Index 1947
Kleeman & Engel p. 175
PDR pp. 1703, 1771
OCDS Vol. 2 p. 440 (1980)
DOT 9 (3) 89 (1973)
I.N. p. 199
REM p. 1188
Weisenborn, F.L., Dolfini, J.E., Bach, G.G. and Bernstein, J.; U.S. Patent 3,485,819; December 23, 1969; assigned to E.R. Squibb & Sons, Inc.