C

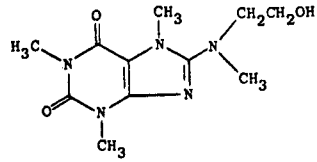
CAFAMINOL

Therapeutic Function: Nasal decongestant

Chemical Name: 3,7-Dihydro-8-[(2-hydroxyethyl)methylamino]-1,3,7-trimethyl-1H-purine-2,6-dione

Common Name: Methylcoffanolamine

Structural Formula:



Chemical Abstracts Registry No: 30924-31-3

Trade Name	Manufacturer	Country	Year Introduced
Rhinoptil	Promonta	W. Germany	1974
Rhinetten	Arzneimittelwerk Dresden	E. Germany	–

Raw Materials

8-Chlorocaffeine
β-N-methylaminoethanol

Manufacturing Process

21 g 8-chlorocaffeine and 15 g β-N-methylaminoethanol are heated to 140°-160°C for 30 minutes. Then the temperature is increased for 15-20 minutes to 165°-170°C. On cooling a colorless mass of crystals results. This is boiled with 50-60 ml ethanol and crystallized. Colorless crystals result which are soluble in water up to about 6%; pH of the aqueous solution is 6.9. The yield is 19 g while the MP is 162°-164°C.

References

Merck Index 1603
I.N. p. 173
Klosa, J.; U.S. Patent 3,094,531; June 18, 1963; assigned to Delmar Chemicals Ltd. (Canada)

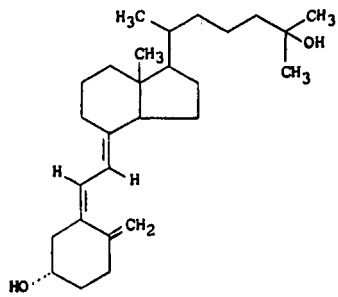
CALCIFEDIOL

Therapeutic Function: Regulator (calcium)

Chemical Name: 9,10-Secocholesta-5,7,10(19)-triene-3,25-diol

Common Name: 25-Hydroxyvitamin D_3; 25-Hydroxycholecalciferol

Structural Formula:



Chemical Abstracts Registry No.: 19356-17-3

Trade Name	Manufacturer	Country	Year Introduced
Dedrogyl	Roussel	France	1976
Delakmin	Roussel	W. Germany	1978
Calderol	Upjohn	U.S.	1980
Didrogyl	Roussel/Maestrett	Italy	1980
Dedrogyl	Hoechst	Switz.	1982
Hidroferol	Juventus	Spain	–
Calderol	Organon	U.S.	–

Raw Materials

Cholesta-5,7-diene-3β,25-diol

Manufacturing Process

A solution of 125 mg of cholesta-5,7-diene-3β,25-diol in 125 ml of benzene and 10 ml of absolute ethanol is placed in a photo reactor equipped with a quartz lampwell cooled with water and a nitrogen inlet. The reaction mixture is cooled to about 16°C, and purged with N_2. A Hanovia 8A36, 100-watt lamp, centered in the lampwell 2.5 cm from the internal surface of the reaction mixture, is turned on for 15 minutes, including the 5–6 minutes required for the lamp to reach full brilliance. The lamp is a typical actinic energy source suitable for the irradiation step in the known synthesis of Vitamin D, and can be replaced by any such available lamp. The specific lamp used is a 100-watt high-pressure quartz mercury-vapor lamp, producing approximately 11.5 watts total radiated energy distributed over the range of 220–1400 mμ. A fast stream of water is necessary to keep the outlet water temperature below 20°C. The reaction mixture is concentrated to dryness in a rotary evaporator below room temperature. The semisolid residue is triturated with 5 ml of 35% ethyl acetate-65% Skellysolve B hexanes mixture and filtered and another 5 ml of the same solvent is used for wash. The solid contains unreacted starting material and the liquor contains the product. The liquor is poured onto a 40 g column containing TLC grade Florisil, 150–200 mesh packed wet with 35% ethyl acetate-Skellysolve B hexanes, and the products are eluted with the same solvent mixture collecting 10 ml fractions. The fractions containing the product, located by spotting on a TLC plate, are combined and evaporated to dryness below room temperature to give an oily residue. A few drops of absolute ether are added and removed under vacuum to give 25-hydroxyprecholecalciferol as a fluffy foam; yield 60 mg.

A solution of about 300 mg of 25-hydroxyprecholecalciferol prepared as described above in 5 ml of chloroform is heated for 3½ hours at 70°–75°C under N_2 in a sealed flask. The solvent is evaporated and the residue is chromatographed through a 60 g column containing TLC grade Florisil, 150–200 mesh packed wet with 35% ethyl acetate in Skellysolve B hex-

anes. The column is eluted with the same solvent mixture, collecting 10 ml fractions. The fractions which crystallize on trituration with aqueous methanol are combined and recrystallized twice from aqueous methanol to give 25-hydroxycholecalciferol hydrate; yield 120 mg, MP 81°-83°C (sinters 75°C).

A solution of 20 mg of 25-hydroxycholecalciferol hydrate, prepared as described above, in 20 ml of methylene chloride is dried with 200 mg of anhydrous sodium sulfate. The solution is filtered and the filtrate is evaporated to yield 25-hydroxycholecalciferol essentially anhydrous as an amorphous oil.

References

Merck Index 1610
Kleeman & Engel p. 133
PDR p. 1285
OCDS Vol. 3 p. 101 (1984)
DOT 13 (6) 225 (1977)
I.N. p. 174
Babcock, J.C. and Campbell, J.A.; U.S. Patent 3,833,622; September 3, 1974; assigned to The Upjohn Company
Salmond, W.G.; U.S. Patent 4,001,096; January 4, 1977; assigned to The Upjohn Company

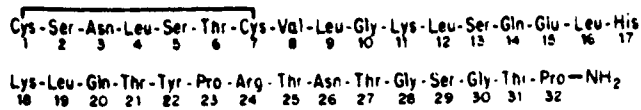
CALCITONIN

Therapeutic Function: Regulator (calcium)

Chemical Name: Complex hormone of molecular weight about 4,500

Common Name: Thyrocalcitonin

Structural Formula:



Chemical Abstracts Registry No.: 9007-12-9

Trade Name	Manufacturer	Country	Year Introduced
Calcitar	Yamanouchi	Japan	1978
Cibacalcin	Ciba Geigy	Switz.	1978
Elcitonin	Toyo Jozo	Japan	1981
Calcimar	Armour	U.S.	—
Calcitonin-Sandoz	Sandoz	Switz.	—
Calsyn	Armour	U.K.	—
Calsynar	Armour	U.K.	—
Miacalcic	Sandoz	Switz.	—
Staporos	Roussel	France	—

Raw Materials

C-cell-rich thyroid gland carcinoma

Manufacturing Process

The process for the manufacture of human calcitonin in pure form from C-cell rich medulla

carcinoma of the thyroid gland or from C-cell metastasis material is one wherein medullar carcinoma of the thyroid gland or C-cell metastasis material, which has been defatted, for example with acetone or ether, and which may have been first purified with alcohol or with aqueous trichloroacetic acid, is extracted one or more times with a solvent system containing water and an alkanol having at most 5 carbon atoms, at a pH of from about 1 to 6, and the extracted product subjected to gel chromatography using aqueous formic acid as eluant. The calcitonin may be separated into its constituents by countercurrent distribution, for example by Craig distribution using a solvent system advantageously containing n-butanol and acetic acid.

References

Merck Index 1611
DFU 8 (2) 105 (1983)
PDR p. 1809
DOT 14 (4) 139 (1978)
I.N. p. 174
REM p. 979
Ciba-Geigy A.G.; British Patent 1,270,595; April 12, 1972

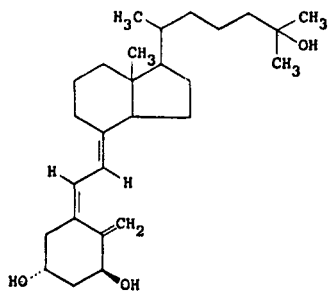
CALCITRIOL

Therapeutic Function: Calcium regulator

Chemical Name: 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol

Common Name: 1α,25-Dihydroxycholecalciferol; 1α,25-dihydroxyvitamin D_3

Structural Formula:



Chemical Abstracts Registry No.: 32222-06-3

Trade Name	Manufacturer	Country	Year Introduced
Rocaltrol	Roche	U.S.	1978
Rocaltrol	Roche	W. Germany	1980
Rocaltrol	Roche	U.K.	1980
Rocaltrol	Roche	Switz.	1980
Rocaltrol	Roche	Italy	1981

Raw Materials

1α,25-Diacetoxyprecholecalciferol
Potassium hydroxide

Manufacturing Process

1α,25-Dihydroxyprecholecalciferol: A solution of 1α,25-diacetoxyprecholecalciferol (0.712 g, 1.42 mmols), potassium hydroxide (2.0 g, 35.6 mmols) and methanol (40 ml) was stirred at room temperature under argon for 30 hours. The reaction mixture was concentrated under reduced pressure. Water (50 ml) was added to the residue and the mixture was extracted with methylene chloride (3 x 100 ml). The combined organic extracts were washed with saturated sodium chloride solution (3 x 50 ml), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give 0.619 g of 1α,25-dihydroxyprecholecalciferol as a thick oil.

1α,25-Dihydroxycholecalciferol: A solution of 1α,25-dihydroxyprecholecalciferol [0.619 g in dioxane (30 ml)] was heated under reflux for 30 minutes under an atmosphere of argon. The reaction mixture was concentrated under reduced pressure and the residue was purified with a Waters Associates liquid chromatograph model 202 using a 8 foot X 3/8 inch Porasil A column and a 5:1 mixture of ethyl acetate-n-hexane as the eluent to give 0.474 g (80% yield based on 1α,25-diacetoxyprecholecalciferol) of pure 1α,25-dihydroxycholecalciferol. Recrystallization from methyl formate afforded 0.340 g of 1α,25-dihydroxcholecalciferol as colorless crystals, MP 113°-114°C.

References

Merck Index 1612
Kleeman & Engel p. 134
PDR p. 1498
OCDS Vol. 3 p. 103 (1984)
DOT 16 (5) 149 (1980)
I.N. p. 175
REM p. 1012
Uskokovic, M.R., Narwid, T.A., Iacobelli, J.A. and Baggiolini, E.; U.S. Patent 3,993,675; November 23, 1976; assigned to Hoffmann-La Roche, Inc.

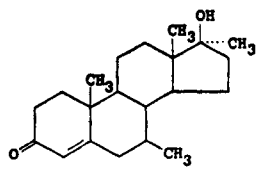
CALUSTERONE

Therapeutic Function: Antineoplastic

Chemical Name: 17β-hydroxy-7β,17-dimethylandrost-4-en-3-one

Common Name: 7,17-dimethyltestosterone

Structural Formula:



Chemical Abstracts Registry No.: 17021-26-0

Trade Name	Manufacturer	Country	Year Introduced
Methosarb	Upjohn	U.S.	1973
Riedemil	Upjohn	U.S.	–

Raw Materials

6-Dehydro-17-methyltestosterone
Methyl magnesium bromide

Manufacturing Process

As described in U.S. Patent 3,029,263, one possibility is a multistep synthesis starting from 3β,17β-dihydroxy-17α-methyl-5-androstene.

Alternatively, as described in U.S. Patent 3,341,557, 6-dehydro-17-methyltestosterone may be used as the starting material. A mixture of 0.4 g of cuprous chloride, 20 ml of 4 M methylmagnesium bromide in ether and 60 ml of redistilled tetrahydrofuran was stirred and cooled in an ice bath during the addition of a mixture of 2.0 g of 6-dehydro-17-methyltestosterone, 60 ml of redistilled tetrahydrofuran and 0.2 g of cuprous chloride. The ice bath was removed and stirring was continued for four hours. Ice and water were then carefully added, the solution acidified with 3 N hydrochloric acid and extracted several times with ether. The combined ether extracts were washed with a brine-sodium carbonate solution, brine and then dried over anhydrous magnesium sulfate, filtered and then poured over a 75-g column of magnesium silicate (Florisil) packed wet with hexanes (Skellysolve B). The column was eluted with 250 ml of hexanes, 0.5 liter of 2% acetone, two liters of 4% acetone and 3.5 liters of 6% acetone in hexanes.

Four 250-ml fractions were collected followed by 150 ml fractions. The residues from fractions 8 to 16 were combined and rechromatographed over a 125-g column of magnesium silicate. The solumn was eluted with 6% acetone in hexanes which was collected in 150 ml portions. Fractions 18 to 29 were combined and dissolved in acetone, decolorized with charcoal, and recrystallized from acetone. One gram of a crystalline mixture of the 7-epimers of 7,17-dimethyltestosterone was obtained melting at 120° to 140°C.

References

Merck Index 1701
Kleeman & Engel p. 138
OCDS Vol. 2 p. 154 (1980)
DOT 10 (3) 85 (1974)
I.N. p. 177
REM p. 1001
Campbell, J.A. and Babcock, J.C.; U.S. Patents 3,029,263; April 10, 1962 and 3,341,557; September 12, 1967; both assigned to The Upjohn Company

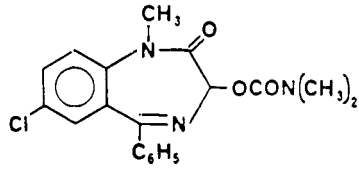
CAMAZEPAM

Therapeutic Function: Anxiolytic

Chemical Name: 3-N,N-dimethylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 36104-80-0

Trade Name	Manufacturer	Country	Year Introduced
Albego	Simes	Italy	1977

Trade Name	Manufacturer	Country	Year Introduced
Albego	Boehringer-Ingel.	W. Germany	1978
Albego	Inpharzam	Switz.	1978
Albego	Farmasimes	Spain	—
Limpidon	Crinos	Italy	—
Nebolan	—	—	—

Raw Materials

7-Chloro-5-phenyl-1-methyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepine-2-one
Phenyl chlorocarbonate
Dimethylamine

Manufacturing Process

A suspension of 100 g of 7-chloro-5-phenyl-1-methyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 700 ml of anhydrous pyridine, kept stirred between 0°C and +5°C, is slowly treated, during 20 to 30 minutes, with 54.5 ml phenyl chlorocarbonate. The temperature is gradually allowed to rise to 20°–25°C and stirring is maintained at this temperature during 24 hours.

2 ℓ of water are then slowly added (during about 30 minutes) and stirring is maintained during 1 hour. The precipitate which has been formed is collected on a filter, washed thoroughly with water, dried in a vacuo at 50°C and recrystallized by dissolving it at 60°C in 1,400 ml dioxane, the solution thus obtained being evaporated under reduced pressures to one-half of its volume, and 1,700 ml of ligroin (BP 80°C to 120°C) being added thereto.

7-chloro-5-phenyl-1-methyl-3-phenoxycarbonyloxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one is thus obtained, with a melting point of 162°C to 164°C.

A suspension of 45 g 3-phenoxycarbonyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 450 ml methanol is treated with stirring, with 43 ml of a solution of dimethylamine in methanol (containing 31 g dimethylamine in 100 ml). Stirring is maintained at 20°C to 25°C during 5 hours. The reaction mixture is filtered, and the filtrate is diluted with 450 ml water. The precipitate thus formed, is 3-(N,N-dimethylcarbamoyloxy)-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, which is collected on a filter, dried and recrystallized from ethyl acetate, and has a melting point of 173°C to 174°C.

References

Merck Index 1703
DFU 1 (10) 458 (1976)
Kleeman & Engel p. 139
DOT 11 (5) 182 (1975); 13 (12) 521 (1977)
I.N. p. 177
Ferrari, G. and Casagrande, C.; U.S. Patent 3,799,920; March 26, 1974; assigned to Siphar SA

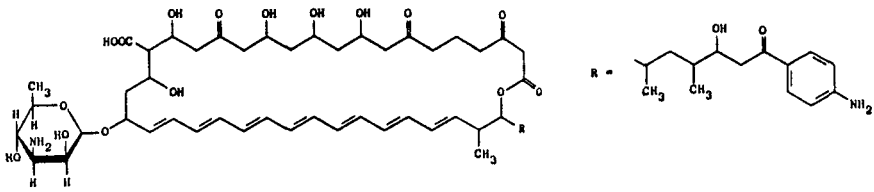
CANDICIDIN

Therapeutic Function: Topical antifungal

Chemical Name: Heptaene macrolide antibiotic

Common Name: —

Structural Formula: –



Chemical Abstracts Registry No.: 1403-17-4

Trade Name	Manufacturer	Country	Year Introduced
Candeptin	Schmid	U.S.	1964
Candimon	Ayerst	U.S.	–
Prostatin	Schmidt	U.S.	–
Vanobid	Merrell Dow	U.S.	–

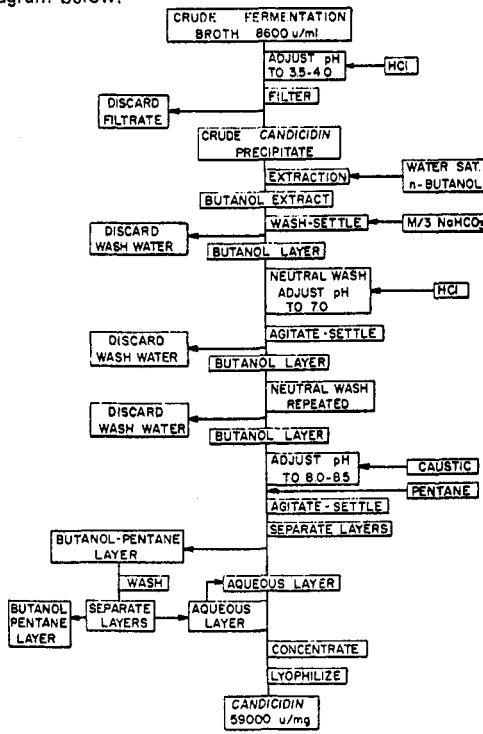
Raw Materials

Yeast-glucose medium

Streptomyces Griseus No. 3570 bacterium

Manufacturing Process

Hubert Lechevalier et al were the first to describe "Candicidin, a New Antifungal Antibiotic," in *Mycologia* XLV, No. 2, 155-171, March-April 1953. They produced candicidin by growing a culture of the organism *Streptomyces griseus* No. 3570 on a yeast-glucose medium, isolating a "crude candicidin" from the resulting broth and purifying it. An improved extraction and purification method is described in U.S. Patent 2,872,373 and is shown in the flow diagram below.



Another extraction and separation process is described in U.S. Patent 2,992,162.

References

I.N. p. 178
REM p. 1226
Siminoff, P.; U.S. Patent 2,872,373; February 3, 1959; assigned to S.B. Penick & Company, Inc.
Waksman, S.A. and Lechevalier, H.A.; U.S. Patent 2,992,162; July 11, 1961; assigned to Rutgers Research and Educational Foundation

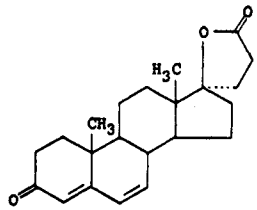
CANRENOATE POTASSIUM

Therapeutic Function: Aldosterone antagonist, Diuretic

Chemical Name: 17-hydroxy-3-oxo-17α-pregna-4,6-diene-21 carboxylic acid potassium salt

Common Name: —

Structural Formula: The corresponding lactone, canrenone, has the formula following.



(base)

Chemical Abstracts Registry No.: 2181-04-6; 976-71-6 (Canrenone base)

Trade Name	Manufacturer	Country	Year Introduced
Spiroctan	Boehringer-Mannheim	Switz.	1968
Soldactone	Diethelm	Switz.	1968
Osyrol	Hoechst	W. Germany	1968
Soludactone	Searle	France	1971
Venactone	Lepetit	Italy	1978
Spiroctan-M	MCP Pharm.	U.K.	1981
Soldacton	Dainippon	Japan	1981
Aldactone	Boehringer-Mannheim	W. Germany	—
Aldatense	Searle	France	—
Aldatense	Spa	Italy	—
Phanurane	Specia	France	—
Sincomen	Schering	W. Germany	—
Soldactone	Searle	U.S.	—

Raw Materials

17α-Carboxyethyl-17β-hydroxyandrost-4-en-3-one lactone
Chloranil

Manufacturing Process

The lactone is prepared as follows: A solution of 5 parts of 17α-carboxyethyl-17β-hydroxy-androst-4-en-3-one lactone and 5 parts of chloranil in 400 parts of xylene containing a trace of p-toluenesulfonic acid is heated at the boiling point of the solvent under reflux overnight. The solution is then cooled and filtered through approximately 200 parts of silica gel. The gel is successively washed with 5%, 10%, and 15% ethyl acetate-benzene

solutions, and the washings comprising 15% ethyl acetate are thereupon purified by chromatography on a further quantity of silica gel, using benzene and ethyl acetate as developing solvents. From the 15% ethyl acetate eluate there is obtained pure 17α-carboxyethyl-17β-hydroxyandrosta-4,6-dien-3-one lactone, melting at 148° to 151°C. The product solidifies above this melting point and melts again at 165°C.

References

Merck Index 1726
Kleeman & Engel p. 507
OCDS Vol. 2 p. 174 (1980)
DOT 12 (2) 45 (1976)
I.N. p. 178
Cella, J.A.; U.S. Patent 2,900,383; August 18, 1959; assigned to G.D. Searle & Co.

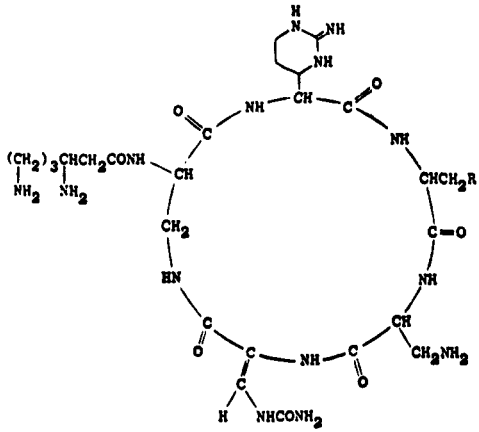
CAPREOMYCIN SULFATE

Therapeutic Function: Antitubercular

Chemical Name: Cyclic polypeptide antibiotic

Common Name: Caprolin

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1405-37-4 (Base = 11003-38-6)

Trade Name	Manufacturer	Country	Year Introduced
Capastat	Lilly	U.K.	1966
Capastat	Serum Impfinst	Switz.	1967
Ogostac	Lilly	W. Germany	1967
Capastat	Lilly	U.S.	1971
Capastat	Lilly	Italy	1973
Capastat	Shionogi	Japan	—

Raw Materials

Glucose
Culture of NRRL-2773 bacterium

Manufacturing Process

A culture of NRRL 2773 is produced by growing the organism on a nutrient agar slant having the following composition:

Oatmeal-Tomato Paste Agar

	Grams
Tomato paste	20
Precooked oatmeal	20
Agar	15
Tap water, added to make a final volume of 1 liter.	

The slant is inoculated with spores of NRRL 2773 and is incubated for 10 days at about 30°C. The culture growth on the slant is covered with 6 ml of nutrient broth, and the slant is scraped gently to remove the organisms to provide an aqueous suspension. Employing aseptic techniques, the inoculum obtained from one 1-inch agar slant is used to inoculate a 2-liter Erlenmeyer flask containing a 500-ml portion of a sterilized vegetative culture medium having the following composition: soluble starch, 10 g; peptones, 5 g; beef extract, 5 g; sodium chloride, 5 g; yeast extract, 2.5 g; and tap water, 1,100 ml. The incubation is carried on at 28°C for 48 hours with shaking at 250 cycles per minute on a rotary shaker having a 1-inch stroke.

To produce a larger quantity of vegetative inoculum, 500 ml of the vegetative inoculum is added aseptically to a stainless steel 350-gallon fermentation tank containing 250 gallons of sterile medium having the following composition (weight/volume): glucose, 1.5%; yeast, 1.5%; and antifoam (Polyglycol No. 2000, Dow Chemical Co.), 0.02%. The inoculum is allowed to grow for about 22 hours at a temperature of 30°C. Throughout the growth period, the medium is aerated with sterile air at the rate of 17 cfm and is agitated with two 16-inch impellers rotating at 160 revolutions per minute. To a 1,700-gallon stainless steel fermentor are added 1,100 gallons of a medium having the following composition (weight/volume):

Peptone No. 159 Medium

	Percent
Glucose	2.5
Molasses	1.0
Peptones	4.0
Calcium carbonate	0.2
Hydrolyzed casein	0.6
Antifoam (Polyglycol No. 2000, Dow Chemical Co.)	0.005

The medium after sterilization is inoculated with 100 gallons of the inoculum grown in the fermentation tank. The fermentation is carried on at 30°C for about five days. The foam is controlled by the addition, when needed, of Larex No. 1 (an antifoam product, Swift and Co.). Throughout the fermentation, the medium is aerated by the addition of sterile air at the rate of 96 cfm and is agitated with two 22-inch impellers operated at 140 revolutions per minute. At the end of the fermentation, 240 lb of Dicalite 476 (a perlite filter product, Great Lakes Carbon Corporation) are added to 1,000 gallons of the antibiotic broth, and the mixture is stirred and filtered. The filter cake is washed with tap water and the wash water and the filtrate are combined to provide a total volume of 1,000 gallons.

To 500 gallons of the combined liquids are added 132 lb of Darco G-60. The mixture is stirred thoroughly and filtered, and the filtrate is discarded. The carbon filter cake is washed with 200 liters of tap water, the wash water being discarded. The washed carbon cake on which the capreomycin is adsorbed is further washed with 200 liters of 0.05 N aqueous hydrochloric acid. The acid wash is discarded. The washed carbon cake is eluted during a one-hour period with 400 liters of an aqueous acetone mixture containing 1.65 liters of 11.7 N hydrochloric acid and 80 liters of acetone. The filter cake is further eluted by washing the cake with 200 liters of an aqueous acetone mixture containing 825 ml of 11.7 N hydrochloric acid and 40 liters of acetone during a 15-minute period. The combined eluates, having a total volume of 575 liters, are concentrated in vacuo to 52.5 liters.

The concentrate is added with stirring to 525 liters of acetone and the acetone mixture is permitted to stand overnight at room temperature, during which time an oily precipitate of capreomycin separates. The supernatant is decanted and discarded, and the oily precipitate which remains is dissolved in 20 liters of distilled water. The aqueous solution is concentrated in vacuo to 12 liters to remove any residual acetone. The aqueous concentrate containing capreomycin is filtered to remove a small amount of a precipitate, which is discarded.

The filtrate containing the capreomycin is added to 240 liters of methanol with stirring. The methanolic solution of capreomycin is acidified by the addition of one liter of 10 N sulfuric acid, whereupon the precipitation of the sulfuric acid addition salt of capreomycin commences. The mixture is permitted to stand overnight for more complete precipitation. The supernatant is removed by decanting and filtering. The precipitate, consisting of the capreomycin disulfate, is washed with 10 liters of methanol and is dried in vacuo. Yield: 2,510 grams.

References

Merck Index 1732
Kleeman & Engel p. 141
PDR p. 1039
DOT 1 (1) 33 (1965)
I.N. p. 179
REM p. 1202
Herr, E.B., Jr., Hamill, R.L. and McGuire, J.M.; U.S. Patent 3,143,468; August 4, 1964; assigned to Eli Lilly and Company

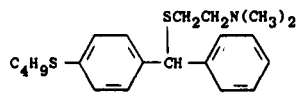
CAPTODIAMINE

Therapeutic Function: Sedative

Chemical Name: 2-[[[4-(Butylthio)phenyl] phenylmethyl] thio] -N,N-dimethylethanamine

Common Name: Captodiam; captodramine

Structural Formula:



Chemical Abstracts Registry No.: 486-17-9; 904-04-1 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Covatine	Bailly	France	1958
Suvren	Ayerst	U.S.	1958
Covatix	Lundbeck	Denmark	–

Raw Materials

p-Butylmercaptobenzhydryl chloride
Sodium hydroxide
Diethylaminoethyl chloride
Thiourea
Sodium metal

Manufacturing Process

p-Butylmercaptobenzhydryl chloride was boiled with thiourea in alcohol thereby yielding p-

butylmercaptobenzhydrylisothiouronium chloride which was then subjected to hydrolysis with dilute aqueous sodium hydroxide solution whereupon p-butylmercaptobenzhydryl mercaptan was formed.

p-Butylmercaptobenzhydryl mercaptan (28.5 g) was added to a solution of sodium (2.3 g) in absolute alcohol (75 ml), followed by the addition of a solution of diethylaminoethyl chloride (13.6 g) in toluene (50 ml). The mixture was boiled on a steam bath for 3 hours and the sodium chloride which separated out was removed by filtration. The filtrate was concentrated to one-third of its volume and dissolved in ether. The ether solution was shaken with 2N hydrochloric acid (100 ml), and the resulting middle oily layer was separated, dissolved in water and the resulting aqueous solution was washed with ether, then treated with aqueous sodium hydroxide solution to precipitate an oil. The latter was dissolved in ether, dried with anhydrous potassium carbonate, filtered and then treated with anhydrous hydrogen chloride whereupon the desired p-butylmercaptobenzhydryl 2-diethylaminoethyl sulfide hydrochloride precipitated as a white, crystalline substance which was filtered and dried in a desiccator. The melting point of the product was 124°C.

References

Merck Index 1746
Kleeman & Engel p. 141
OCDS Vol. 1 p. 44 (1977)
I.N. p. 179
Hubner, O.F. and Petersen, P.V.; U.S. Patent 2,830,088; April 8, 1958

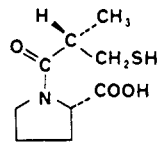
CAPTOPRIL

Therapeutic Function: Antihypertensive

Chemical Name: 1-(3-Mercapto-2-D-methylpropanoyl)-L-proline

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 62571-86-2

Trade Name	Manufacturer	Country	Year Introduced
Lopirin	Von Heyden	W. Germany	1980
Capoten	Squibb	U.S.	1981
Lopirin	Squibb	Switz.	1981
Capoten	Squibb	U.K.	1981
Capoten	Squibb	Italy	1981
Lopril	Squibb	France	1982
Captoril	Sankyo	Japan	1983
Dilabar	Vita	Spain	–
Isopresol	Elea	Argentina	–

Raw Materials

L-proline

Isobutylene

Benzyloxycarbonyl chloride	Hydrogen
3-Acetylthiomethyl propanoic acid	Ammonia
Trifluoroacetic acid	

Manufacturing Process

The first step is the manufacture of L-proline tert-butyl ester. L-proline (230 g) is dissolved in a mixture of water (1 ℓ) and 5 N sodium hydroxide (400 ml). The solution is chilled in an ice bath, and under vigorous stirring, 5 N sodium hydroxide (460 ml) and benzyloxycarbonyl chloride (340 ml) are added in five equal aliquots during a half-hour period. After one hour stirring at room temperature, the mixture is extracted twice with ether and acidified with concentrated hydrochloric acid. The precipitate is filtered and dried. Yield is 442 g; MP 78°C to 80°C.

The benzyloxycarbonyl-L-proline thus obtained (180 g) is dissolved in a mixture of dichloromethane (300 ml), liquid isobutylene (800 ml) and concentrated sulfuric acid (7.2 ml). The solution is shaken in a pressure bottle for 72 hours. The pressure is released, the isobutylene is allowed to evaporate and the solution is washed with 5% sodium carbonate, water, dried over magnesium sulfate and concentrated to dryness in vacuo, to obtain benzyloxycarbonyl-L-proline tert-butyl ester, yield 205 g.

Benzyloxycarbonyl-L-proline tert-butyl ester (205 g) is dissolved in absolute ethanol (1.2 ℓ) and hydrogenated at normal pressure with 10% Pd on carbon (10 g) until only a trace of carbon dioxide is observed in the hydrogen exit gas (24 hours). The catalyst is filtered off and the filtrate is concentrated in vacuo at 30 mm Hg. The residue is distilled in vacuo, to obtain L-proline tert-butyl ester, BP_{1mm} 50°C to 51°C.

The next step yields 1-(3-acetylthio-2-methylpropanoyl)-L-proline tert-butyl ester. L-proline tert-butyl ester (5.1 g) is dissolved in dichloromethane (40 ml) and the solution stirred and chilled in an ice bath. Dicyclohexylcarbodiimide (15 ml) is added followed immediately by a solution of 3-acetylthio-2-methylpropanoic acid (4.9 g) in dichloromethane (5 ml). After 15 minutes stirring in the ice bath and 16 hours at room temperature, the precipitate is filtered off and the filtrate is concentrated to dryness in vacuo. The residue is dissolved in ethyl acetate and washed neutral. The organic phase is dried over magnesium sulfate and concentrated to dryness in vacuo. The residue 1-(3-acetylthio-2-methylpropanoyl)-L-proline tert-butyl ester is purified by column chromatography (silica gel-chloroform), yield 7.9 g.

Then, 1-(3-acetylthio-2-methylpropanoyl)-L-proline is produced. The 1-(3-acetylthio-3-methylpropanoyl)-L-proline tert-butyl ester (7.8 g) is dissolved in a mixture of anisole (55 ml) and trifluoroacetic acid (110 ml). After one hour storage at room temperature the solvent is removed in vacuo and the residue is precipitated several times from ether-hexane. The residue (6.8 g) is dissolved in acetonitrile (40 ml) and dicyclohexylamine (4.5 ml) is added. The crystalline salt is boiled with fresh acetonitrile (100 ml), chilled to room temperature and filtered, yield 3.8 g, MP 187°C to 188°C. This material is recrystallized from isopropanol $[\alpha]_D$ -67° (C 1.4, EtOH). The crystalline dicyclohexylamine salt is suspended in a mixture of 5% aqueous potassium bisulfate and ethyl acetate. The organic phase is washed with water and concentrated to dryness. The residue is crystallized from ethyl acetate-hexane to yield the 1-(3-acetylthio-2-D-methylpropanoyl-L-proline, MP 83°C to 85°C.

Finally, Captopril is produced. The thioester (0.85 g) is dissolved in 5.5 N methanolic ammonia and the solution is kept at room temperature for 2 hours. The solvent is removed in vacuo and the residue is dissolved in water, applied to an ion exchange column on the H^+ cycle (Dowex 50, analytical grade) and eluted with water. The fractions that give positive thiol reaction are pooled and freeze dried. The residue is crystallized from ethyl acetate-hexane, yield 0.3 g. The 1-(3-mercapto-2-D-methylpropanoyl)-L-proline has a melting point of 103°C to 104°C.

References

Merck Index 1747
DFU 3 (11) 795 (1978)
Kleeman & Engel p. 142

PDR p. 1736
OCDS Vol. 3 p. 128 (1984)
DOT 17 (6) 233 (1981); 18 (10) 554 (1982)
I.N. p. 180
REM p. 850
Ondetti, M.A. and Cushman, D.W.; U.S. Patent 4,046,889; September 6, 1977; assigned to E.R. Squibb & Sons, Inc.
Ondetti, M.A. and Cushman, D.W.; U.S. Patent 4,105,776; August 8, 1978; assigned to E.R. Squibb & Sons, Inc.
Ondetti, M.A. and Cushman, D.W.; U.S. Patent 4,154,840; May 15, 1979; assigned to E.R. Squibb & Sons, Inc.

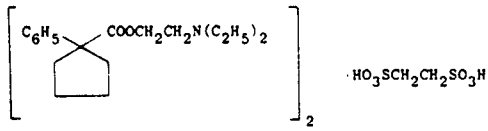
CARAMIPHEN EDISYLATE

Therapeutic Function: Antitussive

Chemical Name: 1-Phenylcyclopentanecarboxylic acid 2-(diethylamino)-ethyl ester 1,2-ethanedisulfonate

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 125-86-0

Trade Name	Manufacturer	Country	Year Introduced
Panparnit	Geigy	U.S.	1949
Toryn	Smith Kline	U.S.	1953
Tuss-Ade	Schein	U.S.	—
Tuss-Ornade	Smith Kline	U.S.	—

Raw Materials

1-Phenylcyclopentyl-1-carboxylic acid chloride
Diethylaminoethanol
Ethanedisulfonic acid

Manufacturing Process

20.8 parts of 1-phenyl-cyclopentyl-1-carboxylic acid chloride, obtained from the acid (cf. Am. Soc. 1934, 56, 715) by means of thionyl chloride, are dissolved in 250 parts by volume of absolute ether, then, while stirring and cooling with a mixture of common salt and ice a solution of 12 parts of diethylaminoethanol in 50 parts by volume of absolute ether is allowed to drop thereinto, the temperature being maintained below 0°C, whereupon stirring is continued during 2 hours at room temperature. The whole is then twice shaken out with water and once with diluted hydrochloric acid, the combined aqueous solutions are made alkaline with a potassium carbonate solution and shaken out with ether. The ethereal solution is washed with water, dried over potassium carbonate and the solvent is distilled off. The base boils at a pressure of 0.07 mm at 112°C to 115°C.

The base may then be converted to the hydrochloride or to the ethanedisulfonic acid salt (edisylate).

References

Merck Index 1750
PDR pp. 1606, 1730
OCDS Vol. 1 pg. 90 (1977)
I.N. p. 180
Martin, H. and Hafliger, F.; U.S. Patent 2,404,588; July 23, 1946; assigned to J.R. Geigy A.G. (Switzerland)

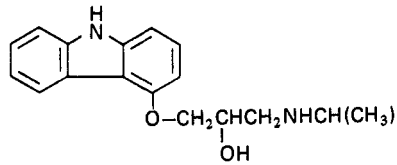
CARAZOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 4-(3-Isopropylamino-2-hydroxypropoxy)carbazole

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 57775-29-8

Trade Name	Manufacturer	Country	Year Introduced
Conducton	Klinge	W. Germany	1980

Raw Materials

Hydroxycarbazole
Epichlorohydrin
Isopropylamine

Manufacturing Process

The 4-(2,3-epoxypropoxy)carbazole used as starting material is prepared as follows. A solution of 16.3 g 4-hydroxycarbazole in a mixture of 190 ml dioxan and 98 ml 1 N sodium hydroxide is, after the addition of 66 ml epichlorohydrin, stirred for 2 hours at 40°C to 45°C. The reaction mixture is then diluted with water and shaken out with methylene chloride. The methylene chloride phase is washed with water, dried over anhydrous sodium sulfate and evaporated. There are obtained 16.8 g 4-(2,3-epoxypropoxy)carbazole.

A solution of 3.5 g 4-(2,3-epoxypropoxy)carbazole in 50 ml absolute alcohol is mixed with 30 ml isopropylamine and heated for 3 hours under reflux. When the reaction is finished, the reaction mixture is evaporated to dryness. The residue obtained is taken up in methylene chloride and chromatographed over an aluminum oxide column (300 g basic aluminum oxide, activity stage IV; eluent methylene chloride). The eluted fractions are evaporated and the residue is dissolved in methanol and acidified with 2 N ethereal hydrochloric acid.

The precipitate obtained is filtered off and recrystallized from methanol. There are obtained 3.1 g (62% of theory) 4-(3-isopropylamino-2-hydroxypropoxy)carbazole hydrochloride; MP 234°C to 235°C.

References

Merck Index 1753
DFU 2 (11) 715 (1977)
Kleeman & Engel p. 143
DOT 17 (2) 53 (1981) and 18 (10) 551 (1982)
I.N. p. 180
Boehringer Mannheim GmbH; British Patent 1,369,580; October 9, 1974

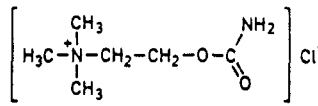
CARBACHOL

Therapeutic Function: *Cholinergic*

Chemical Name: 2-[(Aminocarbonyl)oxy]-N,N,N-trimethyl-ethanaminium chloride

Common Name: *Carbocholine*

Structural Formula:



Chemical Abstracts Registry No.: 51-83-2

Trade Name	Manufacturer	Country	Year Introduced
Miostat	Alcon	U.S.	1979
Atonyl	Ferrosan	Denmark	—
Cacholitin	Vaise	Denmark	—
Carbacel	Warner-Lambert	U.S.	—
Carbamiotin	Tilden-Yates	U.S.	—
Carbyl	Tubi Lux Farma	Italy	—
Carcholin	Merck Sharpe & Dohme	U.S.	—
Doryl	Merck	W. Germany	—
Iricoline	Lematte et Boinot	France	—
Isopto-Carbachol	Alcon	U.S.	—
Jestryl	Ankerwerk	E. Germany	—
Lentin	Merck	W. Germany	—
Lentivasan	Kwizda	Austria	—
Mistura	Lederle	U.S.	—
Moryl	Savory & Moore	U.K.	—
Oftan-Karbakol	Star	Finland	—
P.V. Carbachol	Allergan	U.S.	—
Rilentol	Richter	Austria	—
Secretin	Streuli	Switz.	—
Spersacarbachol	Dispersa	Switz.	—
Tonocholin	A.F.I.	Norway	—

Raw Materials

Choline chloride
Phosgene

Manufacturing Process

About 14 g of choline chloride are stirred with a solution of about 20 g of phosgene in 100 g of chloroform for about two hours at room temperature. The mixture becomes a two-phase liquid mixture. Hydrochloric acid and excess phosgene are removed by distillation in vacuo. Chloroform is added to the syrup, and the mixture is then added to a solution of excess ammonia in chloroform which was cooled with solid carbon dioxide-acetone. The mixture is

filtered, and the solid is extracted with hot absolute alcohol. The solid in the alcoholic solution is precipitated with ether, and filtered. It is recrystallized from a methyl alcohol-ether mixture; the carbaminoyl-choline chloride obtained has a melting point of about 208°-210°C.

References

Merck Index 1754
Kleeman & Engel p. 144
I.N. p. 180
REM p. 896
Major, R.T. and Bonnett, H.T.; U.S. Patent 2,374,367; April 24, 1945; assigned to Merck & Co., Inc.

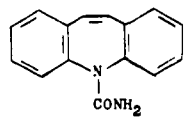
CARBAMAZEPINE

Therapeutic Function: Analgesic, Anticonvulsant

Chemical Name: 5H-dibenz[b,f]azepine-5-carboxamide

Common Name: 5-carbamyl iminostilbene

Structural Formula:



Chemical Abstracts Registry No.: 298-46-4

Trade Name	Manufacturer	Country	Year Introduced
Tegretal	Geigy	W. Germany	1964
Tegretol	Geigy	U.K.	1964
Tegretol	Geigy	France	1964
Tegretol	Geigy	U.S.	1968
Tegretol	Geigy	Italy	1972
Biston	Spofa	Czechoslovakia	—
Convuline	Protea	Australia	—
Finlepsin	Arzneimittelwerk Dresden	E. Germany	—
Hermolepsin	Laake	Finland	—
Lexin	Fujinaga	Japan	—
Mazepine	ICN	Canada	—
Neuritol	Eczacibasi	Turkey	—
Neurotol	Farmos	Finland	—
Nordotol	Farmos	Finland	—
Servimazepine	Servipharm	Switz.	—
Stazepine	Polfa	Poland	—
Telesmin	Yoshitomi	Japan	—
Temporol	Orion	Finland	—
Teril	Taro	Israel	—
Timonil	Desitin	W. Germany	—

Raw Materials

Iminostilbene
Phosgene
Ammonia

Manufacturing Process

19.3 parts of iminostilbene are dispersed in 100 parts by volume of toluene. Phosgene is then introduced whereupon the temperature of the reaction mixture rises to 70°C. While boiling under reflux, further phosgene is introduced until all the iminostilbene has dissolved and the hydrogen chloride development is complete. The reaction mixture is then cooled and the 5-chlorocarbonyl iminostilbene which has crystallized out is filtered off under suction. It melts at 168° to 169°C.

12.8 parts of 5-chlorocarbonyl iminostilbene are dispersed in 128 parts by volume of absolute ethanol and ammonia gas is introduced for three hours into this mixture while stirring at boiling temperature. The reaction is complete after this time; the reaction mixture is cooled and the crystals which precipitate are filtered off under suction. The ammonium chloride is washed from the crystals with water and the residue is recrystallized first from absolute ethanol and then from benzene. 5-carbamyl iminostilbene is obtained which melts at 204° to 206°C.

References

Merck Index 1758
Kleeman & Engel p. 144
PDR p. 900
OCDS Vol. 1 p. 403 (1977)
DOT 1 (3) 82 (1965)
I.N. p. 181
REM p. 1077
Schindler, W.; U.S. Patent 2,948,718; August 9, 1960; assigned to Geigy Chemical Corporation

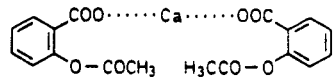
CARBASPIRIN CALCIUM

Therapeutic Function: Analgesic, antipyretic, antirheumatic

Chemical Name: 2-(Acetyloxy)benzoic acid calcium salt

Common Name: Calcium aspirin; calcium acetylsalicylate

Structural Formula:



Chemical Abstracts Registry No.: 69-46-3

Trade Name	Manufacturer	Country	Year Introduced
Calurin	Dorsey	U.S.	1959
Iromin	Iromedica	Switz.	—
Soluspan	UPSA	France	1983
Iromin	Omegin	W. Germany	—
Fiogesic	Sandoz	U.S.	—
Ursinus	Dorsey	U.S.	—

Raw Materials

Acetylsalicylic acid
Calcium carbonate

Manufacturing Process

500 g of finely powdered acetylsalicylic acid and 160 g of calcium carbonate (precipitated chalk), are intimately mixed and 3,000 cc of water are added. The mixture is stirred for 15 minutes or until the reaction is completed, which is indicated by the cessation of the liberation of carbon dioxide. The temperature is desirably maintained below 20°C by any suitable means. The mass is allowed to settle until the supernatant liquor is almost clear; this usually takes about 5 minutes, and the mixture is then filtered to remove unreacted material. This part of the process is carried out as quickly as possible so as to minimize any tendency of the calcium aspirin to hydrolyze in the solution. The filtrate is cooled to about 10°C and 1 to 1½ volumes of 97% methanol, or pure wood alcohol is added. This causes the calcium aspirin to precipitate and the mass is then filtered to remove as thoroughly as possible the mother liquor. The residue of calcium aspirin is then suspended in a quantity of methanol equivalent to the volume previously used as a precipitant, and it is allowed to stand there for one hour or more with occasional or continuous agitation. The mass is again filtered, the filtrate being employed for the precipitation of calcium aspirin in a later batch. After the filtering of the first wash liquor, the calcium aspirin is again suspended in another quantity of methanol of an equivalent volume. This constitutes the second wash and it is carried out in the same way as the first wash. The filtrate is employed as a first wash in a later batch and this filtrate in turn is used, as is the filtrate of the first wash, for the precipitation of more calcium aspirin. Fresh alcohol is used as a new wash in a later batch and the washes are carried out in series. After the second wash the calcium aspirin is dried in a suitable manner, as by passing dry warm air over it, the temperature not being allowed to rise to such an extent as to decompose the aspirin; preferably the temperature is not permitted to rise above 50°C, but should be high enough to avoid deposition of water vapor, and the drying is completed when there is no longer an odor of methanol.

References

Merck Index 1615
Kleeman & Engel p. 145
PDR p. 1583
Lawrence, W.H., Jr.; U.S. Patent 2,003,374; June 4, 1935; assigned to Lee Laboratories, Inc.

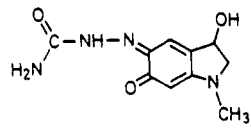
CARBAZOCHROME

Therapeutic Function: Hemostatic

Chemical Name: 3-Hydroxy-1-methyl-5,6-indolinedione semicarbazone

Common Name: Adrenochrome

Structural Formula:



Chemical Abstracts Registry No.: 69-81-8; 13051-01-9 (Salicylate)

Trade Name	Manufacturer	Country	Year Introduced
Adrenosem	Beecham	U.S.	1953
Adrestat	Organon	U.S.	1957
Adrenoxyl	Labaz	France	1957
Adrenoxyl	Nordmark	W. Germany	—

Trade Name	Manufacturer	Country	Year Introduced
Anaroxyl	Organon	U.S.	–
Cromosil	Zambeletti	Italy	–
Cromoxin	R. Rius	Spain	–
Meronyl	Santen	Japan	–

(Many other Trade Names also for Carbazochrome Salicylate and Carbazochrome Sodium Sulfonate)

Raw Materials

Adrenalin
Silver oxide
Semicarbazide hydrochloride

Manufacturing Process

A suspension containing 1 part by weight of adrenalin and 2 to 6 parts by weight of silver oxide in 150 to 250 parts by weight of methanol or ethanol is stirred for about 10 minutes. The alcoholic adrenochrome solution obtained is separated by draining and the filtrate is quickly evaporated to dryness at low temperature and in vacuo. The red crystals of adrenochrome obtained are dissolved in 45 to 55 parts by weight of water. To this solution, 2 parts of sodium acetate dissolved in 2 to 3 parts of water and 2 parts of semicarbazide hydrochloride dissolved in 2 to 3 parts of water are added. The formed precipitate consisting of red-orange prismatic needles is separated by filtration and recrystallized from diluted ethanol. There is obtained 0.30 to 0.40 part by weight of adrenochrome monosemicarbazone dihydrate, melting at 203°C with decomposition.

References

Merck Index 1767, 1768
Kleeman & Engel p. 146
I.N. p. 182
REM p. 832
Dechamps, G., Le Bihan, H. and Baudet, C.; U.S. Patent 2,506,794; May 2, 1950; assigned to Societe Belge de l'azote et des Produits Chimiques du Marly (Belgium)

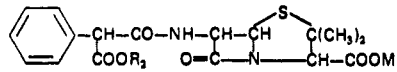
CARBENICILLIN DISODIUM

Therapeutic Function: Antibacterial

Chemical Name: N-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] hept-6-yl)-2-phenylmalonamic acid sodium salt

Common Name: Carboxybenzylpenicillin sodium salt

Structural Formula:



where R_2 and M are both Na.

Chemical Abstracts Registry No.: 4800-94-6; 4697-36-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pyopen	Beecham	Switz.	1968
Pyopen	Beecham	U.K.	1968

Trade Name	Manufacturer	Country	Year Introduced
Carindapen	Pfizer	W. Germany	1968
Pyopen	Beecham	U.S.	1970
Geopen	Roerig	U.S.	1970
Gripenin	Fujisawa	Japan	1970
Geopen	Pfizer Taito	Japan	1971
Pyocianil	Farmitalia	Italy	1972
Anabactyl	Beecham	W. Germany	—
Carbapen	C.S.L.	Australia	—
Carbecin	Beecham	—	—
Fugacillin	Astra	Sweden	—
Microcillin	Bayer	W. Germany	—
Rexcilina	Wolner	Spain	—

Raw Materials

Phenylmalonic acid
Benzyl alcohol
Thionyl chloride
6-Amino penicillanic acid
Hydrogen
Sodium bicarbonate

Manufacturing Process

The required monobenzyl phenylmalonate, MP 68°C, was prepared by treating a mixture of phenylmalonic acid (18 g) and benzyl alcohol (13 g) in carbon tetrachloride (80 ml) with dry hydrogen chloride.

Monobenzyl phenylmalonate (13.3 g) in dry benzene (100 ml) was refluxed with thionyl chloride (6.45 g) for 90 minutes, then concentrated in vacuo. The residual oil was dissolved in dry acetone (50 ml) and added to a stirred, ice-cooled solution of 6-aminopenicillanic acid (9.7 g) in N sodium bicarbonate solution (135 ml), water (150 ml), and acetone (300 ml). The mixture was stirred for 30 minutes at 0°C and then for 90 minutes at room temperature, then concentrated under reduced pressure to remove acetone. The aqueous solution was brought to pH 2 with dilute hydrochloric acid and extracted with ether (3 x 100 ml). The ether solution was washed with water and then itself extracted with sufficient N sodium bicarbonate solution to give an aqueous phase of pH 7.5. The aqueous layer was separated and evaporated at low temperature and pressure to leave the impure sodium salt of α-(benzyloxycarbonyl) benzylpenicillin.

This crude product (15.8 g) in water (360 ml) was added to a prehydrogenated suspension of 10% palladium on charcoal (4 g) in water (400 ml), and hydrogenation was continued for 30 minutes. The catalyst was removed and the filtrate was adjusted to pH 7.5 with sodium bicarbonate, then evaporated at low temperature and pressure. The residue was purified by chromatography on a column of cellulose powder, eluting first with butanol/ethanol/water mixture and then with acetone/isopropanol/water. The main fraction was evaporated at low temperature and pressure to give a 32% yield of the sodium salt of α-carboxybenzylpenicillin as a white powder. The product was estimated by manometric assay with penicillinase to be 58% pure.

References

Merck Index 1773
Kleeman & Engel p. 147
PDR p. 1404
OCDS Vol. 1 p. 414 (1977) & 2 p. 437 (1980)
DOT 4 (3) 96 (1968)
I.N. p. 183
REM p. 1194
Brain, E.G. and Nayler, J.H.C.; U.S. Patents 3,282,926; November 1, 1966 and 3,492,291; January 27, 1970; both assigned to Beecham Group Limited, England

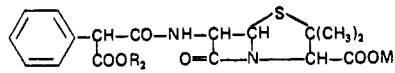
CARBENICILLIN INDANYL SODIUM

Therapeutic Function: Antibacterial

Chemical Name: N-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] hept-6-yl)-2-phenylmalonamic acid, 1-(5-indanyl ester), monosodium salt

Common Name: Carindacillin, Indanylcarbenicillin

Structural Formula:



where R_2 is 5-indanyl, M is Na.

Chemical Abstracts Registry No.: 26605-69-6; 35531-88-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Geocillin	Roerig	U.S.	1972
Carindapen	Pfizer	W. Germany	1973
Geopen	Pfizer	Switz.	1973
Geopen-U	Pfizer-Taito	Japan	1976
Unipen	Pfizer-Roerig	U.S.	—
Urobac	Pfizer-Roerig	—	—

Raw Materials

Phenylmalonic acid
5-Indanyl alcohol
6-Aminopenicillanic acid
Phosphorus pentachloride
Triethylamine

Manufacturing Process

(A) Preparation of Phenylchlorocarbonyl Ketene: To phenylmalonic acid (20 g) in ethyl ether (100 ml) there is added phosphorus pentachloride (46 g). A vigorous reaction occurs. The reaction mixture is refluxed for 4 hours then the ether partially removed by heating on a steam bath. The reaction mixture becomes black when about half the ether is removed and the remaining ether is removed under reduced pressure (at 100 mm). The residue is distilled under vacuum and the fraction boiling at 75° to 90°C at 1.5 to 4 mm collected. The product, a yellow liquid, is redistilled at 74°C and 1.5 mm. It shows a strong peak in the infrared region of the spectrum at 4.69 μ. Repetition of this procedure but using 10 g of phenylmalonic acid instead of 20 g produces a less vigorous reaction on addition of the phosphorus pentachloride. The same product is obtained.

(B) Acylation of 6-Aminopenicillanic Acid: To a solution of the aryl halocarbonyl ketene (0.1 mol) in methylene chloride (sufficient to provide a clear solution and generally from about 5 to 10 ml per gram of ketene) there is added the proper alcohol R_2OH (0.1 mol), in this case 5-indanyl alcohol. The reaction mixture is maintained under an atmosphere of nitrogen and stirred for a period of from 20 minutes to 3 hours, care being taken to exclude moisture. The temperature may range from about -70° to about -20°C. The infrared spectrum of the mixture is then taken to determine and confirm the presence of the ketene ester. A solution of 6-aminopenicillanic acid-triethylamine salt (0.1 mol) in methylene chloride (50 ml) is added and the mixture stirred at -70° to -20°C for 10 minutes. The cooling bath is then removed and the reaction mixture stirred continuously and allowed to warm to room temperature.

Various isolation methods are then spelled out in U.S. Patent 3,679,801.

References

Merck Index 1823
Kleeman & Engel p. 155
PDR p. 1524
DOT 8 (8) 310 (1972 & 9 (4) 128 (1973)
I.N. p. 189
REM p. 1195
Butler, K.; U.S. Patents 3,557,090; January 19, 1971; 3,574,189; April 6, 1971; and 3,679,801; July 25, 1962; all assigned to Chas. Pfizer & Co., Inc.

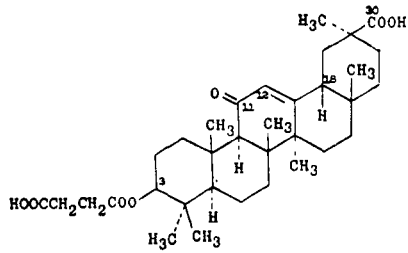
CARBENOXOLONE

Therapeutic Function: Antiinflammatory (Gastric)

Chemical Name: 3β-hydroxy-11-oxo-20β-olean-12-en-29-oic acid hydrogen butanedioate

Common Name: Glycyrrhetinic acid hydrogen succinate

Structural Formula:



Chemical Abstracts Registry No.: 5697-56-3; 7421-40-1 (Sodium salt)

Trade Name	*Manufacturer*	*Country*	*Year Introduced*
Biogastrone	Winthrop	U.K.	1963
Biogastrone	Homburg	W. Germany	1970
Gastrausil	Italseber	Italy	1971
Biogastrone	Richardson-Merrell	Switz.	1978
Biogastron	Shionogi	Japan	1979
Biogastrone	Abic	Israel	—
Bioral	Biorex, Berk	U.K.	—
Duogastrone	Merrell	France	—
Duogastrone	Abic	Israel	—
Karbenol	Yutoglu	Turkey	—
Neogel	Homburg	W. Germany	—
Neutrogastrol Ulcus	Septa	Spain	—
Pyrogastone	Winthrop	U.K.	—
Sanodin	Leo	Spain	—
Sustac	Sintyal	Argentina	—
Terulcon	ISF	Italy	—
Ulcofer	Mulda	Turkey	—
Ulcus-Tablinen	Sanorania	W. Germany	—
Ulkon	Eczacibasi	Turkey	—
Ventroxol	Medica	Finland	—

Raw Materials

Glycyrrhetinic acid

Succinic anhydride

Manufacturing Process

23.5 g of glycyrrhetinic acid were dissolved in 50 cc of dry pyridine. A solution of 6.0 g of succinic anhydride in 30 cc of dry pyridine was added, followed by 30 cc of dry triethylamine and then, for washing purposes, 5 cc of dry pyridine. The solution was heated on a boiling water bath for ten hours and then poured into excess of dilute hydrochloric acid and ice. The fine gray precipitate formed was filtered off, washed with water, dissolved in chloroform, and the solution repeatedly extracted with dilute hydrochloric acid and later with water. It was dried over sodium sulfate and evaporated to dryness. Crystallization from methanol, using charcoal to effect decolorization, gave the hydrogen succinate as cream-colored crystals, MP 291° to 294°C, with previous softening.

One molecular proportion of glycyrrhetinic acid hydrogen succinate was ground with a dilute (5%) aqueous solution containing two molecular proportions of sodium hydroxide. The solution was filtered and evaporated in vacuum over concentrated sulfuric acid. The sodium salt is then obtained as a creamy white water-soluble solid. Glycyrrhetinic acid is obtainable from licorice root.

References

Merck Index 1774
Kleeman & Engel p. 147
I.N. p. 183
Gottfried, S. and Baxendale, L.; U.S. Patent 3,070,623; December 25, 1962; assigned to Biorex Laboratories Limited, England

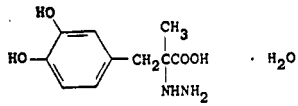
CARBIDOPA

Therapeutic Function: Muscle relaxant–Parkinsonism

Chemical Name: S-α-hydrazino-3,4-dihydroxy-α-methylbenzenepropanoic acid monohydrate

Common Name: Methyldopahydrazine

Structural Formula:



Chemical Abstracts Registry No.: 38821-49-7; 28860-95-9 (Anhydrous)

Trade Name	Manufacturer	Country	Year Introduced
Sinemet	Merck Sharp & Dohme	Italy	1974
Sinemet	Merck Sharp & Dohme	U.K.	1974
Nacom	Sharp & Dohme	W. Germany	1975
Sinemet	Chibret	France	1975
Lodosyn	Merck Sharp & Dohme	U.S.	1977
Menesit	Merck Banyu	Japan	1980
Neo-Dopaston	Sankyo	Japan	1980

Raw Materials

Vanillin
Nitroethane
Potassium cyanide
Hydrazine hydrate

Butylamine	Hydrogen chloride
Acetic acid	Hydrobromic acid
Iron	Hydrochloric acid

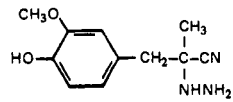
Manufacturing Process

To a solution of vanillin in toluene is added nitroethane, butylamine and glacial acetic acid. The mixture is refluxed and the water of reaction is steadily azeotropically removed by distillation. After the theoretical amount of water is distilled out, distillation is continued to remove excess reactants. The last trace of excess reactants is then removed at room temperature under a vacuum. The product is then triturated with a hydrocarbon solvent such as Skellysolve B and is thus obtained in a crystalline state. In general, however, it is preferred to dissolve the residue directly in toluene for use in the next step, without isolating the 1-(2-nitropropen-1-yl)-4-hydroxy-3-methoxybenzene.

A mixture of iron, ferric chloride and water is added to the toluene solution. The mixture is heated to reflux and concentrated hydrochloric acid is added dropwise at a rate calculated to keep the mixture refluxing vigorously. After the hydrochloric acid is all added, the refluxing is continued by the application of heat for several hours. A siliceous filter aid is then added to the cooled reaction mixture and the material is removed by filtration. The filter cake is washed four times, each time with 90 ml of benzene. The organic layer is then separated from the filtrate. The water layer is acidified to a pH of 2 and extracted three times with 90 ml portions of benzene.

These extracts are then combined with the organic solvent layer and the combined organic phase is extracted four times with 100 ml portions of water. It is then stirred for an hour with 230 ml of 10% sodium bisulfite solution. The organic solvent phase is then separated, washed seven times with 100 ml portions of water and dried over magnesium sulfate. Evaporation of the solvent gives 1-(4-hydroxy-3-methoxyphenyl)-2-propanone in the form of an oil.

A mixture of 59.5 g of that oily product, 1.85 liters of benzene and 1 kg of potassium bisulfite in 200 liters of water is stirred at room temperature for two hours. The precipitated bisulfite addition product of the ketone is isolated by filtration and washed with isopropanol and then with ether. Five hundred grams of the adduct is mixed with 119.5 g of potassium cyanide, 292 ml of 85% hydrazine hydrate and 910 ml of water. The mixture is stirred overnight at room temperature after which the product is isolated by filtration. The product is washed 3 times with 250 ml portions of water and then 3 times with 230 ml portions of ether. It is then air dried and vacuum dried at room temperature. The intermediate so produced has the following formula:



Fifty cubic centimeters of concentrated hydrochloric acid is saturated with hydrogen chloride gas at -10°C. To the solution is then added 2.5 g of the intermediate product, of the formula shown above, slowly with vigorous stirring. The mixture is allowed to stir overnight while warming at room temperature gradually. It is then concentrated in vacuo to a syrup. To the residual syrup is added 100 ml of 48% hydrobromic acid. The reaction vessel is purged with nitrogen and the reaction mixture is then refluxed for 3 hours after which it is concentrated in vacuo to a mixture of a syrup and a solid. The residue is taken up in sufficient water to form a clear solution. Activated charcoal is added and the mixture is heated to boiling and filtered.

The filtrate is concentrated to dryness in vacuo and the residue is taken up in 25 cc of ethanol. The residual ammonium bromide is removed by filtration and to the filtrate

there is added sufficient diethylamine to change the pH to 6.4. The mixture is warmed to 60°C and then cooled to room temperature. It is then allowed to stand overnight to effect complete crystallization. It is then cooled to 0°C and the product is isolated by filtration, washed with methanol and air dried. The product (α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)-propionic acid) is recrystallized once from water using a proportion of 15 cc water per gram of product.

References

Merck Index 1778
Kleeman & Engel p. 148
PDR p. 1210
OCDS Vol. 2 p. 119 (1980)
DOT 10 (9) 322 (1974)
I.N. p. 184
REM p. 929
Chemerda, J.M., Sletzinger, M. and Bollinger, F.W.; U.S. Patent 3,462,536; August 19, 1969; assigned to Merck & Co., Inc.

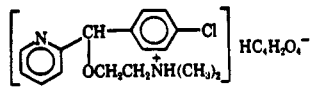
CARBINOXAMINE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: 2-[(4-chlorophenyl)-2-pyridinyl-methoxy] ,N,N-dimethylethanamine maleate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 3505-38-2; 486-16-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Clistin	McNeil	U.S.	1953
Allergefon	Lafon	France	1962
Polistin	Trommsdorf	W. Germany	1963
Cardec	Schein	U.S.	–
Cibelon	Taisho	Japan	–
Hislosine	Toho	Japan	–
Histex	Sigma	Australia	–
Histine	Pharbil	Belgium	–
Lergefin	Larma	Spain	–
Polistine	Pharbil	Netherlands	–
Rondec	Boss	U.S.	–
Ziriton	Importex	Italy	–

Raw Materials

p-Bromochlorobenzene
2-Pyridine aldehyde
2-Dimethylaminoethyl chloride
Magnesium
Sodium metal

Manufacturing Process

As described in U.S. Patent 2,800,485 a solution of p-chlorophenylmagnesium bromide is prepared by adding dropwise a solution of 230 g (1.2 mols) of p-bromochlorobenzene in 900 cc of anhydrous ether to 26.7 g (1.1 g-atoms) of magnesium suspended in 100 cc of anhydrous ether containing a small crystal of iodine. To this solution, 107 g (1 mol) of 2-pyridinealdehyde are added slowly with stripping at a rate to maintain refluxing. The reaction mixture is then stirred for one hour at room temperature. The mixture is then poured onto an equal volume of crushed ice and water and acidified with concentrated hydrochloric acid. The ether layer is removed. The aqueous layer is made basic with ammonia and extracted with ether. The ether solution is evaporated and the residue dried by addition of benzene and removal by distillation to give 208 g (95%) of solid α-(p-chlorophenyl)-2-pyridinemethanol melting at 78° to 80°C. The p-chlorophenyl pyridinemethanol may alternatively be prepared from 4-chloroacetophenone, pyridine and granular aluminum as described in U.S. Patent 2,606,195. In either case, the synthesis then proceeds as described in U.S. Patent 2,800,485.

A solution of 219 g (1 mol) of α-(p-chlorophenyl)-2-pyridinemethanol in one liter of dry toluene is heated to 100°C with stirring. Twenty-three grams (1 g-atom) of sodium are then added in portions. After all the sodium has reacted, a dried solution of 2-dimethylaminoethyl chloride in benzene is added. This benzene solution is prepared by dissolving 173 g (1.2 mols) of 2-dimethylaminoethyl chloride hydrochloride in the minimum amount of water, adding 500 cc of benzene followed by 300 g of sodium carbonate decahydrate, stirring, separating the benzene layer and drying.

The mixture is refluxed with stirring for ten hours, cooled and filtered. The filtrate is extracted three times with 200 cc portions of 6 N acetic acid. The aqueous acetic acid solution is then made strongly basic with 10% sodium hydroxide solution, and extracted three times with 200 cc portions of ether. The ether extract is dried with anhydrous sodium sulfate, stirred with 5 g of activated carbon and filtered to provide 2-[p-chloro-α(2-dimethylaminoethoxy)benzyl] pyridine in solution. Addition of a solution of 116 g (1 mol) of maleic acid in 1,500 cc of ether gives 323 g (79%) of solid which, on recrystallization from ethyl acetate, gives white solid 2-[p-chloro-α(2-dimethylaminoethoxy)benzyl] pyridine maleate melting at 117° to 119°C.

References

Merck Index 1780
Kleeman & Engel p. 150
PDR pp. 1561, 1606
OCDS Vol. 1 p. 43 (1977) and 2 p. 32 (1980)
I.N. p. 184
REM p. 1126
Tilford, C.H. and Shelton, R.S.; U.S. Patent 2,606,195; August 5, 1952; assigned to The Wm. S. Merrell Company
Swain, A.P.; U.S. Patent 2,800,485; July 23, 1957; assigned to McNeil Laboratories, Inc.

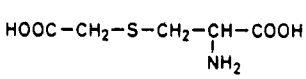
CARBOCYSTEINE

Therapeutic Function: Mucolytic; expectorant; nasal antiinfective

Chemical Name: S-(carboxymethyl)-L-cysteine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 638-23-3

Trade Name	Manufacturer	Country	Year Introduced
Rhinathiol	Kramer	Switz.	–
Rhinathiol	Jouille	France	1961
Mucodyne	Berk	U.K.	1963
Transbronchin	Homburg	W. Germany	1975
Lisomucil	Lirca	Italy	1975
Mucodyne	Kyorin	Japan	1981
Actithiol	Funk	Spain	–
Bronchette	Continental Ethicals	S. Africa	–
Bronchipect	Mepros	Netherlands	–
Bronchokod	Genekod	France	–
Broncodeterge	Valderrama	Spain	–
Carbocit	C.T.	Italy	–
Flemex	Parke Davis	U.S.	–
Fluifort	Lampugnani	Italy	–
Loviscol	Robins	U.S.	–
Muciclar	Parke Davis	U.S.	–
Mucocaps	Berk	U.K.	–
Mucocis	Crosara	Italy	–
Mucolex	Warner Lambert	U.S.	–
Mucopront	Mack	W. Germany	–
Mucosirop	Berk	U.K.	–
Mucospect	Lennon	S. Africa	–
Mucoliz	Yurtoglu	Turkey	–
Pectox	Infar-Nattermann	Spain	–
Pulmoclase	UCB	Belgium	–
Reodyn	Remeda	Finland	–
Reomucil	Tosi	Italy	–
Siroxyl	Sopar	Belgium	–
Solvopect	Mepros	Netherlands	–

Raw Materials

L-Cysteine
Sodium metal
Chloroacetic acid

Manufacturing Process

There were placed 120 g of L-cysteine (0.5 mol) in a 2 liter three-necked flask equipped with a stirrer thermometer and methanol/dry ice cooling and 1.5 liters of liquid ammonia were allowed to enter at -40°C. Then there were added under continuous cooling 50 g (2.17 mols) of sodium metal in portions of 1 to 2 g during the course of one hour. The end of the reaction was recognized by the continuation of the blue color. After the end of the reaction the excess sodium was destroyed by the addition of ammonium chloride and the ammonia vaporized at normal pressure. The residue was taken up in 500 ml of water and concentrated in a vacuum to 200 ml in order to remove residual ammonia, and again treated with 300 ml of water. The entire operations were carried out under a nitrogen atmosphere.

The aqueous solution of the disodium salt of L-cysteine obtained is then reacted at 20°C to 30°C under a nitrogen atmosphere in the course of 30 minutes with stirring with a solution of 104 g of chloroacetic acid (1.1 mols) and 4 g of sodium pyrosulfite in 200 ml of water. It is also allowed to post react for 15 minutes at 20°C, the solution clarified over activated carbon and the filtrate treated with 90 ml of concentrated hydrochloric acid to a pH of 2.5.

Thereby the S-carboxymethyl-L-cysteine precipitates out in crystalline form. The product is filtered off with suction, well stirred in 500 ml of water, again filtered with suction and dried in a vacuum at 70°C. The yield is 92% based on L-cysteine.

References

Merck Index 1785
Kleeman & Engel p. 151
I.N. p. 185
Maierhofer, A. and Wagner, H.; U.S. Patent 4,129,593; December 12, 1978; assigned to Deutsche Gold- und Silber-Scheideanstalt vormals Roessler (Germany)

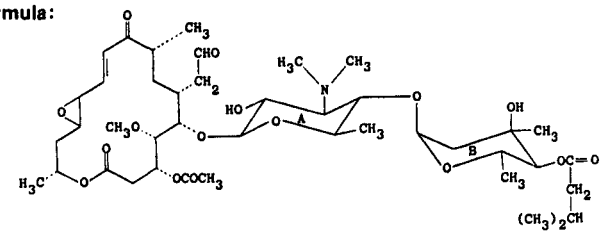
CARBOMYCIN

Therapeutic Function: Antibiotic

Chemical Name: 9-Deoxy-12,13-epoxy-9-oxo-leucomycin V-3-acetate-4^B-(3-methyl-butanoate)

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 4564-87-8

Trade Name	Manufacturer	Country	Year Introduced
Magnamycin	Pfizer	U.S.	1953

Raw Materials

Nutrient broth
Streptomyces halstedii bacterium

Manufacturing Process

A selected strain of *Streptomyces halstedii* was cultivated in an aqueous nutrient medium under aerobic conditions and the resulting broth containing carbomycin antibiotics was filtered. The solutions was extracted twice at pH 6.5 with one-quarter volume of methyl isobutyl ketone. The combined extracts were concentrated to one-tenth volume under vacuum, and the antibiotics were extracted into water adjusted to a pH of about 2 with sulfuric acid. After adjusting the separated aqueous solution to pH 6.5, the antibiotic was extracted into benzene and the solution was concentrated to a small volume. Addition of hexane resulted in the separation of a solid product containing the benzene complexes of carbomycin A and carbomycin B, present in the fermentation broth.

References

Merck Index 1790

I.N. p. 186
Tanner, F.W. Jr., Lees, T.M. and Routien, J.B.; U.S. Patent 2,771,392; November 20, 1956; assigned to Chas. Pfizer & Co., Inc.
Friedman, I.J., Martin, E.G., Taylor, R.J. and Wagner, R.L. Jr.; U.S. Patent 2,960,438; November 15, 1960; assigned to Chas. Pfizer & Co., Inc.

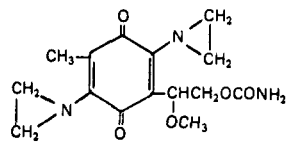
CARBOQUONE

Therapeutic Function: Antineoplastic

Chemical Name: 2,5-Bis(1-aziridinyl)-3-(1-methoxy-2-carbamoyloxyethyl)-6-methyl-1,4-benzoquinone

Common Name: Carbazilquinone

Structural Formula:



Chemical Abstracts Registry No.: 24279-91-2

Trade Name	Manufacturer	Country	Year Introduced
Esquinon	Sankyo	Japan	1974

Raw Materials

2-Methyl-5-(1-methoxy-2-carbamoyloxyethyl)-1,4-benzoquinone
Aziridine

Manufacturing Process

In 10 ml of ethanol was dissolved with heating 200 mg of 2-methyl-5-(1-methoxy-2-carbamoyloxyethyl)-1,4-benzoquinone and the resulting solution was cooled. To the cooled solution was added 0.5 ml of aziridine and then the resulting mixture was allowed to stand in a refrigerator at 5°C to 8°C for 4 days. Thereafter, the crystalline substance which precipitated *in situ was recovered by filtration and washed with ethanol to give 50 mg of the desired product* as red crystals melting at 200°C (with decomposition).

References

Merck Index 1806
Kleeman & Engel p. 151
DOT 11 (9) 344 (1975)
I.N. p. 186
Nakao, H., Arakawa, M. and Nakamura, T.; U.S. Patent 3,631,026; December 28, 1971; assigned to Sankyo Co., Ltd.

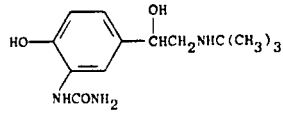
CARBUTEROL

Therapeutic Function: Bronchodilator

Chemical Name: [5-[2-[(1,1-Dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxyphenyl]urea

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 34866-47-2

Trade Name	Manufacturer	Country	Year Introduced
Bronsecur	SK&F	W. Germany	1980
Bronsecur	SK&F	Italy	1980
Pirem	Sasse	W. Germany	1982
Dilabron	Warner-Lambert	–	–
Rispan	SK&F	–	–

Raw Materials

3-Amino-4-benzyloxyacetophenone
Ammonia
N-Benzyl-N-t-butylamine
Phosgene
Bromine
Hydrogen

Manufacturing Process

A stirred solution of 40 g (0.41 m) of phosgene in 150 ml of toluene is held at 25°C with a cooling bath while a mixture of 25.2 g (0.105 m) of 3-amino-4-benzyloxyacetophenone and 220 ml of toluene are added slowly. The mixture is heated to reflux and continued for 30 minutes. Nitrogen is passed through the mixture and then concentrated in vacuo to give a crystalline isocyanate, MP 105°-106°C.

A stirred solution of the isocyanate (28.0 g) in 500 ml of dry benzene is saturated with ammonia. After one hour, the mixture is cooled to give the crystalline 4-benzyloxy-3-ureidoacetophenone, MP 184°-186°C.

To a stirred solution of 5.7 g (0.02 m) of 4-benzyloxy-2-ureidoacetophenone in 100 ml of chloroform is added 3.2 g (0.02 m) of bromine. The mixture is stirred at room temperature for about 45 minutes and the solution is concentrated in vacuo at 25°-30°C. The amorphous residue (hydrobromide salt of 4-benzyloxy-α-bromo-3-ureidoacetophenone) is dissolved in 80 ml of acetonitrile and 9.8 g (0.06 m) of N-benzyl-N-t-butylamine is added. The mixture is stirred and refluxed for 1.5 hours, then it is cooled to 0°C in an ice bath. Crystalline N-benzyl-N-t-butylamine hydrobromide is filtered. The filtrate is acidified with ethereal hydrogen chloride. The semicrystalline product is filtered after diluting the mixture with a large excess of ether. Trituration of the product with 60 ml of cold ethanol gives 4-benzyloxy-α-(N-benzyl-N-t-butylamino)-3-ureidoacetophenone hydrochloride, MP 200°-221°C (decomposition).

A solution of 10.5 g (0.0218 m) of 4-benzyloxy-α-(N-benzyl-N-t-butylamino)-3-ureidoacetophenone hydrochloride in 65 ml of methanol and 25 ml of water is added to a suspension of 1.5 g of 10% palladium-on-carbon in 10 ml of water. The mixture is hydrogenated on the Parr apparatus at room temperature, using an initial pressure of 60 psi of hydrogen. After 4 hours about 80% of the theoretical volume of hydrogen has been absorbed. The mixture is filtered, an additional 1.5 g of 10% palladium-on-carbon is added and the mixture is again hydrogenated on the Parr apparatus under the same conditions. After hydrogenating for an additional 3 hours, the mixture is filtered and the filtrate is concentrated in vacuo. The residue is stripped twice with toluene and crystallized with ether-ethanol to give α-(t-butylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol hydrochloride, MP 214°-215°C.

References

Merck Index 1817
DFU 1 (9) 412 (1976)
Kleeman & Engel p. 153
OCDS Vol. 2 p. 41 (1980)
DOT 12 (2) 483 (1976)
I.N. p. 187
Kaiser, C. and Ross, S.T.; U.S. Patent 3,763,232; October 2, 1973; assigned to Smith Kline & French Laboratories
Kaiser, C. and Ross, S.T.; U.S. Patent 3,917,847; November 4, 1975; assigned to Smith Kline Corp.

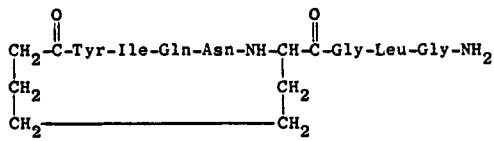
CARGUTOCIN

Therapeutic Function: Oxytoxic

Chemical Name: 1-Butanoic acid-7-glycine-1,6-dicarbaoxytocin

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 33065-67-3

Trade Name	Manufacturer	Country	Year Introduced
Statocin	Yoshitomi	Japan	1982

Raw Materials

Cyclic polypeptide
Hydrogen

Manufacturing Process

To a suspension of Z-Tyr(Bz)-Ile-Gln-Asn-Asu(OTCP)-Gly-Leu-Gly-NH_2 (1,310 mg) in DMF (350 ml) is added a suitable amount of palladium black. Hydrogen gas is introduced with stirring at room temperature (25°C) for about 40 hours. After stirring the mixture at 30°-35°C for several hours, the catalyst is filtered off and the filtrate is concentrated under reduced pressure. A large amount of ether is added to the residue, and the white coagulum is collected by filtration, washed with ether and dried. This is dissolved in water (30 ml), and the solution is filtered. The filtrate is passed through a column (3 x 11.5 cm) of Amerlite IR-45 (OH-form). The fractions which show a UV-absorption maximum at 280 mμ are combined and passed through a column (3 x 12.5 cm) of CM-Sephadex C-25 to remove the noncyclic compound and obtain neutral parts. The detection of the objective compound is made by UV-absorption at 280 mμ. The aqueous solution of the neutral parts is concentrated below 35°C, under reduced pressure, and the concentrate is lyophilized to give 504 mg of the crude title compound in the form of 5 hydrate.

References

Merck Index 1822

DFU 8 (3) 188 (1983)
DOT 19 (3) 130 (1983)
Sakakibara, S. and Yamanaka, T.; U.S. Patent 3,749,705; July 31, 1973; assigned to Yoshitomi Pharmaceutical Industries Ltd. (Japan)

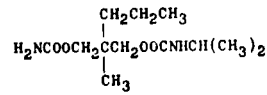
CARISOPRODOL

Therapeutic Function: Skeletal muscle relaxant

Chemical Name: (1-methylethyl)carbamic acid 2-([(aminocarbonyl)oxy] methyl)-2-methylpentyl ester

Common Name: Isopropyl meprobamate

Structural Formula:



Chemical Abstracts Registry No.: 78-44-4

Trade Name	Manufacturer	Country	Year Introduced
Soma	Wallace	U.S.	1959
Rela	Schering	U.S.	1959
Sanoma	Heilit	W. Germany	—
Flexartal	Clin Midy	France	1961
Caprodat	Ferrosan	Denmark	—
Carisol	AFI	Norway	—
Carisoma	Wallace	U.S.	—
Diolene	Pharma. Farm. Spec.	Italy	—
Erbasoma	Erba	Italy	—
Meprodat	Star	Finland	—
Mioril	Rossini	Italy	—
Mioxom	Dessy	Italy	—
Myobutazolidin	Fujisawa	Japan	—
Relasom	Rafa	Israel	—
Relaxo-Powel	Erba	Italy	—
Soma	Horner	Canada	—
Soma	Guidotti	Italy	—
Somadril	Dumex	Denmark	—
Somalgit	Wallace	U.S.	—
Somalgit Simple	Inibsa	Spain	—
Somanil	Banyu	Japan	—
Soprodol	Schein	U.S.	—

Raw Materials

2-Methyl-2-propyl-1,3-propanediol
Isopropylamine
Phosgene
Sodium Cyanate

Manufacturing Process

A cooled 10% solution of 1 mol of phosgene in toluene was added with stirring to a cooled solution of 1 mol of 2-methyl-2-propyl-1,3-propanediol and 2 mols of dimethylaniline also dissolved in toluene, at such a rate that the temperature of the mixture was maintained at about 25°C. The mixture was allowed to remain at this temperature for several hours, then

cooled and extracted with cold 5% hydrochloric acid solution to remove the dimethylaniline. The toluene layer was dried using a suitable drying agent and the 2-methyl-2-propyl-3-hydroxypropyl chlorocarbonate used in subsequent reactions in the form of its solution in anhydrous toluene.

A quantity of solution obtained as described containing 0.1 mol of the chlorocarbonate was treated with 0.2 mol of anhydrous isopropylamine and allowed to react at ordinary room temperature. The solution was cooled, extracted with dilute hydrochloric acid and the organic layer concentrated by evaporation of the solvent. The crude monocarbamate was purified by distilling at 86° to 88°C at about 0.01 mm. It was a clear, viscous liquid.

21.7 g (0.1 mol) of N-isopropyl-2-methyl-2-propyl-3-hydroxypropyl carbamate and 7.5 g (0.11 mol) of anhydrous sodium cyanate are stirred in 200 ml anhydrous chloroform in a suitable vessel equipped with a gas inlet tube, stirrer and thermometer. While cooling the vessel, anhydrous hydrogen chloride is passed into the stirred mixture slowly for 5 hours maintaining the temperature between 0° and 5°C. Alternatively ethyl urethane in the presence of aluminum isopropylate as a catalyst may be used in place of the sodium cyanates and HCl. The mixture is then allowed to stand at room temperature overnight.

The solid material is separated by filtration and the chloroform solution concentrated to an oil under reduced pressure. The oil is dissolved in 50 ml of trichloroethylene, the solution treated with charcoal, filtered and the filtrate added to 125 ml of hexane. The crystalline material which forms on standing at refrigerator temperature is removed by filtration, washed with light petroleum ether and dried at about 50°C. Approximately 20 g of product are obtained. On recrystallizing from trichloroethylene-hexane, 17.8 g of purified compound are obtained, MP 89° to 91°C.

References

Merck Index 1824
Kleeman & Engel p. 155
PDR pp. 830, 1606, 1883
OCDS Vol. 1 p. 219 (1977)
I.N. p. 189
REM p. 926
Berger, F.M. and Ludwig, B.J.; U.S. Patent 2,937,119; May 17, 1960; assigned to Carter Products, Inc.

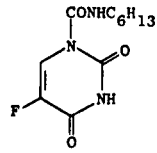
CARMOFUR

Therapeutic Function: Antineoplastic

Chemical Name: 5-Fluoro-N-hexyl-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinecarboxamide

Common Name: HCFU

Structural Formula:



Chemical Abstracts Registry No.: 61422-45-5

Trade Name	Manufacturer	Country	Year Introduced
Mifurol	Mitsui	Japan	1981
Yamafur	Yamanouchi	Japan	1981

Raw Materials

5-Fluorouracil
n-Hexyl isocyanate

Manufacturing Process

13.0 g (0.10 mol) of 5-fluorouracil was suspended in 60 ml of dimethyl acetamide, then 14.0 g (0.11 mol) of n-hexyl isocyanate was added thereto at room temperature and stirred at 50°C for 8 hours. After the reaction mixture was concentrated under reduced pressure, the residue was poured into 400 ml of water and resultant precipitate was filtered off. The precipitate was washed and dried and 19.3 g (75.0% yield) of 5-fluoro-1-(n-hexylcarbamoyl)uracil was obtained.

The product was recrystallized from ether and there were obtained white crystals melting at 283°C (decomposition).

References

Merck Index 1828
DFU 1 (4) 235 (1982)
DOT 18 (9) 424 (1982)
I.N. p. 190
Ozaki, S. and Mori, H.; U.S. Patent 4,071,519; January 31, 1978; assigned to Mitsu Toatsu Chemicals, Inc.

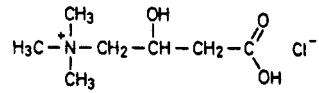
CARNITINE

Therapeutic Function: Gastric and pancreatic stimulator

Chemical Name: 3-Carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium hydroxide, inner salt

Common Name: —

Structural Formula:



Carnitin
(Hydrochlorid)

Chemical Abstracts Registry No.: 461-06-3; 5842-94-8 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Flatistine	Sauba	France	1978
Carnetina	Sigma Tau	Italy	1981
Nefrocarnit	Nefro Pharma	W. Germany	1983
Carnitene	Refarmed SA	Switz.	1983
Abedine	Nippon Zoki	Japan	—
Bicarnesine	Labaz	France	—
Carn	Benvegna	Italy	—

Trade Name	Manufacturer	Country	Year Introduced
Carnitan	Kakenyaku	Japan	–
Carnitine	Tyson	U.S.	–
Carnitolo	Sirt-B.R.P.	Italy	–
Entomin	Maruko	Japan	–
Metina	Francia Farm	Italy	–
Monocamin	Tanabe	Japan	–
Polycartin	Daigo Eiyo	Japan	–

Raw Materials

Trimethylamine
Sodium cyanide
Epichlorohydrin
Hydrogen chloride

Manufacturing Process

9.3 g of epichlorohydrin was added at a temperature of 40°-50°C under stirring to 9.6 g of trimethylamine hydrochloride dissolved in 10 cc of water. Continuing the reaction for an hour at the above temperature, the reaction product was concentrated under reduced pressure to obtain the crystals of 3-chloro-2-oxypropyl trimethyl ammonium chloride which were recrystallized with 25 cc of ethanol. The crystals obtained by concentrating the mother liquor were also recrystallized. The yield was 17.4 g (MP 190°C, yield 91.5%). This substance occurs as white, somewhat hygroscopic crystals and is readily soluble in water or alcohol, but insoluble in benzene, toluene, ether, acetone or chlorororm.

The result of analysis assuming $(C_6H_{15}C_{10}N)^+Cl^-$—calculated value: N, 7.45%; total Cl, 37.7%; Cl^-, 18.88%. Observed value: N, 7.36%; total Cl, 37.54%; Cl^-, 18.98%.

18.8 g of 3-chloro-2-oxypropyl trimethyl ammonium chloride was dissolved in a mixed solvent composed of 19 cc of methanol and 1 cc of water. 5.1 g of sodium cyanide dissolved in 8 cc of water was dropped into the solution at 50°C under stirring. After dropping, the mixture was held at this temperature for 30 minutes under stirring. The reaction product was then neutralized with 6N hydrochloric acid toward pH 5, and, after cooling, sodium chloride separated out and was filtered. The filtrate was concentrated to dryness under reduced pressure, and the residue was washed with small quantity of ethanol. Drying the residue, dissolving in hot methanol, filtering off insoluble matters, and cooling mother liquor, the crystals of 3-cyano-2-oxypropyl trimethyl ammonium chloride which deposited out were filtered and dried. Yield 16.7 g [MP (decomposition) 220°-223°C, yield 93.4%].

12.5 cc of concentrated hydrochloric acid was added to 17.9 g of 3-cyano-2-oxypropyl trimethyl ammonium chloride. Gradually heating the mixture on a water bath under stirring, so bringing the temperature up to 98°C at the end of about 3 hours, 9 cc of water was added. After cooling, free hydrochloric acid was neutralized with 3 cc of 6N sodium hydroxide, and then by adding 1 g of active charcoal, the reaction product was decolorized and filtered. The filtrate was concentrated to almost dryness under reduced pressure. Then, this concentrate was, after washing with 10 cc of ethanol, dried. Yield 24.7g.

The dried product was dissolved in 46.5 cc of glacial acetic acid by heating on a boiling water bath. The insoluble matter is removed by filtering hot, and on cooling the mother liquor, crystals of carnitine hydrochloride separated out. The crystals were filtered, washed with 10 cc of ethanol, and dried. Recrystallizing 19.7 g of the crude carnitine with methanol, 17 g of the refined carnitine was obtained [MP 195°-198°C (decomposing point), yield 86%]. The overall yield of the refined carnitine through whole steps was about 74%. Carnitine thus prepared was an odorless, white, crystalline powder, having a strong acid taste.

References

Merck Index 1833
Kleeman & Engel p. 156
PDR p. 1807

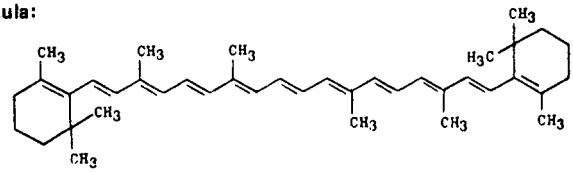
DOT 19 (4) 185 (1983)
I.N. p. 190
Noguchi, J. and Sakota, N.; U.S. Patent 3,135,788; June 2, 1964; assigned to Nihon Zoki Seiyaku Kabushikikaisha (Japan)

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