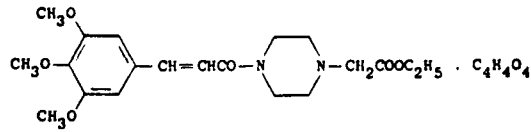
CINEPAZET MALEATE

Therapeutic Function: Antianginal

Chemical Name: 4-[1-Oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-1-piperazineacetic acid ethyl ester (Z)-2-butenedioate (1:1)

Common Name: Ethyl cinepazate maleate

Structural Formula:



Chemical Abstracts Registry No.: 50679-07-7; 23887-41-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Vascoril	Delalande	France	1971
Vascoril	Delalande	Italy	1974

Raw Materials

1-Piperazino ethyl acetate
3,4,5-Trimethoxy cinnamoyl chloride
Sodium bicarbonate
Maleic acid

Manufacturing Process

A solution of 1-piperazino ethyl acetate (0.2 mol) in benzene (300 ml) is treated with 3,4,5-trimethoxy cinnamoyl chloride (0.2 mol) in the presence of sodium bicarbonate (0.3 mol). After contacting for one hour at room temperature, the mixture is refluxed for a further hour. The benzene solution is then treated with an aqueous solution of sodium bicarbonate. After evaporation of the solvent, a solid product is obtained which is recrystallized from isopropyl ether. Melting point = 96°C. This base, when treated with hydrochloric acid, gives a hydrochloride having a melting point of 200°C with decomposition. By the action of maleic acid the acid maleate is obtained, having a melting point of 130°C.

References

Merck Index 2266
Kleeman & Engel p. 210
OCDS Vol. 3 p. 157 (1984)
DOT 10 (12) 336 (1974)
I.N. p. 233
Fauran, C., Huguet, G., Raynaud, G., Pourrias, B. and Turin, M.; U.S. Patent 3,590,034; June 29, 1971; assigned to Delalande S.A. (France)

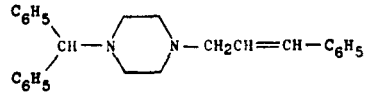
CINNARIZINE

Therapeutic Function: Antihistaminic

Chemical Name: 1-(diphenylmethyl)-4-(3-phenyl-2-propenyl)piperazine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 298-57-7

Trade Name	Manufacturer	Country	Year Introduced
Stugeron	Janssen	U.K.	1961
Stutgeron	Janssen	W. Germany	1961
Midronal	Delalande	France	1962
Sturgeron	Janssen	Italy	1970
Aplactan	Janssen	Belgium	1970
Stugeron	Cilag-Chemie	Switz.	1980
Amynoral	Delalande	France	—
Annarizine	Sioe	Japan	—
Antigeron	Farmasa	Brazil	—
Aplactan	Eisai	Japan	—
Aplexal	Taiyo	Japan	—
Apomiterl	Teizo	Japan	—
Apotomin	Kowa	Japan	—
Apsatan	Wakamoto	Japan	—
Artate	Nippon Chemiphar	Japan	—
Carecin	Zensei	Japan	—
Cerebolan	Tobishi	Japan	—
Cerepar	Merckle	W. Germany	—
Cero-Aterin	Chassot	Switz.	—
Cinaperazine	Kinki	Japan	—
Cinazin	Siegfried	Switz.	—
Cinazyn	Italchimici	Italy	—
Cinnabene	Merckle	W. Germany	—
Cinnacet	Schwarzhaupt	W. Germany	—
Cinnageron	Streuli	Switz.	—
Cinnarizine	Green Cross	Japan	—
Cinnipirine	A.C.F.	Neth.	—
Coldrin	J&J	U.S.	—
Corathiem	Ohta	Japan	—
Cysten	Tsuruhara	Japan	—
Denapol	Teikoku	Japan	—
Dismaren	Gerardo Ramon	Argentina	—
Ederal	Esteve	Spain	—
Eglen	Tatsumi	Japan	—
Folcodal	Syncro	Argentina	—
Giganten	Tropen	W. Germany	—
Glanil	Leo	Sweden	—
Hilactan	Kyoritsu	Japan	—
Hirdsyn	Fuso	Japan	—
Izaberizin	Tohu	Japan	—
Katoseran	Hishiyama	Japan	—
Midronal	Delalande	France	—
Milactan	Miwa	Japan	—
Myodel	Delalande	France	—
Olamin	Siegfried	Switz.	—
Pericephal	Hofmann	Austria	—
Plegitux	Carrion	France	—
Processine	Sankyo	Japan	—
Purazine	Lennon	S. Africa	—
Razlin	S.S. Pharm.	Japan	—
Ribrain	Endopharm	W. Germany	—

Trade Name	Manufacturer	Country	Year Introduced
Roin	Maruishi	Japan	–
Salarizine	Iwaki	Japan	–
Sapratol	Takeda	Japan	–
Sedatromin	Takata	Japan	–
Sefal	Nobel	Turkey	–
Sigmal	Fuji Zoki	Japan	–
Siptazin	Isei	Japan	–
Spaderizine	Kotobuki	Japan	–
Stunarone	Abic	Israel	–
Toliman	Corvi	Italy	–
Tolesmin	Sato	Japan	–
Torizin	Towa	Japan	–

Raw Materials

Cinnamoyl chloride
Benzhydryl piperazine
Lithium aluminum hydride

Manufacturing Process

This compound can be prepared by the reaction of cinnamoyl chloride with benzhydryl-piperazine. The reaction is carried out in dry benzene under reflux. The benzene is then evaporated, the residue taken up in chloroform, washed with dilute HCl and then made alkaline.

The chloroform layer is washed with a dilute aqueous sodium hydroxide solution, thereafter with water, and is finally dried over potassium carbonate. The residue, which is obtained after evaporation of the chloroform, is dissolved by heating in a mixture of 25% of toluene and 75% of heptane. On cooling this solution to about 20°C the product precipitates. That compound is reduced with $LiAlH_4$ to give cinnarizine.

References

Merck Index 2281
DFU 3 (8) 572 (1978)
Kleeman & Engel p. 272
OCDS Vol. 1 p. 58 (1977)
DOT 16 (10) 360 (1974) & 18 (1) 27 (1982)
I.N. p. 234
Janssen, P.A.J.; U.S. Patent 2,882,271; April 14, 1959; assigned to Laboratoria Pharmaceutica Dr. C. Janssen, Belgium

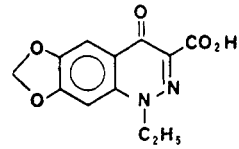
CINOXACIN

Therapeutic Function: Antibacterial

Chemical Name: 1-Ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 28657-80-9

Trade Name	Manufacturer	Country	Year Introduced
Cinobac	Lilly	U.K.	1979
Cinobac	Lilly	Switz.	1979
Cinobactin	Lilly	W. Germany	1980
Cinobac	Lilly	U.S.	1981
Cinobact	Shionogi	Japan	1983
Cinobactin	Lilly	Sweden	1983

Raw Materials

1-Ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile
Hydrogen chloride

Manufacturing Process

About 23 g (0.095 mol) of 1-ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile were added to a mixture of 200 ml of concentrated hydrochloric acid and 200 ml of acetic acid. The resultant reaction mixture was heated under reflux for 18 hours. The excess acids were removed under vacuum, and the residue was taken up in 150 ml of a 5% sodium bicarbonate solution. The resultant solution was treated with 5 g of charcoal and filtered. The filtrate was made acidic by the addition of hydrochloric acid and the resulting precipitate was removed by filtration. 23 g, representing a yield of 91.6% of 1-ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carboxylic acid as light tan crystals which melted at 261°C to 262°C with decomposition were recovered.

References

Merck Index 2284
DFU 3 (1) 22 (1978)
Kleeman & Engel p. 213
PDR p. 836
OCDS Vol. 2 p. 388 (1980)
DOT 11 (10) 402 (1975) & 16 (2) 45 (1980)
I.N. p. 235
REM p. 1216
White, W.A.; U.S. Patent 3,669,965; June 13, 1972; assigned to Eli Lilly & Company

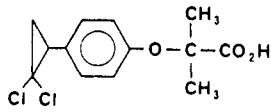
CIPROFIBRATE

Therapeutic Function: Hypolipemic

Chemical Name: 2-[4-(2',2'-Dichlorocyclopropyl)phenoxy]-2-methylpropionic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 52214-83-3

Trade Name	Manufacturer	Country	Year Introduced
Lipanor	Winthrop	France	1983

Raw Materials

p-(2,2-Dichlorocyclopropyl)phenol
Sodium hydroxide
Acetone
Chloroform

Manufacturing Process

A mixture of 8 g (0.0356 mol) of p-(2,2-dichlorocyclopropyl)phenol, 11.2 g (0.28 mol) of sodium hydroxide pellets, 11 g of chloroform and 350 ml of acetone was prepared at 0°C. The cooling bath was removed, the mixture stirred for a minute and then heated on a steam bath to reflux temperature. The reaction mixture was stirred at reflux for three hours and then concentrated in vacuo. The residual gum was partitioned between dilute hydrochloric acid and ether, and the ether layer was separated, dried and concentrated in vacuo. The residual oil (14 g) was partitioned between dilute aqueous sodium bicarbonate and ether. The sodium bicarbonate solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and concentrated. The residue (9.5 g of yellow oil) was crystallized twice from hexane to give 6.0 g of 2-[p-(2,2-dichlorocyclopropyl)phenoxy] -2-methyl propionic acid in the form of a pale cream-colored solid, MP 114°C to 116°C.

References

Merck Index 2286
DFU 2 (5) 297 (1977)
OCDS Vol. 3 p. 44 (1984)
I.N. p. 235
Phillips, D.K.; U.S. Patent 3,948,973; April 6, 1976; assigned to Sterling Drug, Inc.

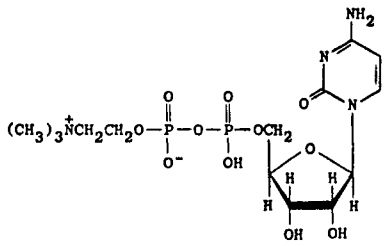
CITICOLINE

Therapeutic Function: Cerebral circulation stimulant

Chemical Name: Cytidine 5'-(trihydrogen diphosphate)mono[2-(trimethylammonio)ethyl] - ester hydroxide inner salt

Common Name: Citidoline; cytidine diphosphate choline

Structural Formula:



Chemical Abstracts Registry No.: 987-78-0

Trade Name	Manufacturer	Country	Year Introduced
Nicholin	Cyanamid	Italy	1971
Rexort	Cassenne Takeda	France	1977
Alaton	Zambon	Italy	–
Andes	Nippon Kayaku	Japan	–
Brassel	Alfa Farmaceutici	Italy	–
CDP-Choline	Kowa	Japan	–
Cereb	Ohta	Japan	–
Ceregut	Kodama	Japan	–
Cidifos	Neopharmed	Italy	–
Colite	Nippon Chemiphar	Japan	–
Corenalin	Kaken	Japan	–
Cyscholin	Kanto	Japan	–
Daicoline	Daisan	Japan	–
Difosfocin	Magis	Italy	–
Emicholine	Dojin	Japan	–
Emilian	Beppu	Japan	–
Ensign	Yamanouchi	Japan	–
Erholen	Nichiiko	Japan	–
Haibrain	Ono	Japan	–
Haocolin	Fuso	Japan	–
Hornbest	Hoei	Japan	–
Intelon	Takata	Japan	–
Meibis	Sanken	Japan	–
Neucolis	Nippon Shinyaku	Japan	–
Nicholin	Takeda	Japan	–
Niticolin	Morishita	Japan	–
Plube	Mochida	Japan	–
Recognan	Toyo Jozo	Japan	–
Rupis	Vitacain	Japan	–
Sauran	Abello	Spain	–
Sinkron	Ripari-Gero	Italy	–
Sintoclar	Pulitzer	Italy	–
Somazina	Ferrer	Spain	–
Startonyl	Cyanamid	–	–
Suncholin	Mohan	Japan	–

Raw Materials

Cytidine-5'-monophosphate
Choline
Brevibacterium ammoniagenes

Manufacturing Process

A 250 ml conical flask containing 30 ml of a reaction liquor (pH 7.0) having a composition of 7.38 mg/ml of disodium salt of CMP (cytidine-5'-monophosphate), 24 mg/ml of choline, 10 mg/ml of glucose, 100 mg/ml of acetone-dried cells of *Brevibacterium ammoniagenes* ATCC 6872, 11.6 mg/ml of monopotassium phosphate, 20 mg/ml of dipotassium phosphate and 2.96 mg/ml of magnesium sulfate, ($MgSO_4 \cdot 7H_2O$), was subjected to culturing at 30°C for 4 hours. Cytidine diphosphate choline was formed and accumulated at a concentration of 3.8 mg/ml in the culture liquor.

The pH of 1.2 liters of filtrate containing 3.8 mg/ml of cytidine diphosphate choline, obtained by removing solid matters from the culturing liquor, was adjusted to a pH of 8.5 with a 0.5N KOH solution. The filtrate was passed through a column of strongly basic anion exchange resin, Dowex 1 x 2 (formic acid type). After washing the resin with water, a formic acid

solution was passed through the column with gradual increase in the concentration of formic acid (until 0.04N max.). A fraction of cytidine diphosphate choline was collected by elution according to the so-called gradient elution method and absorbed onto carbon powders. Then, elution was effected with acetone, and the eluate was concentrated and dried. 1.3 g of cytidine diphosphate choline powders were obtained.

References

Merck Index 2290
Kleeman & Engel p. 214
DOT 4 (2) 68 (1968)
I.N. p. 237
Nakayama, K. and Hagino, H.; U.S. Patent 3,684,652; August 15, 1972; assigned to Kyowa Hakko Kogyo Co., Ltd. (Japan)
Nakamachi, H., Kamiya, K. and Nishikawa, M.; U.S. Patent 3,687,932; August 29, 1972; assigned to Takeda Chemical Industries, Ltd. (Japan)

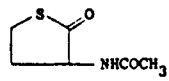
CITIOLONE

Therapeutic Function: Treatment of hepatic disorders

Chemical Name: 2-Acetamido-4-mercaptobutyric acid γ-lactone

Common Name: Acetylhomocystein thiolactone; acetamido thiobutyrolactone

Structural Formula:



Chemical Abstracts Registry No.: 1195-16-0

Trade Name	Manufacturer	Country	Year Introduced
Citiolase	Roussel Maestretti	France	1970
Thioxidrene	Bottu	France	1972
Citiolase	Roussel Maestretti	Italy	1976
Mucorex	Berenguez-Beneyto	Spain	—
Reducdyn	Nordmark	W. Germany	—
Sitilon	Roussel	—	—
Thioncycline	Merrell	France	—

Raw Materials

Acetyl methionine
Sodium
Ammonia
Hydrogen chloride

Manufacturing Process

12.73 kg of acetyl methionine are gradually introduced into a brine-cooled pressure-tight apparatus provided with a stirrer and containing 140 liters of liquid ammonia at -50°C. The amino acid is dissolved after a short time; 6.5 kg of sodium metal are then introduced over a period of from 4 to 5 hours at a temperature of from -40°C to -50°C. Eventually, a persistent blue coloration of the ammoniacal solution indicates the end of the reaction. The ammonia is distilled off and the residue is taken up in 70 liters of methanol. In order to remove ammonia which has been formed from sodium amide, 30 to 40 liters of methanol are distilled off and the residue is made up with methanol to 80 liters. The strongly alkaline solution is neutralized with 22 liters of concentrated aqueous hydrochloric acid. The solution is filtered

off from the precipitated sodium chloride and evaporated to dryness *in vacuo*. The closing of the thiolactone ring takes place as a result of the evaporation of the solution to dryness in the acid pH range and the N-acetyl homocystein originally present is converted into N-acetyl homocystein thiolactone. In order to isolate this compound, the residue is recrystallized from 25% aqueous alcohol.

9 kg of N-acetyl homocystein thiolactone are obtained, this corresponding to a yield of 85% of the theoretical.

References

Merck Index 2291
Kleeman & Engel p. 215
DOT 7 (1) 14 (1971)
I.N. p. 237
British Patent 955,231; April 15, 1964; assigned to Deutsche Gold- und Silber- Scheideanstalt Vormals Roessler (Germany)

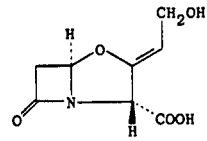
CLAVULANIC ACID

Therapeutic Function: Antibacterial

Chemical Name: 3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 58001-44-8

Trade Name	Manufacturer	Country	Year Introduced
Augmentin	Beecham	U.K.	1981
Augmentin	Beecham	Switz.	1982
Augmentan	Beecham	W. Germany	1982
Synulox	Beecham	–	–

Raw Materials

Dextrin
Soybean flour
Bacterium Streptomyces Clavuligerus

Manufacturing Process

100 ml of sterile water was added to a sporing culture which had been grown on Bennetts agar in a Roux bottle for 10 days at 26°C. A mycelium/spore suspension was produced and used to inoculate 75 liters of steam sterilized medium of the following composition in tap water.

Dextrin	2% W/V
Arkasoy '50'*	1% W/V
10% Pluronic L81 in soybean oil	0.03% V/V

*Arkasoy is soybean flour supplied by British Arkady Co., Old Trafford, Manchester, UK

The pH of the medium was adjusted to 7.0

The medium was contained in a 100 liter stainless steel baffled fermenter, agitated by a 7½ inch vaned disc impeller at 140 rpm. Sterile air was supplied at 75 liters per minute and the tank incubated for 72 hours at 26°C.

The contents of the seed fermenter were used to inoculate 1,500 liters of steam sterilized medium of the following composition in tap water.

Arkasoy '50'	1.5% W/V
Glycerol	1.0% W/V
KH_2PO_4	0.1% W/V
10% Pluronic L81 in soybean oil	0.2% V/V

The pH of the medium was adjusted to 7.0

The medium was contained in a 2,000 liter stainless steel fully baffled fermenter agitated by two 19 inch vaned disc impellers at 106 rpm.

Sterile air was supplied at 1,200 liters per minute. Antifoam was added in 25 ml amounts as required. (10% Pluronic L81 in soybean oil.) The fermentation was controlled at 26°C until a maximum yield of clavulanic acid was obtained between 3-5 days when 200-300 μg/ml of clavulanic acid were produced.

References

Merck Index 2311
DFU 2 (6) 372 (1977)
PDR p. 659
DOT 19 (3) 169 (1983)
I.N. p. 18
REM p. 1200
Cole, M., Howarth, T.T. and Reading, C.; U.S. Patent 4,110,165; August 29, 1978; assigned to Beecham Group, Ltd. (U.K.)

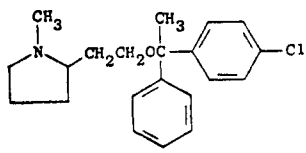
CLEMASTINE FUMARATE

Therapeutic Function: Antihistaminic

Chemical Name: 2-[2-[1-(4-chlorophenyl)-1-phenylethoxy] ethyl] -1-methylpyrrolidine hydrogen fumarate

Common Name: Meclastin

Structural Formula:



(base)

Chemical Abstracts Registry No.: 14976-57-9; 15686-51-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tavegyl	Sandoz	France	1967
Tavegyl	Sandoz	Switz.	1967
Tavegil	Sandoz	W. Germany	1967
Tavegyl	Sandoz	Italy	1968
Tavegyl	Sankyo	Japan	1970
Tavegil	Sandoz	U.K.	1971
Tavist	Dorsey	U.S.	1978
Agasten	Sandoz	—	—
Alagyl	Sawai	Japan	—
Aloginan	Tobishi	Japan	—
Alphamin	S.S. Pharm.	Japan	—
Anhistan	Nippon Zoki	Japan	—
Antriptin	Nippon Yakuhin	Japan	—
Arrest	Taisho	Japan	—
Batomu	Zensei	Japan	—
Benanzyl	Isei	Japan	—
Chlonaryl	Ohta	Japan	—
Clemanil	Kyoritsu	Japan	—
Fuluminol	Tatsumi	Japan	—
Fumalestine	Hishiyama	Japan	—
Fumaresutin	Hishiyama	Japan	—
Inbestan	Maruko	Japan	—
Kinotomin	Toa Eiyo	Japan	—
Lacretin	Toyo Tanabe	Japan	—
Lecasol	Kaken	Japan	—
Maikohis	Nichiiko	Japan	—
Mallermin-F	Taiyo Yakuko	Japan	—
Marsthine	Towa	Japan	—
Masletine	Shioe	Japan	—
Piloral	Nippon Kayaku	Japan	—
Raseltin	Maruishi	Japan	—
Reconin	Toyama	Japan	—
Romien	Fuji Zoki	Japan	—
Telgin G	Taiyo	Japan	—
Trabest	Hoei	Japan	—
Xolamin	Sanko	Japan	—

Raw Materials

α-Methyl p-chlorobenzhydrol
N-Methyl-pyrrolidyl-(2)-ethyl chloride
Sodium amide
Fumaric acid

Manufacturing Process

9.9 g of α-methyl-p-chlorobenzhydrol are added to a suspension of 2.3 g of powdered sodamide in 30 cc of benzene. Subsequently 7.4 g of N-methylpyrrolidyl-(2)-ethyl chloride are added and the solution is heated to the boil at reflux for 20 hours. Then shaking is first effected with water and then 4 times each time with 25 cc of 2N hydrochloric acid. The acid extracts are made alkaline with potassium hydroxide solution while cooling strongly, and the precipitated oil is extracted with ether. After drying of the ethereal solution over potassium carbonate, the solvent is evaporated and the residue is fractionally distilled in a high vacuum, whereby N-methyl-2-[2'-(α-methyl-p-chlorobenzhydryloxy)-ethyl] -pyrrolidine boils over at 154°C/0.02 mm Hg. The base is converted to the fumarate by reaction with fumaric acid.

References

Merck Index 2314

Kleeman & Engel p. 216
PDR p. 1597
OCDS Vol. 2 p. 32 (1980)
I.N. p. 239
REM p. 1127
British Patent 942,152; November 20, 1963; assigned to Sandoz Ltd.

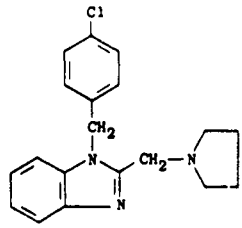
CLEMIZOLE

Therapeutic Function: Antihistaminic

Chemical Name: 1-[(4-Chlorophenyl)methyl]-2-(1-pyrrolidinylmethyl]-1H-benzimidazole

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 442-52-4; 1163-36-6 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Allercur	Roerig	U.S.	1960
Reactrol	Purdue Frederick	U.S.	1961
Allercur	Schering	Switz.	–
Allerpant	Panther-Osfa	Italy	–
Deliproct	S.E.P.S.S.	France	–
Penargyl	Morgan	Italy	–
Ultralan	S.E.P.S.S.	France	–
Ultraproct	S.E.P.S.S.	France	–

Raw Materials

o-Nitrochlorobenzene
p-Chlorobenzylamine
Chloroacetyl chloride
Hydrogen
Pyrrolidine

Manufacturing Process

From 13.1 g of N-p-chlorobenzyl-2-nitroaniline (MP 110°C, obtained in the form of orange-red needles, from o-nitrochlorobenzene and p-chlorobenzylamine by reaction for 3 hours at 150°C) by reduction with Raney-nickel and hydrogen, in which reaction the substance may be suspended in methanol or dissolved in methanol-ethyl acetate at normal pressure and at about 40°C with combination of the theoretical quantity of hydrogen, 12.2 g are obtained of o-amino-N-p-chlorobenzylaniline, which after recrystallization from aqueous methanol has a MP of 90°C.

8 g of o-amino-N-p-chlorobenzylaniline and 2.8 g of pyridine are dissolved in dry ether and reacted with an ethereal solution of 3.9 g of chloracetyl chloride with cooling in a mixture of

ice and common salt. 8 g of N-p-chlorobenzyl-N'-chloracetyl-o-phenylene diamine are obtained which can be worked up in the form of the crude product and, in the slightly colored form, has a MP of 130°C.

7.6 g of this compound are boiled with 3.9 g of pyrrolidine in 70 cc of toluene for some hours under reflux. After extraction by shaking with water and treatment with hydrochloric acid the hydrochloride is produced of N-p-chlorobenzyl-N'-pyrrolidylacetyl-o-phenylene diamine together with some 1-p-chlorobenzyl-2-N-pyrrolidylmethyl-benzimidazole. The former, after recrystallization from butanol, melts with foaming at 205°C, the latter, after recrystallization from butanol melts at 239°C to 241°C, and is in the form of white microscopic rods. Boiling in nitrobenzene converts the former compound into the latter.

References

Merck Index 2315
Kleeman & Engel p. 217
OCDS Vol. 1 p. 324 (1977)
I.N. p. 239
Schenck, M. and Heinz, W.; U.S. Patent 2,689,853; September 21, 1954; assigned to Schering A.G. (Germany)

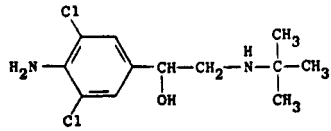
CLENBUTEROL

Therapeutic Function: Antiasthmatic

Chemical Name: 4-Amino-3,5-dichloro-[[(1,1-dimethylethyl)amino] methyl] benzenemethanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 37148-27-9

Trade Name	Manufacturer	Country	Year Introduced
Spiropent	Thomae	W. Germany	1977
Monores	Valeas	Italy	1981

Raw Materials

1-(4'-Aminophenyl)-2-t-butylaminoethanol-(1)-HCl
Chlorine
Hydrogen chloride

Manufacturing Process

127 g of 1-(4'-aminophenyl)-2-t-butylaminoethanol-(1)-hydrochloride were dissolved in a mixture of 250 cc of glacial acetic acid and 50 cc of water, and chlorine added while stirring the solution and maintaining the temperature of the reaction mixture below 30°C by cooling with ice water. After all of the chlorine had been added, the reaction mixture was stirred for thirty minutes more, then diluted with 200 cc of water, and made alkaline with concen-

trated ammonia while cooling with ice, taking care that the temperature of the reaction mixture did not rise above 40°C. The alkaline mixture was extracted three times with 200 cc portions of chloroform, and the chloroform extract solutions were combined, dried with sodium sulfate and evaporated. The residue, the free base 1-(4'-amino-3',5'-dichlorophenyl)-2-t-butylaminoethanol-(1), was dissolved in absolute ethanol, gaseous hydrogen chloride was passed through the solution, and the precipitate formed thereby was collected. It was identified to be 1-(4'-amino-3',5'-dichlorophenyl)-2-t-butylaminoethanol-(1)-hydrochloride, melting point 174.0°C to 175.5°C (decomp.).

References

Merck Index 2316
DFU 1 (5) 221 (1976)
Kleeman & Engel p. 218
DOT 14 (2) 59 (1978) & 17 (8) 339 (1981)
I.N. p. 240
Keck, J., Kruger, G., Machleidt, H., Noll, K., Engelhardt, G. and Eckenfels, A.; U.S. Patent 3,536,712; October 27, 1970; assigned to Boehringer Ingelheim G.m.b.H. (Germany)

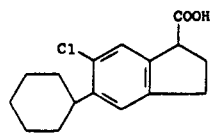
CLIDANAC

Therapeutic Function: Antiinflammatory; antipyretic

Chemical Name: 6-Chloro-5-cyclohexyl-2,3-dihydro-1H-indene-1-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 34148-01-1

Trade Name	Manufacturer	Country	Year Introduced
Indanal	Takeda	Japan	1981
Britai	Bristol Banyu	Japan	1981

Raw Materials

N-Chlorosuccinimide
5-Cyclohexyl-1-indancarboxylic acid

Manufacturing Process

N-chlorosuccinimide (8.2 g, 0.0614 mol) was added to a stirred, cooled (ice-water) solution of (±)-5-cyclohexyl-1-indancarboxylic acid (10.0 g, 0.0409 mol) in dimethylformamide (82 ml). The solution was stirred for fifteen minutes at 0°C, thirty minutes at 25°C, nine hours at 50°C, followed by eight hours at 25°C. The solution was diluted with cold water (400 ml) and stirred until the precipitated product turned granular (fifteen minutes). The crude product was collected, washed with cold water, and dried. Crystallization from Skellysolve B with charcoal treatment gave colorless crystals (6.65 g, 58%), MP 149°C to 150°C. The product was recrystallized twice from Skellysolve B to give (±)-6-chloro-5-cyclohexyl-1-indancarboxylic acid as colorless crystals, MP 150.5°C to 152.5°C.

References

Merck Index 2319
DFU 4 (3) 229 (1979)
DOT 17 (8) 319 (1981)
I.N. p. 240
Juby, P.F., DeWitt, R.A.P. and Hudyma, T.W.; U.S. Patent 3,565,943; February 23, 1971; assigned to Bristol-Myers Co.

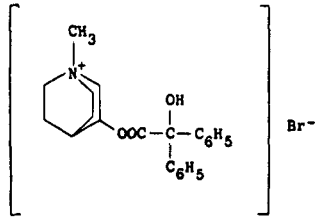
CLIDINIUM BROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: 3-[(hydroxydiphenylacetyl)oxy]-1-methyl-1-azoniabicyclo[2.2.2] octane bromide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 3485-62-9

Trade Name	Manufacturer	Country	Year Introduced
Librax	Roche	U.S.	1961
Quarzan	Roche	U.S.	1976
Dolibrax	Roche	France	–

Raw Materials

1-Azabicyclo[2.2.2]-3-octanol
Diphenylchloroacetyl chloride
Sodium
Methyl bromide

Manufacturing Process

5.12 g of 1-azabicyclo[2.2.2]-3-octanol were refluxed with a suspension of 0.92 g of finely divided sodium in 50 cc of toluene, until most of the sodium had reacted (about 4 hours). The thus-obtained suspension of the white amorphous alcoholate was cooled with ice, and reacted with 10.16 g of diphenylchloroacetyl chloride, which was added in form of a solution in approximately 40 cc of toluene. The mixture was stirred for 1 hour at room temperature. Small amounts of unreacted sodium were destroyed with isopropanol, and 120 cc of 1 N hydrochloric acid were then added. The mixture was refluxed for ½ hour, in order to convert the first formed product, diphenylchloroacetic acid ester of 1-azabicyclo[2.2.2]-3-octanol, into the corresponding benzilic acid ester.

The toluene phase was separated and discarded. The aqueous phase, together with a precipitated water- and toluene-insoluble oil, was made alkaline and extracted repeatedly with chloroform. The chloroform solution was concentrated in vacuo. The residue was re-

crystallized from a mixture of acetone and ether (alternatively, from chloroform and ether), and formed needles melting at 164° to 165°C. It was identified as 3-benziloyloxy-1-azabicyclo[2.2.2]octane.

3-Benziloyloxy-1-azabicyclo[2.2.2]octane methobromide was prepared by adding 20 cc of a 30% solution of methyl bromide in ether to a solution of 2.5 g of 3-benziloyloxy-1-azabicyclo[2.2.2]octane in 20 cc of chloroform. After standing for 3 hours at room temperature and 15 hours at +5°C, a crystalline precipitate had formed. This was filtered off and recrystallized from a mixture of methanol, acetone, and ether; prisms melting at 240° to 241°C.

References

Merck Index 2320
Kleeman & Engel p. 219
PDR pp. 1510, 1606, 1999
I.N. p. 240
REM p. 914
Sternbach, L.H.; U.S. Patent 2,648,667; August 11, 1953; assigned to Hoffmann-LaRoche, Inc.

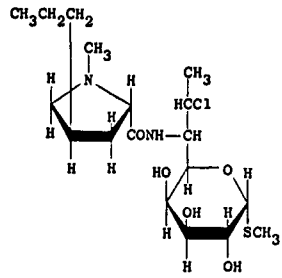
CLINDAMYCIN HYDROCHLORIDE

Therapeutic Function: Antibacterial

Chemical Name: 7(S)-chloro-7-deoxylincomycin hydrochloride

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 21462-39-5; 18323-44-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dalacin-C	Diethelm	Switz.	1968
Sobelin	Upjohn	W. Germany	1968
Cleocin	Upjohn	U.S.	1970
Dalacin-C	Upjohn	U.K.	1970
Dalacin	Sumitomo	Japan	1971
Dalacin C	Upjohn	Italy	1975
Dalacin	Alter	Spain	—

Raw Materials

Lincomycin hydrochloride
Triphenyl phosphine
Acetonitrile
Hydrogen chloride

Manufacturing Process

The following procedure is described in U.S. Patent 3,475,407. A solution of 50 g of lincomycin hydrochloride, 120 g of triphenylphosphine, and 500 ml of acetonitrile in a 3 liter flask equipped with a stirrer was cooled in an ice bath and 500 ml of carbon tetrachloride was added in one portion. The reaction mixture was then stirred for 18 hours without addition of ice to the cooling bath. The reaction was evaporated to dryness under vacuum on a 50° to 60°C water bath, yielding a clear, pale yellow viscous oil. An equal volume of water was added and the mixture shaken until all of the oil was dissolved. The resulting suspension of white solid (ϕ_3PO) was filtered through a sintered glass mat and discarded. The filtrate was adjusted to pH 11 by addition of 6 N aqueous sodium hydroxide. A solid precipitated.

The resulting slurry was extracted with four 300 ml portions of chloroform. The aqueous phase was discarded. The combined chloroform extract was washed once with 100 ml of saturated aqueous sodium chloride solution and the sodium chloride phase was discarded. The chloroform phase was evaporated to dryness under vacuum on a 50° to 60°C water bath and an equal volume of methanol was added to the residue and the resulting solution heated at reflux for 1 hour. The methanol solution was evaporated to dryness under vacuum on a 50° to 60°C water bath. The residue was a clear pale yellow viscous oil. An equal volume of water and 10 ml of 37% aqueous HCl was added and the resultant was shaken until the oil dissolved and a white solid (more ϕ_3PO) remained in suspension. The suspension was filtered through a sintered glass mat at pH 1 to 2 and the solid discarded.

The filtrate was extracted twice with 100 ml of carbon tetrachloride. The carbon tetrachloride phase was discarded. The aqueous phase was adjusted to pH 11 by addition of 6 N aqueous sodium hydroxide and extracted four times with 300 ml portions of chloroform. The combined chloroform extract was washed three times with 100 ml of saturated aqueous sodium chloride solution and the sodium chloride phase was discarded. The chloroform extract was dried over anhydrous magnesium sulfate, filtered and the filtrate evaporated to dryness under vacuum on a 50° to 60°C water bath. The residue was a clear, colorless glass weighing 45 g analyzing about 95% 7(S)-chloro-7-deoxylincomycin. To the crude product there was added 100 ml of ethanol with warming until a clear solution was obtained. Then 150 ml ethyl acetate was added and the resultant filtered through a glass mat and the filtrate adjusted to pH 1 by the addition of saturated ethanolic HCl. Crystallization soon occurred. The resultant was allowed to stand at 0°C for 18 hours and then filtered through a sintered glass mat. The solid was dried under vacuum at 60°C for 18 hours yielding 35 g, a 67% yield of 7(S)-chloro-7-deoxylincomycin hydrochloride as an ethanol solvate.

References

Merck Index 2321
Kleeman & Engel p. 220
PDR p. 1827
DOT 5 (1) 32 (1969) & 7 (5) 188 (1972)
I.N. p. 240
REM p. 1209
Birkenmeyer, R.D.; U.S. Patent 3,475,407; October 28, 1969; assigned to The Upjohn Company
Kagan, F. and Magerlein, B.J.; U.S. Patent 3,509,127; April 28, 1970; assigned to The Upjohn Company

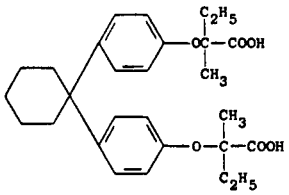
CLINOFIBRATE

Therapeutic Function: Antihyperlipoproteinemic

Chemical Name: 2,2'-[Cyclohexylidenebis(4,1-phenyleneoxy)] bis[2-methylbutanoic acid]

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 30299-08-2

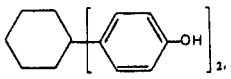
Trade Name	Manufacturer	Country	Year Introduced
Lipocrin	Sumitomo	Japan	1981
Lipocyclin	Sumitomo	Japan	–

Raw Materials

Bis-(phenyleneoxy)cyclohexane
Methyl ethyl ketone

Manufacturing Process

Into a mixture of 6.0 g of a bishydroxyphenyl derivative,



and 44.0 g of methyl ethyl ketone was added 16.2 g of crushed potassium hydroxide or sodium hydroxide. Chloroform was added dropwise into the above mixture with stirring at 20°C to 80°C, and the resultant mixture was heated for 20 hours under reflux to complete the reaction. Thereafter the reaction mixture was concentrated to give a residue. Into the residue was added water. After cooling, the resultant mixture was treated with activated charcoal and acidified by diluted hydrochloric acid or sulfuric acid to give an oily substance. The oily substance was extracted by ether and the ether solution was contacted with aqueous diluted Na_2CO_3 solution. The separated aqueous layer was washed with ether, acidified and again extracted with ether. The obtained ester layer was dried over anhydrous sodium sulfate and concentrated to give 1.0 g of a crude product which was purified by recrystallization or chromatography, to give crystals MP 143°C to 146°C (decomp.).

References

Merck Index 2322
DFU 3 (12) 905 (1978)
DOT 18 (5) 221 (1982)
I.N. p. 241
Nakamura, Y., Agatsuma, K., Tanaka, Y. and Aono, S.; U.S. Patent 3,716,583; February 13, 1973; assigned to Sumitomo Chemical Co., Ltd. (Japan)

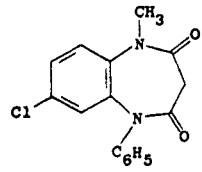
CLOBAZAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4(3H,5H)-dione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 22316-47-8

Trade Name	Manufacturer	Country	Year Introduced
Urbanyl	Diamant	France	1975
Frisium	Albert-Pharm.	Italy	1977
Frisium	Hoechst	W. Germany	1978
Urbanul	Hoechst	Switz.	1979
Frisium	Hoechst	U.K.	1979
Castilium	Hoechst	–	–
Clarmyl	Roussel-Iberica	Spain	–
Clopax	Prodes	Spain	–
Karidium	Hoechst	–	–
Noiafren	Hoechst	–	–
Sentil	Hoechst	–	–
Urbadan	Roussel	–	–
Urbanil	Sarsa	Brazil	–
Urbanol	Roussel	–	–

Raw Materials

N-Phenyl-N-(2-amino-5-chlorophenyl)malonic acid ethyl ester amide
Sodium
Ethanol
Methyl iodide

Manufacturing Process

1.65 g of N-phenyl-N-(2-amino-5-chlorophenyl)-malonic acid ethyl ester amide of MP 108° to 109°C are added to a sodium ethoxide solution, prepared from 20 ml of absolute alcohol and 150 mg of sodium. The solution is allowed to rest for 5 hours at room temperature. Then 1 ml of methyl iodide is added and the reaction mixture is refluxed for 7 hours. After evaporation of the solution in vacuo it is mixed with water and the solution is shaken with methylene chloride. The methylene chloride phase is dried and evaporated. By treatment of the residue with ethyl acetate/charcoal are isolated 500 mg of 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4-(3H,5H)-dione of MP 180° to 182°C. The yield amounts to 34% of theory.

References

Merck Index 2325
Kleeman & Engel p. 221
OCDS Vol. 2 p. 406 (1980)
DOT 9 (6) 240 (1973), 11 (1) 39 (1975) & 16 (1) 9 (1980)
I.N. p. 241
REM p. 1083
Hauptmann, K.H., Weber, K.-H., Zeile, K., Danneberg, P. and Giesemann, R.; South African Patent 68/0803; February 7, 1968; assigned to Boehringer Ingelheim GmbH, Germany

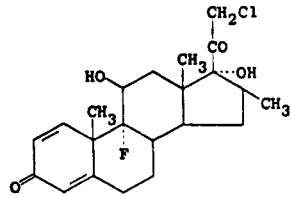
CLOBETASOL

Therapeutic Function: Corticosteroid, Antiinflammatory

Chemical Name: 21-chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 25122-41-2; 25122-46-7 (Propionate)

Trade Name	Manufacturer	Country	Year Introduced
Dermovate	Glaxo	U.K.	1973
Dermoxin	Glaxo	W. Germany	1976
Clobesol	Glaxo	Italy	1977
Dermoval	Glaxo	France	1978
Dermovate	Glaxo	Japan	1979
Dermadex	Glaxo	–	–

Raw Materials

Betamethasone-21-methanesulfonate
Lithium chloride
Propionic anhydride

Manufacturing Process

A solution of betamethasone 21-methanesulfonate (4 g) in dimethylformamide (25 ml) was treated with lithium chloride (4 g) and the mixture heated on the steam bath for 30 minutes. Dilution with water gave the crude product which was recrystallized to afford the title compound, MP 226°C.

Clobetasol is usually converted to the propionate as the useful form by reaction with propionic anhydride.

References

Merck Index 2330
Kleeman & Engel p. 222
DOT 9 (8) 339 (1973)
I.N. p. 242
Elks, J., Phillipps, G.H. and May, P.J.; U.S. Patent 3,721,687; March 20, 1973; assigned to Glaxo Laboratories Limited, England

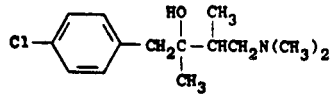
CLOBUTINOL

Therapeutic Function: Antitussive

Chemical Name: 4-chloro-α-[2-(dimethylamino)-1-methylethyl]-α-methylbenzeneethanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 14860-49-2; 1215-83-4 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Silomat	Boehr./Ingel.	Switz.	1960
Silomat	Thomae	W. Germany	1960
Camaldin	Boehr./Ingel.	Italy	1962
Silomat	Badrial	France	1969
Silomat	Morishita	Japan	1975
Biotertussin	Bioter	–	–
Lomisat	Boehr./Ingel.	–	–
Pertoxil	Violani-Farmavigor	Italy	–

Raw Materials

3-Methyl-4-dimethylamino-butanone-(2)
p-Chlorobenzyl chloride
Magnesium
Hydrogen chloride

Manufacturing Process

A solution of 0.2 mol (33 g) of 3-methyl-4-dimethylamino-butanone-(2) [produced according to Mannich, *Arch. Pharm.*, vol. 265, page 589 (1927)] in 50 cc absolute ether was added dropwise, while stirring and cooling with ice, to a Grignard solution of 0.4 mol p-chlorobenzylmagnesium-chloride which was produced from 64.5 g p-chlorobenzyl-chloride and 9.8 g magnesium in 200 cc absolute ether. The reaction product was heated for an additional one-half hour under reflux to bring the reaction to completion, and thereafter the reaction mixture was decomposed into an ether phase and an aqueous phase with about 50 cc concentrated hydrochloric acid and about 200 g ice. The ether phase was discarded and the aqueous phase was adjusted to an alkaline pH with ammonia and then thoroughly extracted with ether. After concentrating the united, dried ether extract solutions, the oily residue was fractionally distilled. The reaction product was obtained in the form of a colorless oil having a boiling point of 179° to 181°C. The yield was 48.5 g corresponding to 95% of theory.

The hydrochloride addition salt of the above reaction product was prepared in customary fashion, that is, by reaction with hydrochloric acid, followed by fractional crystallization from a mixture of alcohol and ether. The two possible racemic forms were obtained thereby. The difficultly soluble racemate had a melting point of 169° to 170°C and the more readily soluble racemate had a boiling point of 145° to 148°C.

References

Merck Index 2332
Kleeman & Engel p. 224
OCDS Vol. 2 p. 121 (1980)
I.N. p. 242
Berg, A.; U.S. Patent 3,121,087; February 11, 1964; assigned to Dr. Karl Thomae GmbH, Germany

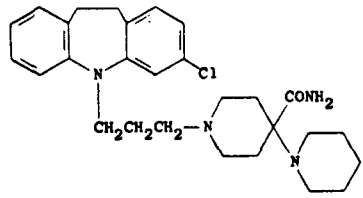
CLOCAPRAMINE

Therapeutic Function: Neuroleptic

Chemical Name: 1'-[3-(3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)propyl][1,4-bi-piperidine]-4-carboxamide

Common Name: Clocarpramine

Structural Formula:



Chemical Abstracts Registry No.: 47739-98-0

Trade Name	Manufacturer	Country	Year Introduced
Clofekton	Yoshitomi	Japan	1974

Raw Materials

3-Chloro-5-(3-chloropropyl)-10,11-dihydro-5H-dibenz(b,f)azepine
4-Carbamoyl-4-piperidinopiperidine

Manufacturing Process

A mixture of 5.0 g of 3-chloro-5-(3-chloropropyl)-10,11-dihydro-5H-dibenz(b,f)azepine, 5.0 g of 4-carbamoyl-4-piperidinopiperidine and 50 ml of dimethylformamide is heated at 100°C for 10 hours. The solvent is distilled off. After the addition of a 2% sodium carbonate solution to the flask, the content is scratched to yield a semisolid, which is dissolved in 50 ml of isopropanol. A solution of 5 g of maleic acid in 50 ml of isopropanol is added, and the precipitate is collected by filtration and recrystallized from isopropanol to give 5.6 g of crystalline 3-chloro-5-[3-(4-carbamoyl-4-piperidino-piperidino)propyl]-10,11-dihydro-5H-dibenz-(b,f)azepine di(hydrogen maleate) with 1/2 molecule of water of crystallization melting at 181°C to 183°C.

References

Merck Index 2334
Kleeman & Engel p. 224
OCDS Vol. 2 p. 416 (1980)
DOT 10 (5) 161 (1974)
I.N. p. 243
Nakanishi, M. and Tashiro, C.; U.S. Patent 3,668,210; June 6, 1972; assigned to Yoshitomi Pharmaceutical Industries, Ltd. (Japan)

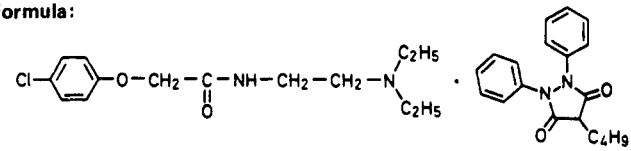
CLOFEZONE

Therapeutic Function: Analgesic; antiinflammatory

Chemical Name: Equimolar mixture of Clofexamide which is 2-(p-chlorophenoxy)-N-[2-(diethylamino)ethyl]acetamide with phenylbutazone

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 17449-96-6; 60104-29-2 (Dihydrate)

Trade Name	Manufacturer	Country	Year Introduced
Perclusone	Anphar-Rolland	France	1967
Perclusone	Heinrich Mack	W. Germany	1974
Panas	Grelan	Japan	1976
Perclusone	Pierrel	Italy	1976
Perclusone	Abic	Israel	–
Perclustop	Uquifa	Spain	–

Raw Materials

Phenylbutazone
p-Chlorophenoxyacetic acid diethylamino ethylamide (Clofexamid)

Manufacturing Process

935 g of phenylbutazone are dissolved, with heating to a lukewarm state, in 2.7 liters of acetone containing 20% water, and the mixture is filtered if necessary. 853.5 g of p-chlorophenoxyacetic acid diethylamino ethylamide are dissolved in 300 cc of acetone containing 20% water, and the solution is poured into the phenylbutazone solution. There is slight heating, and the solution clarifies. The salt crystallizes rapidly. Drying is effected on a Buchner funnel and the mixture is washed in 450 cc of acetone containing 20% of water. The 1,702 g of product obtained is recrystallized in 2,450 cc of acetone containing 20% of water and, after drying in an oven at 37°C, 1,585 g (86%) of product are obtained. The product is in the form of a white crystalline powder having a melting point of from 87°C to 89°C in the Maquenne block.

References

Kleeman & Engel p. 227
I.N. p. 245
Rumpf, P. and Thuillier, J.E.; U.S. Patent 3,491,190; January 20, 1970

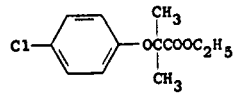
CLOFIBRATE

Therapeutic Function: Cholesterol reducing agent

Chemical Name: 2-(4-chlorophenoxy)-2-methylpropanoic acid ethyl ester

Common Name: Ethyl p-chlorophenoxyisobutyrate

Structural Formula:



Chemical Abstracts Registry No.: 637-07-0

Trade Name	Manufacturer	Country	Year Introduced
Atromid-S	I.C.I.	U.K.	1963
Skleromexe	Merckle	W. Germany	1964
Atromid-S	Ayerst	U.S.	1967
Atromidin	I.C. Pharma	Italy	1969
Liposid	Ohta	Japan	1970
Amotril	Sumitomo	Japan	–
Apoterin A	Seiko	Japan	–
Arterioflexin	Arcana	Austria	–
Arterioflexin	Protea	Australia	–
Artes	Farmos	Finland	–
Artevil	N.C.S.N.	Italy	–
Ateculon	Nippon Chemiphar	Japan	–
Ateles	Tokyo Hosei	Japan	–
Atemarol	Kowa	Japan	–
Ateriosan	Finadiet	Argentina	–
Aterosol	Ferrosol	Denmark	–
Athebrate	Karenyaku	Japan	–
Atherolate	Fuji Zoki	Japan	–
Atheromide	Ono	Japan	–
Atherolip	Solac	France	–
Atheropront	Mack	W. Germany	–
Atmol	Taisho	Japan	–
Atosterine	Kanto	Japan	–
Atrofort	Dif-Dogu	Turkey	–
Atrolen	Firma	Italy	–
Atromidin	I.C.P.	Italy	–
Atrovis	Novis	Israel	–
Auparton	Samya	Japan	–
Binograc	Zeria	Japan	–
Bioscleran	Pfleger	W. Germany	–
Bresit	Toyo Jozo	Japan	–
Cartagyl	Sopar	Belgium	–
Cholenal	Yamanouchi	Japan	–
Cholestol	Toho	Japan	–
Cholesrun	Hokuriku	Japan	–
Citiflus	C.T.	Italy	–
Claresan	Sarbach	France	–
Claripex	I.C.N.-Usafarma	Brazil	–
Clarol	Toyama	Japan	–
Climinon	Meiji	Japan	–
Cloberat	Negroni	Italy	–
Clobrat	Weifa	Norway	–
Clobrate	Chugai	Japan	–
Clobren	Morishita	Japan	–
Clof	Siegfried	Switz.	–
Clofbate	Mohan	Japan	–
Clofibral	Farmochimica	Italy	–
Clofinit	Gentili	Italy	–
Clofipront	Mack	W. Germany	–
Clofirem	Roland-Marie	France	–
Deliva	Nippon Kayaku	Japan	–
Geromid	Zoja	Italy	–
Healthstyle	Sawai	Japan	–
Hyclorate	Funay	Japan	–
Hypocerol	Fuso	Japan	–
Ipolipid	Isnardi	Italy	–

Trade Name	Manufacturer	Country	Year Introduced
Klofiran	Remeda	Finland	—
Levatrom	Abic	Israel	—
Lipavil	Farmades	Italy	—
Lipavlon	Avlon	France	—
Lipidicon	Aristochimica	Italy	—
Liprinal	Bristol	U.K.	—
Liprinal	Banyu	Japan	—
Miscleron	Chinoin	Hungary	—
Normolipol	Delagrange	France	—
Novofibrate	Novopharm	Canada	—
Recolip	Benzon	Denmark	—
Sclerovasal	I.T.I.	Italy	—
Scrobin	Nikken	Japan	—
Sklero-Tablinen	Sanorania	W. Germany	—
Ticlobran	Siegfried	Switz.	—
Xyduril	Dorsh	W. Germany	—
Yoclo	Shinshin	Japan	—

Raw Materials

p-Chlorophenoxyisobutyric acid
Ethanol

Manufacturing Process

The ethyl p-chlorophenoxyisobutyrate may be obtained by heating a mixture of 206 parts of dry p-chlorophenoxyisobutyric acid, 1,000 parts of ethanol and 40 parts of concentrated sulfuric acid under reflux during 5 hours. The alcohol is then distilled off and the residue is diluted with water and extracted with chloroform. The chloroform extract is washed with sodium hydrogen carbonate solution, dried over sodium sulfate and the chloroform removed by distillation. The residue is distilled under reduced pressure and there is obtained ethyl p-chlorophenoxyisobutyrate, BP 148° to 150°C/20 mm.

The p-chlorophenoxyisobutyric acid used as starting material may be obtained as follows. A mixture of 200 parts of p-chlorophenol, 1,000 parts of acetone and 360 parts of sodium hydroxide pellets is heated under reflux and 240 parts of chloroform are gradually added at such a rate that the mixture continues to reflux without further application of heat.

When addition is complete the mixture is heated under reflux during 5 hours and then the acetone is removed by distillation. The residue is dissolved in water, acidified with hydrochloric acid and the mixture extracted with chloroform. The chloroform extract is stirred with sodium hydrogen carbonate solution and the aqueous layer is separated. The alkaline extract is acidified with hydrochloric acid and filtered. The solid product is drained free from oil on a filter pump, then washed with petroleum ether (BP 40° to 60°C), and dried at 50°C. The solid residue, MP 114° to 116°C, may be crystallized from methanol (with the addition of charcoal) to give p-chlorophenoxyisobutyric acid, MP 118° to 119°C.

References

Merck Index 2340
Kleeman & Engel p. 227
PDR p. 613
OCDS Vol. 1 p. 119 (1977) & 2 pp. 79, 101, 432 (1980)
DOT 11 (4) 141 (1975)
I.N. p. 245
REM p. 863
Jones, W.G.M., Thorp, J.M. and Waring, W.S.; U.S. Patent 3,262,850; July 26, 1966; assigned to Imperial Chemical Industries Limited, England

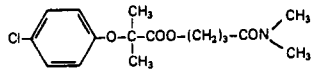
CLOFIBRIDE

Therapeutic Function: Hypocholesterolemiant

Chemical Name: 3-(Dimethylaminocarbonyl)-propyl-4'-chlorophenoxyisobutyrate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Lipenan	Charpentier	France	1974
Evimot	Muller Rorer	W. Germany	1978

Raw Materials

Ethyl 4'-chlorophenoxyisobutyrate
4-Hydroxy-N,N-dimethylbutyramide

Manufacturing Process

48.5 parts of ethyl 4'-chlorophenoxyisobutyrate are dissolved in 200 parts by volume of dry toluene in the presence of 26.2 parts of 4-hydroxy-N,N-dimethyl butyramide and 2 parts of aluminum isopropylate. The solution is heated for 8 hours, while collecting the toluene-ethanol azeotrope, in an apparatus provided with a distillation column at a controllable rate of reflux. After this it is filtered, the solvent is evaporated in vacuo and the residue is distilled. An almost colorless, slightly yellow oil is obtained, the purity of which by chromatographic examination in the gaseous phase is of the order of 99.5%. Its boiling point is 175°C under 0.1 torr.

This oil is kept supercooled at the ambient temperature. Crystallization may be obtained by cooling or by seeding with crystals of the product. The melting point is 34°C (instantaneous on the Maquenne block).

The product can be recrystallized. For this, it is dissolved, for example, at the ambient temperature in petrol ether, ethyl ether or isopropyl ether, and this solution is cooled at about -50°C while stirring. After drying over sulfuric acid under vacuum, white needles of very great purity are thus obtained.

References

DOT 9 (5) 169 (1973)
I.N. p. 246
Nordmann, J., Mattioda, G.D. and Loiseau, G.P.M.H.; U.S. Patent 3,792,082; February 12, 1974; assigned to Ugine Kuhlmann

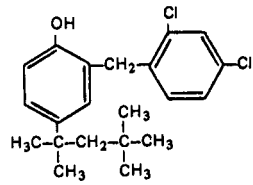
CLOFOCTOL

Therapeutic Function: Antiinfective; bacteriostatic

Chemical Name: 2-(2,4-Dichlorobenzyl)-4-(1,1,3,3-tetramethylbutyl)-phenol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 37693-01-9

Trade Name	Manufacturer	Country	Year Introduced
Octofene	Debat	France	1978

Raw Materials

p-(1,1,3,3-Tetramethylbutyl)phenol
2,4-Dichlorobenzyl chloride
Zinc chloride

Manufacturing Process

The following were introduced into a 1 liter flask provided with a reflux condenser: 206 g (1 mol) of p-(1,1,3,3-tetramethylbutyl)-phenol, 147 g (0.75 mol) of 2,4-dichlorobenzyl chloride, 27 g (0.2 mol) of pure melted zinc chloride, and 750 ml of anhydrous chloroform.

The mixture was heated to reflux for 24 hours. The chloroformic reaction mixture was washed with water, and then dried over anhydrous sodium sulfate. The chloroform was evaporated off and the oil obtained was fractionally distilled under a pressure of 0.2 mm Hg. The fraction distilling at 140°C to 160°C, being the desired product indicated above, was collected and crystallized. Yield: 94 g (32% of theory); MP 78°C (after recrystallization in petroleum ether).

References

Kleeman & Engel p. 228
DOT 15 (4) 171 (1979)
I.N. p. 246
Debat, J.; U.S. Patent 3,830,852; August 20, 1974; assigned to Institute de Recherches Chimiques et Biologiques Appliquees (I.R.C.E.B.A.) (France)

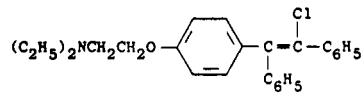
CLOMIPHENE DIHYDROGEN CITRATE

Therapeutic Function: Antiestrogen (fertility inducer)

Chemical Name: 2-[4-(2-Chloro-1,2-diphenylethenyl)-phenoxy] N,N-diethylethanamine dihydrogen citrate

Common Name: Clomifen citrate

Structural Formula:



(base)

Chemical Abstracts Registry No.: 50-41-9; 911-45-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Clomid	Lepetit	Italy	1966
Clomid	Merrell Dow	U.K.	1966
Clomid	Doetsch Grether	Switz.	1967
Clomid	Merrell National	U.S.	1967
Dyneric	Merrell	W. Germany	1967
Clomid	Merrell	France	1968
Serophene	Serono	U.S.	1982
Clomivid	Draco	Sweden	–
Clostilbegyt	Egyt	Hungary	–
Gravosan	Spofa	Czechoslovakia	–
Ikaclomine	Ika	Israel	–
Omifin	Inibsa	Spain	–
Prolifen	Chiesa	Italy	–

Raw Materials

4-(β-Diethylaminoethoxy)benzophenone
Benzyl magnesium chloride
N-Chlorosuccinimide
Hydrogen chloride
Citric acid

Manufacturing Process

A mixture of 20 g of 1-[p-(β-diethylaminoethoxy)phenyl]-1,2-diphenylethanol in 200 cc of ethanol containing an excess of hydrogen chloride was refluxed 3 hours. The solvent and excess hydrogen chloride were removed under vacuum, and the residue was dissolved in a mixture of ethyl acetate and methylene chloride. 1-[p-(β-diethylaminoethoxy)phenyl]-1,2-diphenylethylene hydrochloride was obtained, melting at 148° to 157°C. This hydrochloride salt was treated with N-chlorosuccinimide in dry chloroform under reflux. The product then obtained was converted to the free base and treated with citric acid. The dihydrogen citrate salt of 1-[p-(β-diethylaminoethoxy)phenyl]-1,2-diphenylchloroethylene was obtained, melting at 116.5° to 118°C.

The intermediate 1-[p-(β-diethylaminoethoxy)phenyl]-1,2-diphenylethanol was obtained by treating 4-(β-diethylaminoethoxy)benzophenone with benzylmagnesium chloride. It melted at 95° to 96°C.

References

Merck Index 2349
DFU 3 (11) 850 (1978)
Kleeman & Engel p. 230
PDR pp. 1225, 1699
OCDS Vol. 1 pp. 105, 148 (1977) & 2 p. 127 (1980)
I.N. p. 247
REM p. 990
Allen, R.E., Palopoli, F.P., Schumann, E.L. and Van Campen, M.G. Jr.; U.S. Patent 2,914,563; November 24, 1959; assigned to The Wm. S. Merrell Company

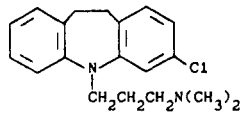
CLOMIPRAMINE

Therapeutic Function: Antidepressant

Chemical Name: 3-Chloro-10,11-dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine

Common Name: Chlorimipramine

Structural Formula:



Chemical Abstracts Registry No.: 303-49-1; 17321-77-6 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Anafranil	Ciba Geigy	Switz.	1968
Anafranil	Ciba Geigy	W. Germany	1968
Anafranil	Fujisawa	Japan	1970
Anafranil	Ciba Geigy	Italy	1970
Anafranil	Ciba Geigy	U.K.	1970
Anafranil	Ciba Geigy	Australia	1983
Marunil	Unipharm	Israel	—
Hydiphen	Arzneimittelwerk Dresden	E. Germany	—

Raw Materials

3-Chloroiminodibenzyl
Sodium amide
γ-Dimethylaminopropyl chloride

Manufacturing Process

22.9 parts of 3-chloroiminodibenzyl are dissolved in 300 parts by volume of xylene, and 4 parts of sodium amide, pulverized and suspended in toluene, are added thereto while stirring and maintaining the whole under a nitrogen atmosphere. The xylene solution immediately turns dark colored, but upon crystallization of the sodium salt therefrom it becomes again light-colored. The reaction mixture is stirred for about 2 hours at 80°C until the development of ammonia has terminated. A solution of γ-dimethylaminopropyl chloride in toluene, prepared by setting free a corresponding amount of the free base from 17.4 parts of its hydrochloride salt by addition of aqueous sodium hydroxide solution in about 10% excess, extraction with toluene and drying for 2 hours over anhydrous sodium sulfate is added to the xylene solution containing the sodium salt mentioned above and the whole is stirred under reflux for 15 hours. Precipitated sodium chloride is filtered off and the filtrate is concentrated. The residue is diluted with ether, and the hydrochloride of 3-chloro-5-(γ-dimethylaminopropyl)-iminodibenzyl is precipitated by introducing dry, gaseous hydrogen chloride. It is filtered off under suction and purified by repeated recrystallization from acetone; the pure substance melts at 191.5°C to 192°C.

References

Merck Index 2350
Kleeman & Engel p. 231
DOT 4 (4) 143 (1968) & 9 (6) 218 (1973)
I.N. p. 248
Schindler, W. and Dietrich, H.; U.S. Patent 3,515,785; June 2, 1970; assigned to Geigy Chemical Corp.

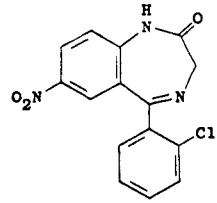
CLONAZEPAM

Therapeutic Function: Anticonvulsant

Chemical Name: 5-(o-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 1622-61-3

Trade Name	Manufacturer	Country	Year Introduced
Rivotril	Roche	France	1973
Rivotril	Roche	U.K.	1974
Clonopin	Roche	U.S.	1975
Rivotril	Roche	Italy	1975
Rivotril	Roche	W. Germany	1976
Rivotril	Roche	Switz.	1976
Rivotril	Roche	Japan	1980
Rancedon	Sumitomo	Japan	1981
Antelepsin	Arzneimittelwerk Dresden	E. Germany	–
Clonex	Teva	Israel	–
Iktorivil	Roche	–	–
Landsen	Sumitomo	Japan	–

Raw Materials

2-Amino-2'-nitrobenzophenone
Hydrogen chloride
Bromoacetyl bromide
Pyridine
Sulfuric acid
Sodium nitrite
Hydrogen
Ammonia
Potassium nitrate

Manufacturing Process

The following description is taken from U.S. Patent 3,116,203. A stirred solution of 75 g of 2-amino-2'-nitrobenzophenone in 700 ml of hot concentrated hydrochloric acid was cooled to 0°C and a solution of 21.5 g of sodium nitrite in 50 ml of water was added in the course of 3 hours. The temperature of the suspension was kept at 2° to 7°C during the addition. The resulting clear solution was poured into a stirred solution of 37 g of cuprous chloride in 350 ml of hydrochloric acid 1:1. The solid which had formed after a few minutes was filtered off, washed with water and recrystallized from ethanol. Crystals of 2-chloro-2'-nitrobenzophenone melting at 76° to 79°C were obtained.

A solution of 20 g of 2-chloro-2'-nitrobenzophenone in 450 ml of ethanol was hydrogenated at normal pressure and room temperature with Raney nickel. After uptake of about 6 liters of hydrogen the catalyst was filtered off, and the alcohol then removed in vacuo. The residue was distilled in a bulb tube at 0.4 mm and a bath temperature of 150° to 165°C giving a yellow oil. The oil was dissolved in alcohol, and on addition of water, needles of 2-amino-2'-chlorobenzophenone melting at 58° to 60°C were obtained.

To a solution of 42 g of 2-amino-2'-chlorobenzophenone in 500 ml of benzene, 19 ml of bromoacetyl bromide was added dropwise. After refluxing for 2 hours, the solution was cooled, washed with 2 N sodium hydroxide and evaporated. The residue was recrystallized from methanol giving crystals of 2-bromo-2'-(2-chlorobenzoyl) acetanilide melting at 119° to 121°C.

To a solution of 14.5 g of 2-bromo-2'-(2-chlorobenzoyl)acetanilide in 100 ml of tetrahydrofuran, an excess of liquid ammonia (ca 150 ml) was added. The ammonia was kept refluxing with a dry-ice condenser for 3 hours after which time the ammonia was allowed to evaporate and the solution was poured into water. Crystals of 2-amino-2'-(2-chlorobenzoyl)acetanilide were collected, which after recrystallization from ethanol melted at 162° to 164°C.

A solution of 3 g of 2-amino-2'-(2-chlorobenzoyl)acetanilide in 50 ml of pyridine was refluxed for 24 hours after which time the pyridine was removed in vacuo. The residue was recrystallized from methanol and a mixture of dichloromethane and ether giving crystals of 5-(2-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one melting at 212° to 213°C.

To a solution of 13.5 g of 5-(2-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one in 60 ml of concentrated sulfuric acid, a solution of 5.5 g of potassium nitrate in 20 ml concentrated sulfuric acid was added dropwise. The solution then was heated in a bath at 45° to 50°C for 2½ hours, cooled and poured on ice. After neutralizing with ammonia, the formed precipitate was filtered off and boiled with ethanol. A small amount of white insoluble material was then filtered off. The alcoholic solution on concentration yielded crystals of 7-nitro-5-(2-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one which, after recrystallization from dichloromethane, melted at 238° to 240°C.

References

Merck Index 2352
Kleeman & Engel p. 232
PDR p. 1481
DOT 9 (6) 237 (1973) & 9 (12) 487 (1973)
I.N. p. 248
REM p. 1077
Kariss, J. and Newmark, H.L.; U.S. Patents 3,116,203; December 31, 1963; and 3,123,529; March 3, 1964; both assigned to Hoffmann-LaRoche, Inc.
Keller, O., Steiger, N. and Sternbach, L.H.; U.S. Patents 3,121,114; February 11, 1964; and 3,203,990; August 31, 1965; both assigned to Hoffmann-LaRoche, Inc.
Focella, A. and Rachlin, A.I.; U.S. Patent 3,335,181; August 8, 1967; assigned to Hoffmann-LaRoche, Inc.

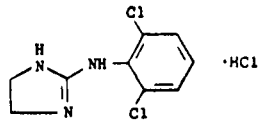
CLONIDINE HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 2-(2,6-dichloroanilino)-2-imidazoline hydrochloride

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 4205-91-8; 4205-90-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Catapresan	Boehr./Ingel	W. Germany	1966
Catapresan	Boehr./Ingel	Switz.	1966
Catapresan	Boehr./Ingel	Italy	1970

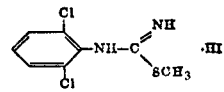
Trade Name	Manufacturer	Country	Year Introduced
Catapres	Tanabe	Japan	1970
Catapres	Boehr./Ingel	U.K.	1971
Catapresan	Boehr./Ingel	France	1971
Catapres	Boehr./Ingel	U.S.	1974
Bapresan	Chemie Linz.	Austria	—
Caprysin	Star	Finland	—
Clonilou	Hermes	Spain	—
Clonisin	Leiras	Finland	—
Clonnirit	Rafa	Israel	—
Dixarit	W.B. Pharm	U.K.	—
Haemiton	Arzneimittelwerk Dresden	E. Germany	—
Ipotensium	Pierrel	Italy	—
Isoglaucon	Boehr./Ingel	W. Germany	—
Normopresan	Rafa	Israel	—
Tensinova	Cheminova	Spain	—

Raw Materials

2,6-Dichloroaniline
Methyl iodide
Hydrogen chloride
Ammonium thiocyanate
Ethylene diamine

Manufacturing Process

N-(2,6-dichlorophenyl)thiourea (MP 149°C) was prepared in customary manner from 2,6-dichloroaniline (*Organic Synthesis* III, 262-263) and ammonium thiocyanate. 16.0 g of this thiourea derivative were refluxed for 2½ hours together with 16 g of methyl iodide in 150 cc of methanol. Thereafter, the methanol was evaporated out of the reaction mixture in vacuo, leaving as a residue 22 g of N-(2,6-dichlorophenyl)-S-methyl-isothiouronium hydroiodide of the formula



having a melting point of 170°C. The entire residue was then admixed with an excess (120%) above the molar equivalent of ethylenediamine, and the mixture was heated for about one hour at 130° to 150°C. Methyl mercaptan was given off. Thereafter, the reaction mixture comprising 2-(2',6'-dichloroanilino)-1,3-diazacyclopentene-(2) hydroiodide was taken up in hot dilute acetic acid, and the resulting solution was made alkaline with 2 N NaOH. A precipitate formed which was separated by vacuum filtration, washed with water and dried. 4.0 g of 2-(2',6'-dichloroanilino)-1,3-diazacyclopentene-(2) were obtained. The product had a melting point of 130°C.

The free base was then dissolved in absolute methanol, and the resulting solution was then adjusted to an acid pH value with an ethereal hydrochloric acid solution. The acidified solution was purified with charcoal and then dry ether was added thereto until crystallization took place. The hydrochloride, prepared in this customary manner, had a melting point of 305°C according to U.S. Patent 3,202,660.

References

Merck Index 2353
Kleeman & Engel p. 232
PDR p. 675
OCDS Vol. 1 p. 241 (1977)
DOT 9 (3) 97 (1973)
I.N. p. 249
REM p. 845

Zeile, K., Hauptmann, K.-H. and Stahle, H.; U.S. Patents 3,202,660; August 24, 1965; and 3,236,857; February 22, 1966; both assigned to Boehringer Ingelheim GmbH, Germany

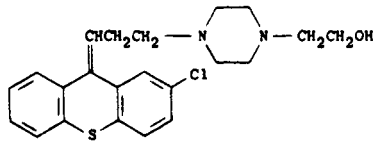
CLOPENTHIXOL

Therapeutic Function: Antipsychotic

Chemical Name: 4-[3-(2-Chloro-9H-thioxanthen-9-ylidene)propyl]-1-piperazineethanol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 982-24-1; 633-59-0 (Dihydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Ciatyl	Tropon	W. Germany	1961
Sordinol	Bracco	Italy	1967
Clopixol	Lundbeck	U.K.	1978
Cisordinol	Lundbeck	—	—
Sordenac	Lundbeck	—	—
Thiapax	Ikapharm	Israel	—

Raw Materials

2-Chloro-9-(3'-dimethylaminopropylidene)-thiaxanthene
N-(β-hydroxyethyl)-piperazine

Manufacturing Process

A mixture of 31.5 g (0.1 mol) of 2-chloro-9-(3'-dimethylaminopropylidene)-thiaxanthene (MP 97°C) and 100 g of N-(β-hydroxyethyl)-piperazine is heated to 130°C and boiled under reflux at this temperature for 48 hours. After cooling, the excess of N-(β-hydroxyethyl)-piperazine is evaporated in vacuo, and the residue is dissolved in ether. The ether phase is washed with water and extracted with dilute acetic acid, and 2-chloro-9-[3'-N-(N'-β-hydroxyethyl)-piperazinylpropylidene]-thiaxanthene separated from the aqueous acetic acid solution by addition of dilute sodium hydroxide solution to basic reaction. The free base is extracted with ether, the ether phase dried over potassium carbonate, the ether evaporated and the residue dissolved in absolute ethanol. By complete neutralization of the ethanolic solution with a solution of dry hydrogen chloride in absolute ethanol, the dihydrochloride of 2-chloro-9-[3'-N-(N'-β-hydroxyethyl)-piperazinylpropylidene]-thiaxanthene is produced and crystallizes out as a white substance melting at about 250°C to 260°C with decomposition. The yield is 32 g.

References

Merck Index 2357
Kleeman & Engel p. 234
OCDS Vol. 1 p. 399 (1977)
DOT 9 (6) 229 (1973)

I.N. p. 249
Petersen, P.V., Lassen, N.O. and Holm, T.O.; U.S. Patent 3,149,103; September 15, 1964; assigned to Kefalas A/S (Denmark)

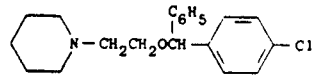
CLOPERASTINE

Therapeutic Function: Antitussive

Chemical Name: 1-[2-[(p-chloro-α-phenylbenzyl)oxy] ethyl] piperidine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 3703-76-2

Trade Name	Manufacturer	Country	Year Introduced
Hustazol	Yoshitomi	Japan	1972
Seki	Symes	Italy	1981

Raw Materials

p-Chlorobenzhydryl bromide
Ethylene chlorohydrin
Piperidine

Manufacturing Process

The manufacture of a related compound is first described. 28.1 parts of p-chloro-benzhydryl bromide are heated to boiling, under reflux and with stirring, with 50 parts of ethylene chlorohydrin and 5.3 parts of calcined sodium carbonate. The reaction product is extracted with ether and the ethereal solution washed with water and dilute hydrochloric acid. The residue from the solution in ether boils at 134° to 137°C under 0.2 mm pressure and is p-chloro-benzhydryl-(β-chloroethyl) ether.

28.1 parts of this ether are heated with 12 parts of methylethylamine (100%) in a sealed tube for 4 hours at 110°C. The product of the reaction is extracted several times with dilute hydrochloric acid, the acid solution made alkaline, in the cold, with concentrated caustic soda solution and the base which separates taken up in ether. The ether extract is washed with concentrated potassium carbonate solution, evaporated down, and the residue distilled in vacuo. The product is β-methylethyl aminoethyl p-chlorobenzhydryl ether, BP 152° to 153°C/0.1 mm.

Reaction with dimethylethylamine instead of methylethylamine leads directly to a quaternary compound, which type of compound can also be obtained by reacting the tertiary aminoethyl ether with reactive esters.

If 18 parts of piperidine are used instead of 12 parts of methylethylamine then the same procedure results in the formation of p-chloro-benzyhydril-(β-piperidino-ethyl) ether, boiling at 178° to 180°C under 0.15 mm pressure.

References

Merck Index 2358
Kleeman & Engel p. 234

I.N. p. 250
British Patent 670,622; April 23, 1952; assigned to Parke, Davis & Company

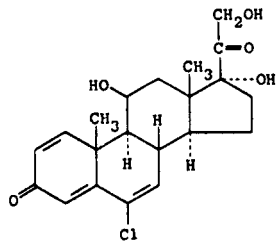
CLOPREDNOL

Therapeutic Function: Glucocorticoid

Chemical Name: 6-Chloro-11,17,21-trihydroxypregna-1,4,6-triene-3,20-dione

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 5251-34-3

Trade Name	Manufacturer	Country	Year Introduced
Syntestan	Syntex	W. Germany	1980
Novacort	Syntex	Switz.	1983
Synclopred	Syntex	—	—

Raw Materials

6α-Chlorohydrocortisone 21-acetate
Chloranil

Manufacturing Process

A mixture of 5 g of the 21-acetate of 6α-chlorohydrocortisone, 7 g of chloranil and 100 cc of n-amyl alcohol was refluxed for 16 hours, cooled and diluted with ether. The solution was successively washed with water, 5% sodium carbonate solution and water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure. Chromatographic purification of the residue yielded the 21-acetate of 6-chloro-$\Delta^{1,4,6}$-pregnatriene-11β,17α,21-triol-3,20-dione.;

References

Merck Index 2361
DFU 2 (1) 18 (1977)
OCDS Vol. 2 p. 182 (1980)
DOT 17 (10) 393 (1981)
I.N. p. 250
Ringold, H.J. and Rosenkranz, G.; U.S. Patent 3,232,965; February 1, 1966; assigned to Syntex Corp.

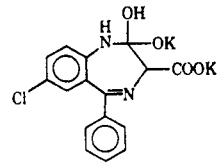
CLORAZEPATE DIPOTASSIUM

Therapeutic Function: Tranquilizer

Chemical Name: 7-chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid dipotassium salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 15585-90-7; 20432-69-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tranxene	Clin Comar	France	1968
Tranxilium	Mack	W. Germany	1969
Tranxilium	Cun Midy	Switz.	1969
Transene	Zambeletti	Italy	1970
Tranxene	Abbott	U.S.	1972
Tranxene	Boehr./Ingel.	U.K.	1973
Mendon	Dainippon	Japan	1980
Anxidin	Orion	Finland	–
Azene	Endo	U.S.	–
Belseren	Mead Johnson	–	–
Enadine	York	Argentina	–
Nansius	Prodes	Spain	–
Noctran	Clin-Comar-Byla	France	–
Tranex	Idravlje	Yugoslavia	–
Tranxilen	Leo	Sweden	–

Raw Materials

2-Amino-5-chlorobenzonitrile
Methyl aminomalonate
Potassium hydroxide
Bromobenzene
Magnesium

Manufacturing Process

(A) Preparation of (2-Amino-5-Chlorophenyl)Phenylmethaneimine (4356 CB): A solution of 228.7 g (1.5 mols) of 2-amino-5-chlorobenzonitrile in 1,800 ml of dry ether is added slowly in the course of about 3.5 hours to a solution of phenyl magnesium bromide prepared from 109 g (4.5 g-atoms) of magnesium turnings and 848 g (5.4 mols) of bromobenzene in 3,600 ml of anhydrous ether, and the mixture then heated under reflux for 15 hours.

The complex is decomposed by stirring the reaction mixture into a solution prepared from 500 g of ammonium chloride in 2,000 ml of water to which 3 kg of crushed ice have been added. After extraction and washing, the ether is evaporated in vacuo at 40°C. The oily residue is taken up in 500 ml of petroleum ether and left to crystallize by cooling at -20°C. The yellowish crystals formed are dried (309 g); MP_K (Kofler block): 74°C; yield: 92%.

(B) Preparation of 7-Chloro-3-Methoxycarbonyl-5-Phenyl-2-Oxo-2,3-Dihydro-1H-Benzo [f]-1,4-Diazepine (4347 CB): A solution of 9.2 g (0.04 mol) of compound 4356 CB in 20 ml of methanol is added dropwise, in the course of one hour and 30 minutes, to a boiling solution of 9.2 g (0.05 mol) of the hydrochloride of methyl aminomalonate in 30 ml of methanol. When this is completed, heating under reflux is continued for 30 minutes and the product then concentrated to dryness under reduced pressure. The residue is taken up in water and ether, the ethereal layer separated, the product washed with water and dried over sodium sulfate. The solvent is evaporated under reduced pressure. The residue, which consists of the methyl ester, could not be obtained in the crystalline state. It is dissolved in 25 ml of acetic acid, heated under reflux for 15 minutes, the product evaporated to dryness and the residual oil taken up in ether. A colorless solid separates which is filtered by suction and recrystallized from methanol. Colorless crystals are obtained (4.7 g); MP_k (Kofler block): 226°C. A second crop (1.5 g) is obtained on concentration of the mother liquor; MP_k (Kofler block): 222°C; total quantity 6.2 g, corresponding to a yield of 47%.

(C) Preparation of Dipotassium Salt of [2-Phenyl-2-(2-Amino-5-Chlorophenyl)-1-Azavinyl] Malonic Acid (4306 CB): 50 g of caustic potash are dissolved in 1,350 ml of 96% ethyl alcohol, and 82 g (0.25 mol) of compound 4347 CB are then added all at once at a temperature of about 70°C. The solid dissolves rapidly to form a yellow solution which then loses color while simultaneously an abundant colorless precipitate appears.

After cooling, the solid is filtered by suction and washed with alcohol at 96°C. The product is dried at ordinary temperature in a high vacuum. A colorless solid is obtained (quantitative yield), which is completely soluble in water. The aqueous solution is strongly alkaline in reaction; when acidified with acetic acid and heated on a water bath, it yields a precipitate of 7-chloro-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine.

References

Merck Index 2364
Kleeman & Engel p. 311
PDR p. 553
DOT 4 (4) 137 (1968) & 9 (6) 238 (1973)
I.N. p. 251
REM p. 1061
Schmitt, J.; U.S. Patent 3,516,988; June 23, 1970

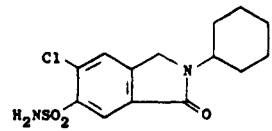
CLOREXOLONE

Therapeutic Function: Diuretic

Chemical Name: 6-Chloro-2-cyclohexyl-2,3-dihydro-3-oxo-1H-isoindole-5-sulfonamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 2127-01-7

Trade Name	Manufacturer	Country	Year Introduced
Speciatensol	Specia	France	1966
Flonatril	Specia	France	–
Nefrolan	May & Baker	U.K.	–
Nefrolan	Teikoku Zoki	Japan	–

Raw Materials

4-Chlorophthalimide
Cyclohexylamine
Tin
Hydrogen chloride
Potassium nitrate
Sulfuric acid
Stannous chloride
Sodium nitrite
Sulfur dioxide
Ammonia

Manufacturing Process

4-chlorophthalimide (263 g) was reacted in amyl alcohol (2.6 ℓ) with cyclohexylamine (143.5 g, 1 mol) at reflux temperature for 16 hours to give N-cyclohexyl-4-chlorophthalimide (250 g, 66%) as a solid, MP 134°C to 136°C.

N-cyclohexyl-1-chlorophthalimide (250 g) was dissolved in glacial acetic acid (2.5 ℓ), concentrated hydrochloric acid (555 ml) and tin (278 g) were added and the suspension was heated on a steam bath for 16 hours. The cooled solution was filtered and concentrated to dryness in vacuo to give a white solid. This solid was dissolved in water and the precipitated oil extracted with chloroform. The chloroform solution was dried and concentrated in vacuo to give a solid which, after recrystallization, yielded 5-chloro-2-cyclohexylisoindolin-1-one (43%), MP 140°C to 142°C.

5-chloro-2-cyclohexylisoindolin-1-one (102.9 g) was dissolved in concentrated sulfuric acid (665 ml); potassium nitrate (723 g) in concentrated sulfuric acid (166 ml) was added at 0°C. The reaction mixture was allowed to warm to room temperature and stirred at 25°C for 12 hours. The reaction mixture was poured onto ice to give a cream solid which, after recrystallization from benzene, gave 5-chloro-2-cyclohexyl-6-nitroisoindolin-1-one (46.7 g, 44%) as a white solid, MP 164°C to 168°C.

5-chloro-2-cyclohexyl-6-nitroisoindolin-1-one (93.9 g) was reduced in concentrated hydrochloric acid (1,970 ml) with stannous chloride (376 g). The reaction temperature rose to 70°C. The resulting solution was cooled in ice and filtered. The product was washed well with water, filtered and dried to give 6-amino-5-chloro-2-cyclohexylisoindolin-1-one (74.1 g, 87.6%) which, after recrystallization from benzene, had a MP of 216°C to 218°C.

6-amino-5-chloro-2-cyclohexylisoindolin-1-one (42.5 g) was dissolved in concentrated hydrochloric acid (425 ml) and the solution diazotized by the addition of sodium nitrite (21.25 g) in water (125 ml). The resulting diazonium salt solution was added to a solution of liquid sulfur dioxide (93 ml) in glacial acetic acid (243 ml) containing cuprous chloride (2.25 g). A yellow solid was precipitated; this was filtered off, washed, dried and recrystallized from benzene to give 5-chloro-2-cyclohexylisoindolin-1-one-6-sulfonyl chloride (45 g, 80%) as a cream solid, MP 171°C to 174°C.

This sulfonyl chloride (23.7 g) was reacted with liquid ammonia (237 ml) to give 5-chloro-2-cyclohexyl-6-sulfamoylisoindolin-1-one (14.2 g, 53%), MP 259°C to 261°C.

References

Merck Index 2365
Kleeman & Engel p. 235
DOT 2 (4) 128 (1966)
I.N. p. 251
Lee, G.E. and Wragg, W.R.; U.S. Patent 3,183,243; May 11, 1965; assigned to May & Baker, Ltd.

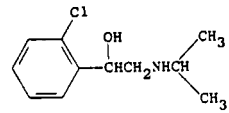
CLORPRENALINE

Therapeutic Function: Bronchodilator

Chemical Name: 2-chloro-α-[[(1-methylethyl)amino] methyl] benzenemethanol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 3811-25-4; 5588-22-7 (Hydrochloride monohydrate)

Trade Name	Manufacturer	Country	Year Introduced
Asthone	Eisai	Japan	1970
Aremans	Zensei	Japan	—
Asnormal	Sawai	Japan	—
Bronocon	Wakamoto	Japan	—
Clopinerin	Nippon Shoji	Japan	—
Clorprenaline	Kongo	Japan	—
Conselt	Sana	Japan	—
Cosmoline	Chemiphar	Japan	—
Fusca	Hoei	Japan	—
Kalutein	Tatsumi	Japan	—
Pentadoll	Showa	Japan	—
Propran	Kobayashi Kako	Japan	—
Restanolon	Isei	Japan	—
Troberin	Nippon Zoki	Japan	—

Raw Materials

o-Chloroacetophenone
Sodium borohydride
Bromine
Isopropylamine

Manufacturing Process

To a solution of 279 g of o-chloroacetophenone in 2 liters of anhydrous diethyl ether were added about 3 g of dibenzoyl peroxide. 5 g of bromine were added to the resulting solution, and after 3 minutes, the color of bromine had been discharged, indicating that the formation of ω-bromo-o-chloroacetophenone had been initiated. A further amount of 288 g of bromine was added dropwise to the reaction mixture over a 1½ hour interval. After the addition of the bromine had been completed, the reaction mixture was stirred for one-half hour and poured over about 1 kg of crushed ice.

After the ice had melted, the resulting aqueous and ethereal layers were separated. The ethereal layer containing ω-bromo-o-chloroacetophenone was washed with successive 500 ml quantities of water, 5% sodium carbonate solution and again with water to remove the hydrogen bromide formed as a by-product in the reaction. The ethereal layer was dehydrated by contacting with anhydrous magnesium sulfate. The drying agent was removed by filtration and the ether was evaporated from the filtrate. The residue remaining after the evaporation consisted of about 400 g of ω-bromo-o-chloroacetophenone.

A solution of 400 g of ω-bromo-o-chloroacetophenone in one liter of methanol was cooled to about 25°C. A cold solution of 92.5 g of sodium borohydride in one liter of methanol was added as rapidly as possible to this cooled solution while maintaining the temperature

below about 25°C. After the addition had been completed, the reaction mixture was allowed to stand for 4 hours at ambient room temperature, to complete the reduction of the keto group of the ω-bromo-o-chloroacetophenone. The reaction mixture containing a mixture of o-chlorophenyl ethylene-β-bromohydrin and o-chlorophenyl ethylene oxide was then evaporated in vacuo at room temperature to a syrup which was poured into about one liter of 5% hydrochloric acid to decompose any borate-alcohol complexes.

The two compounds were dissolved in diethyl ether by extracting the acidic layer three times with successive 500 ml portions of diethyl ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered, and the ether was removed by evaporation in vacuo. A residue consisting of 400 g of a mixture of o-chlorophenyl ethylene-β-bromohydrin and o-chlorophenyl ethylene oxide was obtained.

400 g of a mixture of o-chlorophenyl ethylene-β-bromohydrin and o-chlorophenyl ethylene oxide were dissolved in one liter of anhydrous ethanol. To this solution was added a solution of 306 g of isopropylamine in one liter of anhydrous ethanol. The reaction mixture was heated at refluxing temperature for about 16 hours, thus forming N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine. The solvent was removed in vacuo, and to the residue was added a solution containing 200 ml of 12 N HCl in 2,500 ml of water.

The acidic solution was washed twice with 500 ml portions of ether which were discarded. The acidic layer was then made basic by the addition of 250 ml of 5% (w/v) sodium hydroxide, thus liberating the free base of N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine. The free base was extracted with two successive one liter portions of diethyl ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to remove all of the solvents. N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine was thus obtained, according to U.S. Patent 2,887,509.

The N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine obtained by the foregoing procedure was dissolved in about 3 liters of ether and dry hydrogen chloride gas was bubbled into the solution until it was saturated, whereupon the hydrochloride salt of N-[β-(o-chlorophenyl)-β-(hydroxy)-ethyl] isopropylamine precipitated. The salt was separated from the ether by filtration, and was dissolved in two liters of anhydrous ethanol. The alcoholic solution was decolorized with charcoal and filtered.

Three liters of anhydrous ether were added thereto and the N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine hydrochloride precipitated in crystalline form as the monohydrate. The mixture was maintained at about 0°C for 40 hours and then filtered. The filter cake was washed with ether and dried. About 209 g of N-[β-(o-chlorophenyl)-β-(hydroxy)-ethyl] isopropylamine hydrochloride monohydrate, melting at about 163° to 164°C, were obtained according to U.S. Patent 2,816,059.

References

Merck Index 2368
Kleeman & Engel p. 236
OCDS Vol. 2 p. 39 (1980)
I.N. p. 252
Mills, J.; U.S. Patent 2,816,059; December 10, 1957; assigned to Eli Lilly and Company
Nash, J.F.; U.S. Patent 2,887,509; May 19, 1959; assigned to Eli Lilly and Company

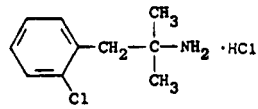
CLORTERMINE HYDROCHLORIDE

Therapeutic Function: Antiobesity drug

Chemical Name: 2-chloro-α-α-dimethylbenzeneethanamine hydrochloride

Common Name: 1-(o-chlorophenyl)-2-methyl-2-aminopropane hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 10389-72-7; 10389-73-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Voranil	USV	U.S.	1973

Raw Materials

o,α-Dichlorotoluene
Acetone
Sodium cyanide
Magnesium
Sulfuric acid
Hydrogen chloride

Manufacturing Process

To a Grignard reagent (prepared from 50.0 g of o,α-dichloro-toluene and 7.45 g of magnesium in diethyl ether) is added 18.0 g of acetone at such rate that constant reflux is maintained. The reaction mixture is allowed to stand overnight at room temperature, and is then poured onto a mixture of 20% sulfuric acid and ice. The organic layer is separated, washed with water, an aqueous solution of sodium hydrogen carbonate and again with water, dried over magnesium sulfate and evaporated to dryness. The residue is distilled under reduced pressure to yield 42.6 g of 1-(o-chlorophenyl)-2-methyl-2-propanol, BP 120° to 122°C/12.5 mm.

To 29.0 ml of glacial acetic acid, cooled to 15°C, is added 11.5 g of sodium cyanide (98%) while stirring, and then dropwise 32.4 ml of concentrated sulfuric acid, dissolved in 29 ml of glacial acetic acid, while maintaining a temperature of 20°C. The 1-(o-chlorophenyl)-2-methyl-2-propanol is added moderately fast, allowing the temperature to rise spontaneously. After completing the addition, the reaction mixture is heated to 70°C and stirred, and is then poured onto a mixture of water and ice. The aqueous mixture is neutralized with sodium carbonate and extracted with diethyl ether. The organic solution is washed with water, dried over magnesium sulfate and evaporated to dryness.

The oily residue is taken up in 100 ml of 6 N aqueous hydrochloric acid and refluxed until a clear solution is obtained. The latter is made basic with aqueous ammonia and extracted with diethyl ether; the organic solution is separated, washed, dried and evaporated. The residue is distilled under reduced pressure to yield 26.3 g of 1-(o-chlorophenyl)-2-methyl-2-propylamine, BP 116° to 118°C/16 mm.

The 1-(o-chlorophenyl)-2-methyl-2-propylamine hydrochloride is prepared by adding ethanolic hydrogen chloride to an ice-cold solution of the free base in ethanol; the desired salt precipitates and is recrystallized from ethanol, MP 245° to 246°C.

References

Merck Index 2369
Kleeman & Engel p. 236
I.N. p. 253
REM p. 891
Finocchio, D.V. and Heubner, C.F.; U.S. Patent 3,415,937; December 10, 1968; assigned to Ciba Corporation

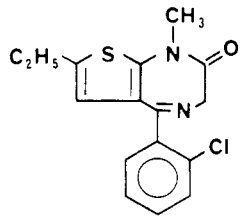
CLOTIAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 5-(o-Chlorophenyl)-7-ethyl-1,3-dihydro-1-methyl-1H-thieno[2,3-e]-1,4-diazepin-2-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 33671-46-4

Trade Name	Manufacturer	Country	Year Introduced
Rize	Yoshitomi	Japan	1979
Trecalmo	Trpon	W. Germany	1979

Raw Materials

2-N-Methyl-aminoacetamido-3-o-chlorobenzyl-5-ethylthiophene
Acetic acid

Manufacturing Process

To a solution of 10 g of 2-N-methyl-aminoacetamido-3-o-chlorobenzoyl-5-ethylthiophene in 50 ml of pyridine are added 20 ml of benzene and 1.9 g of acetic acid. The resulting mixture is refluxed with stirring for 10 hours in a flask provided with a water-removing adaptor. The reaction mixture is concentrated, and the residue is extracted with chloroform. The chloroform layer is washed with water and then with a sodium hydrogen carbonate solution, then dried over magnesium sulfate. The chloroform is distilled off under reduced pressure, and toluene is added to the residue. Thus is precipitated white crystalline 5-o-chlorophenyl-7-ethyl-1-methyl-1,2-dihydro-3H-thieno-[2,3-e] [1,4] diazepin-2-one, MP 105°C to 106°C.

References

Merck Index 2373
DFU 1 (8) 363 (1976)
Kleeman & Engel p. 237
DOT 16 (1) 13 (1980)
I.N. p. 254
Nakanishi, M., Araki, K., Tahara, T. and Shiroki, M.; U.S. Patent 3,849,405; November 19, 1974; assigned to Yoshitomi Pharmaceutical Industries, Ltd.

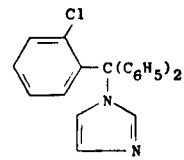
CLOTRIMAZOLE

Therapeutic Function: Antifungal

Chemical Name: 1-[(2-chlorophenyl)diphenylmethyl]-1H-imidazole

Common Name: 1-(o-chlorotrityl)imidazole

Structural Formula:



Chemical Abstracts Registry No.: 23593-75-1

Trade Name	Manufacturer	Country	Year Introduced
Canesten	Bayer	U.K.	1973
Canesten	Bayer	Italy	1973
Canesten	Bayer	W. Germany	1973
Lotrimin	Schering	U.S.	1975
Empecid	Bayer	Japan	1976
Trimysten	Bellon	France	1978
Mycelex	Miles	U.S.	1979
Baycuten	Bayropharm	W. Germany	—
Gyne-Lotrimin	Debay	U.S.	—
Micoter	Cusi	Spain	—
Myclo	Boehr./Ing.	—	—
Mycosporin	Bayer	—	—

Raw Materials

o-Chlorophenyldiphenylmethyl chloride
Imidazole

Manufacturing Process

156.5 g (0.5 mol) o-chlorophenyldiphenylmethyl chloride and 34 g (0.5 mol) imidazole are dissolved in 500 ml acetonitrile, with stirring, and 51 g (0.5 mol) triethylamine are added, whereupon separation of triethylamine hydrochloride occurs even at room temperature. In order to complete the reaction, heating at 50°C is carried out for 3 hours. After cooling, one liter of benzene is added and the reaction mixture is stirred, then washed salt-free with water. The benzene solution is dried over anhydrous sodium sulfate, filtered and concentrated by evaporation; giving 167 g crude 1-(o-chlorophenylbisphenylmethyl)-imidazole. By recrystallization from acetone, 115 g (= 71% of the theory) of pure 1-(o-chlorophenylbisphenylmethyl)-imidazole of MP 154° to 156°C are obtained.

References

Merck Index 2374
Kleeman & Engel p. 238
PDR pp. 1257, 1631
DOT 10 (1) 32 (1974)
I.N. p. 254
REM p. 1227
Buechel, K.H., et al; South African Patent 69/0039; January 3, 1969; assigned to Farbenfabriken Bayer AG, Germany
Buechel, K.H., Regel, E. and Plempel, M.; U.S. Patent 3,660,577; May 2, 1972; and U.S. Patent 3,705,172; Dec. 5, 1972; both assigned to Farbenfabriken Bayer A.G. (Germany)