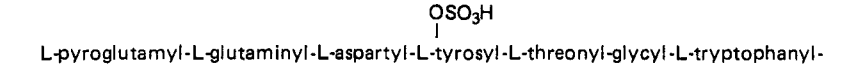
CERULETIDE

Therapeutic Function: Stimulant (gastric secretory)

Chemical Name: Decapeptide of empirical formula $C_{58}H_{73}N_{13}O_{21}S_2$

Common Name: Cerulein; caerulein

Structural Formula:



Chemical Abstracts Registry No.: 17650-98-5

Trade Name	Manufacturer	Country	Year Introduced
Ceosunin	Kyowa Hakko	Japan	1976
Takas	Carlo Erba	W. Germany	1978
Takus	Essex	Switz.	1981
Tymtran	Adria	U.S.	1982
Cerulex	Farmitalia Erba	France	1983

Raw Materials

L-Pyroglutamyl-L-glutaminyl-L-aspartyl-L-tyrosine azide
L-Threonyl-glycyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalaninamide
Pyridine sulfuric anhydride
Sodium carbonate

Manufacturing Process

The tetrapeptide, L-pyroglutamyl-L-glutaminyl-L-aspartyl-L-tyrosine-azide (I), is condensed with the hexapeptide, L-threonyl-glycyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalaninamide (II), having the hydroxyl of the threonyl radical blocked by an acyl radical in a suitable solvent, such as dimethylformamide, to obtain the decapeptide, L-pyroglutamyl-L-glutaminyl-L-aspartyl-L-tyrosyl-L-threonyl-glycyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylaninamide (III) having the hydroxy group of the threonyl radical blocked by an acyl radical. The decapeptide (III) is treated, at low temperature, with the complex anhydrous pyridine sulfuric anhydride finally to obtain the decapeptide, L-pyroglutamyl-L-glutaminyl-L-aspartyl-L-tyrosyl-L-threonyl-glycyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalaninamide (IV) having the phenolic group of the tyrosyl radical protected by a sulfate radical and the hydroxyl of the threonyl radical protected by an acyl radical.

Finally, by mild alkaline hydrolysis of the decapeptide (IV) one obtains the decapeptide product.

References

Merck Index 1963
DFU 1 (8) 359 (1976)
Kleeman & Engel p. 178
DOT 15 (11) 13 (1979)
I.N. p. 203
REM p. 1274
Bernardi, L., Bosisio, G., De Castiglione, R. and Goffredo, O.; U.S. Patent 3,472,832; Oct. 14, 1969; assigned to Societa Farmaceutici Italia (Italy)

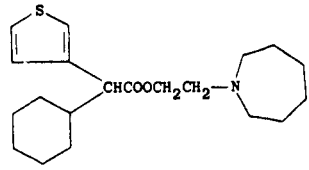
CETIEDIL

Therapeutic Function: Vasodilator (peripheral)

Chemical Name: α-Cyclohexyl-3-thiopheneacetic acid 2-(hexahydro-1H-azepin-1-yl)ethyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 14176-10-4; 16286-69-4 (Citrate)

Trade Name	Manufacturer	Country	Year Introduced
Stratene	Innothera	France	1973
Stratene	Sigmatau	Italy	1976
Fusten	Galenica	Greece	–
Huberdilat	Hubber	Spain	–
Vasocet	Winthrop	–	–

Raw Materials

Sodium metal
1-(2-Chloroethyl)-hexahydro-1H-azepine
(3-Thienyl)-acetonitrile
Cyclohexyl bromide

Manufacturing Process

In a 100 ml flask fitted with a mechanical stirrer, a vertical condensor protected by a calcium chloride stopper, a dropping-funnel and a source of nitrogen were introduced 30 ml of hexamethylenephosphotriamide and 2.3 g (0.1 mol) of finely cut sodium wire. A mixture of 12.3 g (0.1 mol) of (3-thienyl)-acetonitrile and 16.3 g (0.1 mol) of cyclohexyl bromide was then quickly added at a temperature of 20°C. The reaction mixture was then maintained under nitrogen atmosphere and stirred for 12 hours at room temperature. The excess of sodium was destroyed by adding 5 ml of ethanol and the organic solution was slowly poured into 100 ml of a 1 N iced solution of hydrochloric acid. The solution was extracted twice with 100 ml ether. The ethereal phases were collected, washed with water, dried and concentrated under reduced pressure. The crude product was then purified by chromatography on a silica column (150 g of silica) using a 1/1 benzene/cyclohexane mixture as elution agent. The product obtained was rectified by distillation.

In this manner, 3.4 g of α(3-thienyl)-α-cyclohexylacetonitrile were obtained, which represents a yield of 16%.

The nitrile may then be hydrolyzed to cyclohexyl-(3-thienyl)acetic acid which is reacted with 1-(2-chloroethyl)-hexahydro-1H-azepine to give cetiedil. It is commonly used as the citrate.

References

Merck Index 1976
Kleeman & Engel p. 179
OCDS Vol. 3 p. 42 (1984)
DOT 10 (4) 126 (1974)

I.N. p. 204

Pigerol, C., De Cointet De Fillain, P., Grain, C. and Le Blat, J.; U.S. Patent 4,108,865; August 22, 1978; assigned to Labaz (France)

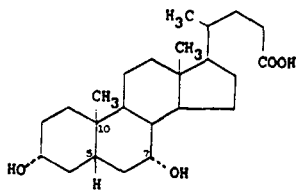
CHENODIOL

Therapeutic Function: Solubilizer for cholesterol gallstones

Chemical Name: 3,7-Dihydroxycholan-24-oic acid

Common Name: Chenodeoxycholic acid; chenic acid

Structural Formula:



Chemical Abstracts Registry No.: 474-25-9

Trade Name	Manufacturer	Country	Year Introduced
Chenofalk	Falk	W. Germany	1974
Chenofalk	Pharmacolor	Switz.	1974
Chenossil	Giuliani	Italy	1975
Chenodex	I.S.H.	France	1977
Chendol	Weddell	U.K.	1978
Regalen	Eisai	Japan	1982
Chenocol	Yamanouchi	Japan	1982
Chenix	Reid-Rowell	U.S.	1983
Aholit	Vetprom	Yugoslavia	–
Bilo	Iltas	Turkey	–
Calcolise	Prodes	Spain	–
Carbilcolina	Ralay	Spain	–
Chelobil	Oftalmiso	Spain	–
Chemicolina	Ern	Spain	–
Chenar	Armour-Montagu	–	–
Chendal	Tika	Sweden	–
Chendix	Weddell	U.K.	–
Chendol	Weddell	U.K.	–
Chenoacid	Falk	W. Germany	–
Chenodecil	Aldon	Spain	–
Chenodex	Houde	France	–
Chenomas	Guadalupe	Spain	–
Chenotar	Armour	–	–
Cholonorm	Gruenenthal	W. Germany	–
Cholasa	Tokyo Tanabe	Japan	–
Cholestex	Ikapharm	Israel	–
Duanox	Roche	–	–
Fluibil	Zambon	Italy	–
Gamiquenol	Gamir	Spain	–
Hekbilin	Hek	W. Germany	–
Henohol	Galenika	Yugoslavia	–

Trade Name	Manufacturer	Country	Year Introduced
Kebilis	Hoechst-Roussel	—	—
Kenolite	Leurquin	France	—
Quenobilan	Estedi	Spain	—
Soluston	Rafa	Israel	—
Ulmenid	Roche	—	—

Raw Materials

7-Acetyl-12-ketochenodeoxycholic acid
Hydrazine hydrate
Potassium hydroxide

Manufacturing Process

To 1,400 ml of an approximately 50% water/triglycol solution of the potassium salt of chenodeoxycholic acid, obtained by the Wolff-Kishner reduction (using hydrazine hydrate and potassium hydroxide) from 50 g of 7-acetyl-12-ketochenodeoxycholic acid, 220 ml of dilute hydrochloric acid is added to bring the pH to 2. The solution is stirred and the crude chenodeoxycholic acid precipitates. The precipitate is recovered and dried to constant weight at about 60°C. About 36 g of the crude chenodeoxycholic acid, melting in the range of 126°-129°C, is obtained.

25 g of crude chenodeoxycholic acid so obtained is dissolved in 750 ml of acetonitrile while stirring and heating. 3 g of activated charcoal is added and then removed by suction filtering. The resulting liquid filtrate is cooled, the pure chenodeoxycholic acid crystallizing out. The crystals are recovered by suction filtering and the recovered crystals dried under vacuum. The yield is 19 g of pure chenodeoxycholic acid with a melting range of 168°-171°C.

References

Merck Index 2007
Kleeman & Engel p. 181
PDR p. 1446
DOT 8 (7) 273 (1972) & 12 (2) 52 (1976)
I.N. p. 17
REM p. 812
Maeke, S. and Rambacher, P.; U.S. Patent 4,163,017; July 31, 1979; assigned to Diamalt A.G. (Germany)

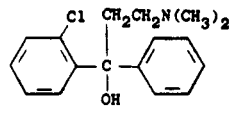
CHLOPHEDIANOL

Therapeutic Function: Antitussive

Chemical Name: 2-Chloro-α-[2-(dimethylamino)ethyl]-α-phenylbenzenemethanol

Common Name: Clofedanol

Structural Formula:



Chemical Abstracts Registry No.: 791-35-5; 511-13-7 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Detigon	Bayer	W. Germany	1958
Detigon	Bayer	Italy	1959
Ulo	Riker	U.S.	1960
Tussiplegyl	Bayer	France	1969
Colorin	Nippon Shinyaku	Japan	1981
Abehol	Pliva	Yugoslavia	–
Anayok	Chibi	Italy	–
Baltix	Kobanyai	Hungary	–
Demax	Orma	Italy	–
Dencyl	Bencard	U.K.	–
Eletuss	Serpero	Italy	–
Eutus	Eupharma	Italy	–
Farmatox	Cifa	Italy	–
Fugatox	Ifisa	Italy	–
Gen-Tos	Morgens	Spain	–
Gutabex	Russi	Italy	–
Pectolitan	Kettelhack Riker	W. Germany	–
Prontosed	Francia	Italy	–
Refugal	Bayer	–	–
Tigonal	I.B.P.	Italy	–
Tuxidin	Gazzini	Italy	–
Tuxinil	Bieffe	Italy	–
Ulone	Riker	–	–

Raw Materials

o-Chlorobenzophenone
Acetonitrile
Sodium amide
Hydrogen
Methyl sulfate

Manufacturing Process

This compound may be produced by reacting o-chlorobenzophenone with acetonitrile in the presence of sodium amide or another strongly basic condensing agent, to form the nitrile of β-phenyl-β-o-chlorophenyl-hydracrylic acid, which is then hydrogenated to yield 1-phenyl-1-o-chlorophenyl-3-aminopropanol-1. The latter intermediate compound is subsequently dimethylated with an agent such as methyl sulfate to provide the desired end product 1-o-chlorophenyl-1-phenyl-3-dimethylaminopropanol.

References

Merck Index 2018
Kleeman & Engel p. 226
I.N. p. 244
REM p. 871
Lorenz, R., Gosswald, R. and Henecka, H.; U.S. Patent 3,031,377; April 24, 1962; assigned to Farbenfabriken Bayer AG, Germany

CHLORAL BETAINE

Therapeutic Function: Sedative

Chemical Name: Adduct of chloral hydrate with betaine

Common Name: –

Structural Formula: $CCl_3CH(OH)_2 \cdot (CH_3)_3N^+CH_2COO^-$

Chemical Abstracts Registry No.: 2218-68-0

Trade Name	Manufacturer	Country	Year Introduced
Beta-Chlor	Mead-Johnson	U.S.	1963

Raw Materials

Betaine hydrate
Chloral hydrate

Manufacturing Process

An intimate mixture of betaine hydrate (67.5 g) and chloral hydrate (100 g) was warmed to ca. 60°C when an exothermic reaction occurred and the mixture became pasty. It was then stirred at 60°C for 30 minutes. The residue solidified on cooling and was crystallized from a small amount of water. The product separated in hard, colorless prisms of MP 122.5° to 124.5°C (corr).

References

Merck Index 2026
Kleeman & Engel p. 184
Petrow, V., Thomas, A.J. and Stephenson, O.; U.S. Patent 3,028,420; April 3, 1962; assigned to The British Drug Houses Limited, England

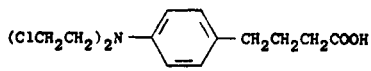
CHLORAMBUCIL

Therapeutic Function: Antineoplastic

Chemical Name: 4-[bis(2-chloroethyl)amino] benzenebutanoic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 305-03-3

Trade Name	Manufacturer	Country	Year Introduced
Leukeran	Burroughs-Wellcome	U.S.	1957
Leukeran	Wellcome	W. Germany	–
Leukeran	Wellcome	Switz.	–
Amboclorin	Simes	Italy	–
Chloraminophene	Techni-Farma	France	–
Linfolysin	I.S.M.	Italy	–

Raw Materials

Acetanilide
Hydrogen
Phosphorus oxychloride
Maleic acid
Ethylene oxide

Manufacturing Process

Acetanilide and maleic acid are condensed to give β-(p-acetaminobenzoyl)acrylic acid which is hydrogenated to give methyl-γ-(p-aminophenyl)butyrate. That is reacted with ethylene oxide and then with phosphorus oxychloride to give the methyl ester which is finally hydrolyzed to give chlorambucil.

References

Merck Index 2031
Kleeman & Engel p. 184
PDR p. 752
DOT 16 (5) 70 (1980)
I.N. p. 208
REM p. 1145
Phillips, A.P. and Mentha, J.W.; U.S. Patent 3,046,301; July 24, 1962; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.

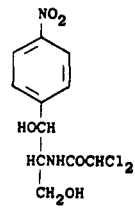
CHLORAMPHENICOL

Therapeutic Function: Antimicrobial

Chemical Name: D(-)-threo-2,2-dichloro-N-[β-hydroxy-α-(hydroxymethyl)-p-nitrophenethyl]-acetamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 56-75-7

Trade Name	Manufacturer	Country	Year Introduced
Leukomycin	Bayer	W. Germany	–
Chloromycetin	Warner-Lambert	Switz.	–
Chloromycetin	Parke-Davis	U.S.	1949
Chloramphenicol	MSD-Chibret	France	1954
Econochlor Sol	Alcon	U.S.	1975
Amboken	Gedeon Richter	Mexico	–
Amphicol	McKesson	U.S.	–
Antacin	Sumitomo	Japan	–
Aquamycin	Winzer	W. Germany	–
Bemacol	Int'l. Multifoods	U.S.	–
Berlicetin	Ankerwerk	E. Germany	–
Biocetin	Tasman Vaccine	U.K.	–
Biophenicol	Biochemie	Austria	–
Cafenolo	Benvegna	Italy	–
Catilan	Hoechst	W. Germany	–
Cebenicol	Chauvin-Blache	France	–

Trade Name	Manufacturer	Country	Year Introduced
Chemicetina	Erba	Italy	—
Chemyzin	S.I.T.	Italy	—
Chlomin	Knoll	W. Germany	—
Chloramex	Dumex	Denmark	—
Chloramol	Protea	Australia	—
Chloramphenicol-POS	Ursapharm	W. Germany	—
Chlorasol	Evsco	U.S.	—
Chlora-Tabs	Evsco	U.S.	—
Chloricol	Evsco	U.S.	—
Chlornitromycin	Farmakhim	Bulgaria	—
Chlorocid	Egyt	Hungary	—
Chloromycetin	Sankyo	Japan	—
Chloronitrin	Jenapharm	E. Germany	—
Chloroptic	Allergan	U.S.	—
Chlorsig	Sigma	Australia	—
Chloramidina	Arco	Switz.	—
Clorbiotina	Wassermann	Spain	—
Clorofenicina	Antibioticos	Spain	—
Clorosintex	Angelini	Italy	—
Cylphenicol	Trent	U.S.	—
Desphen	Despopharm	Switz.	—
Detreomine	Polfa	Poland	—
Devamycetin	Deva	Turkey	—
Dextromycin	V.N.I.Kh.F.J.	USSR	—
Doctamicina	Docta	Switz.	—
Farmicetina	Erba	Italy	—
Globenicol	Gist-Brocades	—	—
Glorous	Sanwa	Japan	—
Halomycetin	Kwizda	Austria	—
Hortfenicol	Hortel	Spain	—
Ismicetina	I.S.M.	Italy	—
Isophenicol	Bouchara	France	—
Kamaver	Engelhard	W. Germany	—
Kemicetin	Aesca	Austria	—
Kemicetine	Fujisawa	Japan	—
Kemicetine	Erba	Italy	—
Kemicetine	Vifor	Switz.	—
Kemicetine	I.C.N.	Canada	—
Kemicotine	Erba	U.K.	—
Kloromisin	Biofarma	Turkey	—
Labamicol	Labatec	Switz.	—
Levomycetin	Provita	Austria	—
Lomecitina	Locatelli	Italy	—
Loromisin	Atabay	Turkey	—
Medichol	Copanos	U.S.	—
Micochlorine	Continental Pharma	Belgium	—
Misetin	Dif-Dogu	Turkey	—
Mycetin	Farmigea	Italy	—
Mychel	Rachelle	U.S.	—
Mycinol	Horner	Canada	—
Neocetin	Uranium	Turkey	—
Novochlorcap	Novopharm	Canada	—
Novaphenicol	Nova	Canada	—
Novophenicol	Solac	France	—
Oftakloram	Tan	Turkey	—
Oftalent	Weifa	Norway	—
Oleomycetin	Winzer	W. Germany	—

Trade Name	Manufacturer	Country	Year Introduced
Ophtaphenicol	Faure	France	–
Oralmisetin	Mulda	Turkey	–
Otachron	Alpine	Austria	–
Otomycin	Pliva	Yugoslavia	–
Pantovernil	Heyden	W. Germany	–
Paraxin	Boehr/Mann.	W. Germany	–
Paraxin	Yamanouchi	Japan	–
Pedimycetin	T.E.M.S.	Turkey	–
Pentamycetin	Pentagone	Canada	–
Pentocetine	Ibsa	Switz.	–
Rivomycin	Rivopharm	Switz.	–
Romphenil	Zeria	Japan	–
Septicol	Streuli	Switz.	–
Serviclofen	Servipharm	Switz.	–
Sificetina	Sifi	Italy	–
Sno-Paenicol	Smith & Nephew	U.K.	–
Sopamycetin	Pharbec	Canada	–
Spersanicol	Dispersa	Switz.	–
Suismycetin	Lagap	Switz.	–
Synthomycetin	Abic	Israel	–
Tevocin	Tevcon	U.S.	–
Thilocanfol	Thilo	W. Germany	–
Tifomycine	Roussel	France	–
Veticol	Copanos	U.S.	–
Viceton	Int'l. Multifoods	U.S.	–
Viklorin	Ilsan	Turkey	–
Vitaklorin	Iltas	Turkey	–

Raw Materials

Sodium
β-Nitroethanol
Methyl dichloroacetate
Acetic anhydride
Benzaldehyde
Nitric acid
Hydrogen

Manufacturing Process

Chloramphenicol may be prepared by fermentation or by chemical synthesis. The fermentation route to chloramphenicol is described in U.S. Patents 2,483,871 and 2,483,892. To quote from U.S. Patent 2,483,892: The cultivation of *Streptomyces venezuelae* may be carried out in a number of different ways. For example, the microorganism may be cultivated under aerobic conditions on the surface of the medium or it may be cultivated beneath the surface of the medium, i.e., in the submerged condition, if oxygen is simultaneously supplied.

Briefly stated, the production of chloramphenicol by the surface culture method involves inoculating a shallow layer, usually less than about 2 cm, of a sterile, aqueous nutrient medium with *Streptomyces venezuelae* and incubating the mixture under aerobic conditions at a temperature between about 20° and 40°C, preferably at room temperature (about 25°C), for a period of about 10 to 15 days. The mycelium is then removed from the liquid and the culture liquid is then treated by methods described for isolating therefrom the desired chloramphenicol.

The synthetic route to chloramphenicol is described in U.S. Patent 2,483,884 as follows: 1.1 g of sodium is dissolved in 20 cc of methanol and the resulting solution added to a solution of 5 g of benzaldehyde and 4.5 g of β-nitroethanol in 20 cc of methanol. After standing at room temperature for a short time the gel which forms on the mixing of the reactants changes to a white insoluble powder. The precipitate is collected, washed with methanol and ether and then dried. The product thus produced is the sodium salt of

1-phenyl-2-nitropropane-1,3-diol.

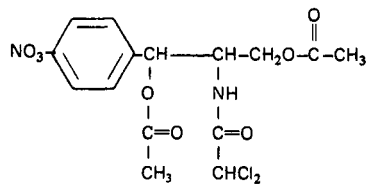
Eighteen grams of the sodium salt of 1-phenyl-2-nitropropane-1,3-diol is dissolved in 200 cc of glacial acetic acid. 0.75 g of palladium oxide hydrogenation catalyst is added and the mixture shaken at room temperature under three atmospheres pressure of hydrogen overnight. The reaction vessel is opened, 2.5 g of 10% palladium on carbon hydrogenation catalyst added and the mixture shaken under three atmospheres pressure of hydrogen for 3 hours. The catalyst is removed from the reaction mixture by filtration and the filtrate concentrated under reduced pressure. Fifty cubic centimeters of n-propanol is added to the residue and the insoluble inorganic salt removed by filtration.

The filtrate is treated with excess hydrochloric acid and evaporated to obtain a pale yellow oil. Five grams of the oil thus obtained is treated with 15 cc of saturated potassium carbonate solution and the mixture extracted with 50 cc of ether, then with 30 cc of ethyl acetate and finally with two 30 cc portions of ethanol. Evaporation of the solvent from the extract gives the following quantities of the desired 1-phenyl-2-aminopropane-1,3-diol: 0.5 g, 1.0 g and 3.1 g.

1.7 g of 1-phenyl-2-aminopropane-1,3-diol is treated with 1.6 g of methyl dichloroacetate and the mixture heated at 100°C for 1¼ hours. The residue is washed with two 20 cc portions of petroleum ether and the insoluble product collected. Recrystallization from ethyl acetate yields the desired (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diol in pure form; MP 154° to 156°C.

Five hundred milligrams of (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diol is added to a solution consisting of 1 cc of pyridine and 1 cc of acetic anhydride and the resulting reaction mixture heated at 100°C for ½ hour. The reaction mixture is evaporated to dryness under reduced pressure and the residue taken up in and crystallized from methanol. Recrystallization from methanol produces the pure diacetate of (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diol (MP 94°C).

Two hundred milligrams of the diacetate of (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diol is added to a mixture consisting of 0.25 cc of concentrated nitric acid and 0.25 cc of concentrated sulfuric acid at 0°C. The reaction mixture is stirred until solution is complete, poured onto 25 g of ice and the mixture extracted with ethyl acetate. The ethyl acetate extracts are evaporated under reduced pressure and the diacetate of (dl)-reg.-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol so produced purified by recrystallization from ethanol; MP 134°C.



Five hundred milligrams of the diacetate of (dl)-reg.-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol is dissolved in a mixture consisting of 25 cc of acetone and an equal volume of 0.2 N sodium hydroxide solution at 0°C and the mixture allowed to stand for one hour. The reaction mixture is neutralized with hydrochloric acid and evaporated under reduced pressure to dryness. The residue is extracted with several portions of hot ethylene dichloride, the extracts concentrated and then cooled to obtain the crystalline (dl)-reg.-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol; MP 171°C.

References

Merck Index 2035
Kleeman & Engel p. 185
PDR pp. 1321, 1379, 1606, 1999

OCDS Vol. 1 p. 75 (1977) & 2 pp. 28, 45 (1980)
I.N. p. 209
REM p. 1208
Bartz, Q.R.; U.S. Patent 2,483,871; October 4, 1949; assigned to Parke, Davis & Company
Crooks, H.M., Jr., Rebstock, M.C., Controulis, J. and Bartz, Q.R.; U.S. Patent 2,483,884; October 4, 1949; assigned to Parke, Davis & Company
Ehrlich, J., Smith, R.M. and Penner, M.A.; U.S. Patent 2,483,892; October 4, 1949; assigned to Parke, Davis & Company
Carrara, G.; U.S. Patent 2,776,312; January 1, 1957
Slack, R.; U.S. Patent 2,786,870; March 26, 1957; assigned to Parke, Davis & Company

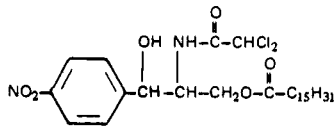
CHLORAMPHENICOL PALMITATE

Therapeutic Function: Antibacterial; antirickettsial

Chemical Name: D(–)-threo-1-p-nitrophenyl-2-dichloroacetamido-3-palmitoyloxypropane-1-ol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 530-43-8

Trade Nme	Manufacturer	Country	Year Introduced
Chloromycetin	Parke Davis	U.S.	1951
B-CP	Biokema	Switz.	–
Berlicetin	Ankerwerk	E. Germany	–
Chlorambon	Biokema	Switz.	–
Chloromisol	Maipe	Spain	–
Colimycin	Biofarma	Turkey	–
Detreopal	Polfa	Poland	–
Hortfenicol	Hortel	Spain	–
Levomicetina	Lepetit	Italy	–
Paidomicetina	Lafare	Italy	–
Protophenicol	Arco	Switz.	–
Sintomicetina	Lepetit	–	–

Raw Materials

Palmitoyl chloride
Chloramphenicol

Manufacturing Process

1,674 g of palmitoyl chloride is added to 1,870 g of D(–)-threo-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol (chloramphenicol) in 2,700 cc of pyridine and the solution stirred for 1 hour. The mixture is poured into 16 liters of water and the solid collected. Recrystallization of the crude product from benzene yields the desired D(+)-threo-1-p-nitrophenyl-2-dichloroacetamido-3-palmitoyloxypropane-1-ol in pure form: MP 90°C.

References

Merck Index 2036
PDR p. 1324
I.N. p. 210
REM p. 1209
Edgerton, W.H.; U.S. Patent 2,662,906; December 15, 1953; assigned to Parke, Davis & Co.

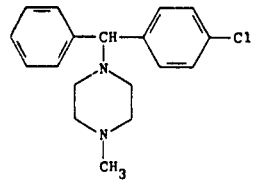
CHLORCYCLIZINE

Therapeutic Function: Antihistaminic

Chemical Name: 1-[(4-Chlorophenyl)phenylmethyl] -4-methylpiperazine

Common Name: Histachlorazine

Structural Formula:



Chemical Abstracts Registry No.: 82-93-9; 1620-21-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Perazil	Burroughs-Wellcome	U.S.	1949
Di-Paralene	Abbott	U.S.	1950
Histantin	Burroughs-Wellcome	–	–
Histofax	Burroughs-Wellcome	U.K.	–
Mantadil	Burroughs-Wellcome	U.S.	–
Prurisedine	Couvreur	Belgium	–
Trihistan	Revit	Switz.	–
Trihistan	Gea	Denmark	–
Trihistan	Weifa	Norway	–

Raw Materials

4-Chlorobenzhydryl chloride
Methyl piperazine

Manufacturing Process

0.08 mol (19 g) of 4-chlorobenzhydryl chloride and 0.16 mol (16 g) of methylpiperazine were mixed in about 20 cc of dry benzene. The flask containing the reaction mixture was covered by a watch glass and set in a steam bath, and heating was continued for 6 hours. The contents of the flask were partitioned between ether and water and the ethereal layer was washed with water until the washings were neutral. The ethereal layer was extracted successively with 30- and 10-cc portions of 3 N hydrochloric acid. On evaporation of the ether layer there remained a residue of 2.5 g. The aqueous extracts were united and basified with concentrated alkali. The oily base was taken into ether and dried over potassium carbonate. On evaporation of the ether, N-methyl-N'-(4-chlorobenzhydryl) piperazine was recovered in the form of a viscous oil in 75% yield. The N-methyl-N'-(4-chlorobenzhydryl) piperazine was dissolved in absolute alcohol and ethanolic hydrogen chloride added in excess. The dihydrochloride crystallized

on addition of absolute ether and was recrystallized from the same solvent mixture in the form of longish prisms melting at about 216°C.

References

Merck Index 2045
Kleeman & Engel p. 188
PDR p. 754
OCDS Vol. 1 p. 58 (1977)
I.N. p. 211
REM p. 1132
Baltzly, R. and Castillo, J.C.; U.S. Patent 2,630,435; March 3, 1953; assigned to Burroughs-Wellcome & Co. (U.S.A.) Inc.

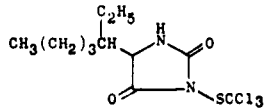
CHLORDANTOIN

Therapeutic Function: Topical antifungal

Chemical Name: 5-(1-Ethylpentyl)-3-[(trichloromethyl)thio]-2,4-imidazolidinedione

Common Name: Clodantoin

Structural Formula:



Chemical Abstracts Registry No.: 5588-20-5

Trade Name	Manufacturer	Country	Year Introduced
Sporostacin	Ortho	U.S.	1960
Sporostacin	Ortho	U.K.	—
Gynelan	Eisai	Japan	—

Raw Materials

Perchloromethyl mercaptan
5-(1-Ethylpentyl)hydantoin sodium salt

Manufacturing Process

Perchloromethylmercaptan is reacted with the sodium salt of 5-(1-ethylpentyl)hydantoin.

References

Merck Index 2047
Kleeman & Engel p. 225
I.N. p. 243
Kittleson, A.R.; U.S. Patent 2,553,770; May 22, 1951; assigned to Standard Oil Development Company
Hawley, R.S., Kittleson, A.R. and Smith, P.V. Jr.; U.S. Patent 2,553,775; May 22, 1951; assigned to Standard Oil Development Company

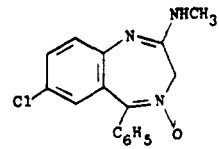
CHLORDIAZEPOXIDE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: 7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amino-4-oxide hydrochloride

Common Name: Metaminodiazepoxide hydrochloride; methaminodiazepoxide hydrochloride

Structural Formula:



(base)

Chemical Abstracts Registry No.: 438-41-5; 58-25-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Librium	Roche	W. Germany	1960
Librium	Roche	U.S.	1960
Librium	Roche	Switz.	1960
Librium	Sauter	U.K.	1960
Librium	Roche	France	1961
Librium	Roche	Italy	1961
SK-Lygen	SKF	U.S.	1976
Diazachel	Rachelle	U.S.	1976
A-Poxide	Abbott	U.S.	1977
Zetran	Hauck	U.S.	1978
Balance	Yamanouchi	Japan	—
Bent	Pharma. Farm. Spec.	Italy	—
Benzodiapin	Lisapharma	Italy	—
Binomil	Uriach	Spain	—
Cebrum	Cifa	Italy	—
Chemdipoxide	Chemo-Drug	Canada	—
Chlordiazachel	Rachelle	U.S.	—
Contol	Takeda	Japan	—
Diapax	Therapex	Canada	—
Dolibrax	Roche	France	—
Elenium	Polfa	Poland	—
Endequil	Panther-Osfa	Italy	—
Equibral	Ravizza	Italy	—
Gene-Poxide	Franca	Canada	—
Huberplex	Hubber	Spain	—
I-Liberty	I-Pharmacal	U.S.	—
Labican	Boniscontro-Gazzone	Italy	—
Lentotran	Farm Patria	Portugal	—
Lixin	I.S.M.	Italy	—
Medilium	Medic	Canada	—
Murcil	Reid-Provident	U.S.	—
Napoton	Chemimportexport	Rumania	—
Normide	Inibsa	Spain	—
Novopoxide	Novopharm	Canada	—
Omnalio	Estedi	Spain	—
Peast C	Sawai	Japan	—
Protensin	Elliott-Marion	Canada	—
Psicofar	Terapeutico	Italy	—

Trade Name	Manufacturer	Country	Year Introduced
Psicoterina	Francia	Italy	–
Radepur	Arzneimittelwerk Dresden	E. Germany	–
Reliberan	Geymonat Sud	Italy	–
Relium	Riva	Canada	–
Risolid	Dumex	Denmark	–
Sakina	Causytn	Italy	–
Sereen	Foy	U.S.	–
Smail	Saita	Italy	–
Solium	Horner	Canada	–
Sophiamin	Santen	Japan	–
Trakipearl	Hishiyama	Japan	–
Tropium	D.D.S.A.	U.K.	–
Untensin	Pharmador	S. Africa	–
Via-Quil	Denver	Canada	–

Raw Materials

2-Amino-5-chlorobenzophenone
Chloroacetyl chloride
Hydrogen chloride
Hydroxylamine
Methylamine

Manufacturing Process

A mixture of 202 g 2-amino-5-chlorobenzophenone, 190 g hydroxylamine hydrochloride, 500 cc pyridine and 1,200 cc alcohol was refluxed for 16 hours, then concentrated in vacuc to dryness. The residue was treated with a mixture of ether and water. The water was separated, the ether layer containing a considerable amount of precipitated reaction product was washed with some water and diluted with petroleum ether. The crystalline reaction product, 2-amino-5-chlorobenzophenone-α-oxime, was filtered off. The product was recrystallized from a mixture of ether and petroleum ether forming colorless prisms, MP 164° to 167°C.

To a warm solution (50°C) of 172.5 g (0.7 mol) of 2-amino-5-chlorobenzophenone-α-oxime in one liter glacial acetic acid were added 110 cc (1.47 mols) chloroacetyl chloride. The mixture was heated for 10 minutes at 50°C and then stirred at room temeprature for 15 hours. The precipitated yellow prisms, 2-chloromethyl-4-phenyl-6-chloroquinazoline 3-oxide hydrochloride, were filtered off, melting range 128° to 150°C with dec.

The acetic acid mother liquor, containing the rest of the reaction product, was concentrated in vacuo. The residue was dissolved in methylene chloride and washed with ice cold sodium carbonate solution. The organic solution was dried, concentrated in vacuo to a small volume and diluted with ether and petroleum ether. Fine yellow needles of 2-chloromethyl-4-phenyl-6-chloroquinazoline 3-oxide precipitated. The pure base was recrystallized from a mixture of methylene chloride, ether and petroleum ether, MP 133° to 134°C.

Ninety-eight grams of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide hydrochloride were introduced into 600 cc of ice cold 25% methanolic methylamine. The mixture was initially cooled to about 30°C and then stirred at room temperature. After 15 hours the reaction product which precipitated was filtered off. The mother liquor was concentrated in vacuo to dryness. The residue was dissolved in methylene chloride, washed with water and dried with sodium sulfate. The methylene chloride solution was concentrated in vacuo and the crystalline residue was boiled with a small amount of acetone to dissolve the more soluble impurities. The mixture was then cooled at 5°C for 10 hours and filtered. The crystalline product, 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide, was recrystallized from ethanol forming light yellow plates, MP 236° to 236.5°C.

A solution of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide in an equivalent amount of methanolic hydrochloric acid was diluted with ether and petroleum ether.

The precipitated hydrochloride was filtered off and recrystallized from methanol, MP 213°C.

References

Merck Index 2049
Kleeman & Engel p. 188
PDR pp. 993, 1510, 1606, 1723, 1999
OCDS Vol. 1 p. 365 (1977) & 2 p. 401 (1980)
DOT 9 (6) 236 (1973)
REM p. 1061
Sternbach, L.H.; U.S. Patent 2,893,992; July 7, 1959; assigned to Hoffmann-LaRoche, Inc.

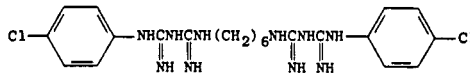
CHLORHEXIDINE

Therapeutic Function: Antimicrobial

Chemical Name: N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecane-di-imidamide

Common Name: 1,6-di(4'-Chlorophenyldiguanido)hexane

Structural Formula:



Chemical Abstracts Registry No.: 55-56-1

Trade Name	Manufacturer	Country	Year Introduced
Hibiclens	Stuart	U.S.	1976
Hibitane	I.C.I.	France	1976
Corsodyl	I.C.I.	U.K.	1977
Souplens	Chauvin-Blache	France	1978
Hibitane	Stuart	U.S.	1979
Hibistat	ICI	U.S.	1980
Abacil	Polfa	Poland	—
Aseptigel	Medicornea	France	—
Bactigras	Smith & Nephew	U.K.	—
Biotensid	Arcana	Austria	—
Cetal	Orapharm	Australia	—
Chlorhexamed	Blendax	W. Germany	—
Chlorohex	Geistlich	Switz.	—
Dacrine	Chibret	France	—
Dentosmin	VEB Leipz. Arz.	E. Germany	—
Desmanol	Schulke & Mayr	W. Germany	—
Desocort	Chauvin-Blache	France	—
Dialens	Chauvin-Blache	France	—
Eludril	Inava	France	—
Hexadol	Green Cross	Japan	—
Hibiscrub	ICI-Pharma	France	—
Hibiscrub	ICI	Japan	—
Hibitane	Sumitomo	Japan	—
Larylin	Beiersdorf	W. Germany	—
Lisium	Brunton Chemists	U.K.	—

Trade Name	Manufacturer	Country	Year Introduced
Manusan	Polfa	Poland	—
Maskin	Maruishi	Japan	—
Nolvasan	Fort Dodge	U.S.	—
Oronine	Otsuka	Japan	—
Pabron	Taisho	Japan	—
Plac Out	Bernabo	Argentina	—
Plak-Out	Hawe-Neos	Switz.	—
Plurexid	Sythemedica	France	—
Rhino-Blache	Chauvin-Blache	France	—
Rotersept	Roter	Neth.	—
Scarlene	Chauvin-Blache	France	—
Secalan	Zyma	Switz.	—
Septalone	Abic	Israel	—
Sterilone	Roter	Neth.	—
Trachitol	Engelhard	W. Germany	—
Vitacontact	Faure	France	—

Raw Materials

Hexamethylene bis-dicyandiamide
p-Chloroaniline hydrochloride

Manufacturing Process

25 parts of hexamethylene bis-dicyandiamide, 35 parts of p-chloroaniline hydrochloride and 250 parts of β-ethoxyethanol are stirred together at 130°C to 140°C for 2 hours under reflux. The mixture is then cooled and filtered and the solid is washed with water and crystallized from 50% aqueous acetic acid. 1,6-di(N_1,N_1'-p-chlorophenyldiguanido-N_5,N_5')hexane dihydrochloride is obtained as colorless plates of MP 258°C to 260°C.

The following is an alternative route: 19.4 parts of p-chlorophenyldicyandiamide, 9.4 parts of hexamethylenediamine dihydrochloride and 100 parts of nitrobenzene are stirred together and heated at 150°C to 160°C for 6 hours. The mixture is cooled, diluted with 200 parts of benzene and filtered. The solid residue is washed with benzene and crystallized from 50% acetic acid. 1,6-di(N_1, N_1'-p-chlorophenyldiguanido-N_5,N_5')hexane dihydrochloride is obtained.

References

Merck Index 2057
Kleeman & Engel p. 189
PDR p. 1781
I.N. p. 212
REM p. 1159
Rose, F.L. and Swain, G.; U.S. Patent 2,684,924; July 27, 1954; assigned to Imperial Chemical Industries, Ltd.

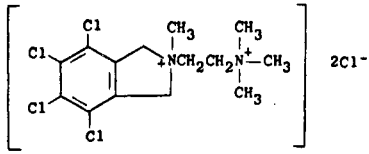
CHLORISONDAMINE CHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 4,5,6,7-Tetrachloro-1,3-dihydro-2-methyl-2-[2-(trimethylammonio)ethyl]-2H-isoindolium dichloride

Common Name: Chlorisondamine dimethochloride

Structural Formula:



Chemical Abstracts Registry No.: 69-27-2

Trade Name	Manufacturer	Country	Year Introduced
Ecolid Chloride	Ciba	U.S.	1956

Raw Materials

3,4,5,6-Tetrachlorophthalic anhydride
2-Dimethylaminoethyl amine
Lithium aluminum hydride
Methyl iodide
Silver chloride

Manufacturing Process

50 parts by weight of 3,4,5,6-tetrachlorophthalic anhydride is added with stirring and cooling to 30 parts by volume of 2-dimethylaminoethyl amine. The mixture is heated at 170°C for 4 minutes and the oily residue then dissolved in 200 parts by volume of hot ethanol. On cooling, N-(2'-dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide separates. It crystallizes from ethanol and melts at 184°-186°C.

6 parts by weight of N-(2'-dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide is extracted continuously with 300 parts by volume of dry ether in which have been dissolved 3.1 parts by weight of lithium aluminum hydride. After 48 hours the excess lithium aluminum hydride is destroyed by cautious addition of 9 parts by volume of ethyl acetate while stirring. There is then added in succession with stirring 3 parts by volume of water, 6 parts by volume of 15% aqueous sodium hydroxide and 9 parts by volume of water. The granular precipitate of lithium and aluminum salts are filtered and washed with ether. The ether is distilled off, yielding the crude, oily 4,5,6,7-tetrachloro-2-(2'-dimethylaminoethyl)-isoindoline. The above base is dissolved in 25 parts by volume of 90% ethanol and refluxed 2 hours with 6 parts by volume of methyl iodide. 4,5,6,7-tetrachloro-2-(2'-dimethylaminoethyl)-isoindoline dimethiodide separates during the reaction. It is collected by filtration and recrystallized from a mixture of ethanol and water; MP 244°-246°C.

4,5,6,7-tetrachloro-2-(2'-dimethylaminoethyl)-isoindoline dimethochloride is prepared by shaking an aqueous solution of the dimethiodide with an excess of freshly prepared silver chloride and evaporating to dryness the aqueous solution after removal of the silver salts. 4,5,6,7-tetrachloro-2-(2'-dimethylaminoethyl)-isoindoline dimethochloride is recrystallized from ethanol-ethylacetate; MP 276°-280°C.

References

Merck Index 2068
I.N. p. 213
Huebner, C.F.; U.S. Patent 3,025,294; March 13, 1962; assigned to Ciba Pharmaceutical Products, Inc.

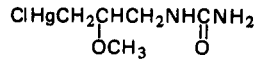
CHLORMERODRIN

Therapeutic Function: Diuretic

Chemical Name: 1-[3-(Chloromercuri)-2-methoxypropyl] urea

Common Name: Chlormeroprin

Structural Formula:



Chemical Abstracts Registry No.: 62-37-3

Trade Name	Manufacturer	Country	Year Introduced
Neohydrin	Lakeside	U.S.	1952
Asahydrin	Pharmacia	Sweden	–
Bucohydral	Vifor	Switz.	–
Mercloran	Parke Davis	U.S.	–
Merilid	Pharmacia	Sweden	–
Oricur	Medix	Denmark	–
Orimercur	Reder	Spain	–
Ormerdan	Parke Davis	U.S.	–

Raw Materials

Allyl urea
Mercuric acetate
Sodium chloride

Manufacturing Process

To a refluxing solution of 100 g of allyl urea and 600 ml of absolute methanol there was added with stirring a suspension of 319 g of mercuric acetate and 600 ml of absolute methanol and 60 ml of glacial acetate acid; complete solution resulted. After 6 hours of refluxing, the solution was cooled and clarified by filtration. To this solution there were added 50 g of sodium chloride and 240 ml of water. After a short time a heavy white precipitate settled out. This precipitate, which was 3-chloromercuri-2-methoxy-propylurea, was filtered, washed and dried.

References

Merck Index 2071
Kleeman & Engel p. 191
I.N. p. 213
REM p. 489
Foreman, E.L; U.S. Patent 2,635,983; April 21, 1953; assigned to Lakeside Laboratories, Inc.

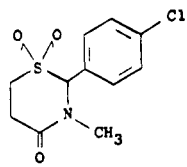
CHLORMEZANONE

Therapeutic Function: Tranquilizer

Chemical Name: 2-(4-Chlorophenyl)tetrahydro-3-methyl-4H-1,3-thiazin-4-one 1,1-dioxide

Common Name: Chloromethazanone

Structural Formula:



Chemical Abstracts Registry No.: 80-77-3

Trade Name	Manufacturer	Country	Year Introduced
Trancopal	Winthrop-Breon	U.S.	1958
Supotran	Winthrop	France	1965
Alinam	Lucien	France	–
Chlomedinon	Taiyo	Japan	–
Lumbaxol	Aldo Union	Spain	–
Metsapal	Leiras	Turkey	–
Muscotal	Farmos	Finland	–
Muskel	Winthrop	W. Germany	–
Myolespen	Dojin	Japan	–
Relizon	Mochida	Japan	–
Rexan	Labif	Italy	–
Rilaquil	Guidotti	Italy	–
Tanafol	A.M.S.A.	Italy	–
Trancote	Sawai	Japan	–
Transanate	Teikoku	Japan	–

Raw Materials

4-Chlorobenzaldehyde
β-Mercaptopropionic acid
Methylamine
Potassium permanganate

Manufacturing Process

A solution of 4-chlorobenzaldehyde is reacted with β-mercaptopropionic acid and with methylamine. The mixture is refluxed in benzene and water is removed from an overhead separator. The reaction mixture was cooled, washed with dilute ammonium hydroxide and water, and the benzene was removed by distillation in vacuo. The oily residue was taken up in ether from which it crystallized. The precipitate was recrystallized twice from ether to yield 2-(4-chlorophenyl)-3-methyl-4-metathiazanone.

A solution of 11.2 g of potassium permanganate in 100 ml of warm water was added dropwise to a well stirred solution of 10 g of 2-(4-chlorophenyl)-3-methyl-4-metathiazanone in 50 ml of glacial acetic acid. The temperature was kept below 30°C with external cooling. An aqueous sodium bisulfite solution was then added to remove the manganese dioxide. The thick whitish oil which separated was taken up in chloroform and the extract was washed with water. Removal of the chloroform by distillation in vacuo yielded an oily residue which solidified. The solid was recrystallized from isopropyl alcohol to give 5 g of the product, 2-(4-chlorophenyl)-3-methyl-4-metathiazanone-1,1-dioxide, MP 116.2° to 118.6°C (corr.).

References

Merck Index 2072
Kleeman & Engel p. 191
PDR p. 1934
DOT 9 (6) 243 (1973)
I.N. p. 214
REM p. 1074
British Patent 815,203; June 17, 1959; assigned to Sterling Drug, Inc.

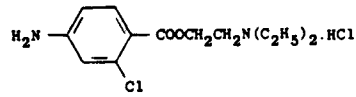
CHLOROPROCAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 4-amino-2-chlorobenzoic acid 2-diethylaminoethyl ester hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 3858-89-7; 133-16-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nesacaine	Astra	U.S.	1956
Nesacaine	Pennwalt	U.S.	–
Nesacaine	Strasenburgh	U.S.	–
Halestyn	–	–	–
Piocaine	Teikoku-Nagase	Japan	–

Raw Materials

2-Chloro-4-amino benzoic acid
β-Diethyl amino ethanol
Thionyl chloride
Hydrogen chloride

Manufacturing Process

In the first step, 2-chloro-4-aminobenzoyl chloride hydrochloride is prepared by refluxing a mixture of 25 cc of purified thionyl chloride and 10 g of 2-chloro-4-aminobenzoic acid until all of the solid has gone into solution. To the cooled solution is added 150 cc of dry ethyl ether. A brisk stream of dry hydrogen chloride is passed into the solution until the precipitation of 2-chloro-4-aminobenzoyl chloride hydrochloride is complete. The acyl halide is removed by filtration and dried in a vacuum desiccator.

In the second step, the diethylaminoethyl 2-chloro-4-aminobenzoate hydrochloride is prepared by refluxing equimolar proportions of the hydrochloride of β-diethylaminoethanol in a suitable inert solvent such as a mixture of dry toluene and tetrachloroethane and the hydrochloride of 2-chloro-4-aminobenzoyl chloride until the reaction as indicated by the cessation of hydrogen chloride evolution is complete. The supernatant solvents are decanted from the reaction product which can be conveniently purified by crystallization from absolute ethanol.

An alternative purification can be effected by dissolving the reaction product in water. The ester base is liberated by rendering the clarified aqueous solution alkaline. Removal of the base from the alkaline solution is achieved by extraction with a suitable solvent such as benzene or ether. The pure hydrochloride of diethylaminoethyl 2-chloro-4-aminobenzoate is then precipitated from the dried extract by the addition of dry hydrogen chloride. After removal by filtration and recrystallization from ethanol it is found to have a melting point of 173° to 174°C.

References

Merck Index 2131
Kleeman & Engel p. 193
PDR p. 594
OCDS Vol. 1 p. 11 (1977)
I.N. p. 220
REM p. 1050
Marks, H.C. and Rubin, M.I.; U.S. Patent 2,460,139; January 25, 1949; assigned to Wallace & Tiernan Products, Inc.

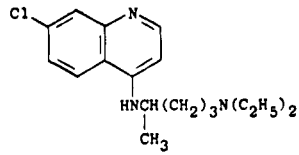
CHLOROQUINE PHOSPHATE

Therapeutic Function: Antimalarial

Chemical Name: N^4-(7-chloro-4-quinolinyl)-N',N'-diethyl-1,4-pentanediamine phosphate

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 50-63-5; 54-05-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nivaquine	Specia	France	1949
Aralen	Winthrop	U.S.	—
Arthrochin	Arcana	Austria	—
Artri	Badrial	France	—
Aspiquinol	Bayer	France	—
Avloclor	I.C.I.	U.K.	—
Chemochin	Pliva	Yugoslavia	—
Clorochina	Bayer	Italy	—
Cidanchin	Cidan	Spain	—
Delagil	Egyt	Hungary	—
Dichinalex	Savonna	Italy	—
Elestol	Bayer	France	—
Heliopar	Farmos	Finland	—
Imagon	Astra	—	—
Lagaquin	Legap	Switz.	—
Letaquine	Letap	Switz.	—
Malarex	Dumex	Denmark	—
Quinachlor	Cophar	Switz.	—
Quinercil	Robert et Carriere	France	—
Quinilon	Sumitomo	Japan	—
Resochin	Bayer	Japan	—
Rivoquine	Rivopharm	Switz.	—
Serviquin	Servipharm	Switz.	—
Silbesan	Atmos	W. Germany	—
Siragon	Biochemie	Austria	—
Tresochin	Bayer	—	—

Raw Materials

4,7-Dichloroquinoline
1-Diethylamino-4-aminopentane
Phosphoric acid

Manufacturing Process

105 g of 4,7-dichloroquinoline (MP 93° to 94°C) are heated with 200 g of 1-diethylamino-4-aminopentane for 7 hours in an oil bath to 180°C while stirring, until a test portion dissolved in diluted nitric acid does not show a precipitation with sodium acetate solution. The mixture is dissolved in diluted acetic acid and made alkaline by adding sodium lye.

The base is extracted with ether, dried with potassium carbonate, the ether removed by distillation and the residue fractionated. The 4-(5'-diethylaminopentyl-2'-amino)-7-chloroquinoline (BP 212° to 214°C/0.2 mm) is obtained. On cooling the compound solidifies crystalline. It melts, recrystallized from benzene, at 88°C. The base combines with phosphoric acid to yield a diphosphate salt.

References

Merck Index 2136
Kleeman & Engel p. 194
PDR p. 1902
OCDS Vol. 1 p. 341 (1977)
I.N. p. 220
REM p. 1218
Andersag, H., Breitner, S. and Jung, H.; U.S. Patent 2,233,970; March 4, 1941; assigned to Winthrop Chemical Company, Inc.

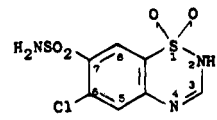
CHLOROTHIAZIDE

Therapeutic Function: Diuretic, Antihypertensive

Chemical Name: 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 58-94-6

Trade Name	Manufacturer	Country	Year Introduced
Diuril	Merck Sharp & Dohme	U.S.	1957
Diurilix	Theraplix	France	1959
Aldoclor	MSD	U.S.	–
Azide	Fawns & McAllan	Australia	–
Chlorosal	Teva	Israel	–
Chloroserpine	Schein	U.S.	–
Chlotride	Sharp & Dohme	W. Germany	–
Clotride	MSD	Italy	–
Diubram	Bramble	Australia	–
Diupres	MSD	U.S.	–
Diuret	Protea	Australia	–
Diurone	Knoll	Australia	–
Fenuril	Pharmacia	Sweden	–
Lyovac	MSD	U.S.	–
Niagar	Cimes	Belgium	–
Ro-Chlorozide	Robinson	U.S.	–
Salisan	Ferrosan	Denmark	–
Saluren	Croce Bianca	Italy	–
Saluretil	Gayoso Wellcome	Spain	–
Saluric	MSD	U.K.	–
Salutrid	Leiras	Finland	–

Trade Name	Manufacturer	Country	Year Introduced
SK-Chlorothiazide	SK&F	U.S.	–
Urinex	Orion	Finland	–

Raw Materials

m-Chloroaniline
Chlorosulfonic acid
Ammonia
Formic acid

Manufacturing Process

(A) m-Chloroaniline (64 g, 0.5 mol) was added dropwise with stirring to 375 ml of chlorosulfonic acid in a 3-liter round bottom, 3-necked flask cooled in an ice bath. Sodium chloride (350 g) was added portionwise over a period of 1 to 2 hours and the mixture then heated gradually in an oil bath to 150°C. After 3 hours at 150° to 160°C, the flask was cooled thoroughly in an ice bath and the contents treated with a liter of cold water. The product was extracted with ether and the extract washed with water and dried over sodium sulfate.

After removal of ether on the steam bath, the residual 5-chloroaniline-2,4-disulfonyl chloride, which may be crystallized from benzene-hexane MP 130° to 132°C, was cooled in an ice bath and treated with 150 ml of 28% ammonium hydroxide in a 2-liter Erlenmeyer flask. The mixture was heated on the steam bath for 1 hour, cooled and the product collected on the filter, washed with water and dried. Upon crystallization from dilute alcohol 5-chloro-2,4-disulfamylaniline was obtained as colorless needles, MP 251° to 252°C.

(B) A solution of 88 g of 5-chloro-2,4-disulfamylaniline in 1.1 liters of 88% formic acid was heated under reflux for 2 hours. After removal of 200 ml of solvent by distillation, one liter of water was added and the product collected, washed with water and dried. Crystallization from dilute alcohol afforded 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide as colorless needles, MP 342.5° to 343°C, as described in U.S. Patent 2,809,194.

References

Merck Index 2143
Kleeman & Engel p. 194
PDR pp. 830, 993, 1133, 1168, 1606, 1723
OCDS Vol. 1 pp. 321, 355 (1977) & 2 p. 395 (1980)
I.N. p. 221
REM p. 938
Novello, F.C.; U.S. Patent 2,809,194; October 8, 1957; assigned to Merck & Co., Inc.
Hinkley, D.F.; U.S. Patent 2,937,169; May 17, 1960; assigned to Merck & Co., Inc.

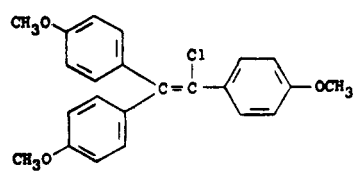
CHLOROTRIANISENE

Therapeutic Function: Estrogen

Chemical Name: 1,1',1"-(1-chloro-1-ethenyl-2-ylidene)tris[4-methoxybenzene]

Common Name: Tri-p-anisylchloroethylene

Structural Formula:



Chemical Abstracts Registry No.: 569-57-3

Trade Name	Manufacturer	Country	Year Introduced
TACE	Merrell	U.S.	1952
TACE FN	Merrell	France	1959
Anisene	Farmila	Italy	—
Clorotrisin	Courtois	Italy	—
Merbentul	Merrell	W. Germany	—
Triagen	Gentili	Italy	—

Raw Materials

Tris-p-methoxyphenyl ethylene
Chlorine

Manufacturing Process

The following method is described in U.S. Patent 2,430,891. To a solution of 10 parts of tris-p-methoxyphenyl ethylene in 35 to 40 parts of carbon tetrachloride is added a solution of 2.0 parts of chlorine in 50 parts of carbon tetrachloride, with stirring, and over a period of ½ hour. The carbon tetrachloride is then removed by distillation on a steam bath and the residual oil is recrystallized from 250 to 400 parts of methanol, decolorizing with charcoal or the like if necessary. Tris-p-methoxyphenyl chloroethylene is obtained in a yield of 65 to 75%. It melts at 113° to 114°C.

References

Merck Index 2149
Kleeman & Engel p. 195
PDR p. 1239
OCDS Vol. 1 p. 104 (1977)
I.N. p. 221
REM p. 988
Shelton, R.S. and Van Campen, M.G. Jr.; U.S. Patent 2,430,891; November 18, 1947; assigned to the Wm. S. Merrell Company

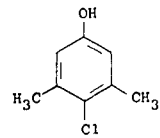
4-CHLORO-3,5-XYLENOL

Therapeutic Function: Topical antiseptic and disinfectant

Chemical Name: 4-Chloro-3,5-dimethylphenol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 88-04-0

Trade Name	Manufacturer	Country	Year Introduced
Septiderm	Fougera	U.S.	1960
Anti-Sept	Seamless	U.S.	—

Trade Name	Manufacturer	Country	Year Introduced
Bacillotox	Bode	W. Germany	—
Baktol	Bode	W. Germany	—
Cruex	Pharmacraft	U.S.	—
Dettol	Reckitt & Coleman	U.K.	—
Fungoid	Pedinol	U.S.	—
Ice-O-Derm	Wampole	U.S.	—
Metasep	Marion	U.S.	—
Micro-Guard	Sween	U.S.	—
Orlex	Baylor	U.S.	—
Otall	Saron Pharmacal	U.S.	—
Pedi-Pro Foot Powder	Pedinol	U.S.	—
Rezamid	Dermik	U.S.	—
Rocapyol	Plurosan	Austria	—
Roxenol	Saunders	Canada	—
Satinasept	Mack	W. Germany	—
Sween-Soft	Sween	U.S.	—
Valvanol	Asid	W. Germany	—
Zetar	Dermik	U.S.	—

Raw Materials

Sulfuryl chloride
m-5-Xylenol

Manufacturing Process

546 g of intermediate xylenol fraction having a crystallizing point of 45°C mixed with an equal weight of m-5-xylenol are placed in a suitable vessel, equipped with stirring gear, and 273 g of sulfuryl chloride are added slowly. The temperature rises in the course of the reaction to about 40°C. When all the sulfuryl chloride is added the reaction mixture is heated to 80°C and the acid gases removed as far as possible by air-blowing or any other suitable means. On cooling a quantity of the required chlor-xylenol separates out and is removed from the mother liquor. Further quantities of the material required can be isolated by vacuum distillation of the mother liquors and further crystallization. In all, 200 to 208 g of material substantially 2-chlor-m-5-xylenol can be obtained having a melting point of 112°C to 115°C. The material can be purified if desired by crystallization from a solvent such as a hydrocarbon.

References

Merck Index 2152
Kleeman & Engel p. 196
PDR pp. 1397, 1662, 1790
I.N. p. 222
REM p. 1168
Gladden, G.W.; U.S. Patent 2,350,677; June 6, 1944; assigned to W.W. Cocker

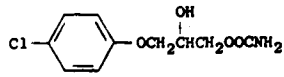
CHLORPHENESIN CARBAMATE

Therapeutic Function: Skeletal muscle relaxant

Chemical Name: 3-(4-chlorophenoxy)-1,2-propanediol-1-carbamate

Common Name: 3-p-chlorophenoxy-2-hydroxypropyl carbamate

Structural Formula:



Chemical Abstracts Registry No.: 886-74-8

Trade Name	Manufacturer	Country	Year Introduced
Maolate	Upjohn	U.S.	1967
Kolpicortin	Doetsch Grether	Switz.	—
Rinlaxer	Taisho	Japan	—

Raw Materials

p-Chlorophenol
Glyceryl monochlorohydrin
Phosgene
Ammonia

Manufacturing Process

1.0 mol of 3-p-chlorophenoxy-1,2-propanediol (chlorphenesin) is suspended in 1,000 ml of benzene in a 5-liter flask equipped with a dropping funnel, thermometer and stirrer. 1.0 mol of phosgene in 500 ml of cold, dry benzene is then added dropwise over a period of 45 minutes, the resulting mixture being maintained at 30°C until all solid material is dissolved. 1.0 mol of triethylamine is added dropwise and the resulting reaction mixture stirred for 45 minutes at 30°C following the addition. The reaction mixture is then cooled to 5°C and extracted repeatedly with 600 ml portions of cold water to remove the triethylamine hydrochloride.

The benzene fraction, containing the intermediate 3-p-chlorophenoxy-3-hydroxypropyl chlorocarbonate, is added to 600 ml of cold concentrated ammonium hydroxide and the resulting reaction mixture agitated vigorously at 5°C for 7 hours. The crude 3-p-chlorophenoxy-2-hydroxypropyl carbamate solid is then filtered off, dissolved in hot benzene, dried to remove all traces of water, and permitted to crystallize out. Several recrystallizations from solvent mixtures of benzene and toluene, with small amounts of acetone, produced a crystalline white solid in about 65% yield. The product is 3-p-chlorophenoxy-2-hydroxypropyl carbamate, melting at 89° to 91°C. The chlorphenesin starting material is made by reacting p-chlorophenol with glyceryl monochlorohydrin as noted in U.S. Patent 3,214,336.

References

Merck Index 2156
Kleeman & Engel p. 198
PDR p. 1850
OCDS Vol. 1 p. 118 (1977)
DOT 2 (4) 138 (1966)
I.N. p. 223
REM p. 927
Collins, R.J. and Matthews, R.J.; U.S. Patent 3,161,567; December 15, 1964; assigned to The Upjohn Company
Parker, H.E.; U.S. Patent 3,214,336; October 26, 1965; assigned to The Upjohn Company

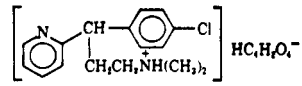
CHLORPHENIRAMINE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: γ-(4-Chlorophenyl)-N,N-dimethyl-2-pyridinepropanamine maleate

Common Name: Chlorophenyl pyridyl propyldimethylamine maleate; chlorphenamine maleate; chlorprophen-pyridamine maleate

Structural Formula:



Chemical Abstracts Registry No.: 113-92-8; 132-22-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Chlor-Trimeton	Schering	U.S.	1949
Teldrin	SKF	U.S.	1954
Drize	Ascher	U.S.	1967
Histaspan	U.S.V.	U.S.	1968
Allerbid	Amfre-Grant	U.S.	1971
Antagonate	Dome	U.S.	1973
Animing	Nisshin Seiyaku	Japan	1981
Ahiston	Ikapharm	Israel	—
Alaspan	Almay	U.S.	—
Alermine	Reid-Provident	U.S.	—
Allerdor	Fellows-Testagar	U.S.	—
Allergex	Protea	Australia	—
Allergin	Dellsberger	Switz.	—
Allergin	Sankyo	Japan	—
Allergisan	Pharmacia	Sweden	—
Allersan	Pharmacia	Sweden	—
Allertab	Tri-State	Italy	—
Allerton	Scalari	Italy	—
Anaphyl	Sam-On	Israel	—
Anthistamin-Sigletten	Rohm Pharma	W. Germany	—
Atalis-D	Kanto	Japan	—
Bismilla	Fuso	Japan	—
Chlo-Amine	Hollister-Stier	U.S.	—
Chlodamine	Maruko	Japan	—
Chloramate	Reid-Provident	U.S.	—
Chloramin	Langley	Australia	—
Chlor-Hab	Danbury	U.S.	—
Chlor-Mal	Rugby	U.S.	—
Chlormene	Robinson	U.S.	—
Chloroton	Cenci	U.S.	—
Chlorphen	Pro Doc	Canada	—
Chlor-Tel	Garden	U.S.	—
Chlortrone	Barlowe Cote	Canada	—
Clorten	Panthox & Burck	Italy	—
C-Meton	S.S. Pharm.	Japan	—
Cotuxinf	Sauba	France	—
Dallergy	Laser	U.S.	—
Decongestant Elixir	Schein	U.S.	—
Demazin	Schering	U.S.	—
Donatussin	Laser	U.S.	—
Dow-Chlorpheniramine	Dow	U.S.	—
Hexapneumine	Doms	France	—
Histachlor	Vitamix	U.S.	—
Histadur	Wynn	U.S.	—
Histaids	Ohio Medical	U.S.	—
Histalen	Len-Tag	U.S.	—
Histamic	Metro-Med	U.S.	—
Histapen	Douglas	New Zealand	—

Trade Name	Manufacturer	Country	Year Introduced
Histol	Blaine	U.S.	–
Isoclor	Arnar-Stone	U.S.	–
Kloromin	Halsey	U.S.	–
Lekrica	Yoshitomi	Japan	–
Lorphen	Geneva	U.S.	–
Neoallermin	Taiyo	Japan	–
Neorestamin	Kowa	Japan	–
Niratron	Progress	U.S.	–
Novahistine	Dow	U.S.	–
Novopheniram	Novopharm	Canada	–
Piriton	Allen & Hanbury	U.K.	–
Pneumopan	Sauba	France	–
Polaronic	Byk Essex	W. Germany	–
Poracemin	Horita	Japan	–
Probahist	Legere	U.S.	–
Propofan	Lepetit	France	–
Pyridamal	Bel-Mar	U.S.	–
Pyrroxate	Upjohn	U.S.	–
Quadrahist	Schein	U.S.	–
Rachelamine	Rachelle	U.S.	–
Rumicine	Cetrane	France	–
Singlet	Dow	U.S.	–
Synistamine	Sigmapharm	Austria	–
Trimeton	Essex	Italy	–
Trymegen	Medco	U.S.	–
U.R.I.	ICN	U.S.	–
Vitac	Egnaro	France	–

Raw Materials

4-Chlorobenzyl cyanide
2-Chloropyridine
Dimethylaminoethyl chloride
Sodium amide
Sulfuric acid

Manufacturing Process

See "Brompheniramine Maleate." The starting material is simply a chlorophenyl compound.

References

Merck Index 2157
Kleeman & Engel p. 196
PDR pp. 992, 1033, 1246, 1606
OCDS Vol. 1 p. 77 (1977)
I.N. p. 222
Sperber, N., Papa, D. and Schwenk, E.; U.S. Patents 2,567,245; September 11, 1951; and 2,676,964; April 27, 1954; both assigned to Schering Corporation

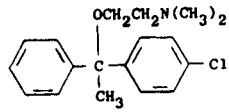
CHLORPHENOXAMINE HYDROCHLORIDE

Therapeutic Function: Muscle relaxant; Antiparkinsonism

Chemical Name: 2-[1-(4-chlorophenyl)-1-phenylethoxy]-N,N-dimethylethanamine hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 562-09-4; 77-38-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Phenoxene	Dow	U.S.	1959
Systral	Lucien	France	1963
Clorevan	Evans	U.K.	–
Contristamine	Noristan	S. Africa	–
Rodavan	Asta	W. Germany	–
Systral	Asta	W. Germany	–
Systral	Kyorin	Japan	–

Raw Materials

Methyl chloride
4-Chlorobenzophenone
Dimethylaminoethyl chloride
Magnesium
Sodium amide
Hydrogen chloride

Manufacturing Process

A Grignard solution is prepared by introducing methyl chloride into a boiling suspension of 36 g of magnesium in 1,000 cc of absolute ether until all the magnesium has reacted. 216 grams of 4-chloro-benzophenone are slowly added to the Grignard solution with ice cooling and stirring; after 15 hours, the thus-obtained product is poured into a mixture of 200 g of ammonium chloride and ice, whereupon it is separated with ether. The separated ether layer is dried with sodium sulfate, and the ether is distilled. The residual carbinol is added to a suspension of 45 g of sodium amide in 500 cc of toluene. To the thus-obtained mixture there are added 125 g of dimethylaminoethyl chloride, and the mixture is heated at boiling temperature for 3 hours with stirring.

The mixture is taken up with water and the base is extracted from the toluene with dilute hydrochloric acid. The hydrochloric solution is rendered alkaline with caustic soda, the base is separated with ether, dried, and after distillation of the ether fractionated in vacuo, BP at 0.05 mm Hg, 150° to 153°C. The basic ether is then dissolved in dry ether, and ether saturated with dry hydrogen chloride is added dropwise with stirring. An excess of hydrogen chloride must be avoided as it may produce decomposition to the corresponding diphenyl ethylene. The ether-moist hydrochloride is preferably dried at once in vacuo and subsequently reprecipitated from acetone-ether and then again dried in vacuo over phosphorus pentoxide. Hydrochloride, MP 128°C.

References

Merck Index 2159
Kleeman & Engel p. 198
OCDS Vol. 1 p. 44 (1977)
I.N. p. 223
REM p. 931
Arnold, H., Brock, N. and Kuhas, E.; U.S. Patent 2,785,202; March 12, 1957; assigned to Asta-Werke A.G. Chemische Fabrik, Germany

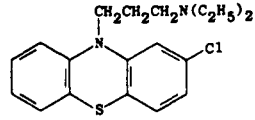
CHLORPROETHAZINE HCl

Therapeutic Function: Muscle relaxant; tranquilizer

Chemical Name: 2-Chloro-N,N-diethyl-10H-phenothiazine-10-propanamine

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 84-01-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Neuriplege	Genevrier	France	1961

Raw Materials

2-Bromo-2'-(3''-dimethylaminopropyl)-amino-4'-chlorodiphenyl sulfide
Copper powder
Potassium carbonate
Hydrogen chloride

Manufacturing Process

2-Bromo-2'-(3''-dimethylaminopropyl)-amino-4'-chlorodiphenylsulfide (10 g) is dissolved in dimethylformamide (80 cc). To this solution is added potassium carbonate (5 g) and copper powder (0.4 g). It is then heated under reflux for 48 hours, cooled, and the insoluble matter filtered off. After washing with dimethylformamide (20 cc), the filtrate is taken up in distilled water (200 cc). The base formed is extracted with ether (3 times with 50 cc), the ethereal solution is dried over sodium sulfate, the ether driven off on a water-bath and the residue distilled. In this way there is obtained 3-chloro-10-(3'-dimethylaminopropyl)-phenthiazine (6.4 g) which boils at 210°C to 225°C under 0.7 mm of mercury. The hydrochloride is made by the action of ethereal hydrogen chloride on the base dissolved in acetone; this hydrochloride melts at 180°C.

References

Merck Index 2161
OCDS Vol. 1 p. 379 (1977)
I.N. p. 224
Buisson, P.J.C., Gaillot, P. and Gaudechon, J.; U.S. Patent 2,769,002; October 30, 1956; assigned to Societe des Usines Chimiques Rhone-Poulenc (France)

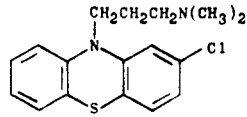
CHLORPROMAZINE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: 2-chloro-N,N-dimethyl-10H-phenothiazine-10-propanamine hydrochloride

Common Name: N-(3-dimethylaminopropyl)-3-chlorophenothiazine

Structural Formula:



(base)

Chemical Abstracts Registry No.: 69-09-0; 50-53-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Thorazine	SKF	U.S.	1954
Chlor-PZ	USV	U.S.	1973
Promapar	Parke Davis	U.S.	1973
Prochel	Rachelle	U.S.	1975
Acemin	Sankyo	Japan	—
Chloractil	D.D.S.A.	U.K.	—
Chlorazin	Streuli	Switz.	—
Chlorpromados	Holz	W. Germany	—
Chlor-Promanyl	Paul Maney	Canada	—
Chlorprom-Ez-Ets	Barlowe Cote	Canada	—
Contomin	Yoshitomi	Japan	—
Copormin	Kaken	Japan	—
Cromedazine	Fellows-Testagar	U.S.	—
Doimazin	Nippon Shinyaku	Japan	—
Elmarine	Elliott-Marion	Canada	—
Epokuhl	Kyowa	Japan	—
Esmind	Otsuka	Japan	—
Fenactil	Polfa	Poland	—
Hibanil	Mekos	Sweden	—
Hibernal	Leo	Sweden	—
Ishitomin	Kanto	Japan	—
Klorazin	Star	Finland	—
Klorproman	Orion	Finland	—
Klorpromex	Dumex	Denmark	—
Largactil	Specia	France	—
Megaphen	Bayer	W. Germany	—
Neurazine	Misr. Co-Pharm.	Egypt	—
Norcozine	Iwaki	Japan	—
Procalm	Bramble	Australia	—
Promachlor	Geneva	U.S.	—
Promacid	Knoll	Australia	—
Promactil	Wassermann	Spain	—
Promexin	Meiji	Japan	—
Promosol	Horner	Canada	—
Propafenin	Deut. Hydrierwerk	E. Germany	—
Protran	Protea	Australia	—
Prozil	Dumex	Denmark	—
Prozin	Lusofarmaco	Italy	—
Psychozine	O'Neal, Jones & Feldman	U.S.	—
Psylkatil	Farmos	Finland	—
Repazine	Lennon	S. Africa	—
Taroctyl	Taro	Israel	—
Wintermin	Shionogi	Japan	—

Raw Materials

Chlorophenthiazine
3-Dimethylamino-1-chloropropane
Sodium amide
Hydrogen chloride

Manufacturing Process

To a boiling suspension of 11.6 g of chlorophenthiazine (consisting of a mixture of two isomers melting at 196° to 198°C and 116° to 117°C, respectively, the latter in minor proportion) and 2.4 g of sodamide (80%) in 60 cc of xylene, there are added over a period of one hour 7.5 g of 3-dimethylamino-1-chloropropane in solution in its own weight of xylene. At the end of the addition, heating is continued for one hour under reflux. After cooling, the contents are taken up in acidified water and the xylene separated. The aqueous layer is made strongly alkaline by means of sodium hydroxide in order to liberate the base and this is extracted with ether. On distillation of the ethereal extract there is obtained 10-(3'-dimethylamino-propyl)-chlorophenthiazine which distills at 200° to 205°C under a pressure of 0.8 mm Hg. Its hydrochloride, recrystallized from chlorobenzene, melts at 177° to 178°C. The chlorophenthiazine may be prepared by reacting m-chlorodiphenylamine with sulfur in the presence of an iodine catalyst.

References

Merck Index 2163
Kleeman & Engel p. 199
PDR p. 1728
OCDS Vol. 1 pp. 319, 378 (1977), 2 p. 409 (1980) & 3 p. 72 (1984)
I.N. p. 224
REM p. 1086
Charpentier, P.; U.S. Patent 2,645,640; July 14, 1953; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

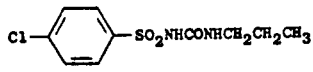
CHLORPROPAMIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: 4-chloro-N-[(propylamino)carbonyl] benzenesulfonamide

Common Name: 1-(p-chlorobenzenesulfonyl)-3-propylurea

Structural Formula:



Chemical Abstracts Registry No.: 94-20-2

Trade Name	Manufacturer	Country	Year Introduced
Diabinese	Pfizer	U.S.	1958
Diabinese	Pfizer	France	1960
Dynalase	Pharmadyne	U.S.	1980
Insulase	Premo	U.S.	1980
Abemide	Kabayashi	Japan	–
Adiaben	Belupo	Yugoslavia	–
Arodoc-C	Sawai	Japan	–
Biadibe	Guidotti	Italy	–
Bioglumin	Uriach	Spain	–
Catanil	De Angeli	Italy	–
Chloronase	Hoechst	W. Germany	–
Chloronase	Hoechst	Japan	–
Clordiabet	Carulla-Vekar	Spain	–
Clordiasan	Santos	Spain	–
Cloro-Hipoglucina	Lefa	Spain	–

Trade Name	Manufacturer	Country	Year Introduced
Diabemide	Guidotti	Italy	–
Diabet	Pages Maruny	Spain	–
Diabetabs	Wolfs	Belgium	–
Diabetasi	Biagini	Italy	–
Diabetoral	Boehr/Mann.	W. Germany	–
Diabexan	Crosara	Italy	–
Diabitex	Irapharm	Israel	–
Diamel-Ex	Ibsa	Switz.	–
Diamide	Kanto	Japan	–
Gliconorm	Gentili	Italy	–
Glucamide	Lemmon	U.S.	–
Glucosulfina	Infale	Spain	–
Meldian	Pliva	Yugoslavia	–
Melisar	Beolet	Italy	–
Melitase	Berk	U.K.	–
Mellitos	Ono	Japan	–
Melormin	Farmos	Finland	–
Normoglic	Salfa	Italy	–
Novopropamide	Novopharm	Canada	–
Orabet	Deva	Turkey	–
Orabines	Biofarma	Turkey	–
Orbin	Biles	Turkey	–
Prodiaben	Labif	Italy	–
Promide	Protea	Australia	–
Shuabate	Toyama	Japan	–
Stabinol	Horner	Canada	–
Toyomelin	Toyo Jozo	Japan	–

Raw Materials

Propyl isocyanate
p-Chlorobenzene sulfonamide
Triethylamine

Manufacturing Process

A solution of 54 g (0.64 mol) of propyl isocyanate in 60 ml of anhydrous dimethylformamide was added to a cold, well-stirred suspension of 81 g (0.42 mol) of dry p-chlorobenzenesulfonamide in 210 ml of anhydrous triethylamine during the course of 20 to 30 minutes. The mildly exothermic reaction was completed by allowing it to stand at room temperature for about 5 hours. The reaction mixture was then slowly added to 3 liters of cold 20% acetic acid during the course of about one hour, constant agitation being maintained throughout the addition.

After the addition was complete, the desired product, which had crystallized out, was filtered and washed well with about 2 liters of cold water. The crude material was then dissolved in 1 liter of cold 5% sodium carbonate and the resulting solution was immediately filtered from an insoluble gum. The product was then reprecipitated, by slowly adding the filtrate to 3 liters of 20% acetic acid. The precipitate, which is very nearly pure N-(p-chlorobenzenesulfonyl)-N'-propylurea, was then dried and subsequently recrystallized from about 800 ml of benzene to give a 59% yield of pure product, MP 129.2° to 129.8°C.

References

Merck Index 2164
Kleeman & Engel p. 200
PDR pp. 830, 993, 1034, 1417, 1999
OCDS Vol. 1 p. 137 (1977)
I.N. p. 225

REM p. 976
McLamore, W.M.; U.S. Patent 3,349,124; October 24, 1967; assigned to Chas. Pfizer Co., Inc.

CHLORPROTHIXENE

Therapeutic Function: Tranquilizer

Chemical Name: 3-(2-chloro-9H-thioxanthen-9-ylidene)-N,N-dimethyl-1-propanamine

Common Name: –

Structural Formula:

Chemical Abstracts Registry No.: 113-59-7; 6469-93-8 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Taractan	Roche	France	1960
Taractan	Roche	U.S.	1962
Clothixen	Yoshitomi	Japan	–
Cloxan	Orion	Finland	–
Minithixen	Spofa	Czechoslovakia	–
Paxyl	Ikapharm	Israel	–
Tra-Quilan	Eisai	Japan	–
Truxal	Tropon	W. Germany	–
Truxal	Toyama	Japan	–
Truxaletten	Tropon	W. Germany	–

Raw Materials

3-Dimethylaminopropyl chloride
2-Chlorothiaxanthone
Acetyl chloride
Magnesium
Ethyl bromide

Manufacturing Process

Chlorprothixene may be prepared as described in U.S. Patent 2,951,082. Magnesium turnings, 4.86 g (0.2 g-atom) was placed in a 500 ml reaction flask fitted with a mercury sealed stirrer, reflux condenser and a dropping funnel. Tetrahydrofuran, 50 ml and calcium hydride, 500 mg, were added. Ethyl bromide, 2.18 g and a crystal of iodine then were added. A vigorous reaction set in that evolved sufficient heat to induce refluxing. After 5 minutes, a solution of 3-dimethylaminopropyl chloride (dried over calcium hydride) in 50 ml of tetrahydrofuran was added to the refluxing solution at such a rate that gentle refluxing was maintained. The addition required 25 minutes.

The reaction mixture was stirred at reflux for an additional 30 minutes when nearly all of the magnesium had dissolved and determination of magnesium in an aliquot of the solution showed that an 82% yield of Grignard reagent had been obtained. The reaction mixture was cooled in an ice bath and stirred while 24.67 g (0.1 mol) of 2-chlorothiaxanthone was added over a period of 10 minutes. The reaction was stirred at room temperature for 30 minutes then allowed to stand overnight in the refrigerator. The tetrahydrofuran was evaporated at 50°C under reduced pressure. Benzene, 150 ml, was added to the residue.

The mixture was hydrolyzed in the cold by the dropwise addition of 50 ml of water. The benzene layer was separated by decantation and the gelatinous precipitate washed with two 100 ml portions of benzene.

The precipitate was then mixed with diatomaceous earth, collected on a filter, and washed with water and extracted with two 100 ml portions of boiling benzene. The aqueous filtrate was extracted with 50 ml of benzene, the combined benzene extracts washed with water and evaporated to dryness under reduced pressure. The crystalline residue, MP 140° to 147°C, weighed 30.8 g. Recrystallization from a mixture of benzene and hexane gave 27.6 g (83%) of 2-chloro-10-(3-dimethylaminopropyl)-10-hydroxythiaxanthene, MP 152° to 154°C. Analytically pure material from another experiment melted at 153° to 154°C.

2-Chloro-10-(3-dimethylaminopropyl)-10-hydroxythiaxanthene, 3.34 g (0.01 mol) obtained as described was dissolved in 15 ml of dry, alcohol-free chloroform. Acetyl chloride, 2.36 g (0.03 mol) was added and the clear yellow solution was refluxed for one hour in a system protected by a drying tube. The solvent then was evaporated on the steam bath under reduced pressure and the residue dissolved in absolute alcohol. The hydrochloride of 2-chloro-10-(3-dimethylaminopropylidene)-thiaxanthene was precipitated by the cautious addition of absolute ether. After drying at 70°C the yield of white crystalline 2-chloro-10-(3-dimethylaminopropylidene)-thiaxanthene hydrochloride, MP 189° to 190°C (to a cloudy melt), was 3.20 g (90%). This material is a mixture of geometric isomers.

Trans-2-chloro-9-(ω-dimethylamino-propylidene)-thioxanthene [MP 98°C, MP of the hydrochloride 225°C (corr.)], is a valuable medicinal agent, being used as a tranquilizer and antiemetic agent, whereas the corresponding cis isomer (MP 44°C, MP of the hydrochloride 209°C) is not useful for these indications, as described in U.S. Patent 3,115,502, which describes procedures for conversion of the cis to the trans form.

References

Merck Index 2166
Kleeman & Engel p. 200
PDR p. 1503
OCDS Vol. 1 p. 389 (1977)
DOT 9 (6) 229 (1973)
I.N. p. 225
REM p. 1087
Sprague, J.M. and Engelhardt, E.L.; U.S. Patent 2,951,082; August 30, 1960; assigned to Merck & Co., Inc.
Schlapfer, R. and Spiegelberg, H.; U.S. Patent 3,115,502; December 24, 1963; assigned to Hoffmann-LaRoche Inc.

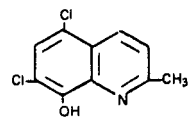
CHLORQUINALDOL

Therapeutic Function: Antibacterial

Chemical Name: 5,7-Dichloro-2-methyl-8-quinolinol

Common Name: Hydroxydichloroquinaldine, chloroquinaldol

Structural Formula:



Chemical Abstracts Registry No.: 72-80-0

Trade Name	Manufacturer	Country	Year Introduced
Sterosan	Geigy	U.S.	1954
Gynotherax	Bouchard	France	1967
Afungyl	Egyt	Hungary	–
Chinosicc	Schering	W. Germany	–
Chinotiol	Bouty	Italy	–
Gyno-Sterosan	Geigy	W. Germany	–
Intensol	Anasco	W. Germany	–
Lonjee	Sampo	Japan	–
Phyletten	Muller-Rorer	W. Germany	–
Quesil	Egyt	Hungary	–
Rub-All T	Toyama	Japan	–
Saprosan	C.I.F.	Rumania	–
Serviderm	Servipharm	Switz.	–
Siogeno	Geigy	W. Germany	–
Siogene	Geigy	France	–
Siosteran	Fujisawa	Japan	–
Steroxin	Geigy	U.K.	–

Raw Materials

8-Hydroxyquinaldine
Chlorine

Manufacturing Process

11.1 parts of 8-hydroxy-quinaldine are dissolved in 140 parts of formic acid. Chlorine is introduced into this solution under cooling, until the increase in weight corresponds to the required quantity of chlorine and a test of the chlorination mixtures gives no more dyestuff formation with diazo-benzene in an acetic acid solution.

When the chlorination is complete, the reaction mixture is poured into 1,000 parts of water and treated with a dilute sodium bisulfite solution, until no more reaction may be observed with starch-potassium iodide paper. Thereby the 5,7-dichloro-8-hydroxy-quinaldine separates out in form of a weakly yellowish colored precipitate. The same is filtered off and thoroughly washed with water.

After drying, 15 parts of 5,7-dichloro-8-hydroxy-quinaldine melting at 111°C to 112°C are obtained. When recrystallized from alcohol, the product is obtained in voluminous, slightly yellowish needles having the melting point of 111,5°C to 112°C.

References

Merck Index 2168
Kleeman & Engel p. 201
I.N. p. 225
Senn, E.; U.S. Patent 2,411,670; November 26, 1946; assigned to J.R. Geigy AG

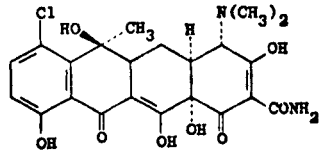
CHLORTETRACYCLINE

Therapeutic Function: Antibacterial

Chemical Name: 7-chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 57-62-5

Trade Name	Manufacturer	Country	Year Introduced
Aureomycin	Lederle	U.S.	1948
Aureomycine	Specia	France	1951
Aureum	Farmigea	Italy	–
Aufofac	Amer. Cyanamid	U.S.	–
B-Aureo	Biokema	Switz.	–
Chevita C-10	Chevita	W. Germany	–
Chlortet	Langley	Australia	–
Chrysomycin	Dispersa	Switz.	–
Clorteta	Pierrel	Italy	–
Colircusi Aureomicina	Cusi	Spain	–
CTC Soluble	Diamond Shamrock	U.S.	–
Vi-Mycin	Vineland Chemical	U.S.	–

Raw Materials

Sucrose
Corn steep liquor
S. aureofaciens bacterium

Manufacturing Process

The following process description is taken from U.S. Patent 2,987,449. An appropriate *S. aureofaciens* strain such as mutant S1308 (ATCC No. 12,748) is grown aerobically in a suitable inoculum medium. A typical medium used to grow the primary inoculum is prepared according to the following formula: sucrose, 20.0 g; corn steep liquor, 16.5 ml; ammonium sulfate, 2.0 g; calcium carbonate, 7.0 g; and water to 1,000 ml.

A 100 ml aliquot of this medium is placed in a 500 ml Erlenmeyer flask and sterilized by autoclaving for 20 minutes under 15 psi pressure. Spores of mutant strain *S. aureofaciens* S1308 (ATCC No. 12,748) are washed from an agar slant into the flask with sterile distilled water to form a suspension containing approximately 10^8 spores per milliliter. A 1.0 ml portion of this suspension is used to inoculate the fermentation media in the example which follows. A fermentation medium consisting of the following ingredients was prepared.

	Grams
$(NH_4)_2SO_4$	5.0
$CaCO_3$	9.0
NH_4Cl	1.5
$MgCl_2 \cdot 6H_2O$	2.0
$FeSO_4 \cdot 7H_2O$	0.06
$MnSO_4 \cdot 4H_2O$	0.05
$CoCl_2 \cdot 6H_2O$	0.005
$ZnSO_4 \cdot 7H_2O$	0.1
Corn steep liquor	25.0
Cornstarch	55.0
Water to 1,000 ml	

25 ml aliquots of this fermentation medium were placed in each of two 250 ml Erlenmeyer flasks and 0.5 ml of lard oil was added to each flask. Then 0.002 mg/ml of riboflavin was added to one flask, the other flask being retained as a control. The flasks were sterilized in an autoclave for 20 minutes under 15 psi pressure, then cooled to room temperature (25°±5°C). At this point, a 1.0 ml portion of inoculum of mutant strain *S. aureofaciens* S1308 (ATCC No. 12,748) was added to each of the two flasks. The flasks were incubated at 25°C for 120 hours on a rotary shaker operating at 180 rpm. Upon completion of the fermentation period the mashes were assayed for 7-chlorotetracycline content.

The increase in production due to the addition of riboflavin was very noticeable in the above example. A similar effect was reported for cupric sulfate pentahydrate addition according to U.S. Patent 3,050,446.

References

Merck Index 2170
Kleeman & Engel p. 203
PDR p. 1007
OCDS Vol. 1 p. 212 (1977)
I.N. p. 226
REM p. 1208
Duggar, B.M.; U.S. Patent 2,482,055; September 13, 1949; assigned to American Cyanamid Company
Niedercorn, J.G.; U.S. Patent 2,609,329; September 2, 1952; assigned to American Cyanamid Company
Winterbottom, R., Mendelsohn, H., Muller. S.A., and McCormick, J.R.D.; U.S. Patent 2,899,422; August 11, 1959; assigned to American Cyanamid Company
Miller, P.A., Goodman, J.J., Sjolander, N.O. and McCormick, J.R.D.; U.S. Patent 2,987,449; June 6, 1961; assigned to American Cyanamid Company
Goodman, J.J.; U.S. Patent 3,050,446; August 21, 1962; assigned to American Cyanamid Company

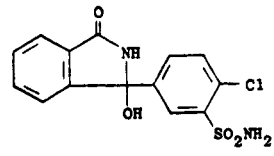
CHLORTHALIDONE

Therapeutic Function: Diuretic, antihypertensive

Chemical Name: 2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzenesulfonamide

Common Name: Chlortalidone

Structural Formula:



Chemical Abstracts Reigstry No.: 77-36-1

Trade Name	Manufacturer	Country	Year Introduced
Hygroton	Geigy	U.S.	1960
Hygroton	Ciba Geigy	France	1960
Hygroton	Ciba Geigy	Switz.	1960
Hygroton	Ciba Geigy	W. Germany	1960

Trade Name	Manufacturer	Country	Year Introduced
Hygroton	Ciba Geigy	U.K.	1960
Igroton	Geigy	Italy	1961
Thalitone	Boehr/Ingel.	U.S.	1982
Aquadon	Ikapharm	Israel	–
Hybasedock	Sawai	Japan	–
Hydoban	Medica	Finland	–
Hydro-Long	Sanorama	W. Germany	–
Hygroton	Pliva	Yugoslavia	–
Hygroton	Geigy	Japan	–
Hypertol	Farmos	Finland	–
Igrolina	Benedetti	Italy	–
Novothalidone	Novopharm	Canada	–
Regretron	U.S.V.	U.S.	–
Renon	Medal	Italy	–
Servidone	Servipharm	Switz.	–
Urid	Protea	Australia	–
Uridon	I.C.N.	Canada	–
Urolin	Sidus	Italy	–
Zambesil	Spemsa	Italy	–

Raw Materials

4-Chloro-3-amino-benzophenone-2'-carboxylic acid
Sodium nitrate
Hydrogen chloride
Sulfur dioxide
Thionyl chloride
Ammonia

Manufacturing Process

15 parts of aqueous 46% sodium nitrite solution are gradually added to a mixture of 27.5 parts of 4-chloro-3-amino-benzophenone-2'-carboxylic acid, 200 parts of glacial acetic acid and 20 parts of 37% hydrochloric acid at 0° to 10°C. The solution of the diazonium salt is poured into an ice-cooled mixture of 200 parts of 30% sulfur dioxide solution in glacial acetic acid and 3 parts of crystallized cupric chloride in 15 parts of water. Nitrogen is developed and, after a short time, the 4-chloro-2'-carboxy-benzophenone-3-sulfochloride crystallizes out. After 1 hour it is filtered off and washed with water. MP 178° to 182°C.

35.9 parts of 4-chloro-2'-carboxy-benzophenone-3-sulfochloride and 50 parts of thionyl chloride are heated first for 3 hours at 30° to 35°C and then for 1 hour at 45°C. The excess thionyl chloride is distilled off in the vacuum, the dichloride, 3-chloro-3-(3'-chlorosulfonyl-4'-chlorophenyl)phthalide, which remains as a crystallized mass is dissolved in 150 parts of chloroform and a mixture of 200 parts of 25% aqueous ammonia solution and 200 parts of ethanol is added dropwise at about 10°C while stirring and cooling. After stirring for 1 hour at 40°C, the solvent is distilled off in the vacuum and diluted hydrochloric acid is added to the residue whereupon the 1-oxo-3-(3'-sulfamyl-4'-chloro-phenyl)-3-hydroxy-isoindoline which is tautomeric to the 4-chloro-2'-carbamyl-benzophenone-3-sulfonamide, separates out. On recrystallizing from diluted ethanol, the isoindoline derivative melts at 215°C on decomposition.

Instead of reacting the dichloride in aqueous solution with ammonia, it can also be reacted at -50° to -40°C with a great excess of liquid ammonia. After removal of the ammonia, the crude product obtained is recrystallized as described above.

References

Merck Index 2171
Kleeman & Engel p. 202

PDR pp. 509, 676, 682, 830, 993, 1326, 1606, 1786, 1813, 1820, 1999
OCDS Vol. 1 p. 322 (1977)
DOT 16 (1) 32 (1980)
I.N. p. 226
REM p. 938
Graf, W., Schmid, E. and Stoll, W.G.; U.S. Patent 3,055,904; September 25, 1962; assigned to Geigy Chemical Corporation

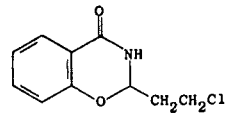
CHLORTHENOXAZINE

Therapeutic Function: Antipyretic; analgesic

Chemical Name: 2-(2-Chloroethyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 132-89-8

Trade Name	Manufacturer	Country	Year Introduced
Reugaril	Farber	Italy	1966
Apirogen	Dessy	Italy	—
Betix	Saba	Italy	—
Fiobrol	Geigy	W. Germany	—
Ossazin	Scalari	Italy	—
Ossazone	Brocchieri	Italy	—
Ossipirina	Radiumpharma	Italy	—
Oxal	Saita	Italy	—
Reulin	Isola-IBI	Italy	—
Reumital	Farge	Italy	—
Valtorin	Boehr./Ingel.	—	—

Raw Materials

Acrolein
Hydrogen chloride
Salicylamide

Manufacturing Process

A mixture of 4 liters chloroform and 1,050 cc ethanol was saturated with dry hydrogen chloride gas at -5°C to +5°C in a vessel having a net volume of 15 liters and provided with a stirring device, reflux cooler, gas feed line, thermometer and dropping funnel. 455 g acrolein which had been precooled to 0°C were added dropwise to the solution over a period of 1 to 2 hours while maintaining the temperature below +5°C and vigorously stirring. 1,070 g salicylamide and 1,080 g glacial acetic acid were added to the resulting solution of β-chloropropionaldehyde acetal, thereby forming a suspension which was heated to 60°C while stirring. A clear solution was formed which was maintained at 60°C for an additional hour. The solution was allowed to cool to about 40°C and was then washed with water by passing a strong stream of water under the surface of the chloroform and continuously withdrawing the upper phase. When the water had reached a pH of 3–4, the precipitated reaction product was separated by

vacuum filtration. The chloroform phase of the filtrate was evaporated under a weak vacuum and the residue was combined with the precipitate first obtained. The combined products were stirred with 2 liters of a 5% sodium hydroxide solution. The raw reaction product was then washed with water, dried and recrystallized from ethanol. The product had the melting point of 146°C to 147°C (decomposition). The yield was 1,260 g, corresponding to 76% of the theoretical yield.

References

Merck Index 2172
Kleeman & Engel p. 203
I.N. p. 226
Ohnacker, G. and Scheffler, H.; U.S. Patent 2,943,087; June 28, 1960; assigned to Dr. Karl Thomae G.m.b.H. (Germany)

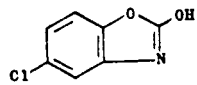
CHLORZOXAZONE

Therapeutic Function: Skeletal muscle relaxant

Chemical Name: 5-chloro-2(3H)-benzoxazolone

Common Name: 5-chloro-2-hydroxybenzoxazole

Structural Formula:



Chemical Abstracts Registry No.: 95-25-0

Trade Name	Manufacturer	Country	Year Introduced
Paraflex	McNeil	U.S.	1958
Benzoflex	Benzon	Denmark	—
Biomioran	Bioindustria	Italy	—
Chroxin	Kanyo	Japan	—
Chlozoxine	Sanko	Japan	—
Deltapyrin	Kodama	Japan	—
Escoflex	Streuli	Switz.	—
Framenco	Fuso	Japan	—
Kiricoron	Sampo	Japan	—
Mesin	Yamanouchi	Japan	—
Myoflex	Pliva	Yugoslavia	—
Myoflexin	Chinoin	Hungary	—
Oxyren	Astra	—	—
Paraflex	Cilag	W. Germany	—
Pathorysin	Kowa	Japan	—
Remoflex	Belupo	Yugoslavia	—
Solaxin	Eisai	Japan	—
Sorazin	Toho	Japan	—
Trancrol	Mohan	Japan	—

Raw Materials

2-Amino-5-chlorobenzoxazole
Hydrogen chloride
Sodium hydroxide

Manufacturing Process

A solution of 16.9 g (0.1 mol) of 2-amino-5-chlorobenzoxazole in 200 ml of 1 N HCl is refluxed until precipitation is complete. The resulting solid is collected by filtration, dissolved in 200 ml of 1 N NaOH and the solution extracted with 50 ml of ether. Acidification of the alkaline solution gives a precipitate which is purified by crystallization from acetone to give 2-hydroxy-5-chlorobenzoxazole melting at 191° to 191.5°C.

References

Merck Index 2174
Kleeman & Engel p. 204
PDR pp. 830, 993, 1093, 1441, 1606, 1999
OCDS Vol. 1 p. 323 (1977)
I.N. p. 227
REM p. 926
Marsh, D.F.; U.S. Patent 2,895,877; July 21, 1959; assigned to McNeil Laboratories, Inc.

CHOLINE DIHYDROGEN CITRATE

Therapeutic Function: Lipotropic

Chemical Name: (2-Hydroxyethyl)trimethylammonium citrate

Common Name: –

Structural Formula: $[HOCH_2CH_2N^+(CH_3)_3]\,[C_6H_7O_7^-]$

Chemical Abstracts Registry No.: 77-91-8

Trade Name	Manufacturer	Country	Year Introduced
Chothyn	Flint	U.S.	1945
Citrocholine	United	U.S.	1949
Lipocholin	–	–	–

Raw Materials

Trimethyl amine
Ethylene oxide
Citric acid

Manufacturing Process

30 lb of trimethylamine were added to 70.4 lb of methyl alcohol to which 9.2 lb of water had previously been added. To the resulting solution in a closed vessel 23 lb of ethylene oxide gas were introduced and the resulting mixture then maintained at a temperature of 16°C to 30°C and agitated for 6 hours. During the reaction the pressure in the reaction vessel varied from about 17.5 psi at the start of the reaction to 0 psi at the end of the reaction. The resulting solution was then added with agitation to a refluxing solution of 40 liters of isopropyl alcohol containing 95 lb of citric acid dissolved therein. This mixture was then cooled to 0°C and held at that temperature overnight. The white crystalline choline dihydrogen citrate which formed was separated from the solvent mixture by filtration and dried in vacuo. 117 lb of anhydrous, crystalline choline dihydrogen citrate having a purity of 99.6% were obtained. This was a yield of 78% based on the amount of trimethylamine employed.

References

Merck Index 2187
I.N. p. 227
REM p. 1026
Klein, H.C., DiSalvo, W.A. and Kapp, R.; U.S. Patent 2,870,198; January 20, 1959; assigned to Nopco Chemical Co.

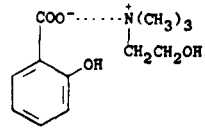
CHOLINE SALICYLATE

Therapeutic Function: *Analgesic, antipyretic*

Chemical Name: 2-hydroxy-N,N,N-trimethyl-ethanaminium salt with 2-hydroxy benzoic acid

Common Name: Choline salicylic acid salt

Structural Formula:



Chemical Abstracts Registry No.: 2016-36-6

Trade Name	Manufacturer	Country	Year Introduced
Arthropan	Purdue Frederick	U.S.	1959
Actasal	Purdue Frederick	U.S.	1959
Atilen	Spofa	Czechoslovakia	–
Audax	Napp	U.K.	–
Audax	Ethimed	S. Africa	–
Audax	Mundipharma	W. Germany	–
Bonjela	Lloyds	U.K.	–
Mundisal	Mundipharma	Switz.	–
Mundisal	Erco	Denmark	–
Otho	Purdue Frederick	U.S.	–
Sachol	Polfa	Poland	–
Rheumavincin	Owege	W. Germany	–
Salicol	Sais	Italy	–
Satibon	Grelan	Japan	–
Syrap	Carrion	France	–
Teejel	Napp	U.K.	–
Tegunor	Mundipharma	W. Germany	–
Trilisate	Purdue Frederick	U.S.	–

Raw Materials

Choline chloride
Sodium salicylate

Manufacturing Process

A method of preparation is to react an acid salt of choline (such as choline chloride or choline bromide) with an alkaline salt of salicylic acid (such as sodium salicylate, potassium salicylate, or magnesium salicylate) in an alcoholic media.

References

Merck Index 2189
Kleeman & Engel p. 205
I.N. p. 228
Broh-Kahn, E.H. and Sasmor, E.J.; U.S. Patent 3,069,321; December 18, 1962; assigned to Laboratories for Pharmaceutical Development, Inc.

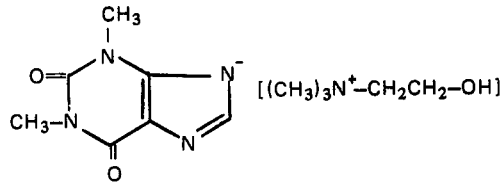
CHOLINE THEOPHYLLINATE

Therapeutic Function: Smooth muscle relaxant

Chemical Name: Theophylline cholinate

Common Name: Oxotriphylline; oxytrimethylline

Structural Formula:



Chemical Abstracts Registry No.: 4499-40-5

Trade Name	Manufacturer	Country	Year Introduced
Sabidal S.R.	Zyma	U.K.	1983
Brondaxin	Ferrosan	Denmark	–
Cholecyl	Substancia	Spain	–
Choledyl	Nepera	U.S.	–
Cholegyl	Substantia	Neth.	–
Chophyllin	Ferraton	Denmark	–
Euspirax	Asche	W. Germany	–
Glomax	Midlands Int. Chem.	U.K.	–
Isoperin	Spofa	Yugoslavia	–
Monofillina	Manetti Roberts	Italy	–
Novotriphyl	Novopharm	Canada	–
Rouphylline	Rougier	Canada	–
Sclerofillina	Medici Domus	Italy	–
Teocolina	Nessa	Spain	–
Teofilcolina	Salfa	Italy	–
Teovent	Ferrosan	Denmark	–

Raw Materials

Theophylline
Choline bicarbonate

Manufacturing Process

18 parts by weight of theophylline are added to 37.8 parts by weight of aqueous choline bicarbonate (47% assay) and the mixture stirred and heated at 80°C to 90°C until the evolution

of carbon dioxide has ceased and complete solution effected. Water is separated from the reaction mixture by distillation under a vacuum sufficient to keep the still temperature between 50°C and 55°C. After about 15 parts by weight of water have been separated, about 80 parts by weight of isopropyl alcohol are added and the mixture subjected to further distillation under a vacuum sufficient to keep the mixture boiling at about 40°C. The distillation removes some of the water as an azeotrope with the isopropyl alcohol. During the removal of the water-isopropyl alcohol azeotrope a crystalline precipitate forms. The mixture is further cooled slowly to 5°C and the crystalline precipitate filtered off. The choline theophyllinate crystals are then washed with isopropyl alcohol and dried under vacuum at about 70°C. A second crop of the product may be obtained from the mother liquor by further reduction in volume and cooling. A yield of 90.5% of theory of choline theophyllinate is obtained completely free of inorganic salts.

References

Merck Index 2190
I.N. p. 228
REM p. 872
Ladenburg, K., Duesel, B.F. and Fand, T.I.; U.S. Patent 2,776,287; January 1, 1957; assigned to Nepera Chemical Co., Inc.

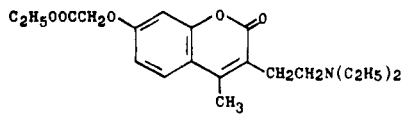
CHROMONAR HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: [[3-[2-(Diethylamino)ethyl]-4-methyl-2-oxo-2H-1-benzopyran-7-yl]oxy] acetic acid ethyl ester hydrochloride

Common Name: Carbocromene

Structural Formula:



(base)

Chemical Abstracts Registry No.: 655-35-6; 804-10-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Intensain	Hoechst	Switz.	1963
Intensain	Cassella	W. Germany	1963
Intensain	Diamant	France	1966
Intensain	Pierrel	Italy	1971
Antiagor	I.S.M.	Italy	—
Beta-Intensain	Cassella	W. Germany	—
Cardiocap	Fidia	Italy	—
Cromene	Scharper	Italy	—
Intensain	Takeda	Japan	—
Intensacrom	Albert Farma	Spain	—
Sedo-Intensain	Diamant	France	—
Intenkordin	Polfa	Poland	—

Raw Materials

Resorcinol
2-(2-Diethylaminoethyl)acetic acid ethyl ester
Bromoacetic acid ethyl ester

Manufacturing Process

18.7 g of 3-β-diethylaminoethyl-4-methyl-7-hydroxy-coumarin chlorhydrate are dissolved in 200 cc methyl ethyl ketone and 18 g anhydrous potassium carbonate are added. The mixture is stirred for 1 hour at 70°C and then 12 g bromoacetic acid ethyl ester are allowed to drop in. The reaction mixture is stirred under reflux for 9 hours and then it is filtered off with suction in the heat. The filtrate is concentrated in the vacuum to dryness and the resultant residue is dissolved in ether. The etheric solution is washed with diluted caustic soda solution for several times and, subsequently, dried with Glauber's salt. By introduction of hydrochloric acid gas into the etheric solution the reaction product is precipitated in the form of chlorhydrate. Yield: 15 g of 3-β-diethylaminoethyl-4-methyl-coumarin-7-ethyl oxyacetate chlorhydrate having a melting point of 154° to 156°C (= 63% of the theory).

The starting material is produced by reacting resorcinol with 2-(2-diethylaminoethyl)acetic acid ethyl ester.

References

Merck Index 2217
Kleeman & Engel p. 150
OCDS Vol. 1 p.331 (1977)
I.N. p. 185
Ritter, H., Hanau, K., Beyerle, R. and Nitz, R.-E.; U.S. Patent 3,282,938; November 1, 1966; assigned to Cassella Fabrwerke Mainkur AG, Germany

CHYMOPAPAIN

Therapeutic Function: Proteolytic enzyme used in chemical nucleolysis

Chemical Name: See "Structural Formula" below.

Common Name: –

Structural Formula: Chymopapain is a sulfhydryl enzyme similar to papain. Has components of molecular weight about 35,000.

Trade Name	Manufacturer	Country	Year Introduced
Chymodiactin	Smith	U.S.	1982
Chemolase	Ortho-Tex	U.S.	–
Discase	Travenol	U.S.	–

Chemical Abstracts Registry No.: 9001-09-06

Raw Materials

Papaya latex
Hydrochloric acid

Manufacturing Process

The undried latex of papaya is mixed with about three times its weight of hundredth normal hydrochloric acid. To this mixture is then added dilute hydrochloric acid (about normal) until a pH of substantially 2 has been attained. The acidified latex is next allowed to stand over night or longer in a cold place (0°C to 10°C). The material still in solution is then separated out, by any convenient means, such as filtration through paper. From the soluble portion, a

small amount of inert protein is precipitated, by half saturation with sodium chloride at about 10°C. The desired enzyme is next precipitated as a nearly pure protein by raising the concentration of salt to full saturation, while the pH is kept at a level of substantially 2, by the addition of normal alkali, if necessary. The precipitate of protein is removed by any suitable means, and may be kept as a thick paste out of contact with the air, and in the cold. The keeping properties at higher temperatures are enhanced by addition of enough alkali to the protein to bring its pH to 4.5-6.0.

This protein may be further purified, if desired, and eventually may be crystallized, by redissolving the paste in saturated sodium chloride solution by adjusting the pH to 4.5-6.0, and reprecipitating the enzyme protein by the gradual addition of acid in the cold, until a pH of approximately 2.0 is obtained; or, the purification may be accomplished by dissolving the protein in acid at a pH of 2, and then precipitating the enzyme, by increasing the concentration of salt.

When the activity and other properties of the several times recrystallized new enzyme protein are compared with those of the uncrystallized precipitate obtained in the first stages of the process, it is found that even in the first stages, the enzyme is present in sufficiently pure form for most purposes.

References

Merck Index 2244
PDR p. 1732
DOT 19 (7) 413 (1983) & (8) 454 (1983)
I.N. p. 229
REM p. 1036
Jansen, E.F. and Balls, A.K.; U.S. Patent 2,313,875; March 16, 1943; assigned to Government of the U.S.A.
Stern, I.J.; U.S. Patent 3,558,433; January 26, 1971; assigned to Baxter Laboratories, Inc.

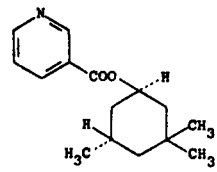
CICLONICATE

Therapeutic Function: Vasodilator

Chemical Name: 3-Pyridinecarboxylic acid 3,3,5-trimethylcyclohexyl ester

Common Name: Cyclonicate

Structural Formula:



Chemical Abstracts Registry No.: 53449-58-4

Trade Name	Manufacturer	Country	Year Introduced
Bled	Poli	Italy	1978
Bled	Poli	Switz.	1981
Cortofludan	Knoll	W. Germany	—
Elastan 200	Byk Liprandi	Argentina	—

Raw Materials

trans-3,3,5-Trimethylcyclohexanol
Niacin chloride hydrochloride
Sodium hydroxide

Manufacturing Process

To a solution of 142 g (1 mol) of trans-3,3,5-trimethylcyclohexanol in 400 cc of anhydrous benzene heated to 70°C is added gradually 178 g (1 mol) of niacin chloride hydrochloride. Heating is carried out under reflux conditions for 3 hours, the solution is cooled, the ester hydrochloride is filtered off and then recrystallized in an ethanol-ethyl ether mixture to obtain 227 g (80% yield) of product melting at 155°C to 157°C.

By treating the hydrochloride with an aqueous solution of NaOH at 0°C, the free base is obtained in the form of a viscous white liquid which boils at 115°C under 0.05 mm.

References

Merck Index 2249
DOT 19 (1) 12 (1983)
I.N. p. 231
British Patent 1,409,990; October 15, 1975; assigned to Poli Industria Chimica S.p.A. (Italy)

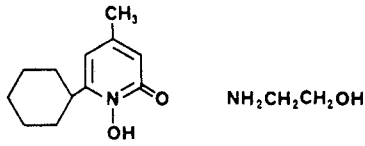
CICLOPIROXOLAMINE

Therapeutic Function: Antifungal

Chemical Name: 6-Cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone ethanolamine salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 41621-49-2; 29342-05-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Batrafen	Cassella-Riedel	W. Germany	1980
Batrafen	Hoechst	Japan	1981
Loprox	Hoechst	Canada	1983
Loprox	Hoechst	U.S.	1983

Raw Materials

4-Methyl-6-cyclohexyl-2-pyrone
Hydroxylamine hydrochloride
Ethanolamine

Manufacturing Process

Ciclopirox may be produced as follows: 2 g of 4-methyl-6-cyclohexyl-2-pyrone were heated with 1 g of hydroxylamine hydrochloride and 5 g of 2-aminopyridine to 80°C for 8 hours.

The reaction mixture was then dissolved in methylene chloride, the amine was removed by shaking with dilute hydrochloric acid, the reaction product was extracted from the organic phase by means of dilute sodium hydroxide solution and the alkaline solution was acidified with acetic acid to a pH value of 6. The 1-hydroxy-4-methyl-6-cyclohexyl-2-pyridone precipitated in crystalline form. It was filtered off with suction, washed with water and dried. The yield was 1.05 g (49% of theory); melting point 143°C.

Reaction of ciclopirox with ethanolamine gives the desired product.

References

Merck Index 2250
DFU 4 (11) 795 (1979)
Kleeman & Engel p. 206
PDR p. 940
OCDS Vol. 2 p. 282 (1980)
DOT 17 (9) 364 (1981)
I.N. p. 231
REM p. 1230
Lohaus, G. and Dittmar, W.; U.S. Patents 3,972,888; August 3, 1976; and 3,883,545; May 13, 1975; both assigned to Hoechst A.G.

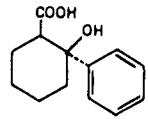
CICLOXILIC ACID

Therapeutic Function: Choleretic

Chemical Name: cis-2-Hydroxy-2-phenylcyclohexanecarboxylic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 57808-63-6

Trade Name	Manufacturer	Country	Year Introduced
Plecton	Guidotti	Italy	1975
Sintiabil	Sintyal	Argentina	—

Raw Materials

2-Hydroxymethyl cyclohexanone
Potassium permanganate
Bromobenzene
Magnesium

Manufacturing Process

25 g of 2-hydroxy-methyl-cyclohexanone, diluted in 20 cc of ether, were dropped into a vessel containing an ether suspension of phenyl-magnesium-bromide (prepared from 19.6 g of magnesium and 128 g of bromobenzene in 300 cc of ether according to usual techniques by stirring and external ice-cooling). The mixture was stirred for some time, then the magnesium compound was decomposed by pouring it carefully into water and ice; the magnesium hydroxide was dissolved in 50 cc of a saturated solution of ammonium chloride, the ether portion was separated and the aqueous portion extracted with further ether.

Collected and dried ether extracts were evaporated and the residue vacuum distilled yielded 15 g of a thick oil of boiling point at 0.1 to 0.2 mm Hg 127°C to 135°C.

This product crystallized by dissolving in ether and reprecipitation with petroleum ether yielded 7 g of 1-phenyl-2-hydroxy-ethylene-cyclohexan-1-ol, melting point (Kofler) 81°C to 83°C.

The thus obtained product was dried and finely powdered, and then suspended in 1.4 liters of an aqueous solution of 14 g of $KMnO_4$ and 7 g of Na_2CO_3, and the suspension was thoroughly stirred for one day.

After filtering off the MnO_2, thus formed, a small amount of Na_2SO_3 was added until the violet coloration disappeared; MnO_2 was filtered again and the alkaline solution was acidified with concentrated HCl.

After one day standing in a refrigerator, the product was filtered and washed with water, thus yielding 5 g of 2-phenyl-2-hydroxy-cyclohexane-carboxylic acid, melting point (Kofler) 143°C to 145°C.

References

Kleeman & Engel p. 207
DOT 15 (4) 185 (1979)
I.N. p. 18
Turbanti, L.; U.S. Patent 3,700,775; October 24, 1972

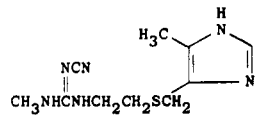
CIMETIDINE

Therapeutic Function: Antiulcer drug

Chemical Name: N-cyano-N'-methyl,N''-[2-[[(5-methyl-1H-imidazol-4-yl)methyl] thio]-ethyl] guanidine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 51481-61-9

Trade Name	Manufacturer	Country	Year Introduced
Tagamet	SKF	U.K.	1977
Tagamet	SKF	U.S.	1977
Tagamet	SKF	France	1977
Tagamet	SKF	W. Germany	1977
Tagamet	SKF	Switz.	1977
Euroceptor	Zambon	Italy	1978
Tagamet	Fujisawa/SKF	Japan	1982
Cimetag	Cehasol	Austria	1983
Acibilin	Exa	Argentina	–
Aciloc	Orion	Finland	–
Altramet	Lek	Yugoslavia	–
Belomet	Belupo	Yugoslavia	–
Biomag	Pulitzer	Italy	–
Brumetidina	Bruschettini	Italy	–

Trade Name	Manufacturer	Country	Year Introduced
Cimetum	Sintyal	Argentina	–
Cinamet	Isis	Yugoslavia	–
Cinulcus	Wassermann	Spain	–
Citius	Prodes	Spain	–
Civent	Medica	Finland	–
Fremet	Antibioticos	Spain	–
Gastromet	Sigurta	Italy	–
Itacem	Italchemie	Italy	–
Mansal	Vita	Spain	–
Peptol	Horner	Canada	–
Stomakon	Andromaco	Brazil	–
Tametin	Giuliani	Italy	–
Tratul	Ricar	Argentina	–
Ulcedin	Agips	Italy	–
Ulcedine	I.C.N.-Usafarma	Brazil	–
Ulcerfen	Finadiet	Argentina	–
Ulcestop	Gibipharma	Italy	–
Ulcimet	Farmasa	Brazil	–
Ulcodina	Locatelli	Italy	–
Ulcomet	Italfarmaco	Italy	–
Ulhys	Farnex	Italy	–

Raw Materials

2-Chloroacetic acid ethyl ester	Formamide
Potassium hydroxide	Sodium
Cysteamine	Ammonia
Carbon disulfide	Cyanamide
Dimethyl sulfate	Methylamine

Manufacturing Process

In an initial step, 2-chloroacetic acid ethyl ester is reacted with formamide to give 5-methyl-imidazole-4-carboxylic acid ethyl ester. Then sodium in ammonia is used to convert that to 4-hydroxymethyl-5-methylimidazole-hydrochloride. Cysteamine HCl ($HSCH_2CH_2NH_2 \cdot HCl$) is then reacted to give 4-(2-aminomethyl)-thiomethyl-5-methyl-imidazole di-HCl. Then N-cyanamido-5,5-dimethyl-dithio-carbonate (from cyanamid, KOH, CS_2 and $(CH_3)_2SO_4$) is reacted to give a further intermediate which is finally reacted with methylamine to give cimetidine.

The preparation of the pyridyl analogs of the imidazolyl compounds of the type of cimetidine are discussed in the patent cited below.

Further references are given by Kleeman & Engel in the reference below.

References

Merck Index 2254
DFU 1 (1) 13 (1976)
Kleeman & Engel p. 208
PDR p. 1725
OCDS Vol. 2 p. 353 (1980)
DOT 13 (5) 187 (1977) & 16 (11) 393 (1980)
I.N. p. 232
REM p. 797
Durant, G.J., Emmett, J.C. and Ganellin, C.R.; U.S. Patent 3,876,647; April 8, 1975; assigned to Smith Kline & French Laboratories Limited