L

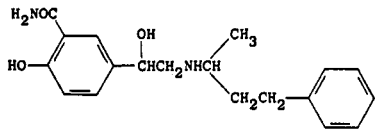
LABETALOL HYDROCHLORIDE

Therapeutic Function: α and β-Adrenergic blocker

Chemical Name: 2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino] ethyl] benzamide hydrochloride

Common Name: Ibidomide

Structural Formula:



(base)

Chemical Abstracts Registry No.: 36894-69-6; 32780-64-6 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Trandate	Allen & Hanburys	U.K.	1977
Trandate	Glaxo	W. Germany	1977
Labetalol	Duncan	Italy	1978
Trandate	Glaxo	Switz.	1979
Trandate	Glaxo	France	1980
Trandate	Glaxo	Japan	1983
Abetol	C.T.	Italy	–
Labelol	Elea	Argentina	–
Lamitol	Pliva	Yugoslavia	–
Lolum	Farmochimica	Italy	–
Mitalolo	Ellem	Italy	–
Normodyne	Schering	U.S.	–
Presdate	Alfa Farm.	Italy	–

Raw Materials

5-Bromoacetylsalicylamide
N-Benzyl-N-(1-methyl-3-phenylpropyl)amine
Hydrogen

Manufacturing Process

(a) 5-Bromoacetylsalicylamide (2.6 g), N-benzyl-N-(1-methyl-3-phenylpropyl)amine (4.8 g) and methyl ethyl ketone (50 ml) were heated at reflux for 40 minutes. The solvent was removed and the residue was treated with benzene. The secondary amine hydrobromide was filtered off and discarded, and the filtrate was evaporated to dryness. The residue was treated with an excess of ethanolic hydrogen chloride when 5-[N-benzyl-N-(1-methyl-3-phenylpropyl)-glycyl] -salicylamide hydrochloride (1.15 g) crystallized out, MP 139°C to 141°C.

(b) 5-[N-benzyl-N-(1-methyl-3-phenylpropyl)glycyl]-salicylamide hydrochloride (0.75 g), 10% mixture of PdO and PtO on carbon catalyst (0.1 g) and ethanol (20 ml) were shaken at room temperature and pressure with hydrogen until uptake ceased. The catalyst was filtered off and the filtrate evaporated to dryness. The residue was crystallized from ethanol to give 5-[1-hydroxy-2-(1-methyl-3-phenylpropyl)aminoethyl] salicylamide hydrochloride as a white solid (0.40 g), MP 188°C.

References

Merck Index 5166
DFU 1 (3) 125 (1976)
Kleeman & Engel p. 513
PDR pp. 913, 1638
OCDS Vol. 3 p. 24 (1984) & 18 (8) 378 (1982)
DOT 13 (11) 493 (1977)
I.N. p. 547
REM p. 904
Lunts, L.H.C. and Collin, D.T.; U.S. Patent 4,012,444; March 15, 1977; assigned to Allen & Hanburys Ltd. (U.K.)

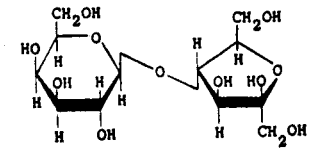
LACTULOSE

Therapeutic Function: Laxative

Chemical Name: 4-O-β-D-galactopyranosyl-D-fructose

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 4618-18-2

Trade Name	Manufacturer	Country	Year Introduced
Duphalac	Philips-Duphar	U.K.	1969
Bifiteral	Philips-Duphar	W. Germany	1971
Duphalac	Duphar	France	1972
Duphalac	Duphar	Italy	1973
Gatinar	Duphar	U.K.	1973
Lactulose	Nikken	Japan	1973
Cephulac	Merrell Dow	U.S.	1976
Duphalac	Philips-Roxane	U.S.	1977
Chronulac	Merrell Dow	U.S.	1979
Dia-Colon	Piam	Italy	–
Epalfen	Zambon	Italy	–
Laevilac	Wander	W. Germany	–
Laevolac	Laevosan	Austria	–
Monilac	Chugai	Japan	–

Raw Materials

Lactose
Sodium aluminate

Manufacturing Process

105 g of lactose monohydrate were dissolved in 500 ml of water. 48 g of $NaAlO_2$ was dissolved in 100 ml of water and was then added to the lactose solution. The mixture was then diluted to one liter to provide a pH of 11.5. The reactant concentrations of 48 g of sodium aluminate and 105 g of lactose are equivalent to a mol ratio of two mols of aluminate to one mol of lactose. The mixture was then heated to 50°C and 100 ml aliquots were removed at periodic intervals to determine the level of conversion. The reaction was terminated after three hours by adding sufficient 30% HCl to lower the pH to 4.2. The pH was then raised to neutrality, i.e., 6.5 to 7.0, with ammonium hydroxide so as to completely precipitate insoluble aluminum hydroxide. The precipitate was then removed by vacuum filtration and the filtrate was analyzed for the presence of ketose sugar by chromatographic analysis. The chromatographic analysis of the filtrate confirmed that the main component of the filtrate was lactulose and not the monosaccharide ketose sugar, fructose.

References

Merck Index 5184
Kleeman & Engel p. 513
PDR p. 1224
I.N. p. 548
REM p. 814
Guth, J.H. and Tumerman, L.; U.S. Patent 3,546,206; December 8, 1970; assigned to Kraftco Corp.

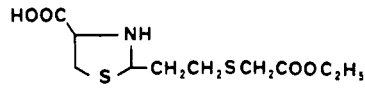
LETOSTEINE

Therapeutic Function: Mycolytic

Chemical Name: 4-Carboxy thiazolidinyl-2-ethylmercapto-acetic acid ethyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53943-88-7

Trade Name	Manufacturer	Country	Year Introduced
Viscotiol	Carlo Erba	France	1979
Viscotiol	Carlo Erba	Switz.	1980
Viscotiol	I.S.F.	Italy	1981

Raw Materials

Acrolein
Thioglyolic acid
Cysteine hydrochloride

Manufacturing Process

In an Erlenmeyer flask placed in an ice bath, and under a well-ventilated hood, a solution of 0.1 mol of acrolein in 100 ml of ether was introduced. With the aid of a bromine ampoule,

0.1 mol (≈11 ml) of the ethyl ester of thioglycolic acid containing 0.5 ml of triethylamine was added drop by drop.

One hour after completion of the addition, there was added 0.1 mol (15.6 g) of chlorhydrate of cysteine in alcoholic solution. The chlorhydrate of the expected derivative, which appeared in the form of a thick oil, was precipitated by addition of 0.1 mol (10 g) of potassium acetate in aqueous solution. The abundant precipitate obtained was filtered and washed in water and ether. The product was recrystallized in a minimum of absolute alcohol.

References

DFU 4 (10) 729 (1979)
Kleeman & Engel p. 516
DOT 16 (4) 109 (1980)
I.N. p. 553
Chodkiewicz, M.X.; U.S. Patent 4,032,534; June 28, 1977; assigned to Ferlus-Chimie SA

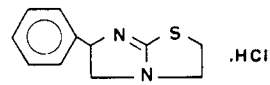
LEVAMISOLE HYDROCHLORIDE

Therapeutic Function: Antiinflammatory

Chemical Name: L-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-b]thiazole hydrochloride

Common Name: L-Tetramisole hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 16695-80-5; 14769-73-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Solaskil	Specia	France	1971
Ergamisol	Janssen	Italy	1978
Ascaryl	Abic	Israel	—
Meglum	Bago	Argentina	—
Niratic-Pur-On	Vet. Med. Handel	W. Germany	—
Tramisol	Lederle	U.S.	—
Vermisol	Andreu	Spain	—

Raw Materials

DL-2-Thio-1-phenyl-imidazolidine
1,2-Dibromoethane
d-10-Camphorsulfonic acid
Potassium hydroxide
Hydrogen chloride
Sodium hydroxide

Manufacturing Process

To a stirred and refluxed suspension of 17 parts of 1,2-dibromoethane, 7.8 parts of sodium hydrogen carbonate and 50 parts of 2-propanol is added a mixture of 3.4 parts of dl-2-thio-1-phenyl-imidazolidine, 9 parts of a 20% potassium hydroxide solution in 40 parts of 2-propanol over a period of about 1 hour. After the addition is complete, the whole is stirred and refluxed for an additional 3 hours. The reaction mixture is evaporated. To the residue are added 18 parts of a 15% potassium hydroxide solution. The whole is extracted with toluene. The extract is dried and evaporated. The oily residue is dissolved in acetone and gaseous hy-

drogen chloride is introduced into the solution. The precipitated solid salt is filtered off and recrystallized from 2-propanol, yielding dl-2,3,5,6-tetrahydro-6-phenyl-imidazo[2,1-b] thiazole hydrochloride; melting point 264°C to 266°C.

dl-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b] thiazole hydrochloride, 188 g (0.785 mol), is suspended in a mixture of 500 ml of water and 500 ml of methylene chloride. The suspension is stirred mechanically while 20% sodium hydroxide solution is added until the solution is basic. Ice is added from time to time to keep the temperature below the boiling point of the methylene chloride. The methylene chloride layer is separated, washed with water, dried over potassium carbonate and evaporated. The oily residue crystallizes with the evolution of the heat when poured into a beaker containing 100 ml of ether. The free base is washed with ether. The yield of dl-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b] thiazole is 151.4 g (0.746 mol), 94%. The product has a melting point of 90°C.

A solution of 204.3 g (1 mol) of dl-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b] thiazole and 232.3 g (1 mol) of d-10-camphorsulfonic acid in 1,750 ml of chloroform is allowed to crystallize overnight at -28°C. The solvate is recovered by filtration and washed with ice cold chloroform (400 ml). The solvate is dried (decomposed) under nitrogen 7 hours and then in air overnight. The yield of d(+)6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b] thiazole d-10-camphorsulfonate is 202.5 g (0.464 mol) 92.8%, melting point 139°C to 140°C $[\alpha]_D^{25}$ + 82.6 (C = 16, H_2O).

A solution of 150 g (0.344 mol) of d(+)6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b] thiazole, d-10-camphorsulfonate in water is treated with 15.5 g (0.378 mol) of 98% sodium hydroxide and the liberated base extracted with chloroform. The chloroform solution is washed with water followed by sodium chloride solution and dried over magnesium sulfate. Evaporation of the solvent left 72.1 g of residue which crystallized shortly. The free base hereby obtained has a melting point of 60°C to 61.5°C and an optical rotation $[\alpha]_D^{25}$ + 85.1 (C = 10, $CHCl_3$).

The free base d(+)6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b] thiazole is dissolved in 112 ml of acetone and 178 ml of isopropanolic hydrogen chloride is added all at once. The hydrochloride crystallizes at once. After cooling to below 0°C, the salt is recovered by filtration and washed with acetone. The product weighs 75.2 g (0.312 mol), 91%, from the camphorsulfonate, melting point 227°C to 227.5°C $[\alpha]_D^{25}$ + 123.1°C (C = 15, H_2O).

References

Merck Index 9055
DFU 4 (6) 420 (1979)
Kleeman & Engel p. 517
DOT 8 (6) 225 (1972) & 16 (10) 327, 359 (1980)
I.N. p. 554
REM p. 1156
Raeymaekers, A.H.M., Thienpont, D.C.I.C. and Demoen, P.J.A.W.; U.S. Patents 3,274,209; September 20, 1966 and 3,364,112; January 16, 1968; both assigned to Janssen Pharmaceutica NV
Bullock, M.W.; U.S. Patent 3,463,786; August 26, 1969; assigned to American Cyanamid Co.
Dewar, R.A., Maier, V.E. and Ingram, M.A.; U.S. Patent 3,579,530; May 18, 1971; assigned to Imperial Chemical Industries of Australia and New Zealand Ltd.
Dewilde, F. and Frot, G.G.; U.S. Patent 3,646,051; February 29, 1972; assigned to Rhone-Poulenc SA

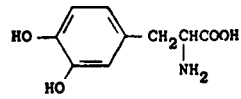
LEVODOPA

Therapeutic Function: Antiparkinsonism

Chemical Name: 3-hydroxy-L-tyrosine

Common Name: β-(3,4-dihydroxyphenyl)-α-alanine; 2-amino-3-(3,4-dihydroxyphenyl)propanoic acid

Structural Formula:



Chemical Abstracts Registry No.: 59-92-7

Trade Name	Manufacturer	Country	Year Introduced
Larodopa	Roche	U.S.	1970
Dopar	Norwich Eaton	U.S.	1970
Dopaidan	De Angeli	Italy	1970
Larodopa	Roche	W. Germany	1970
Larodopa	Roche	U.K.	1970
Larodopa	Roche	France	1970
Larodopa	Roche	Italy	1970
Brocadopa	Brocades	U.K.	1970
Levodopa	SKF	U.S.	1971
Bendopa	I.C.N.	U.S.	1971
Larodopa	Roche	Japan	1972
Biodopa	DDR Pharm	U.S.	–
Ceredopa	Merckle	W. Germany	–
Cidandopa	Cidan	Spain	–
Dehdopa	De Angeli	Brazil	–
Dopacin	I.C.N.	Brazil	–
Dopaflex	Egyt	Hungary	–
Dopaidan	De Angeli	Italy	–
Dopalfher	Fher	Spain	–
Doparkin	Farmos	Finland	–
Doparkine	Armstrong	Argentina	–
Doparl	Kyowa	Japan	–
Dopasol	Daiichi	Japan	–
Dopason	Yurtoglu	Turkey	–
Dopaston	Sankyo	Japan	–
Eldopar	Weifa	Norway	–
Eldopatec	Labatec	Switz.	–
Eurodopa	Castejon	Spain	–
Levopa	Arco	Switz.	–
Maipedopa	Maipe	Spain	–
Medidopa	Medica	Finland	–
Novedopa	Torlan	Spain	–
Parkidopa	Farmos	Finland	–
Parmedin	Kwizda	Austria	–
Prodopa	Faulding	Australia	–
Syndopa	Sankyo	Japan	–
Weldopa	Smith & Nephew	U.K.	–

Raw Materials

Velvet beans
Acetic acid

Manufacturing Process

A charge of 1,000 g of ground velvet beans was extracted with 9 liters of 1% aqueous

acetic acid at room temperature over a 20-hour period with occasional stirring during the first 4 hours. The liquor was decanted and the bean pulp slurry was vacuum filtered through a cake of acid-washed diatomaceous earth in a Buechner funnel. The decanted liquor was combined with the filtrate and concentrated under vacuum and a nitrogen atmosphere to a volume of 900 ml. After treating with acid-washed activated carbon, the concentrate was then filtered through acid-washed diatomaceous earth.

After concentrating the filtrate to approximately 400 ml, solids started crystallizing out at which time the filtrate was cooled by refrigerating at 5°C for several hours. Filtration gave 18.7 g of L-Dopa, MP 284° to 286°C (dec.); $[\alpha]_D$ 8.81° (1% solution in aqueous 4% HCl). The infrared spectrum and paper chromatography indicated very good L-Dopa according to U.S. Patent 3,253,023.

Various synthetic routes are also described by Kleeman & Engel.

References

Merck Index 5298
Kleeman & Engel p. 520
PDR pp. 1210, 1489
DOT 9 (6) 247 (1973) & 10 (9) 317, 332 (1974)
I.N. p. 555
REM p. 930
Wysong, D.V.; U.S. Patent 3,253,023; May 24, 1966; assigned to The Dow Chemical Company
Krieger, K.H., Lago, J. and Wantuck, J.A.; U.S. Patent 3,405,159; October 8, 1968; assigned to Merck & Co., Inc.

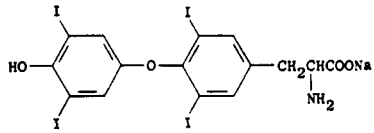
LEVOTHYROXINE SODIUM

Therapeutic Function: Thyroid hormone

Chemical Name: L-3,3',5,5'-Tetraiodothyronine sodium salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 55-03-8; 51-48-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Synthroid	Flint	U.S.	1953
Letter	Armour	U.S.	1965
Eltroxin	Glaxo	U.K.	–
Euthyrox	Merck	W. Germany	–
Eutirox	Bracco	Italy	–
Levaxin	Nyegaard	Norway	–
Levothyrox	Merck-Clevenot	France	–
Levotiron	Abdi Ibrahim	Turkey	–
Ro-Thyroxine	Robinson	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
Syntaroid	Travenol	U.S.	–
Thevier	Glaxo	W. Germany	–
Thyradin-S	Teikoku Zoki	Japan	–
Thyraplex	Erco	Denmark	–
Thyrex	Sanabo	Austria	–

Raw Materials

N-Acetyl-L-diiodotyrosinamide
Manganese sulfate
Sodium hydroxide
Acetic acid
Hydrochloric acid

Manufacturing Process

A 9.30 g portion of N-acetyl-L-diiodotyrosinamide was suspended in 100 ml of 0.05 M boric acid (H_3BO_3) and 100 ml of 95% ethanol, and the solid was dissolved by adjusting the pH to 10.5 with 2 N sodium hydroxide (NaOH). A 15% (by weight) portion of manganese sulfate monohydrate was added and the solution heated at 44°C under conditions of oxygenation while being agitated mechanically. After approximately 24 hours of incubation, the precipitated product was collected and separated from the catalyst, providing the amide of N-acetyl-L-thyroxine in 30.6% yield. On hydrolysis (removal of both amide functions), achieved by refluxing in glacial acetic acid-hydrochloric acid (approximately 2:1), L-thyroxine is obtained. It was isolated as the sodium salt, containing approximately 5 molecules of water of hydration.

References

Merck Index 5303
Kleeman & Engel p. 525
PDR p. 993
OCDS Vol. 1 p. 97 (1977)
I.N. p. 558
REM p. 980
Anthony, P.Z. and Ginger, L.G.; U.S. Patent 2,889,364; June 2, 1959; assigned to Baxter Laboratories, Inc.

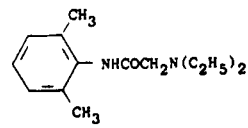
LIDOCAINE

Therapeutic Function: Local anesthetic, antiarrhythmic

Chemical Name: 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide

Common Name: Lignocaine

Structural Formula:



Chemical Abstracts Registry No.: 137-58-6; 73-78-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Xylocaine	Astra	U.S.	1949
Anestacon	Contal	U.S.	1967

Trade Name	Manufacturer	Country	Year Introduced
Octocaine	Novocol	U.S.	1980
Clinicaine	Johnson & Johnson	U.S.	1982
Anestacain	Farmos	Finland	–
Anestecidan	Cidan	Spain	–
Baylocaine	Bay	U.S.	–
Cidancaina	Cidan	Spain	–
Cito-Optadren	Fischer	Switz.	–
Dolicaine	Reid-Provident	U.S.	–
Dulicaine	Dulcis	Monte Carlo	–
Duncaine	Duncan-Flockhart	U.K.	–
Esracain	Hillel	Israel	–
Leotesin-N	Showa	Japan	–
Lida-Mantal	Dome	U.S.	–
Lidocain	Bristol	U.S.	–
Lidocard	Orion	Finland	–
Lidocaton	Pharmaton	Switz.	–
Lidocor	Gebro	Austria	–
Lido Pen	Survival Tech.	U.S.	–
Lignane	Propan-Lipworth	S. Africa	–
Neo-Novutox	Braun	W. Germany	–
Ortodermina	Tiber	Italy	–
Qualigens	Qualipharma	Switz.	–
Rapidocaine	Sintetica	Switz.	–
Sedodent	Belupo	Yugoslavia	–
Xylanaest	Gebro	Austria	–
Xylesin	Amino	Switz.	–
Xylestesin	Espe	W. Germany	–
Xylocard	Hassle	Sweden	–
Xylocitin	Jenapharm	E. Germany	–
Xyloneural	Gebro	Austria	–
Xylonor	Septodont	France	–
Xylotox	Willows-Francis	U.K.	–

Raw Materials

2,6-Xylidine
Chloroacetyl chloride
Diethylamine

Manufacturing Process

One mol of 2,6-xylidine is dissolved in 800 ml glacial acetic acid. The mixture is cooled to 10°C, after which 1.1 mol chloracetyl chloride is added at one time. The mixture is stirred vigorously during a few moments after which 1,000 ml half-saturated sodium acetate solution, or other buffering or alkalizing substance, is added at one time. The reaction mixture is shaken during half an hour. The precipitate formed which consists of ω-chloro-2,6-dimethyl-acetanilide is filtered off, washed with water and dried. The product is sufficiently pure for further treatment. The yield amounts to 70 to 80% of the theoretical amount.

One mole of the chloracetyl xylidide thus prepared and 2.5 to 3 mols diethyl amine are dissolved in 1,000 ml dry benzene. The mixture is refluxed for 4 to 5 hours. The separated diethyl amine hydrochloride is filtered off. The benzene solution is shaken out two times with 3 N hydrochloric acid, the first time with 800 ml and the second time with 400 ml acid. To the combined acid extracts is added an approximately 30% solution of sodium hydroxide until the precipitate does not increase.

The precipitate, which sometimes is an oil, is taken up in ether. The ether solution is dried with anhydrous potassium carbonate after which the ether is driven off. The remain-

ing crude substance is purified by vacuum distillation. During the distillation practically the entire quantity of the substance is carried over within a temperature interval of 1° to 2°C. The yield approaches the theoretical amount. MP 68° to 69°C. BP 180° to 182°C at 4 mm Hg; 159° to 160°C at 2 mm Hg. (Procedure is from U.S. Patent 2,441,498.)

References

Merck Index 5310
DFU 8 (12) 1021 (1983)
Kleeman & Engel p. 526
PDR pp. 607, 888, 1569
OCDS Vol. 1 p. 16 (1977); 2, 95, 449 (1980) & 3, 40 (1984)
I.N. p. 559
REM p. 1051
Löfgren, N.M. and Lundqvist, B.J.; U.S. Patent 2,441,498; May 11, 1948; assigned to AB Astra, Sweden
Brown, C.L.M. and Poole, A.; U.S. Patent 2,797,241; June 25, 1957

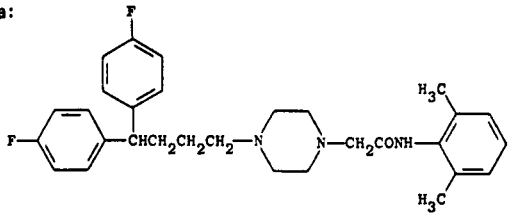
LIDOFLAZINE

Therapeutic Function: Vasodilator (coronary)

Chemical Name: 4-[4,4-Bis(4-fluorophenyl)butyl]-N-(2,6-dimethylphenyl)-1-piperazineacetamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 3416-26-0

Trade Name	Manufacturer	Country	Year Introduced
Clinium	Janssen	W. Germany	1969
Corflazine	Cassenne	France	1972
Clinium	Janssen	Italy	1974
Clinium	Janssen	U.K.	1980
Anginin	Yurtoglu	Turkey	—
Clavidene	Corvi	Italy	—
Clinium	McNeil	U.S.	—
Klinium	Esteve	Spain	—
Klintab	Eczacibasi	Turkey	—

Raw Materials

1-[4,4-Di-4-fluorophenyl)butyl] piperazine
N-(2-Chloroacetyl)-2,6-dimethylaniline

Manufacturing Process

A mixture of 6.6 parts 1-[4,4-di-(4-fluoro-phenyl)butyl] -piperazine, 4.33 parts N-(2-chloro-acetyl)-2,6-dimethyl-aniline, 3.2 parts sodium carbonate, a few crystals of potassium iodide in 200 parts 4-methyl-2-pentanone is stirred and refluxed for 70 hours. After cooling there are added 70 parts water. The organic layer is separated, dried over potassium carbonate, filtered and evaporated. The oily residue is dissolved in 80 parts diisopropyl-ether and the solution is filtered hot. After cooling the filtrate at 0°C, the formed solid is filtered off and recystallized from 80 parts ether, yielding 1-[4,4-di-(4-fluoro-phenyl)butyl] -4-[(2,6-dimethyl-anilino-carbonyl)-methyl] -piperazine; MP 159°C to 161°C.

References

Merck Index 5311
Kleeman & Engel p. 526
OCDS Vol. 1 p. 279 (1977)
DOT 2 (4) 118 (1966) & 6 (1) 21 (1970)
I.N. p. 560
Hermans, H.K.F. and Schaper, W.K.A.; U.S. Patent 3,267,164; August 16, 1966; assigned to Janssen Pharmaceutica N.V. (Belgium)

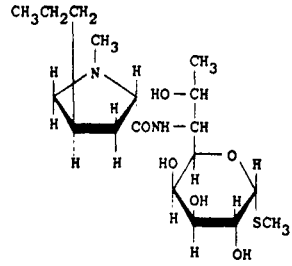
LINCOMYCIN

Therapeutic Function: Antibacterial

Chemical Name: Methyl 6,8-dideoxy-6-(1-methyl-4-propyl-2-pyrrolidinecarboxamido)-1-thio-D-erythro-D-galacto-octopyranoside

Common Name: Lincolnensin

Structural Formula:



Chemical Abstracts Registry No.: 154-21-2; 859-18-7 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Lincocin	Upjohn	U.K.	1964
Lincocin	Upjohn	U.S.	1965
Lincocine	Upjohn	France	1966
Albiotic	Upjohn	W. Germany	1966
Lincocin	Upjohn	Italy	1966
Cillimicina	Albert Farma	Spain	–
Cillimycin	Hoechst	W. Germany	–
Lincolcina	Atral	Portugal	–
Mycivin	Boots	U.K.	–

Raw Materials

Bacterium *Streptomyces lincolnensis*
Nutrient medium

Manufacturing Process

As described in U.S. Patent 3,086,912, the process comprises cultivating *Streptomyces lincolnensis* var. *lincolnensis* in an aqueous nutrient medium containing a source of assimilable carbohydrate and assimilable nitrogen under aerobic conditions until substantial activity is imparted to the medium by production of lincolnensin and isolating the lincolnensin so produced.

References

Merck Index 5328
Kleeman & Engel p. 527
PDR p. 1847
DOT 2 (2) 62 (1966)
I.N. p. 561
REM p. 1212
Bergy, M.E., Herr, R.R. and Mason, D.J.; U.S. Patent 3,086,912; April 23, 1963; assigned to The Upjohn Company
Bergy, M.E., Herr, R.R. and Mason, D.J.; U.S. Patent 3,155,580; November 3, 1964; assigned to The Upjohn Company
Argoudelis, A.D., Bannister, B., Hoeksema, H., Kagan, F. and Magerlein, B.J.; U.S. Patent 3,380,992; April 30, 1968; assigned to The Upjohn Company
Jariwala, S.L.; U.S. Patent 4,091,204; May 23, 1978; assigned to The Upjohn Company

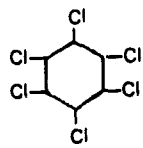
LINDANE

Therapeutic Function: Pediculicide; scabicide

Chemical Name: 1α,2α,3β,4α,5α,6β-hexachlorocyclohexane

Common Name: gamma-BHC

Structural Formula:



Chemical Abstracts Registry No.: 58-89-9

Trade Name	Manufacturer	Country	Year Introduced
Kwell	Reed Carnrick	U.S.	1952
Gamene	Barnes Hind	U.S.	1975
Escabiol	Stiefel	U.S.	1979
Scabene	Stiefel	U.S.	1981
Bicide	Fischer	Israel	–
Gambex	Continental Ethicals	S. Africa	–
HCH-Salbe	VEB Leipziger Arz.	E. Germany	–
Jacutin	Hermal	W. Germany	–
Malice Shampoo	Restan	S. Africa	–
Quellada	Stafford-Miller	U.K.	–

Raw Materials

Benzene
Chlorine

Manufacturing Process

Chlorine gas was gradually passed into 660 parts of benzene contained in a lead-lined reaction vessel until 890 parts of the gas had been absorbed. The mixture was stirred continuously and the temperature maintained at 15°C to 20°C.

The supply of chlorine was then interrupted and the precipitated solid filtered off and dried. In weight, it was found to be equivalent to 900 parts. The mother liquid was then mixed with 330 parts of benzene and the mixture again treated with 890 parts of chlorine in the manner described.

After filtering the reaction mixture resulting from the second chlorination, the filtrate was again mixed with a smaller quantity of benzene and again chlorinated in a similar manner. In this way, a continuous process for the preparation of benzene hexachloride resulted.

That benzene hexachloride isomer mixture is then the raw material for lindane production. The production of lindane per se is not a chemical synthesis operation but a physical separation process. It is possible to influence the gamma isomer content of benzene hexachloride to an extent during the synthesis process. Basically, however, one is faced with the problem of separating a 99%-plus purity gamma isomer from a crude product containing perhaps 12 to 15% of the gamma isomer. The separation and concentration process is done by a carefully controlled solvent extraction and crystallization process. One such process is described by R.D. Donaldson et al. Another description of hexachlorocyclohexane isomer separation is given by R.H. Kimball.

References

Merck Index 5329
PDR pp. 1444, 1606, 1779
I.N. p. 561
REM pp. 1239, 1253
Donaldson, R.D. et al; U.S. Patent 2,767,223; October 16, 1956; assigned to Allied Chemical and Dye Corp.
Kimball, R.H.; U.S. Patent 2,767,224; October 16, 1956; assigned to Hooker Electrochemical Co.
Hay, J.K. and Webster, K.C.; U.S. Patent 2,502,258; March 28, 1950; assigned to Imperial Chemical Industries, Ltd.
Hardie, T.; U.S. Patent 2,218,148; October 15, 1940; assigned to Imperial Chemical Industries, Ltd.

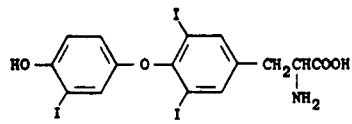
LIOTHYRONINE

Therapeutic Function: Thyroid replacement therapy

Chemical Name: O-(4-hydroxy-3-iodophenyl)-3,5-diiodo-L-tyrosine

Common Name: 3,5,3'-triiodothyronine; L-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]alanine

Structural Formula:



Chemical Abstracts Registry No.: 6893-02-3; 55-06-1 (Sodium Salt)

Trade Name	Manufacturer	Country	Year Introduced
Cytomel	SKF	U.S.	1956
Cynomel	Merrell	France	1961
Cytobin	Norden	U.S.	–
Cytomine	Darby	U.S.	–
Ro-Thyronine	Robinson	U.S.	–
Tertroxin	Glaxo	U.K.	–
Thybon	Hoechst	W. Germany	–
Thyronamin	Takeda	Japan	–
Thyronine	Taisho	Japan	–
Tiromel	Abdi Ibrahim	Turkey	–
Ti-Tre	Glaxo	Italy	–
Trijodthyronin	Nyegaard	Norway	–
Trithyron	Millot	France	–

Raw Materials

L-Diiodothyronine
Iodine

Manufacturing Process

The 3,5-diiodo compound used as a starting material is a known material and may be prepared by the method in British Patents 643,089 and 671,070 and in the *Journal of the Chemical Society*, London, 1949, page 3424.

Synthesis: L-diiodo thyronine (1.05 g) is dissolved in ammonia (specific gravity 0.880) (40 ml) and methanol (40 ml) and iodinated slowly with shaking with N-iodine in KI solution at room temperature. After iodination, most of the ammonia and methanol are removed by evaporation under diminished pressure, water is added to the original volume, the solution is heated to 60°C and brought to pH 4 with hydrochloric acid. A crystalline precipitate is obtained which after cooling to room temperature is collected and washed with water. At this stage, the crude triiodo thyronine is contaminated with thyroxine and a little unchanged diiodo thyronine.

Purification: The crude precipitate is dissolved in boiling 2 N HCl (300 ml) and filtered from the relatively insoluble thyroxine hydrochloride. The hot filtrate is brought to pH 4 with 5 N NaOH and triiodo thyronine again separates; after chilling at 0° to 4°C it is collected, washed with water and dried. The yield of triiodo thyronine is 70 to 75% of the theoretical. This triiodo thyronine still contains some thyroxine (about 10%).

The final purification consists of chromatographic separation of thyroxine and triiodo thyronine on a kieselguhr column using 20% chloroform in n-butanol equilibrated with 0.5 N NaOH as the developing solvent. 80 to 100 mg triiodo thyronine is purified during each run on a 50 g kieselguhr column. Pure L-triiodo thyronine has MP 236° to 237°C (dec.) and $[\alpha]_D^{29.5°} = +21.5$ in a 4.75% solution in a mixture of 1 part of N HCl and 2 parts of ethanol. Liothyronine is commonly used as the sodium salt.

References

Merck Index 5337
Kleeman & Engel p. 527
PDR pp. 1606, 1709
OCDS Vol. 1 p. 97 (1977)
I.N. p. 562
REM p. 980
Pitt-Rivers, R. and Gross, J.; U.S. Patent 2,823,164; February 11, 1958; assigned to National Research Development Corporation, England

Platt, J.T. and Wenner, W.; U.S. Patent 2,784,222; March 5, 1957; assigned to Hoffmann-La Roche Inc.
Razdan, R.K. and Wetherill, L.A.; U.S. Patent 2,993,928; July 25, 1961; assigned to Glaxo Laboratories, Ltd.

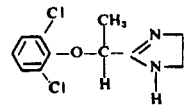
LOFEXIDINE HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 2-[1-(2,6-Dichlorophenoxy)ethyl] -2-imidazoline

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: —

Trade Name	Manufacturer	Country	Year Introduced
Lofetensin	Nattermann	W. Germany	1981

Raw Materials

α-2,6-Dichlorophenoxypropionitrile
Hydrogen chloride
Ethanol
Ethylenediamine

Manufacturing Process

10.4 ml of absolute ethanol are added to 57.5 g of α-2,6-dichlorophenoxypropionitrile, followed by the introduction of 100 ml of chloroform dried over phosphorus pentoxide; 10.4 g of carefully dried hydrogen chloride being slowly introduced with stirring and cooling with ice/common salt. Most of the chloroform and excess hydrogen chloride is then removed by filtration in vacuo at room temperature, and dry ether added to the residue until the imido acid ester hydrochloride is quantitatively precipitated. The α-dichlorophenoxypropionimido acid ethyl ester hydrochloride can be obtained analytically pure in the form of white, strongly hygroscopic crystals by repeated dissolution in a little absolute ethanol in the absence of heat, and precipitation with ether.

The crude α-(2,6-dichlorophenoxy)propionamido acid ethyl ester hydrochloride is added in portions to a stirred, ice-cooled solution of 29.5 g of anhydrous ethylenediamine in 200 ml of absolute ethanol in such a way that the temperature does not exceed 0°C to 5°C. The cooling bath is then removed and the reaction mixture heated for 1 hour on a water bath to approximately 70°C.

After cooling, unreacted ethylenediamine is neutralized in a cooling mixture with the absolute ethanolic hydrochloric acid, filtered off from any components that are insoluble in ethanol and approximately two-thirds of the solvent filtered off under suction in a water jet pump vacuum. Residual quantities of ethylenediamine dihydrochloride are precipitated in fractions by the careful addition of ethyl methyl ketone, after which the imidazoline hydrochloride is separated off by the addition of dry ether. Following repeated recrystallization from ethanol ether, 2-[α-(2,6-dichlorophenoxy)ethyl] -Δ^2-imidazoline hydrochloride is obtained in the form of small white crystals melting at 221°C to 223°C.

References

Merck Index 5388
DFU 3 (8) 592 (1978)
DOT 19 (9) 496 (1983)
I.N. p. 566
Baganz, H. and May, H.J.; U.S. Patent 3,966,757; June 29, 1976; assigned to A. Natterman and Cie GmbH

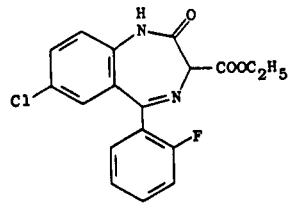
LOFLAZEPATE ETHYL

Therapeutic Function: Minor tranquilizer

Chemical Name: 7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepine-3-carboxylic acid ethyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Victan	Clin Midy	France	1982

Raw Materials

2-Methylimidazole HCl
2-Amino-5-chloro-2'-fluoro-benzophenone
Ethyl aminomalonate hydrochloride

Manufacturing Process

(A) 1-(2-Amino-5-chlorophenyl)-1-(2-fluorophenyl)-2-aza-but-1-en-4-ol: A mixture of 40 g of 2-methylimidazole hydrochloride and of 90 g of 2-amino-5-chloro-2'-fluoro-benzophenone in 240 ml of ethanolamine is heated at 135°C for 2 hours. After cooling, the reaction mixture is poured into an aqueous sodium bicarbonate solution. The mixture is extracted with ether, the organic phase is washed repeatedly with water and is dried over sodium sulfate, and the solvent is evaporated to dryness. The residual oil is chromatographed on a silica column, elution being carried out with a 50/50 mixture of cyclohexane and ethyl acetate.

88 g of the expected amine are thus isolated. Melting point: 105°C to 110°C.

(B) 1-(2-Amino-5-chlorophenyl)-1-(2-fluorophenyl)-3,3-bis-(ethoxycarbonyl)-2-aza-prop-1-ene: A mixture of 88 g of the product obtained above, 300 g of ethyl aminomalonate hydrochloride and 60 ml of acetic acid in 2.3 liters of absolute ethanol is heated to the reflux temperature for 6 hours. The alcohol and the acetic acid are evaporated in vacuo and the residue is taken up in ether. The solution is washed with a dilute sodium bicarbonate solution and

then with water and is dried over sodium sulfate. The solvent is evaporated and the residue is then chromatographed on a silica column, using a 90/10 mixture of chloroform and ethyl acetate for the elution. An oil (64 g) is thus obtained, and is used, without further treatment, for the cyclization.

A sample recrystallized from isopropyl ether has a melting point of 119°C.

(C) Compound of Code No. CM 6912: 25 g of the imine obtained under (B), dissolved in 400 ml of acetic acid, are heated at the reflux temperature for 1 hour. After evaporating the solvent in vacuo, the residue is taken up in methylene chloride. The solution is washed with a dilute sodium bicarbonate solution and then with water. After evaporating the solvent, the residue is chromatographed on silica, elution being carried out with an 80/20 mixture of ether and ethyl acetate. 9 g of benzodiazepine are thus obtained. Melting point: 196°C.

References

Merck Index 3766
DFU 6 (12) 772 (1981)
DOT 19 (1) 24 (1983)
I.N. p. 566
Demarne, H. and Hallot, A.; British Patent 1,538,165; January 17, 1979; assigned to C.M. Industries (France)

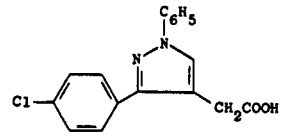
LONAZOLAC

Therapeutic Function: Antiinflammatory

Chemical Name: 3-(4-Chlorophenyl)-1-phenyl-1H-pyrazole-4-acetic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53808-88-1

Trade Name	Manufacturer	Country	Year Introduced
Irriten	Tosse	W. Germany	1981
Irritren	Byk Gulden	Switz.	1982

Raw Materials

1-Phenyl-3-(p-chlorophenyl)-pyrazol-4-acetonitrile
Hydrogen chloride

Manufacturing Process

17.6 g 1-phenyl-3-(p-chlorophenyl)-pyrazol-4-acetonitrile and 180 ml 25% aqueous hydrochloric acid were mixed and heated to the boiling temperature under reflux for 6 hours. To the mixture was then added dropwise concentrated aqueous sodium hydroxide until the pH of the mixture reached a value in the range from 3 to 5. The free pyrazol-4-acetic acid pre-

cipitated thereby was filtered off, redissolved in dilute aqueous sodium hydroxide, the solution cleared by treatment with activated carbon, and the pyrazol-4-acetic acid precipitated by acidifying the solution by the addition of dilute mineral acid, sulfuric acid. The filtered acid was crystallized from a mixture of ethanol and water. 17.1 g 1-phenyl-3-(p-chlorophenyl)-pyrazol-4-acetic acid, melting at 148°C to 150°C, were obtained, representing a yield of 91%.

References

Merck Index 5392
DFU 7 (2) 110 (1982)
DOT 18 (4) 184 (1982)
I.N. p. 567
Rainer, G.; U.S. Patent 4,146,721; March 27, 1979; assgned to Byk Gulden Lomberg Chemische Fabrik G.m.b.H. (W. Germany)

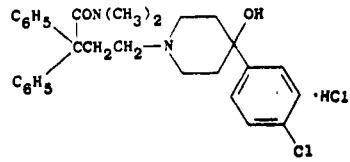
LOPERAMIDE HYDROCHLORIDE

Therapeutic Function: Antidiarrheal

Chemical Name: 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidine-butanamide hydrochloride

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 34552-83-5; 53179-11-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Imodium	Janssen	U.K.	1975
Imodium	Janssen-Le Brun	France	1976
Imodium	Janssen	W. Germany	1976
Imodium	Ortho	U.S.	1977
Dissenten	S.P.A.	Italy	1978
Imodium	Janssen	Italy	1979
Lopemid	Gentili	Italy	1979
Imodium	Janssen	Switz.	1981
Imodium	Dainippon	Japan	—
Blox	Biomedica Foscama	Italy	—
Brek	Irbi	Italy	—
Fortasec	Esteve	Spain	—
Lopermid	Drifen	Turkey	—
Loperyl	Zambeletti	Italy	—
Regulane	Finadiet	Argentina	—
Seldiar	Krka	Yugoslavia	—
Tebloc	Dukron	Italy	—

Raw Materials

2-Oxo-3,3-diphenyl-tetrahydrofuran
Hydrogen bromide

Thionyl chloride
4-(p-Chlorophenyl)-4-piperidinol
Dimethyl amine
Hydrogen chloride

Manufacturing Process

23.6 parts of 2-oxo-3,3-diphenyl-tetrahydrofuran are melted at 100°C in an oil-bath and gaseous hydrogen bromide is introduced into it during 3 hours. The reaction mixture is cooled and triturated in benzene. The product is filtered off, washed with petroleum ether and dried in an exsiccator, yielding 4-bromo-2,2-diphenylbutyric acid; MP 127.5°C.

To a stirred suspension of 16 parts of 4-bromo-2,2-diphenylbutyric acid in 150 parts of chloroform are added dropwise 16 parts of thionyl chloride and the whole is stirred and refluxed for 2 hours. The reaction mixture is evaporated, yielding 4-bromo-2,2-diphenylbutyrylchloride as a residue.

60 parts of 4-bromo-2,2-diphenylbutyrylchloride are dissolved in 400 parts of toluene and gaseous dimethylamine is introduced slowly into the solution while cooling (temperature is kept at about 0°C). The introduction is ceased when dimethylamine escapes from the cooler, and stirring is continued for 2 hours at ordinary temperature. The precipitated product is filtered off and dissolved in a minimum quantity of water. The product is extracted with chloroform. The extract is dried and evaporated. The residue solidifies on triturating in 4-methyl-2-pentanone. The solid is filtered off and dried, yielding dimethyl (tetrahydro-3,3-diphenyl-2-furylidene)ammonium bromide; MP 169° to 171.5°C.

A mixture of 6.33 parts of 4-(p-chlorophenyl)-4-piperidinol, 8 parts of sodium carbonate, 0.2 part of potassium iodide and 240 parts of 4-methyl-2-pentanone is distilled azeotropically. Then there are added 12.12 parts of dimethyl-(tetrahydro-3,3-diphenyl-2-furylidene)ammonium bromide (from the preceding step) and the whole is stirred and refluxed for about 15 hours. The reaction mixture is filtered hot and the filtrate is evaporated.

The oily residue is dissolved in 2-propanol and to this solution is added an excess of 2-propanol previously saturated with gaseous hydrogen chloride. The whole is evaporated and the oily residue is warmed in diluted hydrochloric acid solution. Upon the addition of toluene, the salt is precipitated. It is filtered off, boiled in acetone, and filtered off again after cooling, yielding 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenylpiperidine-1-butyramide hydrochloride; MP 222.1°C.

References

Merck Index 5396
Kleeman & Engel p. 530
PDR p. 953
OCDS Vol. 2 p. 334 (1980)
DOT 10 (6) 220 (1974)
I.N. p. 567
REM p. 814
Janssen, P.A.J., Niemegeers, C.J.E.J., Stokbroekx, R.A. and Vandenberk, J.; U.S. Patent 3,714,159; January 30, 1973; and U.S. Patent 3,884,916; May 20, 1975; both assigned to Janssen Pharmaceutica, NV, Belgium

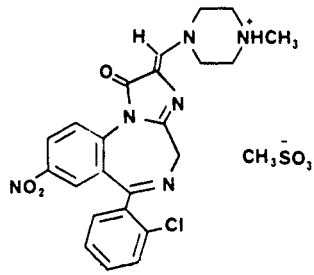
LOPRAZOLAM

Therapeutic Function: Tranquilizer

Chemical Name: 8-Nitro-1,2-dihydro-2-(N-methyl-piperazin-1-yl)methylene-6-(o-chlorophenyl)-1H,4H-imidazo-[1,2-a] [1,4]-benzodiazepin-1-one methanesulfonate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 61197-93-1

Trade Name	Manufacturer	Country	Year Introduced
Avlane	J.A.S.M.	France	1981
Dormonoct	Roussel	U.K.	1983

Raw Materials

8-Nitro-1,2-dihydro-2-(N-methylpiperazin-1-yl)methylene-6-(o-chlorophenyl)-1H,4H-imidazo[1,2-a] [1,4] benzodiazepin-1-one
Methane sulfonic acid

Manufacturing Process

1.1 g of methanesulfonic acid were added dropwise to a mixture of 4.6 g of 8-nitro-1,2-dihydro-2-(N-methylpiperazin-1-yl)methylene-6-(o-chlorophenyl)-1H,4H-imidazo-[1,2-a] [1,4]-benzodiazepin-1-one in 100 ml of anhydrous methylene chloride and 5 ml of methanol. Dry ether was slowly added until crystals formed on scratching and the solution was allowed to crystallize with further ether being added to complete the crystallization. The pale yellow solid was filtered off, washed with ether and crystallized from methylene chloride-methanol to obtain 5.4 g of 8-nitro-1,2-dihydro-2-(N-methylpiperazin-1-yl)methylene-6-(o-chlorophenyl)-1H,4H-imidazo-[1,2-a] [1,4]-benzodiazepin-1-one methanesulfonate melting at 205°C to 210°C.

References

Merck Index 5399
DFU 5 (3) 144 (1980) (As Ru-31,158) & 5 (12) 635 (1980)
Taylor, F.B. and Harrison, D.R.; U.S. Patent 4,044,142; August 23, 1977; assigned to Roussel Uclaf.

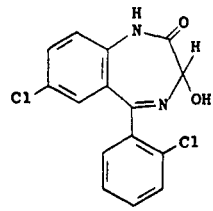
LORAZEPAM

Therapeutic Function: Tranquilizer

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 846-49-1

Trade Name	Manufacturer	Country	Year Introduced
Tavor	Wyeth	Italy	1972
Tavor	Wyeth	W. Germany	1972
Ativan	Wyeth	U.K.	1973
Temesta	Wyeth-Byla	France	1973
Ativan	Wyeth	U.S.	1977
Wypax	Wellcome	Japan	1978
Bonton	Unipharm	Israel	–
Control	Sigurta	Italy	–
Emotion	Alpes	Argentina	–
Emotival	Armstrong	Argentina	–
Idalprem	Prem	Spain	–
Lorans	Schiapparelli	Italy	–
Lorivan	Disco	Israel	–
Lorsilan	Belupo	Yugoslavia	–
Orfidal	Orfi	Spain	–
Piralone	Ferrer	Spain	–
Placidia	Fedal	Spain	–
Pro Dorm	Schurholz	W. Germany	–
Quait	Jamco	Italy	–
Securit	Marxer	Italy	–
Sedarkey	Cuatrecasas-Darkey	Spain	–
Sedatival	Raffo	Argentina	–
Sedicepan	Septa	Spain	–
Sidenar	Syncro	Argentina	–

Raw Materials

2-Amino-2',5-dichlorobenzophenone
Chloroacetylchloride
Acetic anhydride
Hydroxylamine
Methyl amine
Sodium hydroxide

Manufacturing Process

The starting material was 2-amino-2',5-dichlorobenzophenone which was reacted with hydroxylamine and then with chloroacetylchloride. The intermediate thus obtained is reacted with methylamine and then with acetic anhydride.

To a slightly warm suspension of 3-acetoxy-7-chloro-5-(o-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one thus obtained was added 4 N sodium hydroxide solution with stirring. All the solid dissolved and soon a thick white solid precipitated out. The solid was filtered, washed well with water and recrystallized from ethanol. The product was isolated as a solvate with 1 mol of ethanol. When heated it loses the ethanol of solvation and melts at 166°C to 168°C.

References

Merck Index 5400

Kleeman & Engel p. 530
PDR p. 1938
OCDS Vol. 1 p. 368 (1977)
DOT 7 (6) 210 (1971) & 9 (6) 238 (1973)
I.N. p. 568
REM p. 1063
Bell, S.C. British Patent 1,057,492; February 1, 1967; assigned to American Home Products Corporation
Bell, S.C. U.S. Patent 3,176,009; March 30, 1965; assigned to American Home Products Corp.
Bell, S.C.; U.S. Patent 3,296,249; January 3, 1967; assigned to American Home Products Corp.

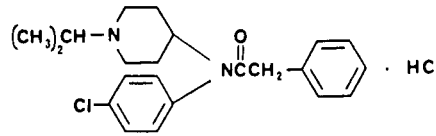
LORCAINIDE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: N-(p-Chlorophenyl)-N-(1-isopropylpiperidin-4-yl)phenylacetamide hydrochloride

Common Name: Isocainide hydrochloride; socalnide hydrochloride

Structural Formula:



Chemical Abstracts Registry no.: 59729-31-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Remivox	Janssen	W. Germany	1980

Raw Materials

N-(4-Chlorophenyl)-N-(piperidinyl)benzeneacetamide
2-Bromopropane
Hydrogen chloride

Manufacturing Process

To a stirred suspension of 5 parts of N-(4-chlorophenyl)-N-(4-piperidinyl)benzeneacetamide, 5 parts of sodium carbonate, a few crystals of potassium iodide in 200 parts of butanol is added dropwise 4 parts of 2-bromopropane at room temperature. After the addition is complete, the whole is stirred and refluxed for 20 hours. Then the second portion of 4 parts of 2-bromopropane is added and stirring and refluxing is continued for another 19 hours. The reaction mixture is cooled, filtered and the filtrate is evaporated. From the oily free base, the hydrochloride salt is prepared in the conventional manner in 1,1'-oxybisethane and 2-propanone. The precipitated solid salt is filtered off and crystallized from a mixture of 2-propanone and 2-propanol, yielding 2 parts of N-(4-chlorophenyl)-N-[1-(1-methylethyl)-4-piperidinyl] benzeneacetamide hydrochloride; melting point 263°C.

References

Merck Index 5401

DFU 3 (7) 518 (1978)
OCDS Vol. 3 p. 40 (1984)
DOT 18 (1) 17 & (10) 548 (1982)
I.N. p. 568
Sanczuk, S. and Hermans, H.K.F.; U.S. Patent 4,196,210; April 1, 1980; assigned to Janssen Pharmaceutica NV

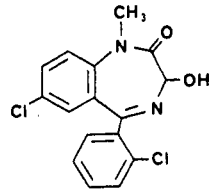
LORMETAZEPAM

Therapeutic Function: Hypnotic

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

Common Name: N-Methyllorazepam

Structural Formula:



Chemical Abstracts Registry No.: 848-75-9

Trade Name	Manufacturer	Country	Year Introduced
Loramet	Wyeth	W. Germany	1980
Noctamid	Schering	W. Germany	1980
Loramet	Wyeth	Switz.	1981
Noctamid	Schering	U.K.	1981
Noctamid	Schering	France	1981
Loramet	Wyeth	U.K.	1983
Loramid	Wyeth	W. Germany	—
Minias	Farmades	Italy	—
Pronoctan	Schering	—	—

Raw Materials

3-Acetoxy-7-chloro-1,3-dihydro-5-(o-chlorophenyl)-2H-1,4-benzodiazepin-2-one
Sodium hydroxide

Manufacturing Process

To a suspension of 3.4 g of 3-acetoxy-7-chloro-1,3-dihydro-5-(o-chlorophenyl)-2H-1,4-benzodiazepin-2-one in 80 ml of alcohol was added 6 ml of 4N sodium hydroxide. After complete solution had taken place a solid precipitated that redissolved upon the addition of 80 ml of water. The solution was acidified with acetic acid to give white crystals. After recrystallization from alcohol the compound melted at 192°C to 194°C.

References

Merck Index 5403
DFU 5 (10) 495 (1980)

Kleeman & Engel p. 531
OCDS Vol. 3 p. 196 (1984)
DOT 17 (4) 137 (1981)
I.N. p. 569
American Home Products Co.; British Patent 1,022,642; March 16, 1966

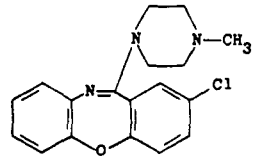
LOXAPINE

Therapeutic Function: Tranquilizer

Chemical Name: 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f] [1,4] oxazepine

Common Name: Oxilapine

Structural Formula:



Chemical Abstracts Registry No.: 1977-10-2

Trade Name	Manufacturer	Country	Year Introduced
Loxitane	Lederle	U.S.	1976
Loxapac	Lederle	France	1980
Loxapac	Cyanamid	Italy	1981
Daxolin	Dome	U.S.	—

Raw Materials

o-(p-Chlorophenoxy)aniline
1-Methylpiperazine
Ethyl chloroformate
Phosphorus oxychloride

Manufacturing Process

One route is described in U.S. Patent 3,412,193 as follows. To a mixture of o-(p-chlorophenoxy)aniline hydrochloride (prepared from 32 g of the base) in 50 ml of pyridine is added gradually while heating under reflux, 25 ml of ethyl chloroformate. After the addition is completed, the mixture is heated under reflux for one hour longer, and then evaporated under reduced pressue to an oily residue. The residue is taken up in 300 ml of water, and extracted with ether (approximately 200 ml).

The ether extract is separated, dried over sodium sulfate, and evaporated to an oily residue (40 g) which contains ethyl o-(p-chlorophenoxy) carbanilate and is used without further purification. The crude ethyl o-(p-chlorophenoxy)carbanilate is dissolved in 20 ml of benzene, and 20 ml of 1-methylpiperazine and a small amount of sodium methylate (approximately 25 to 50 mg) are added. Benzene is then removed by slow distillation; and the mixture is heated overnight under reflux (approximately 16 hours).

Evaporation under reduced pressure then gives a solid residue which is dissolved in 400 ml of ether with heating. Concentration to half-volume under reduced pressure produces a precipitate which is collected, washed with petroleum ether and dried (36 g). A second crop

of product is isolated from the filtrate. This product is dissolved in 200 ml of chloroform and treated with an excess of anhydrous hydrogen chloride. The resulting precipitate is collected and dried at 50°C (in vacuo), and 4-methyl-2'-(p-chlorophenoxy)-1-piperazinecarboxanilide hydrochloride, MP 210° to 213°C, is thereby obtained.

A mixture of 4-methyl-2'-(p-chlorophenoxy)-1-piperazinecarboxanilide hydrochloride (6 g), 50 ml of phosphorus oxychloride and 10 g of phosphorus pentoxide is heated under reflux for about 24 hours, and then concentrated to a gummy residue by evaporation under reduced pressure. This residue is taken up in 150 ml of ether, 200 g of ice is added, and the mixture is made basic with concentrated aqueous ammonium hydroxide. The ether layer is separated, dried over potassium hydroxide pellets and evaporated to a solid residue (approximately 4 g).

This crude product is dissolved in 100 ml of dilute hydrochloric acid, the acid solution is extracted with ether, and the aqueous layer is made basic with sodium hydroxide solution (3 N) in the presence of ether (approximately 250 ml). The ether layer is separated, dried over potassium hydroxide and evaporated to a white solid. Additional purification by repeating the formation of the hydrochloric acid salt and reprecipitation of the base is carried out. When purified in this manner, followed by drying at 80°C in vacuo over phosphorus pentoxide, 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f] [1,4] oxazepine, MP 109° to 111°C, is obtained.

References

Merck Index 5404
Kleeman & Engel p. 532
PDR p. 1012
OCDS Vol. 2 p. 427 (1980)
DOT 14 (6) 248 (1978)
I.N. p. 569
REM p. 1089
Coppola, J.A.; U.S. Patent 3,412,193; November 19, 1968; assigned to American Cyanamid Company
Schmutz, J., Hunziker, F. and Künzle, F.M.; U.S. Patent 3,546,226; December 8, 1970