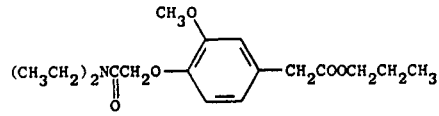
PROPANIDID

Therapeutic Function: Anesthetic (intravenous)

Chemical Name: 4-[2-(Diethylamino)-2-oxoethoxy]-3-methoxybenzene-acetic acid propyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 1421-14-3

Trade Name	Manufacturer	Country	Year Introduced
Epontol	Bayer	W. Germany	1965
Epontol	Bayer	Italy	1967
Epontol	Theraplix	France	1967
Epontol	Bayer	Japan	1970
Fabontal	Bayer	–	–
Sombrevin	Gedeon Richter	Hungary	–

Raw Materials

Homovanillic acid n-propyl ester
Sodium
Chloracetic acid-N,N-diethylamide

Manufacturing Process

To a solution of 4 g of sodium in 200 ml of n-propanol is added 39 g of homovanillic acid-n-propyl ester (boiling point 160°C to 162°C/4 mm Hg) and the mixture is concentrated by evaporation under vacuum. After dissolving the residue in 200 ml of dimethylformamide and the addition of 0.5 g of sodium iodide, 26.2 g of chloracetic acid-N,N-diethylamide are added dropwise with stirring at an internal temperature of 130°C, and the mixture is further heated at 130°C for three hours. From the cooled reaction mixture the precipitated salts are removed by filtering off with suction. After driving off the dimethylformamide under vacuum, the product is fractionated under vacuum, and 44.3 g of 3-methoxy-4-N,N-diethylcarbamidomethoxyphenylacetic acid-n-propyl ester are obtained as a yellowish oil of boiling point 210°C to 212°C/0.7 mm Hg.

References

Merck Index 7705
OCDS Vol. 2 p. 79 (1980)
DOT 2 (3) 110 (1966)
I.N. p. 813
REM p. 1047
Hiltman, R., Wollweber, H., Hoffmeister, F. and Wirth, W.; U.S. Patent 3,086,978; April 23, 1963; assigned to Farbenfabriken Bayer A.G. (Germany)

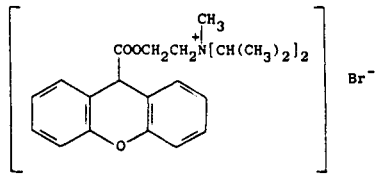
PROPANTHELINE BROMIDE

Therapeutic Function: Antispasmodic

Chemical Name: N-Methyl-N-(1-methylethyl)-N-[2-[(9H-xanthen-9-ylcarbonyl)oxy] ethyl] - 2-propanaminium bromide

Common Name: Diisopropylaminoethyl xanthene-9-carboxylate methobromide

Structural Formula:



Chemical Abstracts Registry No.: 50-34-0

Trade Name	Manufacturer	Country	Year Introduced
Pro-Banthine	Searle	U.S.	1953
Probanthine	Searle	France	1981
Apopant	A.L.	Norway	–
Banlin	Paul Maney	Canada	–
Corigast	Searle	W. Germany	–
Ercoril	Erco	Denmark	–
Giquel	Danal	U.S.	–
Ketaman	Desitin	W. Germany	–
Neo-Banex	Neo	Canada	–
Neo-Dexabine	Nourypharma	Neth.	–
Neo-Gastrosedan	Star	Finland	–
Neo-Metantyl	Zambon	Italy	–
Pantheline	Protea	Australia	–
Panthene	Vangard	U.S.	–
Pervagal	Zambeletti	Italy	–
Probital	Searle	U.S.	–
Prodixamon	A.L.	Norway	–
Propanthel	I.C.N.	Canada	–
Suprantil	Prodotti Erma	Italy	–
Tensilan	Desitin	W. Germany	–

Raw Materials

Xanthene-9-carboxylic acid
β-Diisopropylaminoethyl chloride
Methyl bromide

Manufacturing Process

365 parts of β-diisopropylaminoethyl chloride and 565 parts of xanthene-9-carboxylic acid dissolved in 800 parts of isopropanol is heated to reflux for 5 hours. The solution is then cooled, diluted with dry ether and the crystalline precipitate of β-diisopropylaminoethyl xanthene-9-carboxylate hydrochloride is collected on a filter and dried. This salt melts at 111°-112°C. 38 parts of the foregoing salt are dissolved in the minimum of water and treated with an aqueous solution of potassium carbonate. The suspension of β-diisopropylaminoethyl xanthene-9-carboxylate thus formed is extracted with ether and the ether extract is dried and evaporated. There is thus obtained 33 parts of the free base which are treated with 10 parts of methyl bromide in 100 parts of chloroform for 22 hours at 70°-80°C. The reaction mixture is chilled, diluted with anhydrous ether and the quaternary salt thus precipitated is collected on a filter and washed with dry ether and then with butanone. β-Diisopropylaminoethyl xanthene-9-carboxylate methobromide thus obtained melts at 152°-153°C. After recrystallization from isopropanol it melts at 157°-155°C.

References

Merck Index 7708
Kleeman & Engel p. 771
PDR pp. 830, 1569, 1606, 1694, 1723
OCDS Vol. 1 p. 394 (1977)
I.N. p. 813
REM p. 919
Cusic, J.W. and Robinson, R.A.; U.S. Patent 2,659,732; November 17, 1953; assigned to G.D. Searle & Co.

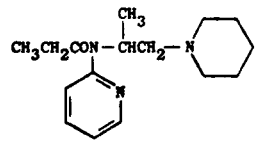
PROPIRAM FUMARATE

Therapeutic Function: Analgesic

Chemical Name: N-[1-Methyl-2-(1-piperidinyl)ethyl]-N-2-pyridinylpropanamide fumarate

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 13717-04-9; 15686-91-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Algeril	Bayropharm	Italy	1974
Algeril	Bayer	W. Germany	1974
Dirame	Schering	–	–

Raw Materials

2-(1-Piperidino-isopropyl)aminopyridine
Propionic anhydride
Fumaric acid

Manufacturing Process

20 g of 2-(1-piperidino-isopropyl)aminopyridine and 50 ml of propionic anhydride are heated to 120°C for 8 hours. The mixture is then evaporated under vacuum and the residue taken up in water. The base is precipitated from the solution with a caustic soda solution, taken up in ether and dried with potassium carbonate. After driving off the ether and distillation under vacuum, there are obtained 18 grams of N-propionyl-2-(1-piperidino-isopropyl)-aminopyridine of BP 162°-163°C/0.5 mm Hg. The base is then reacted with fumaric acid to give the final product.

References

Merck Index 7733
Kleeman & Engel p. 772
DOT 10 (11) 309 (1974)
I.N. p. 815

Hiltmann, R., Wollweber, H., Hoffmeister, F., Wirth, W. and Kroneberg, H.-G.; U.S. Patent 3,163,654; December 29, 1964; assigned to Farbenfabriken Bayer AG, Germany
Wollweber, H., Hiltmann, R., Hoffmeister, F. and Kroneberg, H.-G.; U.S. Patent 3,594,477; July 20, 1971; assigned to Farbenfabriken Bayer AG, Germany

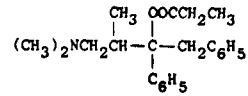
PROPOXYPHENE HYDROCHLORIDE

Therapeutic Function: Analgesic

Chemical Name: (S)-α-[2-(dimethylamino)-1-methylethyl] -α-phenylbenzeneethanol propanoate hydrochloride

Common Name: Dextropropoxyphene hydrochloride

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1639-60-7; 469-62-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Darvon	Lilly	U.S.	1957
Antalvic	Houde	France	1963
SK-65	SKF	U.S.	1973
Propoxychel	Rachelle	U.S.	1973
Dolene-65	Lederle	U.S.	1973
Prophen 65	Halsey	U.S.	1981
Darvocet-N	Lilly	U.S.	–
Depronal SA	Warner	U.K.	–
Develin	Goedecke	W. Germany	–
Doloxene	Lilly	U.K.	–
Erantin	Boehr. Mann.	W. Germany	–
Liberen	Lisapharma	Italy	–
Lorcet	U.A.D. Labs	U.S.	–
Wygesic	Wyeth	U.S.	–

Raw Materials

Benzyl chloride
α-Methyl-β-dimethylaminopropiophenone
Propionic anhydride
Magnesium
Hydrogen chloride

Manufacturing Process

A solution of benzylmagnesium chloride prepared from 63.3 grams (0.5 mol) of benzyl chloride, 30.5 grams (1.25 mol) of magnesium and 750 cc of ether was added dropwise with stirring to a solution of 61.9 grams (0.35 mol) of α-methyl-β-dimethylaminopropiophenone (prepared by the method of Burchalter et al, *JACS* 70 page 4186, 1948), in 150 cc of ether. When all of the Grignard reagent had been added, the solution was refluxed for about 1 hour. The reaction mixture was then decomposed by the addition of saturated aqueous ammonium chloride solution. The ether solution containing the 1,2-diphenyl-2-hydroxy-3-methyl-4-dimethylaminobutane formed in the reaction was decanted from the granular precipitate and dried over anhydrous magnesium sulfate.

Dry hydrogen chloride gas was passed into the ether solution until precipitation was completed. The solid was removed by filtration and was recrystallized from a mixture of methanol and ethyl acetate. The α-dl-1,2-diphenyl-2-hydroxy-3-methyl-4-dimethylaminobutane hydrochloride thus obtained melted at about 231° to 232°C.

A mixture of 50 grams of α-dl-1,2-diphenyl-2-hydroxy-3-methyl-4-dimethylaminobutane hydrochloride, 50 grams of propionic anhydride and 50 cc of pyridine was refluxed for about 5 hours. The reaction mixture was cooled to 50°C and ethyl ether was added to the point of incipient precipitation. The hydrochloride salt of α-dl-1,2-diphenyl-2-propionoxy-3-methyl-4-dimethylaminobutane formed in the reaction precipitated upon cooling and was removed by filtration and washed with anhydrous ether. On recrystallization from a mixture of methanol and ethyl acetate, α-dl-1,2-diphenyl-2-propionoxy-3-methyl-4-dimethylaminobutane hydrochloride melted at 170°-171°C.

References

Merck Index 7739
Kleeman & Engel p. 285
PDR pp. 993, 1044, 1606, 1723, 1808, 1996, 1999
OCDS Vol. 1 pp. 50, 298 (1977) & 2, 57 (1980)
I.N. p. 816
REM p. 1114
Pohland, A.; U.S. Patent 2,728,779; December 27, 1955; assigned to Eli Lilly and Company

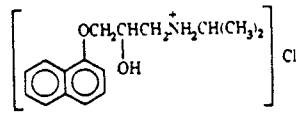
PROPRANOLOL HYDROCHLORIDE

Therapeutic Function: β-adrenergic blocker

Chemical Name: 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 318-98-9; 525-66-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Inderal	I.C.I.	U.K.	1965
Dociton	Rhein Pharma	W. Germany	1965
Avlocardyl	I.C.I.	France	1967
Inderal	Ayerst	U.S.	1968
Angilol	D.D.S.A.	U.K.	—
Arcablock	Arcana	Austria	—
Bedranol	Lagap	Switz.	—
Berkolol	Berk	U.K.	—
Beta-Neg	Ellem	Italy	—
Beta-Tablinen	Sanorania	W. Germany	—
Cardinol	Protea	Australia	—
Caridolol	Sankyo	Japan	—
Corotrend	Siegfried	Switz.	—

Trade Name	Manufacturer	Country	Year Introduced
Deralin	Abic	Israel	–
Detensol	Desbergers	Canada	–
Dideral	Dif-Dogu	Turkey	–
Frekven	Ferrosan	Denmark	–
Herzbase	Nichiiko	Japan	–
Herzul	Ono	Japan	–
Inderide	Ayerst	U.S.	–
Indobloc	Homburg	W. Germany	–
Kemi	Otsuka	Japan	–
Nedis	Omega	Argentina	–
Noloten	Beta	Argentina	–
Novopranol	Novopharm	Canada	–
Obsidan	Iris-Chemie	E. Germany	–
Oposim	Richet	Argentina	–
Pranolol	A.L.	Norway	–
Pronovan	A.L.	Norway	–
Propranolol	Lederle	U.S.	–
Propranur	Henning	W. Germany	–
Pur-Bloka	Lennon	S. Africa	–
Pylapron	Kyorin	Japan	–
Reducor	Leiras	Finland	–
Sawatal	Sawai	Japan	–
Tonum	Tubi Lux Pharma	Italy	–

Raw Materials

1-Naphthol
Isopropyl amine
Epichlorohydrin
Hydrogen chloride

Manufacturing Process

In a first step, 1-naphthol was reacted with epichlorohydrin to give 1-chloro-3-(1-naphthoxy)-2-propanol.

A mixture of 4.4 parts of 1-chloro-3-(1-naphthoxy)-2-propano and 16 parts of isopropylamine is heated in a sealed vessel at 70°-80°C for 10 hours. The vessel is cooled and to the contents there are added 50 parts of water. The mixture is acidified with 2 N hydrochloric acid, and washed with 50 parts of ether. The aqueous phase is decolorized with carbon, and then added to 50 parts of 2N sodium hydroxide solution at 0°C. The mixture is filtered. The solid residue is washed with water, dried, and crystallized from cyclohexane. There is thus obtained 1-isopropylamino-3-(1-naphthoxy)-2-propanol, MP 96°C.

The base may be converted into the hydrochloride as follows. 4.65 parts of the base are dissolved in 60 parts of warm acetone. To the warm solution there are added 2 parts of 10 N hydrochloric acid. The mixture is allowed to cool, and is then filtered. The solid residue is washed with acetone and then dried. The solid is crystallized from propanol, and there is thus obtained 1-isopropylamino-3-(1-naphthoxy)-2-propanol hydrochloride MP 163°C.

References

Merck Index 7740
Kleeman & Engel p. 773
PDR pp. 622, 993, 1999
OCDS Vol. 1 p. 117 (1977) & 2, 105, 107, 212 (1980)
DOT 19 (3) 172 (1983)
I.N. p. 816
REM p. 906

Crowther, A.F. and Smith, L.H.; U.S. Patent 3,337,628; August 22, 1967; assigned to Imperial Chemical Industries Limited, England

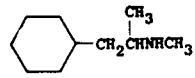
PROPYLHEXEDRINE

Therapeutic Function: Nasal decongestant

Chemical Name: N,α-dimethylcyclohexaneethanamine

Common Name: Hexahydrodesoxyephedrine

Structural Formula:



Chemical Abstracts Registry No.: 101-40-6; 6192-98-9 (Hydrochloride)

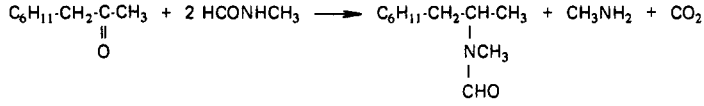
Trade Name	Manufacturer	Country	Year Introduced
Benzedrex	SKF	U.S.	1949
Dristan	Whitehall	U.S.	—
Eggobesin	Fahlberg-List	E. Germany	—
Eventin	Minden	W. Germany	—

Raw Materials

Cyclohexylacetone
Sulfuric acid
N-Methylformamide
Sodium hydroxide

Manufacturing Process

33.6 grams of cyclohexylacetone, a compound known to the art, dissolved in 13 grams of 85% formic acid is caused to interact with 72.0 grams of N-methyl formamide at 160°-180°C for 4 hours. This results in the formation of the formyl derivative of the amine, according to the following reaction:



The formyl derivative is then hydrolyzed by refluxing with 50% sulfuric acid for about 4 hours, after which the hydrolysate is extracted with ether to remove the acid-insoluble material and the aqueous solution made strongly alkaline with any suitable alkalizing agent, for example, sodium hydroxide, to liberate the amine.

The amine is then taken up in ether, dried over potassium hydroxide and purified by distillation, preferably under reduced pressure. β-cyclohexylisopropylmethylamine thus obtained boils at 90.0°-92°C at 22 mm Hg.

References

Merck Index 7761
Kleeman & Engel p. 774
OCDS Vol. 1 p. 37 (1977)
I.N. p. 817

REM p. 890
Ullyot, G.E.; U.S. Patent 2,454,746; November 23, 1948; assigned to Smith, Kline & French Laboratories

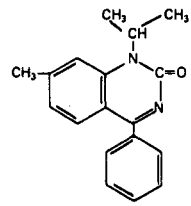
PROQUAZONE

Therapeutic Function: Antiinflammatory

Chemical Name: 1-Isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 22760-18-5

Trade Name	Manufacturer	Country	Year Introduced
Biarison	Sandoz	Italy	1977
Biarison	Sandoz	Japan	1977
Biarison	Sandoz	France	1977
Biarison	Sandoz	Switz.	1977
Biarison	Wander	W. Germany	1979

Raw Materials

4-Methyl-2-isopropylaminobenzophenone
Urethane

Manufacturing Process

A mixture of 5.9 g of 4-methyl-2-isopropylaminobenzophenone, 13.9 g urethane and 500 mg of zinc chloride is heated at a temperature of 190°C for 1½ hours. There is then additionally added 7 g of urethane and 250 mg of zinc chloride, and the heating continued at a temperature of 190°C for an additional 2½ hours. The resulting mixture is cooled to about 100°C and diluted with chloroform. The resulting mixture is then filtered and the filtrate washed first with water and then with brine. The organic phase is separated, dried over anhydrous sodium sulfate and concentrated in vacuo to remove substantially all of the chloroform and obtain an oily residue which is dissolved in a small amount of about 20 ml of methylene chloride. The resulting solution is then diluted with about 40 ml of ethyl acetate and concentrated in vacuo to crystallize 1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone; melting point 137°C to 138°C.

References

Merck Index 7775
DFU 1 (11) 540 (1976)
Kleeman & Engel p. 777

OCDS Vol. 2 p. 386 (1980)
DOT 8 (3) 116 (1972) & 13 (12) 534 (1977)
I.N. p. 818
Linder, J., Mattner, P.G. and Salmond, W.G.; U.S. Patent 3,759,720; September 18, 1973; assigned to Sandoz-Wander Inc.
Denzer, M.; U.S. Patent 3,793,324; February 19, 1974
Ott, H.; U.S. Patent 3,925,548; December 9, 1975; assigned to Sandoz, Inc.

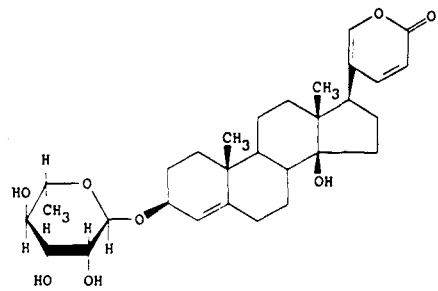
PROSCILLARIDIN

Therapeutic Function: Cardiotonic

Chemical Name: 3-[(6-Deoxy-α-L-mannopyranosyl)oxy]-14-hydroxybufa-4,20,22-trienolide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 466-06-8

Trade Name	Manufacturer	Country	Year Introduced
Talusin	Knoll	W. Germany	1964
Talusin	Biosedra	France	1968
Apocerpin	Kotani	Japan	—
Bunosquin	Seiko	Japan	—
Caradrin	Kowa	Japan	—
Cardimarin	Santen	Japan	—
Cardiolidin	Nichiiko	Japan	—
Cardion	Nippon Chemiphar	Japan	—
Cardon	Kanto	Japan	—
Herzo	Toho	Japan	—
Mitredin	Nippon Shoji	Japan	—
Procardin	Mohan	Japan	—
Procillan	Hokuriku	Japan	—
Proherz	Shinshin	Japan	—
Proscillan	Streuli	Switz.	—
Proscillar	Toyo Jozo	Japan	—
Prosiladin	Sawai	Japan	—
Prostosin	Iwari	Japan	—
Proszin	Teisan	Japan	—
Protasin	Bayropharm	W. Germany	—
Purosin-TC	Tatsumi	Japan	—
Sandoscill	Sandoz	W. Germany	—

Trade Name	Manufacturer	Country	Year Introduced
Scillaridin	Moroshita	Japan	–
Silamarin A	Wakamoto	Japan	–
Stellarid	Tobishi-Mochida	Japan	–
Talusin	Dainippon	Japan	–
Urgilan	Simes	Italy	–
Wirnesin	Inpharzam	W. Germany	–

Raw Materials

Squill

Manufacturing Process

350 g of dried and cut squill were fermented at 50°C for two hours in 1.1 liters of water. The suspension was then extracted three times with 1.1 liters of ethyl acetate. The extracts were united and evaporated to dryness, the residue was dissolved in 2 ml of dioxane and chromatographed in a twenty-fold quantity (based on the amount of dried residue) of silica gel. The proscillaridin was then eluated with toluene to which increasing quantities of a methanol-dioxane mixture were added. The main fraction, containing proscillaridin, was evaporated to dryness. The residue was crystallized out of methanol. Pure proscillaridin was obtained with a melting point of 227°C to 230°C; $\alpha_{20}^{D} = -93.5°C$ (in methanol).

The same result was obtained by fermentation on the aqueous suspension of the cut squill at room temperature for 24 hours and working up in the manner described.

References

Merck Index 7776
Kleeman & Engel p. 777
DOT 3 (3) 97 (1967)
I.N. p. 819
Steidle, W.; U.S. Patent 3,361,630; January 2, 1968; assigned to Knoll A.G. (Germany)

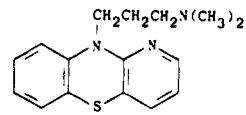
PROTHIPENDYL HYDROCHLORIDE

Therapeutic Function: Sedative; antihistaminic

Chemical Name: N,N-Dimethyl-10H-pyrido[3,2-b] [1,4] benzothiazine-10-propanamine hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1225-65-6; 303-69-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Timovan	Ayerst	U.S.	1960
Dominal	Homburg	W. Germany	–
Prosyl	Kanto	Japan	–
Tolnate	SKF	U.K.	–

Raw Materials

1-Azaphenothiazine	Sodium amide
3-Dimethylaminopropyl chloride	Hydrogen chloride

Manufacturing Process

A mixture of 20 g (0.1 mol) of 1-azaphenothiazine, 4.3 g (0.11 mol) of sodamide and 300 ml of dry toluene is stirred and refluxed for eight hours. A slow stream of dry nitrogen gas is used to sweep out the ammonia as formed. The mixture is cooled and 110 ml of a 1 M solution of 3-dimethylaminopropyl chloride in toluene is added dropwise, with stirring. Subsequently, the mixture is stirred and refluxed for fifteen hours, cooled, and concentrated in vacuo. The viscous residue is refluxed with 500 ml of chloroform and filtered hot. The chloroform filtrate is treated with activated charcoal and again filtered. The filtrate is concentrated and the residue distilled to give about 19.8 g (69% yield) of product, an oil distilling at about 195°C to 198°C (under 0.5 mm pressure of mercury).

To a solution of 16.4 g (0.058 mol) of the free base in 75 ml of dry acetonitrile is added dropwise while cooling (ice bath) and stirring 14.5 ml (0.053 mol) of 3.6N ethereal hydrogen chloride. An equal volume of anhydrous ether is added and the product altered, dried and recrystallized from monochlorobenzene. The product melts at about 177°C to 178°C with sintering at about 176°C. The yield is about 11.0 g (60%).

References

Merck Index 7789
Kleeman & Engel p. 779
OCDS Vol. 1 p. 430 (1977)
I.N. p. 821
Yale, H.L. and Bernstein, J.; U.S. Patent 2,943,086; June 28, 1960; assigned to Olin Mathieson Chemical Corp.

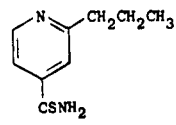
PROTIONAMIDE

Therapeutic Function: Antitubercular

Chemical Name: 2-propyl-4-pyridinecarbothioamide

Common Name: α-propyl-isonicotinic thioamide

Structural Formula:



Chemical Abstracts Registry No.: 14222-60-7

Trade Name	Manufacturer	Country	Year Introduced
Ektebin	Bayer	W. Germany	1969
Protionizina	Farmitalia	Italy	1970
Entelohl	Kyowa	Japan	—
Peteha	Saarstickstoff-Fatol	W. Germany	—
Promid	Biofarma	Turkey	—

Trade Name	Manufacturer	Country	Year Introduced
Prothionamide	Toho	Japan	–
Trevintix	Theraplix	France	–
Tuberamin	Meiji	Japan	–
Tuberex	Shionogi	Japan	–
Tubermide	Sankyo	Japan	–

Raw Materials

Ethyl oxalate
Sodium ethylate
Hydrogen chloride
Hydrogen
Phosphoric anhydride
Methyl-n-propyl ketone
Cyanacetamide
Phosphorus oxychloride
Ammonia
Hydrogen sulfide

Manufacturing Process

(A) Ethyl Butyryl-Pyruvate: 146 grams of ethyl oxalate are condensed with 86 grams of methyl-(n)-propyl-ketone in the presence of sodium ethylate prepared from 25 grams of sodium. 135 grams of product, having a boiling point of 113°C/6 mm, are obtained.

(B) 3-Cyano-4-Carbethoxy-6-(n)-Propyl-2-Pyridone: The 135 grams of the product just obtained are condensed with 62 grams of cyanacetamide in the presence of 24 cc of piperidine in 1200 cc of 95% alcohol. 64 grams of a product, melting at 152°C, are obtained.

(C) 6-(n)-Propyl-2-Pyridone-4-Carboxylic Acid: The 64 grams of the product just obtained are treated with 500 cc of concentrated hydrochloric acid at boiling point. 40 grams of a product, having a melting point of 285°C, are obtained.

(D) Ethyl 2-Chloro-6-(n)-Propyl-Isonicotinate: The 40 grams of the acid just obtained are treated with 80 grams of phosphorus oxychloride and 95 grams of phosphorus pentachloride. The phosphorus oxychloride is distilled and the reaction mixture is treated with 400 grams of absolute alcohol. 40 grams of chlorinated ester, having a BP of 115°-116°C/2 mm, are obtained.

(E) Ethyl 2-(n)-Propyl-Isonicotinate: The product just obtained is dechlorinated by catalytically hydrogenating it in an alcoholic medium in the presence of palladium black and potassium acetate. 30 grams of ester, having a boiling point of 121°-125°C/7 mm, are obtained.

(F) 2-(n)-Propyl-Isonicotinamide: The 30 grams of the ester just obtained are treated with 40 cc of concentrated ammonia saturated with gaseous ammonia. 20 grams of product, having a melting point of 135°C, are obtained.

(G) 2-(n)-Propyl-Isonicotinic-Nitrile: The 20 grams of the amide just obtained are treated with 32 grams of phosphoric anhydride. 11 grams of nitrile, having a BP of 90°-95°C/4 mm, are obtained.

(H) 2-(n)-Propyl-Isonicotinic Thioamide: The 11 grams of nitrile just obtained, dissolved in 40 cc of ethanol containing 4 grams of triethanolamine, are treated with hydrogen sulfide. 8 grams of the desired product, having a melting point of 142°C, are obtained.

References

Merck Index 7791
Kleeman & Engel p. 780
DOT 3 (1) 24 (1967)
I.N. p. 821
Chimie et Atomistique, France; British Patent 800,250; August 20, 1958

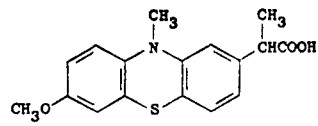
PROTIZINIC ACID

Therapeutic Function: Antiinflammatory

Chemical Name: 7-methoxy-α,10-dimethylphenothiazine-2-acetic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 13799-03-6

Trade Name	Manufacturer	Country	Year Introduced
Pirocrid	Theraplix	France	1974
Pirocrid	Mochida	Japan	1979
P.R.T.	Mochida	Japan	—

Raw Materials

Methyl (7-methoxy-10-methyl-3-phenthiazinyl)acetate
Sodium
Ethanol
Methyl iodide
Diethyl carbonate
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

Methyl ethyl (7-methoxy-10-methyl-3-phenthiazinyl)malonate is prepared by reacting a solution of sodium (4.37 grams) in anhydrous ethanol (110 cc) with a solution of methyl (7-methoxy-10-methyl-3-phenthiazinyl)acetate (59 grams) in ethyl carbonate (180 cc). The reaction mixture is heated at about 105°-110°C for 3 hours and the ethanol formed is distilled off as it is formed.

The reaction mixture is acidified with N hydrochloric acid (200 cc) and the oil formed is extracted with methylene chloride (200 cc). The methylene chloride solution is washed with water (210 cc), treated with decolorizing charcoal (5 grams), dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure (20 mm Hg) giving an oil (77 grams) which is crystallized from methanol (300 cc) to yield methyl ethyl (7-methoxy-10-methyl-3-phenthiazinyl)-malonate (62.4 grams) melting at 80°-82°C.

Methyl ethyl (7-methoxy-10-methyl-3-phenthiazinyl)malonate (62.2 grams) followed by methyl iodide (45.7 grams) is added to a solution of sodium (4.45 grams) in anhydrous ethanol (500 cc). The reaction mixture is heated under reflux for 1 hour at 45°C, then for 6 hours at 55°C, and finally concentrated to dryness under reduced pressure (20 mm Hg). The residue is taken up in methylene chloride (300 cc) and water (250 cc), filtered in the presence of a filtration adjuvant, washed with methylene chloride (150 cc) and water (150 cc), and decanted. The aqueous solution is extracted once again with methylene chloride (100 cc), and the combined organic solutions washed with water (100 cc), aqueous 0.1 N sodium hyposulfite solution (200 cc) and finally with water (200 cc). After drying over anhydrous sodium sulfate and evaporation to dryness under reduced pressure (20 mm Hg), there is obtained an oil (64.8 grams) which is dissolved in methylene chloride (100 cc) and

chromatographed over alumina (650 grams). After elution with methylene chloride, a fraction of 2.5 liters is recovered and concentrated to dryness under reduced pressure (20 mm Hg) to give methyl ethyl methyl-(7-methoxy-10-methyl-3-phenthiazinyl)malonate (59.7 grams) melting at 70°-72°C.

1 N sodium hydroxide solution (296 cc) is poured over a period of 3 hours into a solution of methyl ethyl methyl-(7-methoxy-10-methyl-3-phenthiazinyl)malonate (59.7 grams) in ethanol (600 cc) heated under reflux in an atmosphere of nitrogen. The reaction mixture is concentrated to dryness under reduced pressure (20 mm Hg), the residue obtained acidified with N hydrochloric acid (300 cc) and the gum formed extracted with methylene chloride (150 cc). The organic solution is washed with water (200 cc), treated with decolorizing charcoal (10 grams), dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure (20 mm Hg). The oil obtained (48 grams) is dissolved in N sodium hydroxide solution (200 cc) and the aqueous solution washed with diethyl ether (300 cc), treated with decolorizing charcoal (5 grams) and acidified with N hydrochloric acid (200 cc). The oil formed is dissolved in methylene chloride (350 cc), the solution washed with water (100 cc), treated with decolorizing charcoal (5 grams) and dried over anhydrous sodium sulfate. The solution is concentrated to dryness under reduced pressure (20 mm Hg) to give an oil (35.6 grams) which crystallizes slowly. On recrystallization from diisopropyl ether (180 cc) a product (19.5 grams), melting at 123°-124°C, is obtained. Further recrystallization from diisopropyl ether (290 cc) yields 2-(7-methoxy-10-methyl-3-phenthiazinyl)-propionic acid (12.9 grams) melting at 124°-125°C.

References

Merck Index 7792
Kleeman & Engel p. 782
DOT 8 (12) 452 (1972)
I.N. p. 36
Farge, D., Jeanmart, C. and Messer, M.N.; U.S. Patent 3,450,698; June 17, 1969; assigned to Rhone-Poulenc SA, France

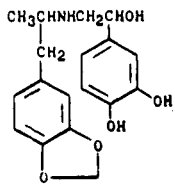
PROTOKYLOL

Therapeutic Function: Bronchodilator

Chemical Name: 4-[2-[[2-(1,3-benzodioxol-5-yl)-1-methylethyl] amino]-1-hydroxyethyl]-1,2-benzenediol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 136-70-9; 136-69-6 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Caytine	Lakeside	U.S.	1959
Ventaire	Marion	U.S.	1974

Trade Name	Manufacturer	Country	Year Introduced
Asmetil	Benvegna	Italy	–
Atma-Sanol	Sanol	W. Germany	–
Beres	Simes	Italy	–
Biturix	Nemi	Argentina	–
Palison	Farmasimes	Spain	–

Raw Materials

3,4-Methylenedioxyphenylisopropanolamine
Chloroacetylcatechol
Hydrogen

Manufacturing Process

3,4-Methylenedioxyphenylisopropanolamine is reacted with chloroacetylcatechol in a 3:1 mol ratio in 60% ethanol at reflux temperature with continuous stirring. Stirring and refluxing were continued for another five hours after which the reaction mixture was cooled and then acidified with 20 cc of concentrated aqueous HCl. The acid solution was concentrated in vacuo to a viscous consistency and the residue dissolved in acetone. On standing, the aminoketone precipitated and was filtered. The precipitate was dissolved in isopropyl alcohol and permitted to recrystallize. An alcoholic solution of this aminoketone precipitate was reduced with PtO_2 and hydrogen, clarified by filtration, concentrated to dryness in vacuo and the residue crystallized from acetone giving the desired product.

References

Merck Index 7798
Kleeman & Engel p. 783
I.N. p. 821
Biel, J.H.; U.S. Patent 2,900,415; August 18, 1959; assigned to Lakeside Laboratories, Inc.

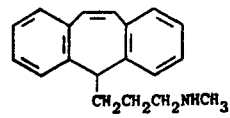
PROTRIPTYLINE

Therapeutic Function: Psychostimulant

Chemical Name: N-methyl-5H-dibenzo[a,d]cycloheptene-5-propylamine

Common Name: Amimetilina; 5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene

Structural Formula:



Chemical Abstracts Registry No.: 438-60-8; 1225-55-4 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Vivactil	MSD	U.S.	1967
Maximed	Sharp & Dohme	W. Germany	1968
Concordin	MSD	Italy	1972
Concordine	MSD	France	1973
Triptil	Merck-Frosst	Canada	–

Raw Materials

3-Methylaminopropanol-1
Thionyl chloride
Potassium amide
Formamide
5H-Dibenzo[a,d]-cycloheptene
Potassium hydroxide

Manufacturing Process

Preparation of 3-(N-Formyl-N-Methyl)-Aminopropanol-1: A mixture of 40 grams of 3-methylaminopropanol-1 and 20 grams of formamide is heated while stirring for 4 hours at 165°C. The crude product is fractionated in vacuo using a Widmer column yielding substantially pure 3-(N-formyl-N-methyl)-aminopropanol-1.

Preparation of 3-(N-Formyl-N-Methyl)-Aminopropyl Chloride: 50 grams of 3-(N-formyl-N-methyl)-aminopropanol-1 obtained above is dissolved in a mixture of 100 ml of chloroform and 25 grams of pyridine. 40 grams of thionyl chloride is then slowly added while maintaining the temperature below 65°C. After 6 hours of refluxing, the mixture is washed with water, then with sodium bicarbonate solution and again with water and then dried over magnesium sulfate and the solvent distilled off in vacuo. Fractional distillation at 1 mm pressure yields substantially pure 3-(N-formyl-N-methyl)-aminopropyl chloride.

Preparation of 5-[3-(N-Formyl-N-Methyl)-Aminopropyl]-5H-Dibenzo[a,d] Cycloheptene: To a suspension of 3.9 grams of potassium amide is slowly added a solution of 19.2 grams (0.1 mol) of 5H-dibenzo[a,d]cycloheptene in 600 ml of ether with stirring. The suspension is refluxed with stirring for 3 hours, then cooled to room temperature and a solution of 0.1 mol of 3-(N-formyl-N-methyl)-aminopropyl chloride in 100 ml of ether added. The mixture is then refluxed with stirring for 5 hours and then 100 ml of water added. The ether layer is then washed with dilute hydrochloric acid, then water and then dried over magnesium sulfate and evaporated to dryness yielding 5-[3-(N-formyl-N-methyl)-aminopropyl]-5H-dibenzo[a,d] cycloheptene.

Preparation of 5-(3-Methylaminopropyl)-5H-Dibenzo[a,d] Cycloheptene from 5-[3-(N-Formyl-N-Methyl)-Aminopropyl]-5H-Dibenzo[a,d] Cycloheptene: 29.5 grams of 5-[3-(N-formyl-N-methyl)-aminopropyl]-5H-dibenzo[a,d]cycloheptene is refluxed for 24 hours under nitrogen in a solution of 36.3 grams of potassium hydroxide in 378 ml of n-butanol. After cooling to room temperature, the solvent is evaporated in vacuo, the residue is stirred with 200 ml of water, 300 ml of n-hexane, the layers separated, the water layer extracted with 100 ml of n-hexane and the combined hexane layers washed with water (2 x 100 ml) and then with 0.5 N sulfuric acid (100, 80, 80 ml). The acid solution is then alkalized and extracted with ether (2 x 150 ml and 1 x 100 ml), dried over $MgSO_4$ and the solution evaporated to dryness yielding substantially pure 5-(3-methylaminopropyl)-5H-dibenzo[a,d] cycloheptene according to U.S. Patent 3,244,748.

References

Merck Index 7804
Kleeman & Engel p. 783
PDR p. 1220
OCDS Vol. 1 p. 152 (1977)
I.N. p. 822
REM p. 1097
Tishler, M., Chemerda, J.M. and Kollonitsch, J.; U.S. Patent 3,244,748; April 5, 1966; assigned to Merck & Co., Inc.
Tishler, M., Chemerda, J.M. and Kollonitsch, J.; U.S. Patent 3,271,451; September 6, 1966; assigned to Merck & Co., Inc.

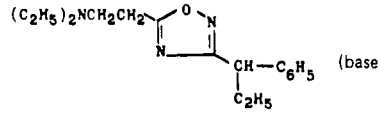
PROXAZOLE CITRATE

Therapeutic Function: Antispasmodic

Chemical Name: N,N-diethyl-3-(1-phenylpropyl)-1,2,4-oxadiazole-5-ethanamine citrate

Common Name: Propaxoline citrate

Structural Formula:



Chemical Abstracts Registry No.: 132-35-4; 5696-09-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Recidol	Lampugnani	Italy	1967
Pirecin	Yoshitomi	Japan	1970
Mendozal	Beaufour	France	1976
Flou	Elea	Argentina	–
Solacil	Finadiet	Argentina	–
Toness	Angelini	Italy	–

Raw Materials

α-Ethylbenzamidoxime
Citric acid
β-Chloropropionyl chloride
Diethylamine

Manufacturing Process

α-Ethylbenzamidoxime and anhydrous potassium carbonate are suspended in chloroform. To this mixture, under continuous stirring and controlling of the reaction temperature to remain beyond 15°C, there is slowly added β-chloropropionyl chloride. After addition of the acid chloride, stirring is continued for a further hour. Then with cooling there is added portionwise a small amount of water. Further amounts of water are introduced into the reaction mixture and the chloroform solution containing the β-chloropropionyl α-ethylbenzamidoxime is separated.

To this solution there is added in about 20 minutes a solution of diethylamine in $CHCl_3$ while the temperature is kept below 35°C. The reacting mixture is heated to boiling, water formed during the reaction being distilled off thereby. After two hours the distillate contains no more water and the reaction is finished. Water is added to dissolve diethylamine hydrochloride formed during the reaction, and the chloroform layer containing the product is separated from the aqueous layer. The product may be purified by distillation; it boils at 132°C at 0.2 mm pressure. It is converted to the citrate by reaction with citric acid.

References

Merck Index 7805
Kleeman & Engel p. 784
OCDS Vol. 2 p. 271 (1980)
I.N. p. 822
Palazzo, G. and Silvestrini, B.; U.S. Patent 3,141,019; July 14, 1964; assigned to Angelini Francesco, Aziende Chimiche Riunite, Italy

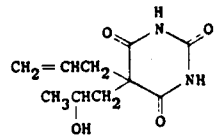
PROXIBARBAL

Therapeutic Function: Sedative

Chemical Name: 5-(2-Hydroxypropyl)-5-(2-propenyl)-2,4,6(1H,3H,5H)pyrimidinetrione

Common Name: Proxibarbital

Structural Formula:



Chemical Abstracts Registry No.: 2537-29-3

Trade Name	Manufacturer	Country	Year Introduced
Axeen	Hommel	W. Germany	1962
Centralgol	Valpan	France	1965
Ipronal	Polfa	Poland	—
Vasalgin	Chinoin	Hungary	—

Raw Materials

Diallylbarbituric acid
Sulfuric acid
Water

Manufacturing Process

9 Parts of diallyl-barbituric acid are added to a precooled mixture of 15.5 parts of concentrated sulfuric acid and 0.5 part of water while stirring intensively, the mixture being cooled so that its temperature does not exceed 25°C. The honey-colored viscous solution is stirred vigorously and all at once into 45 parts of water, whereupon the mixture warms up to 35°C to 40°C and, after several seconds, solidifies into a thick pulp, which is then heated as quickly as possible to 95°C, at which temperature a clear solution is formed. This is cooled slowly until the 5-allyl-5-(β-hydroxypropyl)-barbituric acid begins to form coarse-grained crystals, after which the mass is cooled rapidly to 20°C.

The crystallized 5-allyl-5-(β-hydroxypropyl)-barbituric acid is centrifuged off, 55 to 58 parts of mother liquor and 10 to 13 parts of crude product being obtained. The latter is dispersed in 20 parts of saturated aqueous sodium chloride solution and after two hours is again centrifuged off.

The thus-washed crude product is dissolved in a mixture of 12 parts of ethanol and 20 parts of benzene, with mild warming if necessary. 1 Part of sodium chloride and 1.5 parts of saturated aqueous sodium chloride solution are added to the obtained solution in ethanol-benzene, and whole thoroughly admixed. When the brine layer has settled, it is separated and the aforedescribed washing repeated. The clear solution is concentrated under reduced pressure until incipient formation of crystals and is then poured into 30 parts of benzene, whereupon a thick crystalline pulp is forthwith formed which, after being cooled to room temperature, is centrifuged off. The so-obtained 5-allyl-5-(β-hydroxypropyl)-barbituric acid is dried at 70°C under reduced pressure and can be used for therapeutic purposes without further purification. Melting point 164°C to 165°C. Yield: 5 parts.

References

Merck Index 7806
I.N. p. 822
Hommel A.G.; British Patent 953,387; March 25, 1964

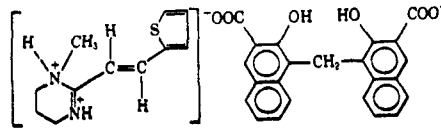
PYRANTEL PAMOATE

Therapeutic Function: Anthelmintic

Chemical Name: E-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl] pyrimidine pamoate

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 22204-24-6; 15686-83-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Antiminth	Roerig	U.S.	1972
Helmex	Roerig	W. Germany	1972
Cobantrin	Pfizer Taito	Japan	1973
Combantrin	Pfizer	France	1973
Combantrin	Pfizer	Italy	1975
Lombriareu	Areu	Spain	—
Piranver	ICN-Usafarma	Brazil	—

Raw Materials

Thiophene-2-carboxaldehyde
1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine
Tartaric acid
Pamoic acid

Manufacturing Process

A solution of 0.1 mol of each of thiophene-2-carboxaldehyde and 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine in dimethyl carbonate (0.2 mol) is held at 27°C for 48 hours. The reaction mixture is then stripped to give a 65% yield of product as the free base.

The base may be isolated as the tartrate as follows: A portion of reaction mixture is added to a well stirred solution of tartaric acid in ethanol at 27°C. The mixture is stirred for two hours and the product recovered by filtration. The filter cake is washed with cold ethanol followed by ether and air-dried. MP 144°-147°C.

The tartrate salt is recrystallized by dissolving in hot methanol, filtering, adding hot ethanol to the filtrate and cooling. The product is collected and air-dried. MP 148°-150°C. A second crop is obtained from the filtrate for a total yield of 59%. The tartrate is then metathesized with pamoic acid (Merck Index #6867) to give pyrantel pamoate as the product.

References

Merck Index 7856
Kleeman & Engel p. 786
PDR p. 1403
OCDS Vol. 1 p. 266 (1977) & 2, 303 (1980)
DOT 8 (11) 431 (1972); 17 (1) 41 (1981); & (6) 262 (1981)
I.N. p. 825
REM p. 1237

Kasubick, R.V. and McFarland, J.W.; U.S. Patent 3,502,661; March 24, 1970; assigned to Chas. Pfizer & Co., Inc.

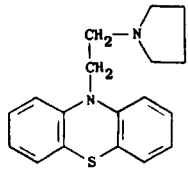
PYRATHIAZINE

Therapeutic Function: Antihistaminic

Chemical Name: 10-[2-(1-Pyrrolidinyl)ethyl] phenothiazine

Common Name: Parathiazine

Structural Formula:



Chemical Abstracts Registry No.: 84-08-2

Trade Name	Manufacturer	Country	Year Introduced
Pyrrolazote	Upjohn	U.S.	1949

Raw Materials

Phenothiazine
Sodium amide
β-Pyrrolidinoethyl chloride

Manufacturing Process

To a stirred suspension of 4.29 g (0.11 mol) of sodium amide in 100 ml of dry toluene was added 19.9 g (0.1 mol) of phenothiazine. The solution was heated at reflux for two hours, the sodium salt of phenothiazine precipitating from solution. The toluene suspension of the sodium salt of phenothiazine was cooled to room temperature, whereupon there was added dropwise with continued stirring 13.36 g (0.1 mol) of β-pyrrolidinoethyl chloride in 50 ml of dry toluene. After addition was complete, the solution was heated under reflux, with stirring, for an additional 15 hours. Upon cooling, the toluene was extracted with dilute hydrochloric acid and the toluene then discarded. The aqueous acid solution was made alkaline with dilute sodium hydroxide, the crude N-(β-pyrrolidinoethyl)-phenothiazine separating as a brownish oil.

The oil was extracted with ether, the ether solution dried with anhydrous magnesium sulfate, and then filtered. Dry hydrogen chloride was passed into the ether solution and a semisolid mass, which crystallized after scratching, separated therefrom. The crude N-(β-pyrrolidinoethyl)-phenothiazine was separated from the ether and, after two crystallizations from isopropanol, 17.0 g of desired product, melting at 196°C to 197°C (uncorr.), was obtained.

References

Merck Index 7857
OCDS Vol. 1 p. 373 (1977)
I.N. p. 731
Hunter, J.H. and Reid, W.B. Jr.; U.S. Patent 2,483,999; October 4, 1949; assigned to The Upjohn Co.

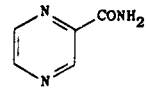
PYRAZINAMIDE

Therapeutic Function: Antibacterial (tuberculostatic)

Chemical Name: Pyrazinecarboxamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 98-96-4

Trade Name	Manufacturer	Country	Year Introduced
Aldinamide	MSD	U.S.	1955
Pirilene	Lepetit	France	1981
Eprazin	Krugmann	W. Germany	–
Isopyratsin	Leiras	Finland	–
Pezatamid	Hefa-Frenon	W. Germany	–
Piraldina	Bracco	Italy	–
Pirazimida	Madaus Cerafarm	Spain	–
Pyrafat	Saarstickstoff-Fatol	W. Germany	–
Pyrazide	SCS Pharmalab	S. Africa	–
P.Z.A.	Servipharm	Switz.	–
Tebrazid	Continental Pharma	Belgium	–
Tisamid	Orion	Finland	–
Zinamide	MSD	U.K.	–

Raw Materials

Pyrazine-2,3-dicarboxamide
Sodium hydroxide

Manufacturing Process

166 Parts of pyrazine-2,3-dicarboxamide (1 mol) is slurried in 1,000 parts of 1 N aqueous sodium hydroxide. The reaction mixture is heated at 95°C to 98°C until a clear solution results. Thereupon the mixture is cooled with ice to about 5°C and acidified to approximately a pH of 1. The cold reaction mixture is allowed to stand until precipitation of the pyrazine-2-carboxamide-3-carboxylic acid is substantially complete whereupon it is recovered by filtration and dried at 50°C to 60°C.

100 Parts of pyrazine-2-carboxamide-3-carboxylic acid is heated in a reaction vessel provided with an intake for inert gas. The reaction mixture is heated in a bath held at 220°C and nitrogen is introduced. The solid material melts and effervesces and sublimed pyrazinamide vapors are carried out of the reaction vessel in the nitrogen stream. They are introduced into a suitably cooled condenser, condensing in the form of a white sublimate. After the reaction is proceeding vigorously the bath temperature is raised to 255°C and then gradually and slowly allowed to drop to 190°C over a period of time sufficient to permit the reaction to go substantially to completion. The sublimed pyrazinamide, if desired, is further purified by recrystallization from water or alcohol.

References

Merck Index 7858
Kleeman & Engel p. 787
OCDS Vol. 1 p. 277 (1977)

I.N. p. 826
REM p. 1216
Webb, J.S. and Arlt, H.G. Jr.; U.S. Patent 2,780,624; February 5, 1957; assigned to American Cyanamid Co.

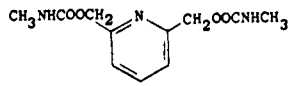
PYRIDINOL CARBAMATE

Therapeutic Function: Antiarteriosclerotic

Chemical Name: Bis[Methylcarbamic acid]-2,6-pyridinediyldimethylene diester

Common Name: Pyricarbate

Structural Formula:



Chemical Abstracts Registry No.: 1882-26-4

Trade Name	Manufacturer	Country	Year Introduced
Movecil	Erba	Italy	1969
Angioxine	Roussel	France	1971
Anginin	Banyu	Japan	—
Angiovital	I.S.M.	Italy	—
Angioxil	Firma	Italy	—
Angiperl	Sawai	Japan	—
Arteriolangal	Lanzas	Spain	—
Aterin	Ilsan	Turkey	—
Aterofal	Nativelle	Italy	—
Atero-Flavin	Indelfar	Spain	—
Aterollano	Llano	Spain	—
Ateronova	Cheminova	Spain	—
Atover	Oti	Italy	—
Carbatona	Turro	Spain	—
Cicloven	A.G.I.P.S.	Italy	—
Colesterinex	Galenica	Switz.	—
Dual-Xol	Lifepharma	Spain	—
Duaxol	Argentia	Argentina	—
Duvaline	Almirall	Spain	—
Gasparol	Castejon	Spain	—
Meduxal	Allard	France	—
Plavolex	Wolner	Spain	—
Prodectin	Kobanyai	Hungary	—
Ravenil	Caber	Italy	—
Sospitan	Kali-Chemie	W. Germany	—
Vasagin	Sidus	Italy	—
Vasapril	Cifa	Italy	—
Vasmol	Lifasa	Spain	—
Vasocil	Magis	Italy	—
Vasoverin	Biochimica	Switz.	—
Veranterol	Asla	Spain	—

Raw Materials

2,6-Dihydroxymethylpyridine hydrochloride
Methyl isocyanate

Manufacturing Process

(A) 15.7 g (0.1 mol) of 2,6-dihydroxymethylpyridine hydrochloride are suspended in 176 ml of acetonitrile, and 20.8 ml (0.15 mol) of triethylamine are added to the suspension. Thereafter 13 ml (0.22 mol) of methyl isocyanate are added dropwise to the reaction mixture at 20°C to 25°C. The reaction mixture is stirred at 20°C to 30°C for one hour, thereafter boiled for 3 hours, and finally the solvent is evaporated under reduced pressure. 35 to 40 g of a greyish, crystalline residue are obtained, which is a mixture of 2,6-dihydroxymethylpyridine-bis-(N-methylcarbamate) and triethylamine hydrochloride. The obtained residue is dissolved in 80 ml of hot water, decolorized with 2 g of activated carbon when hot, and filtered after 30 minutes of stirring. The filtrate is cooled, the resulting crystal suspension is stirred at 0°C to 5°C for 3 hours, the solids are filtered off, and dried at 50°C to 60°C.

23.3 g (94.4%) of 2,6-dihydroxymethylpyridine-bis(N-methylcarbamate) are obtained. The product melts at 134°C to 135°C; its purity is 99.8% (determined by UV spectrophotometry). When examined by thin layer chromatography, the product is uniform.

(B) 23.3 g of 2,6-dihydroxymethylpyridine-bis(N-methylcarbamate), prepared as described above, are dissolved in a boiling mixture of 46.6 ml of methanol and 46.6 ml of water. When the dissolution is complete, the solution is allowed to cool under slow stirring, without applying any external cooling means. The crystals start to separate at 48°C to 50°C. When the temperature of the mixture falls spontaneously below 35°C, it is cooled externally to 0°C to 5°C, and allowed to stand at this temperature for about 8 hours. The separated substance is filtered off and dried at 50°C to 100°C. 22.65 g of 2,6-dihydroxymethylpyridine-bis(N-methylcarbamate) are obtained. The quality of the product meets pharmaceutical requirements.

The yield of this crystallization procedure is 95.7%. The above process provides the γ_2 modification of 2,6-dihydroxymethylpyridine-bis(N-methylcarbamate), which can be tabletted directly. The substance melts at 134°C to 136°C, its purity is 99.9% (determined by UV spectrophotometry).

References

Merck Index 7874
Kleeman & Engel p. 787
DOT 5 (1) 16 (1969)
I.N. p. 826
Sprung, M., Toth, J., Kovatsits, M., Sztrokay, K., Szen, T., Gorgenyi, K., Boor, A., Forgacs, L., Szabo, J. and Kruzics, A.; British Patent 1,548,334; July 11, 1979; assigned to Richter Gedeon Vegyeszeti Gyar R.T. (Hungary)

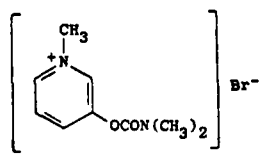
PYRIDOSTIGMINE BROMIDE

Therapeutic Function: Cholinergic

Chemical Name: 3-[[(Dimethylamino)carbonyl] oxy]-1-methylpyridinium bromide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 101-26-8

Trade Name	Manufacturer	Country	Year Introduced
Mestinon	Roche	U.S.	1955
Mestinon	Roche	Japan	1970
Regonol	Organon	U.S.	1973
Mestinon	Roche	France	1981
Kalymin	Arzneimittelwerk Dresden	E. Germany	—

Raw Materials

3-Hydroxypyridine
Dimethyl carbamic acid chloride
Methyl bromide

Manufacturing Process

12 parts by weight of dimethyl-carbamic acid chloride, dissolved in 20 parts by weight of xylol, are added dropwise to a boiling solution of 19 parts by weight of 3-hydroxypyridine in 120 parts by weight of xylol. Heating is continued under reflux for 3 hours. When the solution has cooled down, it is separated from the precipitated 3-hydroxypyridine hydrochloride and washed with water. After drying over sodium sulfate, the xylol is distilled off and the residue fractionated under reduced pressure. The N,N-dimethyl-carbamic acid ester of 3-hydroxypyridine distills at 148°C under a pressure of 15 mm.

A solution of 20 parts by weight of methyl bromide in 30 parts by weight of acetone is added to a solution of 35 parts by weight of N,N-dimethyl-carbamic acid ester of 3-hydroxypyridine in 70 parts by weight of acetone. After standing for a lengthy period (1 or 2 days), the N,N-dimethyl-carbamic acid ester of 3-hydroxy-1-methyl-pyridinium-bromide separates. It can be recrystallized from absolute alcohol. The colorless, strongly hygroscopic crystals melt at 151°-152°C.

References

Merck Index 7877
Kleeman & Engel p. 789
PDR pp. 1289, 1491
I.N. p. 826
REM p. 900
Urban, R.; U.S. Patent 2,572,579; October 23, 1951; assigned to Hoffmann-La Roche Inc.

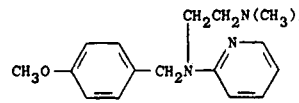
PYRILAMINE

Therapeutic Function: Antihistamine

Chemical Name: N-[(4-Methoxyphenyl)methyl]-N',N'-dimethyl-N-2-pyridinyl-1,2-ethanediamine (often used as the maleate)

Common Name: Mepyramine, pyranisamine

Structural Formula:



Chemical Abstracts Registry No.: 91-84-9; 6036-95-9 (Hydrochloride); 59-33-6 (Maleate)

Trade Name	Manufacturer	Country	Year Introduced
Neo-Antergan	MSD	U.S.	1948
Thylogen	Rorer	U.S.	1949
Statomin	Bowman	U.S.	1950
Pyra-Maleate	Mallinckrodt	U.S.	1950
Copsamine	Durst	U.S.	1950
Stamine	Tutag	U.S.	1951
Albatussin	Bart	U.S.	–
Allergan	Wiedenmann	Switz.	–
Amfeta	Bama-Geve	Spain	–
Anthisan	May & Baker	U.K.	–
Citra Forte	Boyce	U.S.	–
Codimal	Central	U.S.	–
Copsamine	Durst	U.S.	–
Fiogesic	Sandoz	U.S.	–
Histalet	Reid-Rowell	U.S.	–
Histavet-P	Burns-Biotec	U.S.	–
Kontristin	Eczacibasi	Turkey	–
Kriptin	Whitehall	U.S.	–
Kronohist	Ferndale	U.S.	–
Midol PMS	Glenbrook	U.S.	–
Poly-Histine	Bock	U.S.	–
Primatene	Whitehall	U.S.	–
PV-Tussin	Reid-Rowell	U.S.	–
Pyra	Mallinckrodt	U.S.	–
Pyramal	Columbus	U.S.	–
Statomin	Bowman	U.S.	–
Triaminic	Dorsey	U.S.	–

Raw Materials

4-Methoxybenzaldehyde
1-Dimethylamino-2-chloroethane
2-Aminopyridine
Sodium amide

Manufacturing Process

43 g of α-p-methoxybenzylaminopyridine (from 4-methoxybenzaldehyde reaction with 2-aminopyridine) are heated in 60 cc of toluene to 95°C to 100°C. 18 g of sodamide (85%) and 110 cc of a 40% toluene solution of 1-dimethylamino-2-chloroethane are added in small amounts alternately with shaking; the addition takes 1 hour. Toluene is distilled off, first at normal pressure, then under reduced pressure, until there remains a pasty mass. The mass is taken up with dilute hydrochloric acid and ether, neutralized to pH 7, and p-methoxybenzyl-aminopyridine separates. After making alkaline using excess of potash, it is extracted with benzene, dried and distilled. The product thereby obtained, N',N'-dimethylaminoethyl-N-p-methoxybenzyl-α-aminopyridine boils at 185°C to 190°C/2 mm. The monohydrochloride melts at 135°C (block Maquenne).

References

Merck Index 7883
Kleeman & Engel p. 561
PDR pp. 654, 674, 692, 784, 850, 875, 925, 1447, 1583, 1900
OCDS Vol. 1 p. 51 (1977)
I.N. p. 597
REM p. 1129
Horclois, R.J.; U.S. Patent 2,502,151; March 28, 1950; assigned to Societe des Usines Chimiques Rhone-Poulenc

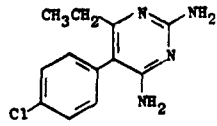
PYRIMETHAMINE

Therapeutic Function: Antimalarial

Chemical Name: 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 58-14-0

Trade Name	Manufacturer	Country	Year Introduced
Daraprim	Burroughs Wellcome	U.S.	1953
Daraprim	Burroughs Wellcome	W. Germany	1969
Erbaprelina	Erba	Italy	—
Fansidar	Roche	France	—
Malocide	Specia	France	—
Pirimecidan	Cidan	Spain	—
Pyrimethamin-Heyl	Heyl	W. Germany	—
Tindurin	Egyt	Hungary	—

Raw Materials

p-Chlorophenylacetonitrile
Sodium ethoxide
Guanidine
Ethyl propionate
Diazomethane

Manufacturing Process

p-Chlorophenylacetonitrile (36.5 grams) and ethyl propionate (25.5 grams) were added to a solution of sodium ethoxide (from 5.75 grams sodium) in absolute ethanol (150 ml). The solution was heated on a steam bath for 6 hours. After cooling, the whole was poured into water and the oil extracted well with ether, the ether solution was discarded and the aqueous solution neutralized with 1 N sulfuric acid. A heavy oil separated which was taken into ether, washed with water, bicarbonate solution and again with water. After drying, the ether was removed to give a thick oil which solidified on standing (34.6 grams). After recrystallization from an ether-petroleum ether mixture it formed needles, MP 108°-112°C.

The above keto-nitrile (15 grams) was methylated with a solution of diazomethane in ether. (The diazomethane solution was prepared using 20 grams of N-nitrosomethylurea.) The ether and excess diazomethane were evaporated on the steam bath and the oil dissolved in ethanol (50 ml). To this was added a solution of guanidine in ethanol (100 ml) (prepared from 8.1 grams of the hydrochloride). The solution was refluxed for 5 hours, the alcohol removed and the residue treated with 5 N sodium hydroxide. The insoluble material was then filtered. After purification by precipitation from dilute acetic acid with sodium hydroxide and by recrystallization from ethanol the product formed clear colorless needles (8.0 grams), MP 218°-220°C as described in U.S. Patent 2,602,794.

References

Merck Index 7884
Kleeman & Engel p. 791
PDR pp. 741, 1484
OCDS Vol. 1 p. 262 (1977)

DOT 16 (5) 174 (1980)
I.N. p. 827
REM p. 1219
Hitchings, G.H., Russell, P.B. and Falco, E.A.; U.S. Patent 2,576,939; December 4, 1951; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Hitchings, G.H. and Falco, E.A.; U.S. Patent 2,579,259; December 18, 1951; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Hitchings, G.H., Russell, P.B. and Falco, E.A.; U.S. Patent 2,602,794; July 8, 1952; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Jacob, R.M.; U.S. Patent 2,680,740; June 8, 1954; assigned to Societe des Usines Chimiques Rhone-Poulenc (France)

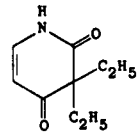
PYRITHYLDIONE

Therapeutic Function: Hypnotic; sedative

Chemical Name: 3,3-Diethyl-2,4-(1H,3H)pyridinedione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 77-04-3

Trade Name	Manufacturer	Country	Year Introduced
Presidon	Roche	U.S.	1948
Persedon	Roche	W. Germany	–

Raw Materials

Methyl formate
Diketene
Ethyl bromide
Sodium methylate
Ammonia

Manufacturing Process

108 g of sodium methylate were suspended in 500 ml of toluene. 120 g of methyl formate were dropped into the sodium methylate suspension thus formed at a rate so that temperature did not exceed 30°C. Thereafter a solution of 157 g of α,α-diethylacetoacetamide in 500 ml of toluene were added so that the temperature did not exceed 50°C. The mixture was stirred for one hour at 50°C and then overnight at room temperature. The reaction mixture was poured into 700 ml of ice water, permitted to stratify, the aqueous layer was separated, covered with a layer of 200 ml of toluene and then treated while stirring with 200 g of 50% sulfuric acid. Finally the reaction mixture, which was acid to congo red, was warmed at 50°C and the toluene-containing layer was separated. The aqueous layer was extracted with four 200 ml portions of toluene at 50°C and then discarded. The toluene extracts were combined and then concentrated in vacuo at 60°C. There were obtained 135 g of crystalline residue which was recrystallized from 200 ml of toluene. The 3,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydropyridine thus obtained melted at 96°C.

The α,α-diethylacetoacetamide used as starting material was obtained by converting diketene with aqueous ammonia to acetoacetamide and alkylating twice with ethyl bromide in the presence of sodium alcoholate.

References

Merck Index 7893
Kleeman & Engel p. 793
I.N. p. 828
Hinderling, R., Lutz, A.H. and Schnider, O.; U.S. Patent 3,019,230; January 30, 1962; assigned to Hoffmann-La Roche Inc.

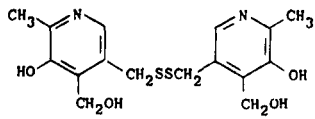
PYRITINOL

Therapeutic Function: Neurotropic agent

Chemical Name: 3,3'-(Dithiodimethylene)bis[5-hydroxy-6-methyl-4-pyridine methanol]

Common Name: Pyrithioxin

Structural Formula:



Chemical Abstracts Registry No.: 1098-97-1; 10049-83-9 (Dihydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Encephabol	Merck	W. Germany	1963
Enbol	Chugai	Japan	1971
Biocefalin	Benvegna	Italy	–
Bonol	Ikapharm	Israel	–
Cefalogen	Montefarmaco	Italy	–
Cerebropirina	Chemil	Italy	–
Cerebrotrofina	N.C.S.N.	Italy	–
Cervitalin	Savoma	Italy	–
Chioebon	Kyowa Yakuhin	Japan	–
Divalvon	Nippon Kayaku	Japan	–
Encebrovit	Sierochimica	Italy	–
Encefabol	Bracco	Italy	–
Encefort	Intersint	Italy	–
Encerebron	Pulitzer	Italy	–
Enerbol	Polfa	Poland	–
Evolubran	A.B.C.	Italy	–
Fulneurina	Fulton	Italy	–
Gladius	SKF	Italy	–
Leonar	Kalopharma	Italy	–
Life	S.I.T.	Italy	–
Maind	Also	Italy	–
Miriplex	Poli	Italy	–
Musa	Poli	Italy	–
Neurotin	Nakataki	Japan	–
Neuroxin	Yamanouchi	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
Piritinol	Magis	Italy	–
Piritiomin	Hishiyama	Japan	–
Sawaxin	Sawai	Japan	–
Scintidin	I.C.I.	Italy	–
Tonobrein	C.T.	Italy	–
Tonomentis	Ion	Italy	–

Raw Materials

Potassium xanthogenate
3,4-Bis-bromoethyl-4-hydroxy-5-methyl-pyridinium bromide
Ammonia
Methanol

Manufacturing Process

To a solution of 60 g of potassium xanthogenate in 240 cc of water there is added dropwise, while being cooled with ice, a solution of 42 g of 3,4-bis-bromomethyl-4-hydroxy-5-methyl-pyridinium-bromide in 1 liter of water so that the temperature remains between 2°C and 5°C. After stirring for 1 hour at the same temperature, the water is decanted off and the residue is triturated with acetone. Yield: 25 g of 4-hydroxymethyl-5-hydroxy-6-methyl-pyridyl-(3)-methylxanthogenate; melting point: 170°C to 171°C (alcohol, decomposition).

40 g of 4-hydroxymethyl-5-hydroxy-6-methyl-pyridyl-(3)-methylxanthogenate are left standing at room temperature for 5 days in a mixture of 800 cc of alcohol and 400 cc of aqueous NH_3-solution, and subsequently concentrated under vacuum to about 50 cc. The precipitated bis(4-hydroxymethyl-5-hydroxy-6-methyl-3 pyridylmethyl) disulfide is sucked off. Yield: 20 g of the disulfide; melting point: 218°C to 220°C (butanol, decomposition).

References

Merck Index 7894
Kleeman & Engel p. 793
DOT 9 (6) 215 (1973)
I.N. p. 828
Zima, O. and Schorre, G.; U.S. Patent 3,010,966; November 28, 1961; assigned to E. Merck A.G. (Germany)

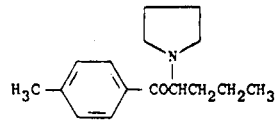
PYROVALERONE HYDROCHLORIDE

Therapeutic Function: Psychostimulant

Chemical Name: 1-(4-methylphenyl)-2-(1-pyrrolidinyl)-1-pentanone hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1147-62-2; 3563-49-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Thymergix	Joullie	France	1973

Raw Materials

p-Methylvalerophenone
Pyrrolidine
Bromine
Hydrogen chloride

Manufacturing Process

23.1 grams of α-bromo-p-methyl-valerophenone, obtained by bromination of p-methyl-valerophenone, are dissolved in 50 ml of benzene and 25 ml of pyrrolidine are added at 0°C. The whole is boiled for 20 minutes, cooled, washed twice with water, dried and acidified with about 50 ml of 2 N hydrochloric acid. After evaporation, it is recrystallized from methanol-acetone-ether. 22.6 grams of α-pyrrolidino-p-methyl-valerophenone hydrochloride, melting point 178°C, equivalent to a yield of 88.5% of the theoretical are obtained according to British Patent 927,475.

References

Merck Index 7914
Kleeman & Engel p. 794
OCDS Vol. 2 p. 124 (1980)
DOT10 (5) 188 (1974)
I.N. p. 829
Dr. A. Wander SA, Switzerland; British Patent 927,475; May 29, 1963
Dr. Karl Thomae, GmbH, Germany; British Patent 933,507; August 8, 1963

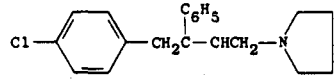
PYRROBUTAMINE

Therapeutic Function: Antihistaminic

Chemical Name: 1-[4-(4-Chlorophenyl)-3-phenyl-2-butenyl]-pyrrolidine

Common Name: –

Structural Formula:



***Chemical Abstracts* Registry No.:** 91-82-7

Trade Name	Manufacturer	Country	Year Introduced
Pyronil	Lilly	U.S.	1952
Co-Pyronil	Lilly	U.K.	–
Proladyl	Lilly	–	–

Raw Materials

Pyrrolidine
Paraformaldehyde
Magnesium
Acetophenone
p-Chlorobenzyl chloride
Hydrogen chloride

Manufacturing Process

A mixture of 1,800 ml of absolute ethanol, 427 g (6 mols) of pyrrolidine, and a trace of methyl

orange is cooled in an ice bath and gaseous hydrogen chloride is bubbled through the mixture until a red color develops, indicating that all of the amine has been converted to the hydrochloride. The addition of hydrogen chloride is stopped, the ice bath is removed and to the solution are added 720 g of acetophenone, 270 g of paraformaldehyde and 10 ml of concentrated hydrochloric acid. The mixture is stirred and refluxed vigorously for one hour. An additional 180 g of paraformaldehyde are then added, and refluxing is continued for about three hours. The hot solution is poured into 6 liters of acetone and the mixture is chilled overnight. A precipitate of ω-(N-pyrrolidino)-propiophenone hydrochloride separates. The precipitate is filtered off, washed with cold acetone, and dried in air.

ω-(N-pyrrolidino)-propiophenone hydrochloride thus prepared melted at about 163°C to 164°C after recrystallization from acetone.

To a suspension of 4 mols of ω-(N-pyrrolidino)-propiophenone hydrochloride in 1,500 ml of water and 100 g of ice in a separatory funnel are added a 50% aqueous solution containing 200 g of sodium hydroxide, and 2 liters of ether. The mixture is shaken vigorously until all of the suspended matter dissolves. The ether is then removed, washed with 1 liter of water and dried over anhydrous magnesium sulfate. The anhydrous ether solution of ω-(N-pyrrolidino)-propiophenone thus prepared is added to a Grignard reagent prepared from 6 mols of p-chlorobenzyl chloride and 6 mols of magnesium turnings in 3,000 ml of anhydrous ether. The ethereal solution of the ketone is added to the Grignard reagent at such a rate that rapid refluxing is maintained. After all of the ketone has been added, the reaction mixture is stirred for 2 hours and is decomposed by pouring it over a mixture of 500 g of ice and 6 mols of concentrated hydrochloric acid. The hydrochloric acid addition salt of 1-p-chlorophenyl-2-phenyl-4-N-(pyrrolidino)-butanol-2 formed in the reaction separates at the ether-water interface as a white crystalline material. The aqueous phase is removed and discarded, and the mixture of ether and hydrochloride salt is converted to 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butanol-2 by treatment with 10% sodium hydroxide solution. The base is removed by extraction with ether, and the ether extracts are dried over magnesium sulfate.

1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino—butanol-2 melted at about 109°C to 110°C after recrystallization from petroleum ether.

A solution of 200 g of 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butanol-2 in 750 ml of concentrated hydrochloric acid is refluxed for 9 hours thereby causing a dehydration of the butanol compound, and the formation of the hydrochloric acid addition salt of a 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butene. The hydrochloride salt formed crystallizes in the oily lower layer of the two phase reaction mixture and is removed therefrom by filtration. The filtrate is again refluxed for 9 hours, cooled to 0°C, and a second crop of the hydrochloric acid addition salt of the dehydration product is obtained and filtered off. The filtrate containing residual amounts of 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butanol-2 is again refluxed for 9 hours to yield an additional crop of the salt of the dehydration product. The several fractions of the butene compound are combined and triturated with several small portions of hot acetone and recrystallized from alcohol-ether mixture. The hydrochloric acid addition salt of the dehydration product, 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butene hydrochloride, melts at about 227°C to 228°C.

References

Merck Index 7916
Kleeman & Engel p. 794
OCDS Vol. 1 p. 78 (1977)
I.N. p. 829
Mills, J.; U.S. Patent 2,655,509; October 13, 1953; assigned to Eli Lilly & Co.

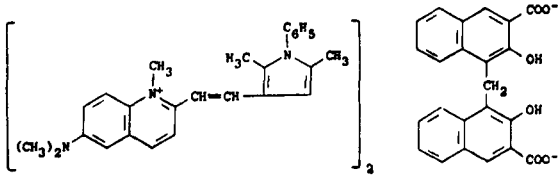
PYRVINIUM PAMOATE

Therapeutic Function: Anthelmintic

Chemical Name: 6-(dimethylamino)-2-[2-(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)ethenyl]-1-methylquinolium salt with pamoic acid (2:1)

Common Name: Pyrvinium embonate; viprynium embonate

Structural Formula:



Chemical Abstracts Registry No.: 3546-41-6

Trade Name	Manufacturer	Country	Year Introduced
Povan	Parke Davis	U.S.	1959
Povanyl	Parke Davis	France	1981
Antioxur	Esteve	Spain	–
Molevac	Parke Davis	W. Germany	–
Neo-Oxypaat	Katwijk	Neth.	–
Oxialum	Wolner	Spain	–
Pamovin	Merck-Frosst	Canada	–
Pamoxan	Uriach	Spain	–
Pirok	Bilim	Turkey	–
Poquil	Parke Davis Sankyo	Japan	–
Privonium	Rivapharm	Switz.	–
Pyrcon	Jenapharm	E. Germany	–
Pyrvin	Farmos	Finland	–
Tolapin	Taro	Israel	–
Tru	Elea	Argentina	–
Vanquin	Parke Davis	Italy	–
Vermitiber	Tiber	Italy	–

Raw Materials

Pyrvinium chloride
Sodium pamoate

Manufacturing Process

A hot, filtered solution of 2.27 grams of pyrvinium chloride dihydrate in 250 ml of water is added slowly to a solution of 2.25 grams of sodium pamoate monohydrate in 50 ml of water. A red precipitate immediately forms. The mixture is heated at about 90°-100°C for 5 minutes more and then filtered. The reaction product is washed with hot water and dried at about 75°C in a vacuum. This preparation melts at about 210°-215°C with prior softening from about 190°C.

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Merck Index 7927
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