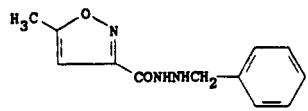
ISOCARBOXAZID

Therapeutic Function: Antidepressant

Chemical Name: 5-Methyl-3-isoxazolecarboxylic acid 2-benzylhydrazide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 59-63-2

Trade Name	Manufacturer	Country	Year Introduced
Marplan	Roche	U.S.	1959
Marplan	Roche	France	1961
Enerzer	Takeda	Japan	–

Raw Materials

5-Methyl-3-isoxazole carboxylic acid hydrazide
Benzaldehyde
Lithium aluminum hydride

Manufacturing Process

800 g of benzaldehyde was added to a hot solution (75°C) of 7 liters of ethanol containing 720 g of 5-methyl-2-isoxazole carboxylic acid hydrazide. The solution was stirred for ten minutes at which time the product began to crystallize. On cooling at 4°C for 14 hours, the solid was filtered off under vacuum and the solid filter cake was washed twice using 250 ml of ice cold ethanol for each washing. The 1-benzylidene-2-(5-methyl-3-isoxazolylcarbonyl)-hydrazine was recrystallized from ethanol, MP 199°C to 200°C.

115 g of 1-benzylidene-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine was added portionwise over the period of an hour to 5 liters of anhydrous ether containing 18.5 g of lithium aluminum hydride. The reaction mixture was stirred for four hours and permitted to stand overnight. The excess lithium aluminum hydride was decomposed with 250 ml of ethyl acetate and 150 ml of water was added to decompose the complex. The solid was separated by filtration and the ether layer was concentrated to about 500 ml. 200 ml of benzene was added to dehydrate the solution. Concentration was continued until a solid remained. The 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine was recrystallized from methanol, MP 105°C to 106°C.

References

Merck Index 5003
Kleeman & Engel p. 500
PDR p. 1490
OCDS Vol. 1 p. 233 (1977) & 2, 266 (1980)
I.N. p. 527
REM p. 1095
Gardner, T.S., Lee, J. and Wenis, E.; U.S. Patent 2,908,688; October 13, 1959; assigned to Hoffmann-La Roche, Inc.

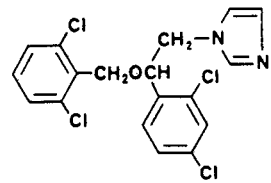
ISOCONAZOLE NITRATE

Therapeutic Function: Antibacterial, antifungal

Chemical Name: 1-[2,4-Dichloro-β-[(2,6-dichlorobenzyl)oxy] phenylethyl] imidazole nitrate

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 24168-96-5; 27523-40-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Fazol	Fournier	France	1979
Travogen	Schering	W. Germany	1979
Travogen	Schering	Switz.	1980
Travogyn	Keymer	U.K.	1981
Adestan	Nihon Schering	Japan	1982
Travogen	Schering	Australia	–
Icaden	Schering	W. Germany	–
Gyno-Travogen	Schering	W. Germany	–

Raw Materials

α-(2,4-Dichlorophenyl)imidazole-1-ethanol
Sodium hydride
2,6-Dichlorobenzyl chloride

Manufacturing Process

To a stirred and refluxing solution of 40 parts of benzene and 35 parts of dimethylformamide (both solvents previously dried azeotropically) are added successively 1.6 parts of sodium hydride and 7.7 parts of α-(2,4-dichlorophenyl)imidazole-1-ethanol, (cooling on ice is necessary). After the addition is complete, stirring and refluxing is continued for 30 minutes. Then there are added 7.8 parts of 2,6-dichlorobenzyl chloride and the whole is stirred at reflux for another 3 hours. The reaction mixture is poured onto water and the product 1-[2,4-dichloro-β-(2,6-dichlorobenzyloxy)phenethyl] imidazole, is extracted with benzene. The extract is washed twice with water, dried, filtered and evaporated in vacuo. The base residue is dissolved in a mixture of acetone and diisopropyl ether and to this solution is added an excess of concentrated nitric acid solution. The precipitated nitrate salt is filtered off and recrystallized from a mixture of methanol and diisopropyl ether, yielding 1-[2,4-dichloro-β-(2,6-dichlorobenzyloxy)phenethyl] imidazole nitrate; melting point 179°C.

References

Merck Index 5007
DFU 4 (11) 814 (1979)
Kleeman & Engel p. 500
DOT 15 (12) 542 (1979) & 17 (9) 388 (1981)
I.N. p. 528
Godefroi, E.F. and Heeres, J.; U.S. Patents 3,717,655; February 20, 1973 and 3,839,574; October 1, 1974; both assigned to Janssen Pharmaceutica NV

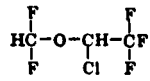
ISOFLURANE

Therapeutic Function: Inhalation anesthetic

Chemical Name: 1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 26675-46-7

Trade Name	Manufacturer	Country	Year Introduced
Forane	Ohio Medical	U.S.	1980
Aerrane	Ohio Medical	Switz.	1983
Aerrane	Ohio Medical	U.K.	1983

Raw Materials

1-Chloro-2,2,2-trifluoroethyl dichloromethyl ether
Hydrogen fluoride

Manufacturing Process

A 1-liter 3-necked stainless steel flask was fitted with a copper "Dry Ice" cold finger condenser, a stainless steel stirring shaft and gland and a copper gas inlet tube. To the flask there was then added 50 g (0.23 mol) of $CF_3CHClOCHCl_2$ and 1.5 g of $SbCl_5$·HF gas was then slowly bubbled through the stirred mixture which was maintained at 0°C. The reaction was run until 0.35 mol of HCl was collected, as indicated by the titration of the effluent gas which was dissolved in water. Following the fluorination 26 g of material were recovered and determined to be 90% pure by vapor phase chromatography. Fractional distillation using a 30 x 0.5 cm column packed with glass helices gave the pure product, BP 48°C to 48.5°C.

References

Merck Index 5021
DOT 16 (11) 374 (1980)
I.N. p. 528
REM p. 1042
Terrell, R.C.; U.S. Patent 3,535,388; October 20, 1970; assigned to Air Reduction Co., Inc.

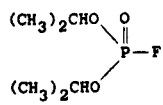
ISOFLUROPHATE

Therapeutic Function: Cholinergic (ophthalmic)

Chemical Name: Phosphorofluoridic acid bis(1-methylethyl)ester

Common Name: Fluostigmine

Structural Formula:



Chemical Abstracts Registry No.: 55-91-4

Trade Name	Manufacturer	Country	Year Introduced
Floropryl	MSD	U.S.	1949
D.F.P.	Sumitomo	Japan	—
D.F.P.	Boots	U.K.	—
D.F.P.	Winzer	W. Germany	—
Diflupyl	Labaz	—	—
Fluopryl	MSD	—	—

Raw Materials

Isopropanol
Chlorine
Phosphorus trichloride
Sodium fluoride

Manufacturing Process

212 lb (3.54 lb-mols) of isopropanol containing less than 0.2 wt % of water was cooled with brine to -5°C in a jacketed reactor. 160 lb (1.16 lb-mols) of phosphorus trichloride was gradually added to the isopropanol with cooling and stirring during a period of 4 hours. The temperature of the reaction was not allowed to exceed 12°C and the system was maintained under slight negative pressure (about 700 mm) to remove undesirable vapors.

After completion of the addition, the mixture was stirred for ½ hour and then subjected to a pressure of 12 to 100 mm of mercury. Chlorine was then passed into the crude reaction product at a rate of 12 lb/hr, the temperature of the reaction being kept below 12°C by brine cooling. The end of the reaction was indicated by a temperature drop which occurred after a total of 122 lb of chlorine (1.72 lb-mols, 48% excess) was used.

To remove excess chlorine, hydrogen chloride and isopropyl chloride, the well-stirred mixture was subjected to a pressure of 12 to 100 mm of mercury for 2 hours. The temperature was gradually raised to 20°C during this time by passing steam into the jacket of the reactor. 10 gallons of benzene was then added and distilled off under reduced pressure, gradually raising the temperature of the reaction mixture to 30°C. The last traces of hydrogen chloride were removed by adding an additional 10 gallons of benzene which was distilled off under reduced pressure at reactor temperatures not exceeding 50°C. The total time required for the removal of the volatile acid components of the reaction mixture was 4 hours.

The mixture was then cooled to 20°C and 19 gallons of benzene was added. This was followed by the introduction of 123.5 lb (2.80 lb-mols) of dry powdered sodium fluoride (95% pure). The mixture was stirred and heated to the refluxing temperature in a period of 1 hour and held at this temperature (95° to 98°C) for 4 hours. The product obtained was cooled and filtered to yield a filter cake which was washed with three 5-gallon portions of benzene. The filtrate and washing were then combined and distilled under reduced pressure. There was obtained 158 lb (74% yield of theory based on PCl_3) of diisopropyl fluorophosphate, BP 62°C at 9 mm and 46°C at 5 mm.

References

Merck Index 5022
Kleeman & Engel p. 501
PDR p. 1179
I.N. p. 437
REM p. 899
Hardy, E.E. and Kosolapoff, G.M.; U.S. Patent 2,409,039; October 8, 1946; assigned to Monsanto Chemical Company

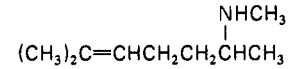
ISOMETHEPTENE

Therapeutic Function: Muscle relaxant

Chemical Name: N,1,5-trimethyl-4-hexenylamine

Common Name: Methyl isooctenylamine

Structural Formula:



Chemical Abstracts Registry No.: 503-01-5

Trade Name	Manufacturer	Country	Year Introduced
Octinum	Knoll	U.S.	1948
Cesal	Dainippon	Japan	–
Midrin	Carnrick	U.S.	–
Migralam	Bart	U.S.	–

Raw Materials

Methyl heptenone
Methylamine

Manufacturing Process

Methyl heptenone dissolved in 75% alcohol is reduced with activated aluminum in the presence of methylamine to give isometheptene.

References

Merck Index 5031
Kleeman & Engel p. 502
PDR pp. 654, 781
I.N. p. 529
REM p. 891
Klavehn, W. and Wolf, A.; U.S. Patent 2,230,753; February 4, 1941; assigned to E. Bilhuber Corporation, Germany
Klavehn, W. and Wolf, A.; U.S. Patent 2,230,754; February 4, 1941; assigned to E. Bilhuber Corporation, Germany

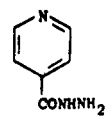
ISONIAZID

Therapeutic Function: Antitubercular

Chemical Name: 4-pyridinecarboxylic acid hydrazide

Common Name: Isonicotinic acid hydrazide

Structural Formula:



Chemical Abstracts Registry No.: 54-85-3

Trade Name	Manufacturer	Country	Year Introduced
Nyrazid	Squibb	U.S.	1952
Niconyl	Parke Davis	U.S.	1952
INH	Lilly	U.S.	1952
Tisin	USV Pharm	U.S.	1952
Pyrizidin	Warner Lambert	U.S.	1952
Cotinazin	Pfizer	U.S.	1952
Tyvid	Merrell National	U.S.	1952
Ditubin	Schering	U.S.	1952
Rimafon	Roche	U.S.	1952
Armazide	Armour	U.S.	1952
Anteben	Dainippon	Japan	–
Cedin	Lyssia	W. Germany	–
Cemidon	Gayoso Wellcome	Spain	–
Cin Vis	Vis	Italy	–
Dardex	Llorente	Spain	–
Diazid	Nippon Shinyaku	Japan	–
Dinacrin	Winthrop-Stearns	Phillipines	–
Dow-Isoniazid	Dow	U.S.	–
Eutizon	Pliva	Yugoslavia	–
Fimazid	Wassermann	Spain	–
Hidrafasa	Lifasa	Spain	–
Hidranic	Efeyn	Spain	–
Hidrazinda	Jorba	Spain	–
Hiperazida	Martin Santos	Spain	–
Hycozid	Takeda	Japan	–
Hydra	Otsura	Japan	–
Hyzyd	Mallinckrodt	U.S.	–
Idrazil	Bracco	Italy	–
INH-Burgthal	Conzen	W. Germany	–
Iscotin	Daiichi	Japan	–
Isobicini	Maggioni	Italy	–
Iso-Dexter	Dexter	Spain	–
Isotamine	I.C.N.	Canada	–
Isozide	I.C.N.	Canada	–
Kridan	Cidan	Spain	–
Lefos	Bicsa	Spain	–
Lubacida	Alfar	Spain	–
Neoteben	Bayer	W. Germany	–
Neo-Tizide	Aesca	Austria	–
Niadrin	Enzo	U.S.	–
Niazid	Sankyo	Japan	–
Nicazide	Wassermann	Italy	–
Niconyl	Parke Davis	U.S.	–
Nicotibina	Zambeletti	Italy	–
Nicotbine	Abic	Israel	–
Nicotubin	Leiras	Finland	–
Nicozid	Piam	Italy	–
Nicozide	Premo	U.S.	–
Niplen	Tanabe	Japan	–
Panazid	Panray	U.S.	–
Pycazide	Smith & Nephew	U.K.	–
Pyrizidin	Nepera	U.S.	–
Rifamate	Merrell Dow	U.S.	–
Rimifon	Roche	France	–
Sumifon	Sumitomo	Japan	–
TB-Phlogin	Heyl	W. Germany	–

Trade Name	Manufacturer	Country	Year Introduced
Tebesium	Hefa-Frenon	W. Germany	–
Tebilon	Kwizda	Austria	–
Tibinide	Ferrosan	Denmark	–
Tibizina	Farmochimica	Italy	–
Tubanox	Morgens	Spain	–
Tuberon	Shionogi	Japan	–
Tubilysin	Orion	Finland	–
Zidafimia	Santos	Spain	–
Zideluy	Miluy	Spain	–

Raw Materials

4-Cyanopyridine
Hydrazine hydrate

Manufacturing Process

4 parts of 4-cyanopyridine in 12 parts of water were reacted with 4 parts of hydrazine hydrate in the presence of 0.08 part of sodium hydroxide at 100°C under reflux for 7 hours. The product, after filtration and evaporation to dryness, was crystallized from ethanol. The yield of isonicotinyl hydrazide amounted to 3.27 parts which is 62% of the theoretical.

References

Merck Index 5032
Kleeman & Engel p. 503
PDR pp. 798, 830, 1237
OCDS Vol. 1 p. 254 (1977) & 2, 266 (1980)
I.N. p. 529
REM p. 1214
Gasson, E.J.; U.S. Patent 2,830,994; April 15, 1958; assigned to The Distillers Company Limited, Scotland
Fox, H.H.; U.S. Patent 2,596,069; May 6, 1952; assigned to Hoffmann-La Roche Inc.

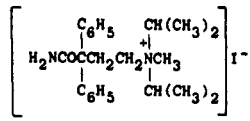
ISOPROPAMIDE IODIDE

Therapeutic Function: Antispasmodic

Chemical Name: γ-(aminocarbonyl)-N-methyl-N,N-bis(1-methylethyl)-γ-phenylbenzenepropanaminium iodide

Common Name: Diisopropylamino diphenyl butyramide methiodide

Structural Formula:



Chemical Abstracts Registry No.: 71-81-8

Trade Name	Manufacturer	Country	Year Introduced
Darbid	SKF	U.S.	1957
Priamide	Delalande	France	1959
Combid	SKF	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
Dipramid	Valeas	Italy	–
Marygin M	Sumitomo	Japan	–
Ornade	SKF	U.S.	–
Prochlor-Iso	Schein	U.S.	–
Pro-Iso	Zenith	U.S.	–
Tyrimide	SKF	U.K.	–

Raw Materials

γ-Diisopropylamino-α,α-diphenylbutyronitrile
Sulfuric acid
Methyl iodide

Manufacturing Process

γ-Diisopropylamino-α,α-diphenylbutyronitrile (60 g) was added in several portions to a mixture of sulfuric acid (150 ml) and water (15 ml) and the solution was heated 3½ hours on the steam bath and then poured on ice and made basic with NH_4OH. The γ-diisopropylamino-α,α-diphenylbutyramide precipitated as a solid, which was taken up in methylene chloride from an aqueous slurry. The methylene chloride was separated and dried by filtering through anhydrous K_2CO_3. The solvent was removed by distillation, leaving the amide which was crystallized from Skellysolve B five times and found then to have MP 87.0° to 88.5°C.

γ-Diisopropylamino-α,α-diphenylbutyramide in propanol was refluxed 4 hours in the presence of excess methyl iodide. Upon dilution of the solution with ethyl acetate (100 ml per 50 ml isopropyl alcohol) and cooling γ-diisopropylamino-α,α-diphenylbutyramide methiodide precipitated, was collected by filtration and recrystallized (9.0 g) by dissolving in a hot mixture of 100 ml isopropyl alcohol and 10 ml methanol and then diluting with 90 ml Skellysolve B, to give 8.3 g recrystallized product, MP 182° to 184°C.

References

Merck Index 5051
Kleeman & Engel p. 504
PDR pp. 1606, 1706, 1711, 1999
I.N. p. 531
REM p. 916
Speeter, M.E.; U.S. Patent 2,823,233; February 11, 1958; assigned to Bristol Laboratories Inc.

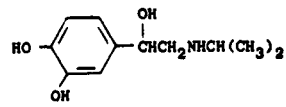
ISOPROTERENOL SULFATE

Therapeutic Function: Bronchodilator

Chemical Name: 4-[1-hydroxy-2-[(1-methylethyl)amino] ethyl] -1,2-benzenediol sulfate

Common Name: Isoprenaline sulfate; isopropylarterenol sulfate

Structural Formula:



(base)

Chemical Abstracts Registry No.: 299-95-6; 7683-59-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Isonorin	Smith Miller & Patch	U.S.	1949
Norisodrine	Abbott	U.S.	1950
Medihaler-Iso	Riker	U.S.	1956
Luf-Iso	Mallinckrodt	U.S.	1974
Aleudrin	Lewis	U.K.	—
Aludrin	Boehr. Ingel.	W. Germany	—
Asmadren	A.F.I.	Norway	—
Asthpul	Nippon Shoji	Japan	—
Bellasthman Medihaler	Kettelhack Riker	W. Germany	—
Dyspnoesan	Nourypharma	Neth.	—
Ingelan	Boehr. Ingel.	W. Germany	—
Isomenyl	Kaken	Japan	—
Meterdos-Iso	West-Silten	U.K.	—
Nebair	Warner-Chilcott	U.S.	—
Novodrin	VEB Berlin-Chemie	E. Germany	—
Prenomiser	Fisons	U.K.	—
Propynalin	Ferrosan	Denmark	—
Proternol	Nikken	Japan	—
Sedansol "Iso"	Nippon Zoki	Japan	—
Vapo-N-Iso	Fisons	U.S.	—

Raw Materials

3,4-Dihydroxy-ω-chloroacetophenone
Hydrogen
Isopropylamine
Sulfuric acid

Manufacturing Process

As described in U.S. Patent 2,308,232, 100 g 3,4-dihydroxy-ω-chloroacetophenone, 200 cc ethyl alcohol and 200 cc of about 50% aqueous isopropylamine solution are boiled during 3 hours on the water bath with the use of a reflux condenser, whereupon neutralizing with diluted sulfuric acid is carried out and the sulfate, obtained upon cooling, from alcohol of 50% is recrystallized; its MP is 245°C.

21 g 3,4-dihydroxy-ω-isopropylaminoacetophenone sulfate are hydrogenated with 50 cc methyl alcohol and 50 cc water, 0.5 g carbon and 3 cc palladium chloride solution of 2%. After 2 hours the hydrogen absorption comes to a standstill, after the theoretical quantity of hydrogen has been absorbed. After concentrating, the isopropylaminomethyl-(3,4-dihydroxyphenyl)carbinolsulfate crystallizes out. It has a MP of 180°C after refining.

References

Merck Index 5065
Kleeman & Engel p. 503
OCDS Vol. 1 p. 63 (1977); 2, 37, 107 (1980) & 3, 20 (1984)
I.N. p. 531
REM p. 886
Scheuing, G. and Thoma, O.; U.S. Patent 2,308,232; January 12, 1943
Delmar, G.S. and Macallum, E.N.; U.S. Patent 2,715,141; August 9, 1955; assigned to Delmar Chemicals Limited, Canada

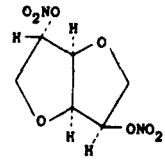
ISOSORBIDE DINITRATE

Therapeutic Function: Vasodilator (coronary)

Chemical Name: 1,4:3,6-Dianhydro-D-glucidol dinitrate

Common Name: Dinitrosorbide

Structural Formula:



Chemical Abstracts Registry No.: 87-33-2

Trade Name	Manufacturer	Country	Year Introduced
Isordil	Ives	U.S.	1959
Sorbitrate	Stuart	U.S.	1968
Isordil	Ayerst	U.K.	1971
Sorquad	Tutag	U.S.	1972
ISDN	Cooper	U.S.	1975
Iso-Bid	Geriatric Pharm.	U.S.	1975
Isomotic	Alcon	U.S.	1980
Dilatrate	Reed Carnrick	U.S.	1981
Cardio-10	Nicholas	W. Germany	—
Cardis	Iwaki	Japan	—
Carvanil	Banyu	Japan	—
Cardopax	Erco	Denmark	—
Carvasin	Ayerst	Italy	—
Cedocard	Tillotts	U.K.	—
Cordil	Disco	Israel	—
Cornilat	Galenika	Yugoslavia	—
Corovliss	Boehr. Mann.	W. Germany	—
Difutrat	Srbolek	Yugoslavia	—
Dilatrate	Reed & Carnrick	U.S.	—
Diretan	Ono	Japan	—
Duranitrate	Durachemie	W. Germany	—
Isobid	Geriatric	U.S.	—
Isocardide	Sam-On	Israel	—
Iso-D	Dunhall	U.S.	—
Isoket	Gebro	Austria	—
Isomack	Mack	W. Germany	—
Isopuren	Klinge	W. Germany	—
Isordil	Wyeth	U.S.	—
Isotrate	Hauck	U.S.	—
Laserdil	Laser	U.S.	—
Marrolingual	Pohl-Boskamp	W. Germany	—
Maycor	Parke-Davis	W. Germany	—
Metonitron	Petazon	Switz.	—
Nitorol R	Eisai	Japan	—
Nitroret	Hishiyama	Japan	—
Nitrosit	Pharmacal	Finland	—
Nitrosorbide	Lusofarmaco	Italy	—
Nitro-Tablinen	Sanorania	W. Germany	—
Nosim	Richet	Argentina	—
Risordan	Theraplix	France	—
Soni-Slo	Lipha	U.K.	—
Sorbangil	Kabi-Vitrum	Sweden	—
Sorbid	I.E. Kimya Evi	Turkey	—

Trade Name	Manufacturer	Country	Year Introduced
Tinidil	Pliva	Yugoslavia	–
Vascardin	Nicholas	U.K.	–

Raw Materials

1,4:3,6-Dianhydro-D-glucitol
Nitric acid

Manufacturing Process

An aqueous syrup of 1,4:3,6-dianhydro-D-glucitol is slowly added to a cooled mixture of HNO_3 and H_2SO_4. After standing a few minutes the mixture is poured into cold water and the precipitated product is collected and recrystallized from ethanol.

References

Merck Index 5074
Kleeman & Engel p. 505
PDR pp. 830, 905, 928, 993, 1442, 1606, 1784, 1951, 1999
I.N. p. 533
REM p. 853
Cordes, G., Munch, U. and Giesselmann, E.; U.S. Patent 4,156,736; May 29, 1979; assigned to Sanol Schwarz-Monheim G.m.b.H. (W. Germany)

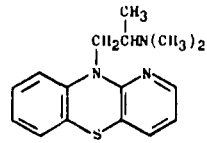
ISOTHIPENDYL HCl

Therapeutic Function: Antihistaminic

Chemical Name: 10-(2-Dimethylamino-2-methylethyl)-10H-pyrido[3,2-b] [1,4]benzothiazine

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1225-60-1; 482-15-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Theruhistin	Ayerst	U.S.	1957
Andantol	Gerda	France	1957
Aczen NS	Kanebo	Japan	–
Adantol	Imidas	Brazil	–
Andanton	Lacer	Spain	–
Nilergex	I.C.I.	U.K.	–
Thiodantol	Teva	Israel	–

Raw Materials

Phenylpyridylamine
Sodium amide
Dimethylaminoisopropyl chloride
Sulfur
Hydrogen chloride

Manufacturing Process

85 parts of phenylpyridyl amine, 21 parts of powdered sulfur and 1.7 parts of iodine were heated to 275°C for two hours. Evolution of hydrogen sulfide began when the mixture reached a temperature of 250°C and became vigorous when it reached 275°C. Such evolution of hydrogen sulfide diminished after about one hour at 275°C. A light oil was distilled from the reaction mixture under vacuum (pressure = 2-3 mm Hg). This oil which contained phenylpyridyl amine in addition to the thiophenylpyridyl amine was then treated at boiling temperature with approximately the theoretical amount of 2-3 normal HCl until complete solution resulted with formation of the HCl salts of the amines. The solution was then treated with 1 to 2% (based upon the substance mixture) of active carbon and then filtered hot. The nitrate was then cooled to 0°C whereupon the thiophenylpyridyl amine hydrochloride crystallized out while the phenylpyridyl amine hydrochloride remained in solution. The thiophenylpyridyl amine hydrochloride was filtered off and suspended in water and the pH adjusted with half concentrated ammonia to 8. The thiophenylpyridyl amine set free was filtered off and dried. It was in the form of gold yellow needles and had a melting point of 114°C to 115°C.

40 parts of thiophenylpyridyl amine were dissolved in 200 parts of water free toluene. After the addition of 16 parts of soda amide, the mixture was refluxed for 1½ hours. Thereafter, 28 parts of dimethylaminoisopropyl chloride in 30 parts of water free toluene were dropped in and the temperature maintained at 20°C to 25°C for 30 minutes. Thereafter, the mixture was heated at 60°C for 30 minutes and subsequently refluxed for 20 minutes. Water and hydrochloride acid were then added to the reaction mixture and this mixture rendered alkaline with NaOH and then the alkalized mixture shaken out with ether. The dimethylaminoisopropyl-N9-thiophenylpyridyl amine base thus obtained was vacuum distilled. It was then converted to hydrochloride salt. The monohydrochloride salt is almost white in color and melts at 213°C to 216°C. The yield was almost 100% of the theoretical.

References

Merck Index 5077
Kleeman & Engel p. 505
OCDS Vol. 1 p. 430 (1977)
I.N. p. 534
Schuler, W.A. and Klebe, H.; U.S. Patent 2,974,139; March 7, 1961; assigned to Degussa (W. Germany)

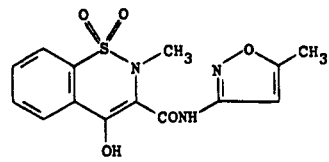
ISOXICAM

Therapeutic Function: Antiinflammatory

Chemical Name: 4-Hydroxy-3-(5-methyl-3-isoxazolocarbamyl)-2-methyl-2H-1,2-benzothiazine 1,1-dioxide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 34552-84-6

Trade Name	Manufacturer	Country	Year Introduced
Pacyl	Warner-Lambert	Switz.	1983
Pacyl	Adenylchemie	W. Germany	1983
Maxicam	Parke Davis	—	—

Raw Materials

3-Carbethoxy-4-hydroxy-2-methyl-2H-1,2-benzothiazine-1,1-dioxide
3-Amino-5-methyl-isoxazole

Manufacturing Process

A mixture of 40.5 g (0.15 mol) of 3-carbethoxy-4-hydroxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide, 20.6 g (0.21 mol) of 3-amino-5-methylisoxazole, and 2,500 ml of xylene was refluxed for 24 hours in a Soxhlet apparatus, the thimble of which contained 60 g of Linde type 4A molecular sieve. The mixture was cooled to 25°C and the resulting crystalline precipitate was collected and washed with ether to give 44 g of crude product. Recrystallization from 1,600 ml of 1,4-dioxan gave 34.7 g of material, MP 265°C to 271°C dec.

References

Merck Index 5085
DFU 1 (3) 123 (1976)
OCDS Vol. 2 p. 394 (1980)
DOT 19 (2) 119 (1983) & 19 (7) 414 (1983)
I.N. p. 534
Zinnes, H., Schwartz, M.L. and Shavel, J. Jr.; U.S. Patent 3,787,324; January 22, 1974; assigned to Warner-Lambert Co.

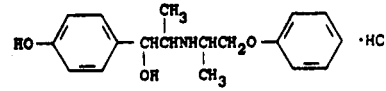
ISOXSUPRINE HYDROCHLORIDE

Therapeutic Function: Vasodilator

Chemical Name: 4-hydroxy-α-[1-[(1-methyl-2-phenoxyethyl)amino] ethyl] benzenemethanol hydrochloride

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 579-56-6; 395-28-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Duvadilan	Duphar	France	1958
Vasodilan	Mead Johnson	U.S.	1959
Cardilan	Ferrosan	Denmark	—
Defencin	Bristol	U.K.	—
Isokulin	Toho Iyaku	Japan	—
Isolait	Elder	U.S.	—
Largiven	Bristol	Italy	—
Suprilent	Duphar	Belgium	—
Synzedrin	Teisan	Japan	—

Trade Name	Manufacturer	Country	Year Introduced
Trophodilan	Duphar	France	–
Vahodilan	Morita	Japan	–
Vascoprin	Guidotti	Italy	–
Vasodilene	Chiesi	Italy	–
Vasolan	Disco	Israel	–
Vasoplex	Frika	Austria	–
Vasosuprina	Lusofarmaco	Italy	–
Xuprin	Duphar	Belgium	–

Raw Materials

1-Phenoxy-2-aminopropane
1-(4'-Benzyloxyphenyl)-2-bromopropanone-1
Hydrogen

Manufacturing Process

To a solution of 30.7 g (0.203 mol) of 1-phenoxy-2-aminopropane in 150 ml of ethanol there was added 31.9 g (0.100 mol) of 1-(4'-benzyloxyphenyl)-2-bromopropanone-1. The mixture was heated to boiling temperature and the solution was then refluxed in a reflux condenser for 3 hours. Most of the ethanol was then distilled off in vacuo. Then to the residue there was added about 150 ml of diethyl ether. The hydrogen bromide salt of 1-phenoxy-2-aminopropane was filtered off and washed with diethyl ether.

The collected ethereal filtrates were acidified with 50 ml of 4 N hydrochloric acid and this solution was stirred vigorously. The hydrochloride of 1-(4'-benzyloxyphenyl)-2-(1'-methyl-2-phenoxy-ethylamino)propanone-1 precipitated out, was filtered off, washed with water and then with diethyl ether. Then this substance was dried in vacuo. The yield was 37.7 g, i.e., 89% of the theoretically possible yield, calculated on 1-(4'-benzyloxyphenyl)-2-bromine propanone-1. This substance had a light yellow color and melted at 197° to 198°C, while decomposing.

Then 21.89 g of the hydrochloride salt was dissolved in 600 ml of 80% aqueous ethanol. With the addition of a palladium carbon catalyst, this solution was hydrogenated at room temperature under a hydrogen pressure of about 1.1 atmospheres. After 2 mols hydrogen had been absorbed, the catalyst was filtered off and the filtrate was evaporated in vacuo *until crystallization occurred. Then the crystals were dissolved* by heating in the smallest possible quantity of water and after cooling, the crystallized substance was filtered off, washed with water and dried in vacuo. The yield was 6.80 g, i.e., 39% of the theoretically possible yield. The resultant product recrystallized from water melted at 203° to 204°C.

References

Merck Index 5086
Kleeman & Engel p. 506
PDR pp. 830, 993, 1129, 1569, 1606, 1999
OCDS Vol. 1 p. 69 (1977)
I.N. p. 534
REM p. 892
Moed, H.D.; U.S. Patent 3,056,836; October 2, 1962; assigned to North American Philips Company