I

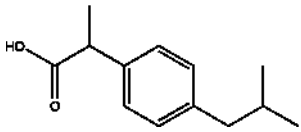
IBUPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: α-Methyl-4-(2-methylpropyl)benzene acetic acid

Common Name: 2-(4-Isobutylphenyl)propionic acid

Structural Formula:



Chemical Abstracts Registry No.: 15687-27-1

Trade Name	Manufacturer	Country	Year Introduced
Brufen	Boots	UK	1969
Brufen	Kakenyaku Kako	Japan	1971
Brufen	Labaz	W. Germany	1971
Brufen	Formenti	Italy	1972
Brufen	Dacour	France	1972
Motrin	Upjohn	US	1974
Rufen	Boots	US	1981
Advil	Whitehall	US	-
Algofen	Ibirn	Italy	-
Andran	Takata	Japan	-
Anflagen	Ohta	Japan	-
Artofen	Lkapharm	Israel	-
Artril	Eczacibasi	Turkey	-
Artril 300	Farmasa	Brazil	-
Bluton	Morishita	Japan	-
Brufamic	Teigo	Japan	-
Buburone	Towa Yakuhin	Japan	-
Butylenin	Sanken	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Daiprophen	Daito	Japan	-
Donjust-B	Horita	Japan	-
Ebufac	D.D.S.A.	UK	-
Epinal	Mitsubishi Yuka	Japan	-
Epobron	Ono	Japan	-
Eputes	Kobayashi Kako	Japan	-
Focus	Angelini	Italy	-
IB-100	Hishiyama	Japan	-
Iborufen	Kyoritsu Yamagata	Japan	-
Ibucasen	Casen	Spain	-
Ibulav	A.L.	Norway	-
Ibumetin	Benzon	Denmark	-
Ibuprocin	Nisshin	Japan	-
Ibo-Slo	Lipha	UK	-
Inflam	Protea	Australia	-
Lamidon	Kowa	Japan	-
Landelun	Tsuruhara	Japan	-
Liptan	Kowa	Japan	-
Manypren	Zensei	Japan	-
Mono-Attritin	Atmos	W. Germany	-
Mynosedin	Toho Yakuhin	Japan	-
Napacetin	Toyama	Japan	-
Neobrufen	Liade	Spain	-
Nobfelon	Toho	Japan	-
Nobfen	Toho	Japan	-
Nobgen	Kanebo, Ltd.	Japan	-
Nurofen	Crookes	UK	-
Opturem	Kade	W. Germany	-
Paduden	Terapia	Rumania	-
Pantrop	Nippon Zoki	Japan	-
Rebugen	Dessy	Italy	-
Roidenin	Showa	Japan	-
Saren	Bracco	Italy	-
Sednafen	Taisho	Japan	-

Raw Materials

Sulfur	Isobutylbenzene
Sodium	Sodium hydroxide
Ethyl iodide	Acetyl chloride
Ethanol	Ethyl carbonate

Manufacturing Process

Isobutylbenzene is first acetylated to give isobutylacetophenone. 4-i-butylacetophenone (40 g), sulfur (11 g) and morpholine (30 ml) were refluxed for 16 hours, cooled, acetic acid (170 ml) and concentrated hydrochloric acid (280 ml) were added and the mixture was refluxed for a further 7 hours. The

mixture was concentrated in vacuo to remove acetic acid and the concentrate was diluted with water.

The oil which separated was isolated with ether, the ethereal solution was extracted with aqueous sodium carbonate and this extract was acidified with hydrochloric acid. The oil was isolated with ether, evaporated to dryness and the residue was esterified by refluxing with ethanol (100 ml) and concentrated sulfuric acid (3 ml) for 5 hours. The excess alcohol was distilled off, the residue was diluted with water, and the oil which separated was isolated with ether. The ethereal solution was washed with sodium carbonate solution; then with water and was dried. The ether was evaporated off and the oil was distilled to give ethyl 4-i-butylphenylacetate.

Sodium ethoxide from sodium (3.67 g) in absolute alcohol (64 ml) was added over 20 minutes with stirring to a mixture of ethyl 4-i-butylphenylacetate (28.14 g) and ethyl carbonate (102 ml) at 100°C. The reaction flask was fitted with a Fenske column through which alcohol and then ethyl carbonate distilled. After 1 hour when the still head reached 124°C heating was discontinued. Glacial acetic acid (12 ml) and water (50 ml) was added to the stirred ice-cooled mixture and the ester isolated in ether, washed with sodium carbonate solution, water and distilled to give ethyl 4-i-butylphenylmalonate.

Ethyl 4-i-butylphenylmalonate (27.53 g) in absolute alcohol (25 ml) was added with stirring to a solution of sodium ethoxide From sodium (2.17 g) in absolute alcohol (75 ml). Ethyl iodide (15 ml) was added and the mixture refluxed for 2% hours, the alcohol distilled and the residue diluted with water, extracted with ether, washed with sodium bisulfite, water, and evaporated to dryness.

The residual oil was stirred and refluxed with sodium hydroxide (75 ml of 5 N), water (45 ml) and 95% ethanol (120 ml). Within a few minutes a sodium salt separated and after 1 hour the solid was collected, washed with ethanol, dissolved in hot water and acidified with dilute hydrochloric acid to give the methyl malonic acid which was collected and dried in vacuo MP 177° to 180°C (dec.).

The malonic acid (9 g) was heated to 210° to 220°C in an oil bath for 20 minutes until decarboxylation had ceased. The propionic acid was cooled and recrystallized from light petroleum (BP 60° to 80°C). Two further recrystallizations from the same solvent gave colorless prisms of 2-(4-isobutylphenyl)propionicacid MP 75° to 77.5°C. (The procedure was reported in US Patent 3,228,831.)

References

Merck Index 4797
Kleeman and Engel p. 482
PDR pp. 687, 728, 830, 1854, 1897
OCDS Vol.1 p.86 (1977) and 2, 218, 356 (1980)
DOT 5 (3) 101 (1969)
I.N. p. 510
REM p. 1117
Nicholson, J.S. and Adams, S.S.; US Patent 3,228,831; January 11, 1966; assigned to Boots Pure Drug Company Limited, England

Nicholson, J.S. and Adams, S.S.; US Patent 3,385,886; May 28, 1968; assigned to Boots Pure Drug Company Limited, England

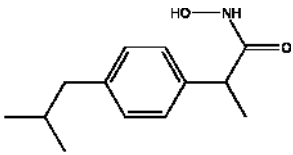
IBUPROXAM

Therapeutic Function: Antiinflammatory

Chemical Name: N-Hydroxy-α-ethyl-4-(2-methylpropyl)benzene-acetamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53648-05-8

Trade Name	Manufacturer	Country	Year Introduced
Ibudros	Manetti-Roberts	Italy	1978
Ibudros	Ferrer	Spain	-

Raw Materials

2-(4-Isobutylphenyl)propionic acid
Hydroxylamine hydrochloride
Ethanol
Potassium hydroxide

Manufacturing Process

In a 1,000 ml three-necked flask equipped with a stirrer, a dropping funnel and a silica gel guard pipe, 46.7 g hydroxylamine hydrochloride are dissolved cold in 480 ml methanol. Separately a solution of 56.1 g KOH in 280 ml methanol is prepared, heated to 30°C and admixed, dropwise under stirring to the hydroxylamine solution. All successive temperature increases during this admixture are prevented by cooling in an ice bath. After the whole KOH solution has been admixed, the mixture is left standing for 5 minutes so as to attain the complete precipitation of the KCl.

Separately, 72.02 g ethyl 2-(4-isobutylphenyl)-propionate, obtained by the esterification of 2-(4-isobutylphenyl)-propionic acid with ethanol and concentrated H_2SO_4, are solved with 100 ml methanol, this solution is introduced drop by drop into the reaction flask, and stirred and cooled for 5

hours on an ice bath. Thereafter it is suction filtered, the residue is washed with all together 50 ml methanol, the wash is added to the filtrate, thereafter the whole is evaporated in a water bath with a rotating evaporator at a reduced pressure, until 100-200 ml of a concentrated solution are obtained. This solution is poured into a 200 ml beaker into which are stirred approximately 1,000 ml 1.25N acetic acid. This mixture is left standing for 24 hours, thereafter suction filtered. The resulting filtrate is taken up with 100 ml petroleum ether at 40°C to 60°C, in order to solve any possible residue of unreacted starting ester, and refiltered. Approximately 50g of 2-(4-isobutylphenyl)-propiohydroxamic acid are obtained, having a melting point of 119°C to 121°C on Kofler's hot stage.

References

Merck Index 4798
DFU 2 (12) 808 (1977)
I.N. p. 511
Orzalesi, G. and Selleri, R.; US Patent 4,082,707; April 4, 1978; assigned to Societa Italo-Britannica L. Manetti-H. Roberts and Co. (Italy)

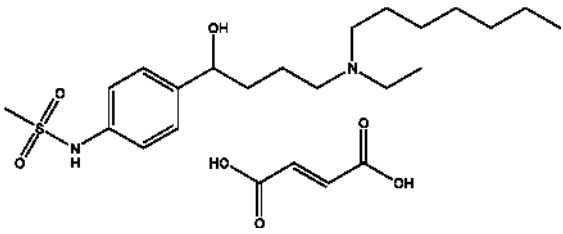
IBUTILIDE FUMARATE

Therapeutic Function: Antiarrhythmic

Chemical Name: Methanesulfonamide, N-(4-(4-(ethylheptylamino)-1-hydroxybutyl)phenyl)-, (2E)-2-butenedioate (2:1) (salt)

Common Name: Ibutilide fumarate

Structural Formula:



Chemical Abstracts Registry No.: 122647-32-9; 122647-31-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Corvert	Pharmacia and Upjohn	USA	-

Raw Materials

Aniline

Methanesulfonyl chloride

Succinic anhydride	1-Hydroxybenzotriazole
Fumaric acid	N,N'-Dicyclohexylcarbodiimide
Ethylheptylamine	Sodium potassium tartrate
Lithium aluminum hydride	

Manufacturing Process

A mechanically stirred solution of aniline (139.7 g, 1.5 mole) in pyridine (2 L), under N_2 is cooled in an ice bath. Methanesulfonyl chloride (171.8 g, 1.5 mole) is added dropwise to this solution while the temperature is maintained at 15°-20°C, which results in a red-orange color change in the reaction mixture. After the addition is complete the ice bath is removed and the reaction is allowed to continue at room temperature. The reaction is complete after 2.5 h. The reaction mixture is concentrated in vacuo and the residue is combined with 700 ml of water which results in crystallization of a dark red material.

This material is filtered and washed several times with water. The filtered material is dissolved in CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue is dissolved in hot ethyl acetate, treated with Darco (decolorizing carbon) and crystallized to yield methanesulfonanilide which had a melting point: 93°-94°C.

A mechanically stirred suspension of aluminum chloride (88.0 g, 0.66 moles) and 150 ml of carbon disulfide under N_2 is cooled in an ice bath. Methanesulfonanilide (30.0 g, 0.175 mol) and succinic anhydride (17.5 g, 0.175 mol) are combined and added rapidly to the cooled reaction mixture. The ice bath is removed and the mixture is stirred at room temperature for 6 h. The reaction mixture is then heated to 55°C and allowed to continue for 18 h. The reaction mixture is separated into two layers the bottom of which solidifies.

The upper layer is decanted and the remaining solid layer is decomposed with ice. The resulting suspension is filtered and the solid is washed several times with methylene chloride and dissolved in a mixture of saturated sodium bicarbonate (500 ml) and water (500 ml). This solution is acidified (pH 2) with HCl and the resulting precipitate is collected by filtration, redissolved in $NaHCO_3$ and reprecipitated with HCl. The solid, 4-[(methylsulfonyl)amino]-γ-oxobenzenebutanoic acid, is collected by filtration. Melting point 198°-200°C.

A stirred solution of 4-[(methylsulfonyl)amino]-γ-oxobenzenebutanoic acid (12.0 g, 0.044 mol) in DMF (100 ml) under N_2 is cooled in an ice bath to 5°C and treated with 1-hydroxybenzotriazole (5.94 g, 0.044 mol) and N,N'-dicyclohexylcarbodiimide (9.08 g, 0.044 mol). After 1 hour, ethylheptylamine (6.3 g, 0.044 mol) is added, after an additional 30 min the ice bath is removed and the mixture is kept at room temperature for 18 h.

The reaction mixture is filtered over a Celite filter aid and the filtrate is concentrated under vacuum. The resulting material is dissolved in CH_2Cl_2, washed with dilute HCl, $NaHCO_3$ and concentrated. The residue is chromatographed over silica gel (1.25 kg) with 5% MeOH : 1% NH4OH : CH_2Cl_2. The N-ethyl-N-heptyl-γ-oxo-4-[(methylsulfonyl)amino]

benzenebutanamide thus obtained is crystallized from EtOAc to yield 10.77 g, melting point 100°-102°C.

To a N_2 covered suspension of 0.29 g (7.57 mmol) of $LiAlH_4$ in 10 ml of THF cooled in an ice bath is added a solution of 1.0 g (2.52 mmol) of N-ethyl-N-heptyl-γ-oxo-4-[methylsulfonyl)amino]benzenebutanamide in 10 ml of THF over 6 min. The ice bath is then removed and the mixture heated at reflux for 27 h and then stirred at room temperature for 2 days. The mixture is cooled in an ice bath and there is added dropwise 10 ml of aqueous sodium potassium tartrate followed by EtOAc and H_2O to keep the mixture fluid.

The aqueous fraction is extracted once with EtOAc and the combined EtOAc fractions are washed in turn with H_2O and concentrated in vacuo. The residue is chromatographed on a 200 ml silica gel column (elution with 6% MeOH : CH_2Cl_2 containing 0.5% NH_4OH) and 9.7 ml fractions were collected and treated with Et2O and aqueous $NaHCO_3$. The organic layer is concentrated in vacuo to yield N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl] methanesulfonamide.

Preparation of fumarate (WO Patent 01/07417). To dichloromethane solution of 4-[4-N-[(Ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide is added hemimolar quantities of fumaric acid and heated to reflux until a clear solution was obtained. Upon cooling the fumarate of 4-[4-N-[(Ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide was obtained.

References

Jackson B.H., Jr.; US Patent No. 5,155,268; Oct. 13, 1992; Assigned: The Upjohn Company (Kalamazoo, MI)

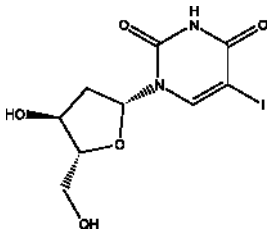
IDOXURIDINE

Therapeutic Function: Antiviral (ophthalmic)

Chemical Name: 2'-Deoxy-5-iodouridine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54-42-2

Trade Name	Manufacturer	Country	Year Introduced
Dendrid	Alcon	US	1963
Stoxil	SKF	US	1963
Herplex	Allergan	US	1963
Idoxene	Spodefeil	UK	1963
Idoviran	Chauvin-Blache	France	1963
Herpetil	Farmila	Italy	1963
Spectanefran	Pharm-Allergan	W. Germany	1964
Cheratil	Francia	Italy	-
Colircusi Virucida	Cusi	Spain	-
Dendrit	Smith and Nephew	UK	-
Gel "V"	P.O.S.	France	-
Herpid	W.B. Pharm.	UK	-
Herpidu	Dispersa	Switz.	-
IDU	Pliva	Yugoslavia	-
IDU Ophthalmic	Sumitomo	Japan	-
Iducher	Farmigea	Italy	-
Iduridin	Ferring	Sweden	-
Idustatin	Isnardi	Italy	-
Kerecid	SKF	UK	-
Oftan-Idurin	Star	Finland	-
Ophthalmadine	S.A.S.Sci.	UK	-
Synmiol	Winzer	W. Germany	-
Virexin	Vinas	Spain	-
Virunguent	Hermal	W. Germany	-
Virusan	Ikapharm	Israel	-
Vistaspectran	Allergan	W. Germany	-
Zostrum	W.B. Pharm.	UK	-

Raw Materials

5-Iodouracil
Acetic anhydride
Acetic acid
3,5-Di-p-toluyl-desoxy-D-ribofuranosyl chloride
Sodium hydroxide

Manufacturing Process

5 g of 5-iodo-uracil (obtained according to T.B. Johnson et al., J. Biol. Chem. 1905/6, 1, 310) in 15 cc of acetic anhydride are heated under reflux for 4,5 hours. The acetylated derivative crystallizes on cooling. The crystallized product is chilled for ½ hour then filtered with suction, washed with acetic anhydride and then with ether and dried. 4.5 g of 1-acetyl-5-iodo-uracil, MP 167°C, are thus obtained.

1.51 g of mercuric acetate are dissolved in 50 cc of methanol under reflux and 1.35 g of 1-acetyl-5-iodo-uracilare added. A white precipitate is soon formed. The reaction mixture is kept under reflux for % hour and then allowed to cool

to room temperature. The precipitate is then filtered with suction, washed with methanol and dried.

2.1 g of monomercuric 5-iodo-uracil, MP 280°C, are thus obtained as a colorless powder, insoluble in water and the majority of the usual organic solvents, such as benzene, chloroform, alcohol, ether and acetone.

1.46 g of 5-iodo-uracil monomercuric derivative are introduced into 50 cc of chloroform and 20 to 30 cc of the solvent are distilled off under normal pressure to ensure good dehydration of the reaction medium. The mixture is cooled to room temperature and 2.59 g of 3,5-di-p-toluyl-desoxy-D-ribofuranosyl chloride added. The mixture is agitated for 6 hours with glass balls, filtered, rinsed with chloroform and the filtrate is successively washed with an aqueous sodium iodide solution, with water, with a saturated solution of sodium bicarbonate and again with water. The product is dried over sodium sulfate, filtered and evaporated to dryness.

The residue crystallizes in ether and yields about 600 mg of β-3',5'-di-p-toluyl-2'-desoxy-5-iodo-uridine which is recrystallized from toluene. The product is obtained as colorless crystals, soluble in chloroform and pyridine, sparingly soluble in acetone, benzene ether and alcohol, insoluble in water, MP 193°C.

206 mg of 3',5'-di-p-toluyl-2'-desoxy-5-iodo-uridineare heated at 80°C with 2.5 cc of caustic soda solution (0.4 N) for ½ hour. The solution obtained is cooled, filtered and then acidified with acetic acid. The desoxy-iodo-uridine and the p-toluic acid crystallize. Ether is added to dissolve the p-toluic acid, the mixture is chilled, filtered with suction, washed with water and ether, and dried. The residue is recrystallized from water and 100 mg of 5-iodo-2'-desoxy-uridine, are obtained.

References

Merck Index 4804
Kleeman and Engel p. 483
DOT 7 (5) 191 (1971) and 10 (10) 268 (1974)
I.N. p. 512
REM p. 1232
Roussel-Uclaf; British Patent 1,024,156; March 30, 1966

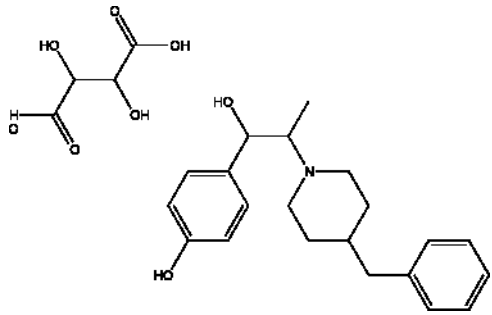
IFENPRODIL TARTRATE

Therapeutic Function: Vasodilator

Chemical Name: α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidineethanol tartrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 23210-58-4; 23210-56-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Vadilex	Carriere	France	1972
Cerocral	Funai	Japan	1979
Angiotrofin	Montpellier	Argentina	-
Dilvax	Promeco	Argentina	-
Validex	Robert and Carriere	France	-

Raw Materials

Benzyl chloride	4-Benzylpiperidine
Hydrogen	4-Hydroxypropiophenone
Bromine	Tartaric acid

Manufacturing Process

The initial steps involve reacting benzyl chloride with 4-hydroxypropiophenone. The benzyloxypropiophene thus obtained is first brominated and then reacted with 4-benzylpiperidine to give 1-(p-benzyloxyphenyl)-2-(4-benzyl-piperidino)propan-1-one.

The neutral tartrate may be prepared directly by reduction of 1-(p-benzyloxyphenyl)-2-(4-benzyl-piperidino)propan-1-one. For the reduction, a mixture of 175 g of ketone (0.425 mol) and 32 g of tartaric acid (0.213 mol) is hydrogenated at 50°C under pressure of 50 kg/cm^2 in 440 ml of methanol in the presence of 12 g of palladium on charcoal.

The catalyst is filtered off at elevated temperature, and the filtrate is concentrated by evaporation under reduced pressure to a volume of 300 ml and added in a thin stream to 2.5 liters of diethyl ether with mechanical agitation. The precipitate is separated, washed with diethyl ether and dried in vacuo at 80° to 85°C for several hours. 325 g (96% yield) of the neutral tartrate of 1-(p-hydroxyphenyl)-2-(4-benzyl-piperidino)propan-1-ol are obtained.

References

Merck Index 4806
Kleeman and Engel p. 484
OCDS Vol. 2 p. 39 (1980)
I.N. p. 513
Carron. M.C.E.. Carron.C.L.C. and Bucher.B.P.; US Patent 3,509,164; April 28, 1970; assigned to societe Anonyme des Laboratoires Robert et Carriere, France

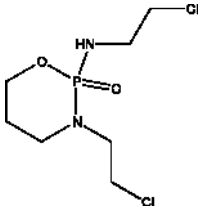
IFOSFAMIDE

Therapeutic Function: Antineoplastic

Chemical Name: N,3-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine-2-oxide

Common Name: Isoendoxan

Structural Formula:



Chemical Abstracts Registry No.: 3778-73-2

Trade Name	Manufacturer	Country	Year Introduced
Holoxan	Lucien	France	1976
Holoxan	Asta	W. Germany	1977
Mitoxana	W.B. Pharm.	UK	1979
Holoxan	Asta-Werke	Switz.	1979
Holoxan	Schering	Italy	1981
Cyfos	Mead Johnson	-	-
Naxamide	Mead Johnson	-	-

Raw Materials

N-(2-Chloroethyl)amine HCl
N-(2-Chloroethyl)-N,O-propylene phosphoric acid ester amide HCl
Triethylamine

Manufacturing Process

127.6 g (1.1 mols) of N-(2-chloroethyl)-amine hydrochloride are suspended in a solution of 218 g (1 mol) of N-(2-chloroethyl)-N,O-propylene phosphoric acid ester amide monochloride in 600 cc of methylene dichloride, and 212 g of triethylamine are added thereto dropwise with stirring. The reaction mixture is heated to boiling by the reaction heat. After termination of the addition, the reaction mixture is heated to boiling for another 2 hours. Thereafter, it is cooled to room temperature and the precipitated triethylamine hydrochloride is separated by filtration with suction. The filtrate is extracted with about 60cc of dilute hydrochloric acid (pH 3), then twice with about 60 cc of water, thereafter with about 60 cc of dilute soda lye and finally twice with about 60 cc of water. After drying over anhydrous sodium sulfate, methylene dichloride is distilled off under normal pressure. The oily residue is dried in a vacuum and thereafter extracted in a perforator with 500 cc of anhydrous ether. The oily extract crystallizes upon inoculation and standing in an ice box. After standing for several hours, the precipitate is filtered off, washed with a small amount of cold ether and dried in a vacuum at room temperature. Yield: 185 g (71% of the theoretical). This material is also identified as 3-(2-chloroethyl)-2-(2-chloroethylamino)-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide; generic name: ifosfamide. F.P.: 39°C to 41°C.

References

Merck Index 4807
Kleeman and Engel p. 485
OCDS Vol. 3 p. 151 (1984)
DOT 12 (11) 450 (1976) and 16 (5) 171 (1980)
I.N. p. 513
REM p. 1155 Arnold, H., Brock, N., Bourseaux, F. and Bekel, H.; US Patent 3,732,340; May 8, 1973; as signed to Asta-Werke A.G. Chemische Fabrik (W. Germany)

IMIPENEM

Therapeutic Function: Antibiotic

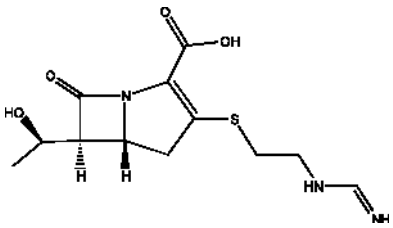
Chemical Name: 1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-(1-hydroxyethyl)-3-((2-((iminomethyl)amino)ethyl)thio)-7-oxo-, (5R-(5-α,6-α(R*)))-

Common Name: Gorillamicin; Imipemide; Imipenem

Chemical Abstracts Registry No.: 64221-86-9

Trade Name	Manufacturer	Country	Year Introduced
Primaxin	Merck and Co., Inc.	-	-

Structural Formula:



Raw Materials

Thienamycin
Methyl formimidate hydrochloride
6-(1)-Hydroxyethyl-1-azabicyclo[3.2.0]heptane-3,7-dione-2-carboxylate
N,S-Bistrimethylsilyl-N-formimidoylcysteamine

Manufacturing Process

Preparation of N-formimidoyl thienamycin:

Thienamycin (517 mg) is dissolved in pH 7 0.1 N phosphate buffer (25 ml) and cooled in an ice bath with magnetic stirring. The solution is adjusted to pH 8.5 using 2.5 N sodium hydroxide solution dispensed from an automatic burette. While maintaining a pH of 8.5, methyl formimidate hydrochloride (711 mg) is added portionwise over 2-3 minutes. After an additional 10 min, the pH of the solution is brought to 7.0 using 2.5 N hydrochloric acid. The solution is chromatographed on a column of XAD-2 resin (150 ml) which is eluted with water. The N-formimidoyl thienamycin derivative (imipenem) elutes in 1.5-2.0 column volumes (200-300 ml) and is lyophilized to a white solid (217 mg). UV (pH 7 0.1 N phosphate buffer); λ_{max}297 nm (8,590); ir (Nujol mull) 1767 Cm-1(β-lactam).

Another method preparation of imipenem:

6-(1)-Hydroxyethyl-1-azabicyclo(3.2.0)heptane-3,7-dione-2-carboxylate is converted to the diphenoxyphosphate enol ester and this in turn reacted with N,S-bistrimethylsilyl-N-formimidoylcysteamine (use of the bistrimethylsilylated reagent is necessary in order to avoid side reactions caused by cyclization reactions). As a result the $(PhO)_2OPO$-groups are converted to Me_3SiN = CHNH-groups. Removal of the protecting groups complete the synthesis of 1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-(1-hydroxyethyl)-3-((2-((iminomethyl)amino)ethyl)thio)-7-oxo-, (5R-(5-alpha,6-alpha(R*)))-.

References

Merck Index, Monograph number: 4954, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Shinkai I. et al.; Tetrahedron Lett.; 1982, 23, 4903

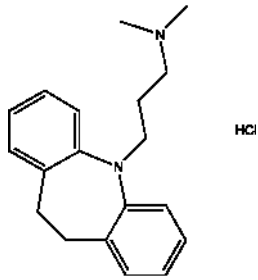
IMIPRAMINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: 10,11-Dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine hydrochloride

Common Name: Imizin

Structural Formula:



Chemical Abstracts Registry No.: 113-52-0; 50-49-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tofranil	Ciba Geigy	France	1959
Tofranil	Ciba Geigy	US	1959
Presamine	U.S.V. Pharm.	US	1971
SK-Pramine	SKF	US	1974
Janim ine	Abbott	US	1975
WDD Tab	Tutag	US	1979
Berkomine	Berk	UK	-
Censtim	Ohio Medical	US	-
Chemipramine	Chemo-Drug	Canada	-
Chemoreptin	Toho Iyaku	Japan	-
Chrytemin	Fujinaga	Japan	-
Depress	Toho	Japan	-
Deprinol	Dumex	Denmark	-
Dimipressin	Drugs, Ltd.	UK	-
Dynaprin	Monico	Italy	-
Eupramin	Pliva	Yugoslavia	-
Feinalmin	Sanko	Japan	-
I.A.-Pram	Inter-Alia Pharm.	UK	-
Imavate	Robins	US	-
Imidol	Yoshitomi	Japan	-
Imilanyle	Takata	Japan	-
Imipramine	Lederle	US	-
Imipranil	Medica	Finland	-
Imiprin	Protea	Australia	-

Trade Name	Manufacturer	Country	Year Introduced
Impranil	Barlow Cote	Canada	-
Impril	I.C.N.	-	-
Intalpran	Inter-Alia Pharm.	UK	-
Iprogen	Genethic	UK	-
Iramil	Knoll	W. Germany	-
Melipramin	EGYT	Hungary	-
Meripramin	Kanebo, Ltd.	Japan	-
Norpramine	Norton	UK	-
Novopramine	Novopharm	Canada	-
Primonil	Ikapharm	Israel	-
Prodepress	Medac	Australia	-
Pryleugan	Arzneimittelwerk Dresden	E. Germany	-
Psychof orin	Pharmachim	Bulgaria	-
Servipramine	Servipharm	Switz.	-
Surplix	Vis	Italy	-

Raw Materials

Iminodibenzyl
3-Dimethylamino n-propyl chloride
Sodium amide
Hydrogen chloride

Manufacturing Process

20 parts of imino dibenzyl are dissolved in 100 parts by volume of absolutely dry benzene. A suspension of 4 parts $NaNH_2$ in 50 parts by volume of absolute benzene are then added dropwise at 50° to 60°C after which the mixture is boiled for an hour under reflux. 13 parts of 3-dimethylamino n-propyl chloride are then added dropwise at 40° to 50°C and the mixture is boiled for 10 hours under reflux. After cooling, the benzene solution is thoroughly washed with water, whereupon the basic constituents are extracted with dilute hydrochloric acid.

The hydrochloric extract is then made alkaline and the separated base is extracted with ether. After drying, the solvent is evaporated and the residue is distilled in the high vacuum, whereby the N-(3-dimethylaminopropyl)-imino dibenzyl passes over at a temperature of 160°C under 0.1 mm pressure. The chlorohydrate with a melting point of 174° to 175°C is obtained therefrom with alcoholic hydrochloric acid.

References

Merck Index 4817
Kleeman and Engel p. 485
PDR pp. 527, 673, 901, 993, 1569, 1606, 1723
OCDS Vol. 1 p.401 (1977); 2, 420 (1980) and 3, 32 (1984)
I.N. p. 514
REM p. 1095

Haefliger, F. and Schindler, W.; US Patent 2,554,736; May 29, 1951; assigned to J.R. Geigy AG, Switzerland

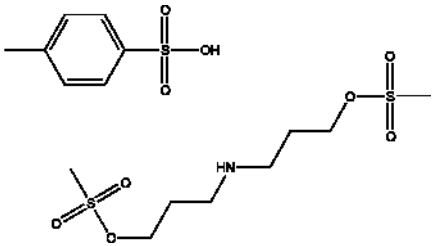
IMPROSULFAN TOSYLATE

Therapeutic Function: Antitumor

Chemical Name: Bis-(3-methanesulfonyloxypropyl)amine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13425-98-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Protecton	Yoshitomi	Japan	1980

Raw Materials

Bis-(3-Methylsulfonyloxypropyl)amine hydrochloride
Sodium carbonate
4-Toluenesulfonic acid

Manufacturing Process

A solution of 5 g of bis(3-methylsulfonyloxypropyl)amine hydrochloride in 20 ml of ice water is neutralized with 1N sodium carbonate solution. The resulting amine base is extracted with five 20 ml portions of chloroform. The combined extract is dried over anhydrous sodium sulfate, the solvent is distilled off under reduced pressure, and the residue is dissolved in 20 ml of ethanol. To the ethanol solution is added slowly with stirring under ice cooling a solution of 2.6 g of p-toluenesulfonic acid in 30 ml of ethanol. The white precipitate formed is collected by filtration and recrystallized from ethanol to give 5.0 g of white crystalline bis(3-methylsulfonyloxypropyl)amine p-toluenesulfonate melting at 115°C to 116°C.

References

Merck Index 4823
DFU 4 (2) 106 (1979)
DOT 16 (12) 422 (1980)
I.N. p. 515
Yoshitomi Pharmaceutical Industries, Ltd.; British Patent 1,272,497; April 26, 1972

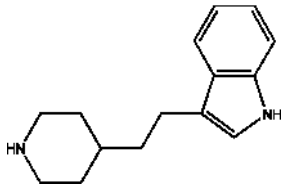
INDALPINE

Therapeutic Function: Antidepressant

Chemical Name: 4-[2-(3-Indolyl)ethyl]piperidine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 63758-79-2

Trade Name	Manufacturer	Country	Year Introduced
Upstene	Fournier	France	1983

Raw Materials

Bis(methoxy-2-ethoxy)sodium aluminum hydride
(Indolyl-3)(piperidinyl-4-methyl)ketone

Manufacturing Process

0.5 g of bis(methoxy-2ethoxy)sodium aluminum hydride in a 70% solution in toluene is added to a solution of 0.29 g of (indolyl-3)(piperidyl-4-methyl) ketone in 10 ml of toluene. The mixture is heated under refluxing conditions for 15 hours, then cooled to 0°C. 10 ml of an aqueous solution of 5N sodium hydroxide is added dropwise thereto, followed by stirring for 1 hour. The organic phase is decanted, washed with water, dried using potassium carbonate and evaporated under partial vacuum. 0.26 g of oil is obtained, which is purified by chromatography and hydrochloride formation. The product

obtained is 0.1 g of (indolyl-3)-2-ethyl-4-piperidine hydrochloride which has a melting point of 167°C.

References

DFU 4 (12) 873 (1979)
DOT 19 (10) 584 (1983)
Champseix, A.A., Gueremy, C.G.A. and LeFur, G.R.; US Patent 4,064,255; December 20, 1977; assigned to Mar-Pha Societe D'Etudes et D'Exploitation De Marques

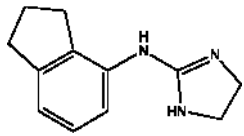
INDANAZOLINE

Therapeutic Function: Nasal decongestant

Chemical Name: 2-(4-Indanylamino)-2-imidazoline

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 40507-78-6

Trade Name	Manufacturer	Country	Year Introduced
Farial	Nordmark-Werke	W. Germany	1980
Farial	Knoll	Switz.	1983

Raw Materials

N-4-Indanyl thiourea
Methyl iodide
Ethylene diamine

Manufacturing Process

38.5 g (0.1 mol) of N-4-indanyl thiourea are dissolved in 250 cc of methanol. 42,6 g (0.3 mol) of methyl iodide are added thereto and the mixture is refluxed for 2,5 hours. The mixture thereafter is cooled and the solvent is removed in a rotation evaporator in a vacuum. Thus, 57.5 g of N-4-indanyl-S-methylisothiuronium hydroiodide (86% of theoretical) are obtained. Melting point 144°C to 146°C.

33.49 (0.1 mol) of N-4-indanyl-S-methylisothiuronium hydroiodide are mixed with 9.0 g (0.15 mol) of anhydrous ethylenediamine. The mixture is slowly heated to 80°C and heating is continued until the termination of the formation of methylmercaptan (about 4 hours). After cooling the residue is dissolved in 2N hydrochloric acid and the solution is extracted with chloroform. The extract is discarded and the aqueous phase is rendered alkaline by the addition of 10% soda lye. The resulting solution is extracted with chloroform and the extract is washed with water, dried over anhydrous sodium sulfate and the solvent is removed. An oily residue is obtained which upon standing soon crystallizes.

The product is recrystallized from petroleum ether having a boiling range of 100°C to 140°C in the presence of activated carbon. Thus, 11.1 g of 2-(4-indanylamino)-2-imidazoline (55% of theoretical) are obtained as the free base. Melting point 109°C to 113°C.

References

Merck Index 4826
DFU 6 (7) 417 (1981)
DOT 17 (10) 413 (1981)
I.N. p. 516
May, H.J. and Berg, A.; US Patent 3,882,229; May 6, 1975; assigned to Nordmark-Werke GmbH

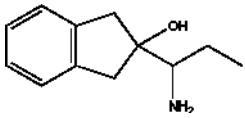
INDANOREX

Therapeutic Function: Anorexic

Chemical Name: 1H-Inden-2-ol, 2-(1-aminopropyl)-2,3-dihydro-

Common Name: Indanorex

Structural Formula:



Chemical Abstracts Registry No.: 16112-96-2

Trade Name	Manufacturer	Country	Year Introduced
Indanorex	Shanghai Lansheng Corporation	-	-
Dietor	Logeais	-	-

Raw Materials

Pyridine	2-Cyano-2-hydroxyindane
Ethyl bromide	Trimethylchlorosilane
Magnesium	Sodium borohydride

Manufacturing Process

125 g (1.15 mol) trimethylchlorosilane was added to 159 g (1 mol) 2-cyano-2-hydroxyindane in 600 ml pyridine by stirring for 2 hours, whereupon the mixture was heated at 1 hour at 40°C for 1 hour. TA light precipitate was filtered off and washed with 1 liter of benzene. The filtrate was washed with water, dried over magnesium sulfate and concentrated in vacuum. The residue was dissolved in benzene 2 times and 2 times the solvent was removed in vacuum in order to any pyridine and water was present. Yield of silano-organic compound as a clear brown liquid was 230 g (100%); BP: 95°C/15 mm Hg.

10.5 g magnesium in 30 ml of dry ether was mixed with 55.5 g of ethyl bromide in 62 ml ether during about 1 hour at the temperature of boiling ether. After that the mixture was heated to 45°C in order to finish the synthesis of ethyl magnesium bromide. On cooling to 0°C it was stood for 2 hours and 50 g the above prepared silano-organic compound in 620 ml ether was added at the temperature about 5°C, whereupon in was stirred else 30 minutes at the ambient temperature and then was placed into ice bath. 82 ml of methanol was added to the prepared mixture during 1 hour. The temperature was kept about 18°C. On 30 minutes stirring the mixture was evaporated to 1/3 volume in vacuum at the temperature about 20°C. The residue was with ethanol diluted, the ethanol was evaporated, whereupon 100 ml methanol was added. 16.4 g sodium borohydride was added to the methanol solution for 1 hour at ice cooling, and stirred 2 hours at 3°C. It stood at ambient temperature overnight. Then the mixture was cooled to 10°C. 250 ml of hydrochloric acid (conc.) was added. After that it was heated at 45°C for 1 hour. The solvent was removed to dryness in vacuum. The pasty residue was in 250 ml of water dissolved and with chloroform washed. The 2-(1-aminopropyl)-2-indanol was precipitated by adding of 750 ml 10% sodium carbonate to pH 10. It was extracted with chloroform and dried over magnesium sulfate.

Chloroform was evaporated to give 13 g desired 2-(1-aminopropyl)-2-indanol. MP: 92°C. Yield 33%. IR spectrum and thin layer chromatography confirmed the structure of prepared compound.

References

Naillard J.G.; DB Patent No. 2,422,879; July 16, 1973; Laboratories Jacques Logeais, Issy-les-Moulineaux, Seine, Frankreich

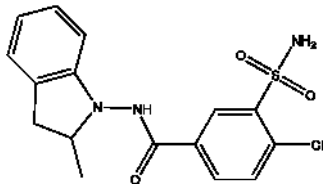
INDAPAMIDE

Therapeutic Function: Diuretic

Chemical Name: 3-(Aminosulfonyl)-4-chloro-N-(2,3-dihydro-2-methyl-1H-indol-1-yl)-benzamide

Common Name: Metindamide

Structural Formula:



Chemical Abstracts Registry No.: 26807-65-8

Trade Name	Manufacturer	Country	Year Introduced
Natrilix	Pharmacodex	W. Germany	1976
Fludex	Eutherapie	France	1977
Natrilix	Servier	UK	1978
Natrilix	Servier	Australia	1983
Lozol	Revlon	US	1983
Arifon	Servier	France	-
Bajaten	Volpino	Argentina	-
Idamix	Gentili	Italy	-
Lozide	Servier	France	-
Nap-Sival	Promeco	Argentina	-
Noranat	Labinca	Argentina	-
Pressural	Polifarma	Italy	-
Tertensil	Servier	France	-

Raw Materials

3-Sulfamyl-4-chloro-benzoyl chloride
N-Amino-2-methyl indoline

Manufacturing Process

A total of 8.9 parts of 3-sulfamyl-4-chloro-benzoylchloride in a solution of 50 parts of anhydrous tetrahydrofuran are added portionwise in the course of 60 minutes, while stirring, to a solution of 5.2 parts of N-amino-2-methyl indoline and 3.5 parts of triethylamine in 150 parts of anhydrous tetrahydrofuran. The reaction mixture is left to stand 3 hours at room temperature, then the precipitated chiorhydrate of triethylamine is filtered off. The filtrate is evaporated under vacuum and the residue is crystallized from a solution of 60 parts of isopropanol in 75 parts of water. There are obtained 9 parts of N-(3-sulfamyl-4-chlorobenzamido)-2-methyl indoline, MP (K) 184° to 186°C, MP (MK) 160° to 162°C (isopropanol/water). [The melting points being

determined on a Kofler heater plate under the microscope (MK) or on a Kofler Bank (K)].

References

Merck Index 4828
Kleeman and Engel p. 487
PDR p. 1816
OCDS Vol. 2 p. 349 (1980)
DOT 12 (8) 313 (1976) and 13 (1) 41 (1977)
I.N. p. 516
REM p. 944
Beregl, L., Hugon, P., Laubie, M.; US Patent 3,56591 1; February 23,1971; assigned to Science Union et Cie, Societe Francaise de Recherche Medicale, France

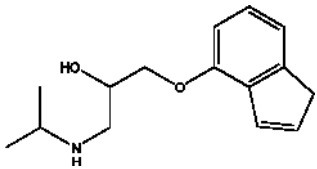
INDENOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 1-[1H-Inden-4(or 7)-yloxy]-3-[(1-methylethyl)amino]-2-propanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 60607-68-3

Trade Name	Manufacturer	Country	Year Introduced
Pulsan	Yamanouchi	Japan	1979
Iambeta	Yamanouchi	Japan	-
Iambeta	Poli	Italy	-

Raw Materials

4-Hydroxyindene
Isopropylamine
Epichlorohydrin
Hydrogen chloride

Manufacturing Process

(a) A mixture of 0.9 g of 4-hydroxyindene, 2.0 g of 1,2-epoxy-3-chloropropane (epichlorohydrin), 2.7 g of potassium carbonate and 15 ml of acetone was refluxed at about 57°C for 24 hours. Acetone was removed by vacuum distillation, the residue was washed with 10 ml of water and then extracted with 20 ml of ether three times. The ether extract was dried with magnesium sulfate, filtered and subjected to column chromatography using a column (having an inside diameter of about 3 cm and a height of about 50 cm) packed with silica gel. The 5th to 7th fractions (volume of one fraction is 50 ml) recovered from the chromatographic column using chloroform as the effluent were combined together and concentrated to provide 0.6 g of 4-(2,3-epoxypropoxy)indene.

(6) A mixture of 0.42 g of 4-(2,3-epoxypropoxy)indene, 1.20 g of isopropylamine and 20 ml of methanol was stirred in a flask at room temperature for 2 hours. Methanol and unchanged isopropylamine were removed by vacuum distillation and the residue was recrystallized from a mixture of n-hexane and ether to yield 0.41 g of 4-(3-isopropylamino-2-hydroxypropoxy)indene having a melting point of 88°C to 89°C.

(c) To a solution of 0.41 g of 4-(3-isopropylamino-2-hydroxypropoxy)indene in 80 ml of absolute ether there was added dropwise a hydrochloric acid-ether mixture at 0°C with stirring. The precipitates thus formed were recovered by filtration and recrystallized from a mixture of ethanol and ether to provide 0.44 g of the hydrochloride of 4-(3-isopropylamino-2-hydroxypropoxy)indene. Melting point 147°C to 148°C.

References

Merck Index 4831
DFU 2 (11) 730 (1977)
Kleeman and Engel p. 487
DOT 16 (1) 24 (1980)
I.N. p. 516
Murakami, M., Murase, K., Niigata, K., Tachikawa, S. and Takenaka, T.; US Patent 4,045,482; August 30, 1977; assigned to Yamanouchi Pharmaceutical Co., Ltd. (Japan)

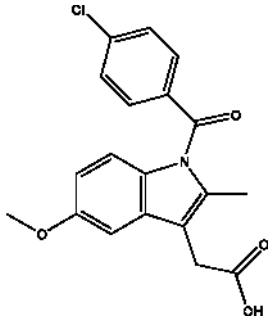
INDOMETHACIN

Therapeutic Function: Antiinflammatory

Chemical Name: 1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53-86-1

Trade Name	Manufacturer	Country	Year Introduced
Indocin	MSD	US	1965
Amuno	MSD	W. Germany	1965
Indocid	MSD-Chibret	France	1966
Indocid	MSD	UK	1966
Mefacen	Chiesi	Italy	1967
Algometacin	Biagini	Italy	-
Argun	Merckle	W. Germany	-
Arthrexin	Lennon	S. Africa	-
Artracin	D.D.S.A.	UK	-
Artrinova	Llorens	Spain	-
Artrivia	Lifasa	Spain	-
Artrobase	Libra	Italy	-
Artrocid	Schoum	Italy	-
Bonidon	Mepha	Switz.	-
Boutycin	Bouty	Italy	-
Calmocin	Mulda	Turkey	-
Cidalgon	Ecobi	Italy	-
Confortid	Dumex	Denmark	-
Durametacin	Durachemie	W. Germany	-
Endol	Deva	Turkey	-
Endomet	Dif-Dogu	Turkey	-
Endsetin	Nobel	Turkey	-
Imbrilon	Berk	UK	-
Imet	Firma	Italy	-
Indacin	Merck-Banyu	Japan	-
Inderapollon	Kaigai	Japan	-
Indetrit	Medica	Finland	-
Indium	Pharma Williams	Italy	-
Indo	Arcana	Austria	-
Indodur	Medica	Finland	-

Trade Name	Manufacturer	Country	Year Introduced
Indolag	Lagap	Switz.	-
Indolene	Italprofar	Italy	-
Indone RC	Sawai	Japan	-
Indomed	Teva	Israel	-
Indomet	Ratiopharm	W. Germany	-
Indomethine	Kowa	Japan	-
Indometin	Orion	Finland	-
Indorektal	Sanorania	W. Germany	-
Indoremed	Remed Econerica	W. Germany	-
Indo-Tablinen	Sanorania	W. Germany	-
Indotard	Benzon	Denmark	-
Indren	Spofa	Czechoslovakia	-
Inflazon	Taisho	Japan	-
Inmecin	Nippon Chemiphar	Japan	-
Inmetocin	Tobishi	Japan	-
Inmetsin	Farmos	Finland	-
Inteban	Sumitomo	Japan	-
Lausit	Showa	Japan	-
Metacen	Chiesi	Italy	-
Metartril	Ifisa	Italy	-
Methabid	Pharmador	S. Africa	-
Methazine	Sankyo	Japan	-
Metindol	Polfa	Poland	-
Mezolin	Meiji	Japan	-
Mobilan	Galen	US	-
Novomethacin	Novopharm	Canada	-
Osmogit	Merck-Frosst	Canada	-
Peralgon	S.A.R.M.	Italy	-
Ralicid	Waldheim	Austria	-
Rheumacin	Protea	Australia	-
Romacid	I.E. Kimya Evi	Turkey	-
Sadoreum	Mediolanum	Italy	-
Salinac	Nippon Kayaru	Japan	-
Takosashin S	Taiho	Japan	-
Tannex	Duncan Flockhart	UK	-
Zalbico	Toyo	Japan	-

Raw Materials

t-Butyl alcohol
Sodium hydride
p-Chlorobenzoyl chloride
Dicyclohexylcarbodiimide
2-Methyl-5-methoxy-3-indolyl acetic acid

Manufacturing Process

(A) 2-Methyl-5-Merhoxy-3-Indolylacetic Anhydride: Dicyclohexylcarbodiimide (10 g, 0.049 mol) is dissolved in a solution of 2-methyl-5-methoxy-3-

indolylacetic acid (22 g, 0.10 mol) in 200 ml of THF, and the solution is allowed to stand at room temperature for 2 hours. The precipitated urea is removed by filtration, and the filtrate is evaporated in vacuo to a residue and flushed with Skellysolve 6. The residual oily anhydride is used without purification in the next step.

(B) t-Butyl 2-Methyl-5-Merhoxy-3-Indolylacetate: t-Butyl alcohol (25 ml) and fused zinc chloride (0.3 g) are added to the anhydride from Part A. The solution is refluxed for 16 hours and excess alcohol is removed in vacuo. The residue is dissolved in ether, washed several times with saturated bicarbonate, water, and saturated salt solution. After drying over magnesium sulfate, the solution is treated with charcoal, evaporated, and flushed several times with Skellysolve B for complete removal of alcohol. The residual oily ester (18 g, 93%) is used without purification.

(C) t-Buryl 1-p-Chlorobenzoyl-2-Methyl-5-Mefhoxy-3-Indolylacetate: A stirred solution of ester (18 g, 0.065 mol) in dry DMF (450 ml) is cooled to 4°C in an ice bath, and sodium hydride (4.9 g, 0.098 mol, 50% susp.) is added in portions. After 15 minutes, p-chlorobenzoyl chloride (15 g, 0.085 mol) is added dropwise during 10 minutes, and the mixture is stirred for 9 hours without replenishing the ice bath. The mixture is then poured into one liter of 5% acetic acid, extracted with a mixture of ether and benzene, washed thoroughly with water, bicarbonate, saturated salt, dried over magnesium sulfate, treated with charcoal, and evaporated to a residue which partly crystallizes. This is shaken with ether, filtered and the filtrate is evaporated to a residue (17 g) which solidifies after being refrigerated overnight.

The crude product is boiled with 300 ml of Skellysolve 6, cooled to room temperature, decanted from some gummy material, treated with charcoal, concentrated to 100 ml, and allowed to crystallize. The product thus obtained (10 g) is recrystallized from 50 ml of methanol and gives 4.5 g of analytically pure material, MP 103° to 104°C.

(D) 1 -p-Chlorobenzoyl-2-Methyl-5-Methoxy-3-Indolylacetic Acid: A mixture of 1 g ester and 0.1 g powdered porous plate is heated in an oil bath at 210°C with magnetic stirring under a blanket of nitrogen for about 2 hours. No intensification of color (pale yellow) occurs during this period. After cooling under nitrogen, the product is dissolved in benzene and ether, filtered, and extracted with bicarbonate. The aqueous solution is filtered with suction to remove ether, neutralized with acetic acid, and then acidified weakly with dilute hydrochloric acid. The crude product (0.4 g, 47%) is recrystallized from aqueous ethanol and dried in vacuo at 65°C: MP 151°C.

References

Merck Index 4852
Kleeman and Engel p. 488
PDR pp.993, 1034, 1187, 1354, 1606, 1999
OCDS Vol. 1 p. 318 (1977); 2, 345 (1980) and 3, 165 (1984)
DOT 1 (4) 125 (1965); 18 (8) 373 (1982) and 19 (5) 286 (1983)
I.N. p. 517
REM p. 1118
Shen, T.-Y.; US Patent 3,161,654; December 15, 1964; assigned to Merck and Co., Inc.

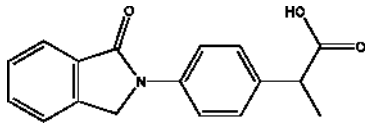
INDOPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: 4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-α-methylbenzeneacetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 31842-01-0

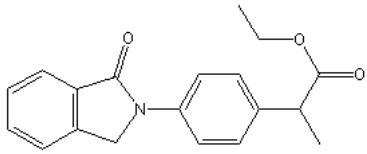
Trade Name	Manufacturer	Country	Year Introduced
Flosint	Carlo Erba	Italy	1976
Flosin	Carlo Erba	W. Germany	1982
Flosin	Carlo Erba	Switz.	1982
Flosint	Carlo Erba	UK	1982
Fenint	Montedison	W. Germany	-
Praxis	Lisapharma	Italy	-

Raw Materials

Ethyl-α-(4-aminophenyl)propionate
Ethyl 2-chloromethyl benzoate
Potassium hydroxide

Manufacturing Process

The mixture of 7.9 g of ethyl α-(4-aminophenyl)propionate and 8.3 g of ethyl 2-chloromethylbenzoate is refluxed under nitrogen for one hour. The residue is recrystallized from hexane, to yield the ethyl α-[4-(1-oxo-isoindolino)-phenyl]-propionate of the formula



melting at 104° to 106°C. The mixture of 4.5 g thereof, 1.6 g of potassium

hydroxide, 2 ml of water and 250 ml of ethanol is refluxed under nitrogen for 2 hours and evaporated under reduced pressure. The residue is taken up in water, the solution washed with chloroform, acidified with hydrochloric acid and extracted with ethyl acetate. The extract is dried, evaporated and the residue recrystallized from ethyl acetate, to yield the corresponding free acid melting at 208° to 210°C. (Procedure reported in US Patent 3,767,805.)

References

Merck Index 4853
DFU 1 (5) 242 (1976)
Kleeman and Engel p. 489
OCDS Vol. 3 p. 171 (1984)
DOT 13 (5) 200 (1977)
I.N. p. 517
Carney, R.W.J. and de Stevens, G.; US Patent 3,767,805; October 23, 1973; assigned to Ciba-Geigy Corporation
Carlo Erba, S.P.A., Italy; British Patent 1,344,663; January 23, 1974

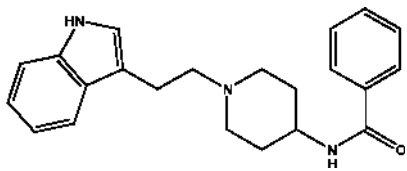
INDORAMIN

Therapeutic Function: Antihypertensive

Chemical Name: N-[1-[2-(1H-Indol-3-yl)ethyl]-4-piperidinyl]benzamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 26844-12-2

Trade Name	Manufacturer	Country	Year Introduced
Baratol	Wyeth	UK	1981
Wydora	Wyeth	W. Germany	1983

Raw Materials

4-Benzamido-1-(2-(3-indolyl)ethyl]pyridinium bromide
Hydrogen

Manufacturing Process

4-Benzamido-1-[2-(3-indolyl)ethyl] pyridinium bromide (3.0 g) was dissolved in 91% ethanol (300 ml) containing triethylamine (0.08 g) and freshly prepared W7 Raney nickel catalyst (ca 3 g) was added. The mixture was hydrogenated in an autoclave at 400 psi hydrogen pressure and 50°C for 4 hours. After filtering off the catalyst the filtrate was evaporated in vacuo and the residue was shaken with a mixture of chloroform and 2N sodium hydroxide solution. The resulting insoluble material was filtered off and dried to give 1.61 g of product, MP 203°C to 206°C. Recrystallization from ethanol gave the title compound as colorless needles (1.34 g), MP 208°C to 210°C.

References

Merck Index 4854
DFU 1 (10) 476 (1976)
OCDS Vol. 2 p. 344 (1980)
DOT 17 (10) 420 (1981)
I.N. p. 518
Archibald, J.L. and Jackson, J.L.; US Patent 3,527,761; September 8,1970; assigned to John Wyeth and Brother, Ltd. (UK)

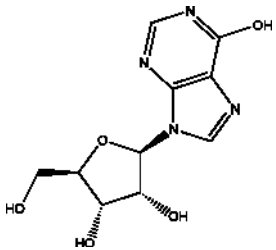
INOSINE

Therapeutic Function: Cardiotonic

Chemical Name: 9-β-D-Ribofuranosylhypoxanthine

Common Name: Hypoxanthine riboside

Structural Formula:



Chemical Abstracts Registry No.: 58-63-6

Trade Name	Manufacturer	Country	Year Introduced
Foreart	Guarnieri	Italy	1970
Oxiamin	Made	Spain	-
Ribonosine	Toyo Jozo	Japan	-
Salinite	Shinshin	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Tebertin	Berenguer-Beneyto	Spain	-
Trophicardyl	Innothera	France	-
Virusina	Dukron	Italy	-

Raw Materials

Adenosine
Barium nitrite
Sulfuric acid

Manufacturing Process

As described in US Patent 3,049,536, inosine may be prepared starting with adenosine.

The Deamination of Adenosine: 20 g of adenosine are dissolved in one liter of water by warming, and after cooling to room temperature 120 g of barium nitrite (monohydrate) are added to the solution. Under stirring there is added in time intervals of one hour 160 cc of 2 N sulfuric acid after each time interval. After the third addition, the reaction mass is allowed to stand for 3 hours at room temperature. The solution is then tested for barium, and if some barium is still present a slight excess of sulfuric acid is added. 300 cc of methanol is then added. In order to drive off the excess of nitrous acid, CO_2 is conducted through the solution until the solution is free of nitrous acid as determined by testing with potassium iodide-starch paper. The precipitated barium sulfate is separated by centrifugation. The residue is washed one time with about 500 cc of water. The total volume of the centrifugate is about 2.3 liters.

Isolation of Inosine by Ion Exchange Method: Half of the above clear centrifugate (1.15 liters) is treated with 250 cc of anion exchange (bicarbonate form) and stirred together therewith for 16 hours at room temperature. The pH value is increased thereby to about 4 to 5. The ion exchanger is filtered off under suction and washed 3 times, each time with 150 cc of water. The solution is brought to a pH value of 7 by means of normal sodium hydroxide (total volume of the solution about 1.55 liters), and concentrated to a volume of about 100 cc under vacuum.

The inosine is crystallized overnight in an ice box and the inosine is then filtered off by suction, washed with a small amount of ice water and dried at a temperature of 105°C. A first fraction of crude inosine consisting of 5.4 g having a purity of 99% is obtained. Further fractions of crude inosine are obtained from the mother liquid by concentration, the total amount constituting 3.2 g having a purity of 96 to 98%. The yield of crude inosine is 8.6 g which is equal to 86%.

Recrystallization of the Crude Inosine: 17.0 g of crude inosine are dissolved in 400 cc of 80% ethanol in a water bath, filtered while hot and brought to crystallization in an ice box. After standing overnight the crystalline material is filtered off under suction and washed with ice water. The pure inosine is dried in a drying chamber at a temperature of 105°C. The yield of pure inosine is 15.0 g which is equal to 75%. The yield can be further increased by working

up the mother liquor of the crystallization as set forth above.

Alternatively, inosine may be made by fermentation as described in US Patent 3,111,459. 3 ml portions of a culture medium consisting of glucose (5 g/dl), ammonium chloride (0.4 g/dl), urea (0.4 g/dl), KH_2PO_4 (0.1 g/dl), $MgSO_4 \cdot 7H_2O$ (0.02 g/dl), Mn^{++} (2 ppm), Fe^{++} (2ppm), casein hydrolyzate (0.2 g/dl), yeast extract (0.2 g/dl), corn steep liquor (0.2 ml/dl), polypeptone (0.1 g/dl), meat extract (0.1 g/dl) and sodium ribonucleate (10 mg/dl) were poured into respective test tubes and each tube was sterilized at 115°C for 10 minutes. Thereafter separately sterilized calcium carbonate was added in the amount of 2 g/dl and then cells of Bacillus subtilis S26910 were inoculated into the above media and cultured with shaking at 30°C for 20 hours.

The resulting culture liquids were utilized for seeding, 20 ml of the medium having the composition described above were poured into a 500 ml shaking flask and sterilized at 115°C for 10 minutes and five drops of the above seed were added, and then cultured with shaking at 30°C for 65 hours. Thereafter 0.15 g/dl of inosine were accumulated.

The inosine-containing solution, which was obtained by separating the cells from the resulting fermentation liquid, was treated with both decolorizing resins and anion exchange resins by means of a conventional method and then acetone was added to crystallize the inosine. 1.47 g of the crude crystals of inosine were obtained from 3.5 liters of the culture liquid containing 1 g of inosine per liter.

References

Merck Index 4858
I.N. p. 519
Reiff, F., Huber, G. and Holle, K.; US Patent 3,049,536; August 14, 1962; assigned to Zellstoff Fabrik Waldhof, Germany
Motozakl, S., Tsunoda, T., Aoki, R., Okumura, S., Kondo, Y., Muramatsu, N., Momose, H. and Tamagawa, Y.;US Patent 3,111,459; November 19, 1963; assigned to Ajinomoto KK, Japan

INOSITOL

Therapeutic Function: Vitamin, Lipotropic

Chemical Name: Myo-Inositol

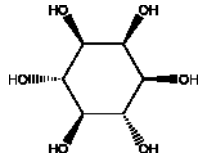
Common Name: Hexahydroxycyclohexane; Cyclohexitol

Chemical Abstracts Registry No.: 87-89-8

Raw Materials

Starch
Calcium hydroxide

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Inositol	Comm. Solvents	US	1949
Amino-Ceru	Milex	US	-
Inosital	Biomedica Foscama	Italy	-
Inositine	Vis	Italy	-
Lipo-BC	Legere	US	-
Mega-B	Arco	US	-
Megadose	Arco	US	-

Manufacturing Process

Inactive inositol may be prepared from starch factory steep water which is the liquid in which corn is steeped to soften the covering of the corn kernel and to thoroughly soften the entire kernel. It contains approximately 1% sulfurous acid (H_2SO_3) in solution. A typical example of such treatment consists in adding to the acid steep water, lime $Ca(OH)_2$ or CaO to approximate neutrality, or to a pH of 6.0 to 8.0, at which range the insoluble "phytin" is precipitated. This precipitate of impure "phytin" or calcium phytate is removed by suitable means, as stated before, and may be mixed with (1) 1 to 10% acid solution; or (2) diluted with water; or (3) the solution may be made alkaline. This alkaline or neutral or acid mixture is placed in a suitable container in an autoclave or steam digester, and the steam turned on whereupon the reaction is allowed to proceed as long as desired. The autoclave in which the mixture has been placed may be heated by generating steam therein, by means of an electric heater, or by suitable heat from outside. A pressure of from 1 to 200 pounds steam for 1 to 18 hours may be used, the time required being correspondingly less for higher pressures. A suitable pressure is 80 pounds. The time expected for 80 pounds is three hours.

After hydrolysis or decomposition is complete, pressure is released, the autoclave cooled, the mixture removed, diluted, and made alkaline with $Ca(OH)_2$, $Ba(OH)_2$,etc., brought to boiling, thoroughly agitated with steam, the insoluble sludge allowed to settle, and the supernatant liquid removed by decantation, siphoning or filtration. The supernatant liquid is concentrated in an open vessel, or in vacuum, to remove the precipitating inorganic impurities as calcium carbonate ($CaCO_3$), magnesium carbonate ($MgCO_3$), etc. The liquid is concentrated until it becomes thick and syrupy. The concentrated solution is filtered, cooled, and agitated by a suitable mechanical means to precipitate i-inositol. The iI-inositol is removed by filtration, the mother liquor concentrated, and the process repeated until the solution becomes too thick to filter advantageously. A filter press may be employed to remove further

quantities of i-inositol, or the thick residue may be diluted with a reagent in which i-inositol is insoluble; as, for example, acetic acid (CH_3COOH) and alcohol-acetic acid (C_2H_5OH, CH_3COOH, etc.). On cooling and stirring the solution, additional i-inositol, etc., results and can be removed by filtration or other mechanical means. The i-inositol may be recrystallized by dissolving the crude product in boiling water, and reprecipitated by cooling and stirring. The final crystallization from a hot water solution to which an equal volume of alcohol is added with cooling and stirring, gives a purer product.

References

Merck Index 4861
PDR pp. 581, 1033, 1263, 1734
I.N. p. 519
REM p. 1015
Bartow, E.and Walker, W.W.; US Patent 2,112,553; March 29, 1938
Elkin, M. and Meadows, C.M.; US Patent 2,414,365; January 14, 1947; assigned to American Cyanamid Co.

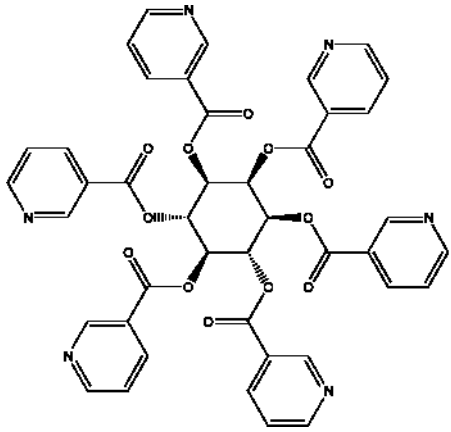
INOSITOL NIACINATE

Therapeutic Function: Vasodilator

Chemical Name: Myo-Inositol hexa-3-pyridine carboxylate

Common Name: Inositol hexanicotinate

Structural Formula:



Chemical Abstracts Registry No.: 6556-11-2

Trade Name	Manufacturer	Country	Year Introduced
Hexanicotol	Philadelphia	US	1962
Dilexpal	Winthrop	France	1968
Bendigon	Bayer	W. Germany	-
Clevamin	Kowa	Japan	-
Cycnate	Toyo	Japan	-
Ebelin	Samva	Japan	-
Hammovenad	Bastian Werk	W. Germany	-
Hexalmin	Maruishi	Japan	-
Hexainosineat	Hishiyama	Japan	-
Hexanate	Nippon Chemiphar	Japan	-
Hexanicit	Yoshitomi	Japan	-
Hexate	Mohan	Japan	-
Hexatin	Kobayashi	Japan	-
Hexit	Toho	Japan	-
Inochinate	Nichiiko	Japan	-
Inosinit	Kanto	Japan	-
Kotanicit	Kotani	Japan	-
Mesonex	Tokyo Tanabe	Japan	-
Mesosit	Toyo Jozo	Japan	-
Nasky	Nikken	Japan	-
Neonitin	Chugai	Japan	-
Nicosamin	Toyama	Japan	-
Nicosinate	Toyo Ono	Japan	-
Nicosinit	Hokuriku	Japan	-
Nicotol	Maruko	Japan	-
Nicoxatin	Fuso	Japan	-
Romanit	Kowa	Japan	-
Salex	Iwaki	Japan	-
Sannecit	Sanko	Japan	-
Secotinen	Seiko	Japan	-
Shikioit	Shiri	Japan	-
Xatolone	Showa	Japan	-
Yonomol	Sawai	Japan	-

Raw Materials

Nicotinic acid
Phosphorus oxychloride
meso-Inositol

Manufacturing Process

100 g of nicotinic acid were suspended in 265 ml of distilled and dried pyridine without stirring. 68 g of phosphorus oxychloride were added dropwise to this mixture under continual stirring. The temperature of the reactants, initially at 20°C, was allowed to rise to about 60°C, and this temperature was maintained for a further 60 minutes. Thereafter 24.5 g of meso-inositol were

added gradually, the temperature being controlled so that it did not exceed about 80°C. The reactants were maintained at this temperature for from 2 to 3 hours, and thereafter the reaction mixture was poured into 500 ml of water. The pyridine salts formed during the reaction readily dissolved, and the meso-inositol hexanicotinate which had formed crystallized out. The ester was filtered off and washed with water and acetone or alcohol. Finally, the meso-inositol hexanicotinate was dried at 100°C.

The yield was 90%, the melting point of the product was 258°C to 260°C. and the chlorine content <0.01%.

References

Merck Index 4863
Kleeman and Engel p. 490
I.N. p. 519
A.B. Bofors; British Patent 1,053,689; January 4, 1967

INSULIN

Therapeutic Function: Antidiabetic

Chemical Name: Complex polypeptide hormone with molecular weight over 6,000

Common Name: -

Structural Formula: A protein that has the normal structure of the natural antidiabetic principle produced by the human pancreas

Chemical Abstracts Registry No.: 9004-10-8

Trade Name	Manufacturer	Country	Year Introduced
Humulin	Lilly	US	1982
Humulin	Lilly	UK	1982
Humulin	Lilly	Switz.	1983
Huminsulin	Lilly	W. Germany	1983
Velosulin	Leo	Switz.	1983
Monotard	Squibb	US	1983
Monotard	Nova	W. Germany	1983
Actrapid	Squibb	US	1983
Actrapid	Novo	W. Germany	1983
Basal-H	Hoechst	W. Germany	1983
Iletin	Lilly	US	-
Insulatard	Nordisk	US	-
Mixtard	Nordisk	US	-
Novolin	Squibb-Novo	US	-
Velosulin	Nordisk	US	-

Raw Materials

Beef pancreas glands
Ethanol

Manufacturing Process

40 pounds of frozen beef pancreas glands were hashed and extracted by stirring with 45,500 cc of 85% alcohol containing 925 cc of phosphoric acid. The acidity of the extraction mixture was pH 3.0 and the alcohol concentration approximately 65% after equilibrium was attained. The pancreatic meat solids removed were then reextracted by stirring in 45,000 cc of 65% alcohol. The pH of the combined filtrates was raised to pH 8.0 by addition of ammonium hydroxide to precipitate inert proteins and phsophoric acid salts. The solids were removed by filtration and sulfuric acid was then added to the filtrate to bring the pH to 3.5. The acidified extracts were then concentrated under reduced pressure to an alcohol concentration of 20%. Lipoidal material was removed by filtration and the filtrate concentrated under reduced pressure to the aqueous phase. Lipoidal material was then removed by filtration and the insulin containing filtrate biologically assayed for insulin activity. The biological assay showed the insulin recovered to be equivalent to 1425 I.U. for each pound of pancreas glands processed.

References

Merck Index 4866
PDR pp. 1054, 1270, 1777
DOT 19 (2) 111 and (5) 262 (1983)
REM p. 973
Maxwell, L.C.and Hinkel, W.P.; US Patent 2,695,861; November 30, 1954; assigned to Armour and Co.

INSULIN ISOPHANE

Therapeutic Function: Hypoglycemic

Chemical Name: See structure

Common Name: Isophane insulin injection

Structural Formula: Isophane insulin

Chemical Abstracts Registry No.: 53027-39-7

Trade Name	Manufacturer	Country	Year Introduced
NPH-Iletin	Lilly	US	1950
Protaphane	Novo	US	1981
Humulin-I	Lilly	UK	1982

Trade Name	Manufacturer	Country	Year Introduced
Insulatard	Leo	Switz.	1983
Novolin N	Squibb-Novo	US	-

Raw Materials

Zinc insulin
Selmiridine sulfate

Manufacturing Process

This is a crystalline product of insulin and an alkaline protein where the protein/insulin ratio is called the isophane ratio. This product gives a delayed and uniform insulin action with a reduction in the number of insulin doses necessary per day. Such a preparation may be made as follows: 1.6 g of zinc-insulin crystals containing 0.4% of zinc are dissolved in 400 ml of water, with the aid of 25 ml of 0.1 N hydrochloric acid. To this are added aqueous solutions of 3 ml of tricresol, 7.6 g of sodium chloride, and sufficient sodium phosphate buffer that the final concentration is 1/75 molar and the pH is 6.9.

Then 0.14 g of salmiridine sulfate dissolved in water is added, while shaking. Salmiridine is a protamine derived from the sperm of Salmo irideus Gibbons, or rainbow trout. Salmiridine-insulin (a protamine-insulin) containing zinc is promptly precipitated. Enough water is now added to make a total of one liter, and the whole is shaken again. After standing for about an hour, the precipitated salmiridine-insulin is found to have become crystalline.

This crystalline salmiridine-insulin can be removed if desired, as by filtration; but it is not necessary to do that, as the suspension of crystalline salmiridine-insulin may be preserved as thus prepared, and dispensed and used (in the same manner as known preparations of protamine insulin and protamine-zinc-insulin are used) in the original suspending medium in which it is formed.

References

PDR p.1778
REM p.974
Krayenbuhl, C.H. and Rosenberg, T,; US Patent 2,538,018; January 16, 1951; assigned to Nordisk Insulinlaboratorium, Denmark

INSULIN ZINC SUSPENSION

Therapeutic Function: Hypoglycemic

Chemical Name: Insulin zinc suspension

Common Name: -

Structural Formula: Sterile suspension, in a buffered water medium, of insulin modified by the addition of zinc chloride in a manner such that the solid phase of the suspension conisists of a mixture of crystals and amorphous material in a ratio of approximately 7:3

Chemical Abstracts Registry No.: 8049-62-5

Trade Name	Manufacturer	Country	Year Introduced
Lente Insulin	Squibb	US	1971
Iletin I	Lilly	US	-
Protamine	Lilly	US	-
Semilente	Squibb-Novo	US	-
Ultralente	Squibb-Novo	US	-

Raw Materials

Insulin
Zinc chloride

Manufacturing Process

First, a series of stock solutions are made.

Stock Solution 1: 2.18 g of recrystallized insulin are dissolved in 25 ml of 0.1 N hydrochloric acid, and distilled water to a volume of 125 ml is added.

Stock Solution 2: To 20 ml of an aqueous zinc chloride solution containing 1% zinc is added distilled water to a volume of 125 ml.

Stock Solution 3: 1.36 g of sodium acetate with 3 mols crystal water are dissolved in distilled water to a volume of 100 ml.

Then, 1.3 ml of glycerine are mixed with 0.5 ml of a 25% solution of methyl p-hydroxybenzoate in ethanol, and 50 ml of distilled water are added. To the produced mixture are, after sterile filtration, added 10 ml of the stock solution 1, 2.5 ml of the stock solution 2 and 10 ml of the stock solution 3, after which 3.0 ml of sterile 0.1 N sodium hydroxide are added, and the mixture is filled up with sterile distilled water to a volume of 100 ml. The insulin will be precipitated amorphously by the admixture of the sodium hydroxide, and the produced suspension acquires the pH value of 7. It will contain approximately 1 gamma zinc per insulin unit.

References

Merck Index 4869
PDR pp. 1055, 1777
REM p.975
Petersen, K., Schlichtkrull, J. and Halias-Moller, K.; US Patent 2,882,203; April 14, 1959 assigned to Novo Terapeutisk Laboratorium A/S, Denmark

INTERFERON

Therapeutic Function: Antineoplastic, Antiviral

Chemical Name: See structural Formula

Common Name: -

Structural Formula: Interferons (complex protein)

Chemical Abstracts Registry No.: 9008-11-1

Trade Name	Manufacturer	Country	Year Introduced
Fiblaferon	Bioferon	W. Germany	1983
Wellferon	Burroughs-Wellcome	-	-

Raw Materials

Semliki Forest arborvirus
Animal kidneys
Trypsin

Manufacturing Process

Semliki Forest arborvirus was grown in chick embryo tissue culture. The infectious tissue culture liquid was decanted and diluted with medium 199 to give a preparation containing between 10^6 and $10^{6.5}$ mouse ID_{50} of virus/ml.

Calf kidneys, dog kidneys and rhesus monkey kidneys were treated with trypsin to give suspensions of cells. The suspensions were centrifuged and the packed cells diluted with 400 volumes (calf cells) or 200 volumes (dog cells and rhesus monkey cells) of a growth medium consisting of 5% horse serum and 0.5% lactalbumen hydrolysate in Earle's saline, with 100 units/ml each of penicillin and streptomycin. These media were used separately to produce Semliki Forest/calf interferon, Semliki Forest/dog interferon and Semliki Forest/rhesus monkey interferon. The cellcontaining growth medium was dispensed into 500 ml medical flat bottles (70 ml in each). The cultures were incubated at 36°C. Confluent sheets of cells (monolayers) were formed in 5 to 6 days. The growth medium was then removed and the monolayers were washed with isotonic phosphate-buffered saline, pH 7.5.

Each bottle for interferon production received the arborvirus preparation in medium 199 (0.5 ml) and further medium 199 (50 ml); some bottles received only medium 199 (50 ml) and no virus and served as controls. The bottles were incubated for 3 to 5 days at 36°C.

The supernatants containing the interferons were decanted from monolayers, pooled, and tested for freedom from bacteria. Residual arborvirus was inactivated by acid and heat as follows. The liquid was brought to pH 2 by the addition of 0.3N hydrochloric acid in Earle's saline (minus sodium chloride and sodium bicarbonate), kept at 4°C for 24 hours, and then brought back to pH 7

by the addition of 0.3N sodium hydroxide in distilled water. The liquid was then heated at 56°C for 30 minutes.

At this stage the interferon preparations were assayed and submitted to safety tests for the absence of contaminating viruses.

Rhesus monkey kidney infected with Semliki Forest arborvirus gave interferon of titre 1.5 log interferon units/2 ml. (The interferon unit, determined in a volume of 2 ml, is the dilution of interferon which produced a half-maximal score for degree of cytopathic effect in virus-infected tissue culture tubes at the time when the control without interferon first showed the maximal score.)

Each interferon preparation was ultracentrifuged at 20,000 revolutions per minute for one hour to remove tissue debris and inactivated virus. The supernatant was dialyzed against distilled water (1:400) for 24 hours at 4°C. The material was then freeze-dried. Thedried product was reconstituted in one-tenth of the original volume in distilled water and dispensed into ampoules. Reconstituted solutions were assayed for interferon activity, examined for toxicity, and tested for sterility.

References

Merck Index 4870
DOT 18 (8) 393 (1982)
I.N. p. 520
REM p. 1233
Sellers,R.F.; British Patent 960,769; June 17, 1964; assigned to The Wellcome Foundation Ltd. (UK)

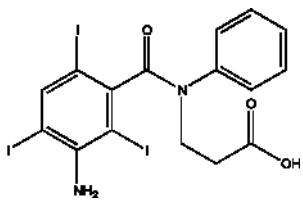
IOBENZAMIC ACID

Therapeutic Function: Diagnostic aid

Chemical Name: β-Alanine, N-(3-amino-2,4,6-triiodobenzoyl)-N-phenyl-

Common Name: Acide iobenzamique; Acidum iobenzamicum; Acidum jobenzamicum; Iobenzamic acid

Structural Formula:



Chemical Abstracts Registry No.: 3115-05-7

Trade Name	Manufacturer	Country	Year Introduced
Bilibyk	Byk Gulden	-	-
Osbil	Upjohn	-	-
Osbil	M and B	-	-

Raw Materials

Methyl β-anilinopropionate
3-Amino-2,4,6-triiodobenzoyl chloride
Hydrogen chloride
Sodium hydroxide

Manufacturing Process

1013.2 g 3-amino-2,4,6-triiodobenzoyl chloride are dissolved in a minimum amount of hot dioxane and caused to flow into 700.6 g molten methyl β-anilinopropionate with stirring. After the ensuing exothermic reaction has gradually terminated the reaction mixture is heated on a steam bath for about 3 h and while boiling hot has then methanol and methanolic 3 N HCl added thereto, where after it is cooled. The precipitated solids are separated and washed with ether. 953.0 g methyl β-N-(3-amino-2,4,6-triiodobenzoyl)-phenylaminopropionate are obtained having a melting paint of 156°-157°C. Yield 74.2% of theory.

The methyl ester may be precipitated as the free acid by dissolving in dioxane, addition of 3.15 N methanolic sodium hydroxide solution, pouring the resulting reaction mixture in water, and acidulating the solution with 6 N HCl. After separation and drying, 553.6 g β-N-(3-amino-2,4,6-triiodobenzoyl)-phenylaminopropionic acid having a melting point of 133°-134.5°C are obtained from 571.0 g methyl ester. Overall yield 73.46% of theory.

References

Obendorf W.H.; US Patent No. 3,051,745; Aug. 28, 1962; Assigned: Osterreichische Stickstoffwerke Aktiengeselischaft, Linz, Austria

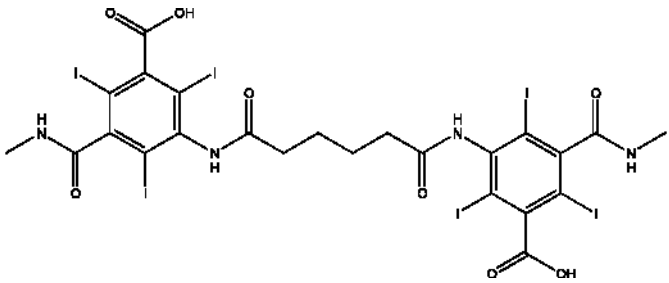
IOCARMIC ACID

Therapeutic Function: Diagnostic aid

Chemical Name: Benzoic acid, 3,3'-((1,6-dioxo-1,6-hexanediyl)diimino) bis(2,4,6-triiodo-5-((methylamino)carbonyl)-

Common Name: Acide iocarmique, Acidum iocarmicum, Acidum jocarmicum, Iocarmate meglumine, Iocarmic acid, Meglumine iocarmate

Structural Formula:



Chemical Abstracts Registry No.: 10397-75-8

Trade Name	Manufacturer	Country	Year Introduced
Myelotrast	Winthrop	-	-
Myelotrast	Guerbet	-	-
Iocarmic acid	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Iocarmic acid	Shanghai Lansheng Corporation	-	-
Dimer-X	Byk Gulden	-	-

Raw Materials

Acetic acid	5-Amino-2,4,6-triiodo-N-methylisophthalamic acid
Adipoyl chloride	Dimethylacetamide
Hydrochloric acid	Sodium hydroxide

Manufacturing Process

5-Amino-2,4,6-triiodo-N-methylisophthalamic acid (228.0 g, 4 mole) was added to stirred, heated dimethylacetamide (400 ml). When the temperature reached 95°C, adipoyl chloride (27.5 g, 0.15 mole) was added all at once, followed by an equal amount added slowly over a period of 15 min (a total of 55.0 g). After addition of the adipoyl chloride the solution was stirred at about 95°C for another 15 min, then poured into 2 L of hot water. As the above mixture cooled to room temperature a gum separated. The mother liquor was discarded and the gum was dissolved in water (2 L) with sufficient sodium hydroxide to complete solution. The solution was acidified with hydrochloric and acetic acids, treated with decolorizing charcoal and filtered. The filtrate was then strongly acidified with hydrochloric acid, which caused the separation of an apparently amorphous granular solid. This was filtered off, digested 0.5 h with hot ethanol (500 ml) collected, washed with ethanol and dried at 110°C. Yield of crude 5,5-(adipoyldiimino)-bis[2,4,6-triiodo-N-methylisophthalamic acid].

The 5,5-(adipoyldiimino)-bis[2,4,6-triiodo-N-methylisophthalamic acid] was precipitated a second and third time from its sodium salt solution. The third precipitate was then dissolved in hot dimethylformamide (400 ml), and water (1.5 L) was slowly added. The mixture was digested and the hot mixture filtered, yielding a crystalline product which, after drying at 110°C, weighed 126.0 g (neutral equivalent, 724). This product was dissolved in dilute sodium hydroxide solution (1 L) and the solution was acidified (pH 5) and filtered into a hot stirred solution of hydrochloric acid (25 ml of concentrated acid in 75 ml water). The mixture was chilled and the solid collected, washed with water and dried at 110°C. Yield of 5,5-(adipoyldiimino)-bis[2,4,6-triiodo-N-methylisophthalamic acid] 114.0 g (45%). Melting point, 302°C (corrected), with decomposition.

References

Hoey G.B.; US Patent No. 3,290,366; Dec. 6, 1966; Assigned: Mallinckrodt Chemical Works, St. Louis, Mo., a corporation of Missouri

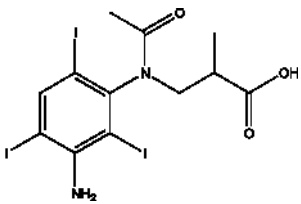
IOCETAMIC ACID

Therapeutic Function: Diagnostic aid

Chemical Name: Propanoic acid, 3-(acetyl(3-amino-2,4,6-triiodophenyl) amino)-2-methyl-

Common Name: Acide iocetamique; Acidum iocetamicum; Acidum jocetamicum; Iocetamic acid

Structural Formula:



Chemical Abstracts Registry No.: 16034-77-8

Trade Name	Manufacturer	Country	Year Introduced
Cholebrine	Nicholas	-	-
Cholimil	Takeda	-	-

Raw Materials

m-Nitroaniline
Pyridine
Methacrylic acid
Sodium chloride

Acetic acid
Aceticanhydride
Iodine monochloride
Ammonia
Nickel Raney

Manufacturing Process

A mixture of equimolecular amounts of m-nitraniline (69.0 g), methacrylic acid (43.0 g), and pyridine (39.5 g) was heated to 125°C for 20 h, and was then poured into 500 ml water. A semi-crystalline product separated from the liquid. The supernatant liquid was decanted and 500 ml fresh water was added. The pH was adjusted to 7-7.5 by means of sodium hydroxide. The precipitate was filtered with suction and washed with water. When the filtrate was acidified with acetic acid, a precipitate of N-(3-nitrophenyl)-β-amino-isobutyric acid was formed. When filtered, washed with water and dried, it weighed 56.0 g and had a melting point of 130°-131°C (recryst. from alcohol). The yield was 50% based on nitraniline.

0.25 mol (56.0 g) N-(3-nitrophenyl)-β-aminoisobutyric acid, prepared as described above, 160 ml glacial acetic acid, and 40 ml acetic anhydride were heated 48 h to 50°C, and the reaction mixture was poured into 600 ml water. A crystalline precipitate of N-acetyl-N-(3-nitrophenyl)-β-aminoisobutyric acid formed gradually. When recovered, it weighed 56.0 g (84% yield). Melting point 146°-148°C.

100.0 g N-acetyl-N-(3-nitrophenyl)-β-amino-isobutyric acid were dissolved in 1 L water and 40 ml 25% aqueous ammonia, and the solution was hydrogenated in the presence of about 10.0 g Raney nickel at 20°C and about 450 p.s.i. until the pressure drop indicated the complete conversion of the NO_2 groups to NH_2. Thus N-acetyl-N-(3-aminophenyl)-β-amino-isobutyric acid was obtained.

The solution of N-acetyl-N-(3-aminophenyl)-β-amino-isobutyric acid was filtered after standing overnight, mixed with an equal volume of acetic acid, and there after with a solution of 275.0 g iodine monochloride and 200.0 g sodium chloride in 1 L water. The mixture was kept at 50°C with stirring for 48 h. Light brown crystals of crude N-acetyl-N-(2,4,6-triiodo-3-aminophenyl)-β-amino-isobutyric acid precipitated, were filtered off, washed with water, and dried. They weighed 195.0 g (84.5% yield based on N-acetyl-N 3-nitrophenyl-p-amino-isobutyric acid).

References

Korver J.A.; US Patent No. 3,661,975; May 9, 1972
GB Patent No. 1,116,586; Nov. 25, 1965; Assigned: Dagra N.V. a limited liability company incorporated, Diemen Nethelands

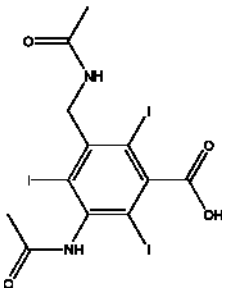
IODAMIDE

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3-(Acetylamino)-5-[(acetylamino)methyl]-2,4,6-triiodobenzoic acid

Common Name: Ametriodinic acid

Structural Formula:



Chemical Abstracts Registry No.: 440-58-4

Trade Name	Manufacturer	Country	Year Introduced
Uromiro	Heyden	W. Germany	1965
Uromiro	Bracco	Italy	1970
Angiomiron	Schering	W. Germany	-
Contraxin	Takeda	Japan	-
Isteropac	Bracco	Italy	-
Opacist	Bracco	Italy	-

Raw Materials

3-Acetylaminomethyl-4-chloro-5-nitrobenzoic acid
Hydrogen
Potassium iodide dichloride
Acetic anhydride

Manufacturing Process

65.4 g (0.24 mol) 3-acetylaminomethyl-4-chloro-5-nitrobenzoic acid were dissolved in a mixture of 48 ml 10N sodium hydroxide and 1,800 ml water. 12 g of a 10% palladium catalyst on a carbon carrier were added, and the nitrobenzoic acid derivative was hydrogenated at slightly elevated temperature and at atmospheric pressure. The hydrogen was avidly absorbed. The nitro group was fully reduced to the corresponding amino radical within about 20 to 40 minutes, and 99 to 100% of the amount of chlorine ions to be theoretically expected was formed. Hydrogen absorption then stopped.

The catalyst was removed by filtration. The filtrate was diluted to about 18 liters, and was acidified with 15 ml concentrated hydrochloric acid. With vigorous stirring, 1,152 ml N $KICl_2$ solution were run into the diluted filtrate

over a period of about 20 to 30 minutes. A solid precipitate was formed, and was filtered off after about six hours. The solid material was washed with water, with sodium bisulfite solution, and again with water. It was dissolved in aqueous ammonium hydroxide solution, the solution was filtered, and the filtrate was acidified with concentrated hydrochloric acid containing a small amount of sodium bisulfite. After a short time, the precipitate formed was filtered with suction, washed with water, and dried.

There were obtained 109 g 3-acetylaminomethyl-5-amino-2,4,6-triiodobenzoic acid which decomposes and melts at approximately 230°C. The equivalent weight was determined experimentally as being 591, as compared to a theoretical value of 586.

A suspension of 40 g 3-acetylaminomethyl-5-amino-2,4,6-triodobenzoic acid in 180 ml acetic anhydride were mixed with 0.4 ml concentrated sulfuric acid. An exothermic reaction was thereby initiated. Acetylation was completed by heating to 80°C for three hours. The reaction mixture was then evaporated to dryness in a vacuum at a temperature not exceeding 50°C. The residue was treated with a mixture of 30 ml concentrated aqueous ammonium hydroxide and 40 ml water, whereby the solid material dissolved with spontaneous heating. Within a few minutes, the ammonium salt of the acetylated product started precipitating. The precipitate and residual liquid were cooled externally with ice after about 15 minutes. The salt was separated from the liquid by filtration with suction, and was washed with ice cold saturated ammonium chloride solution.

The salt was dissolved in 300 ml water, and insoluble matter was removed from the solution by filtration. The free acid was precipitated from the filtrate at 50°C to 60°C by the addition of 40 ml 1:1 hydrochloric acid. The precipitate was filtered off after a few hours, washed with water, and dried. There were obtained 34 g 3-acetylaminomethyl-5-acetylamino-2,4,6-triiodobenzoic acid (79% of theoretical yield) having a melting point of 246°C to 248°C. The equivalent weight of this practically pure acid was found to be 631 as compared to the calculated value of 627.96.

When recrystallized from glacial acetic acid, the pure acid melts at 255°C to 257°C.

References

Merck Index 4878
Kleeman and Engel p. 493
I.N. p. 521
REM p. 1269
Felder, E. and Pitre, D.; US Patent 3,360,436: December 26, 1967; assigned to Eprova Ltd. (Switz.)

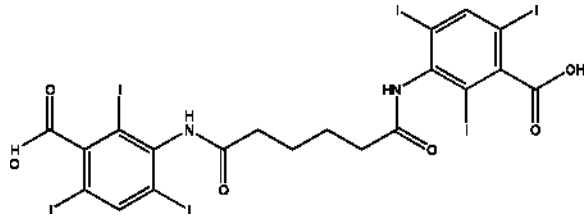
IODIPAMIDE

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3,3'-[(1,6-Dioxo-1,6-hexanediyl)diimino]bis[2,4,6-triiodobenzoic acid]

Common Name: Adipodione

Structural Formula:



Chemical Abstracts Registry No.: 606-17-7

Trade Name	Manufacturer	Country	Year Introduced
Cholografin	Squibb	US	1954
Intralibix	Guerbet	France	1955
Biligrafin	Schering	W. Germany	-
Endocistobil	Bracco	Italy	-
Endografin	Schering	W. Germany	-
Radio-Selectan Biliare	S.E.P.P.S.	France	-
Transbilix	Guerbet	France	-
Ultrabil	Spofa	Czechoslovakia	-

Raw Materials

2,4,6-Triodo-3-amino benzoic acid
Adipic acid dichloride

Manufacturing Process

125 g of 2,4,6-triiodo-3-amino benzoic acid are dissolved in 250 cc of chlorobenzene and 15 g of adipic acid dichloride are added at a temperature between 110° and 130°C drop by drop to the solution. After evolution of hydrochloric acid (about 2 to 3 hours) has ceased, the precipitated crude adipic acid di-(3-carboxy-2,4,6-triiodo anilide) of the above formula is filtered hot with suction, washed with chlorobenzene, extracted by boiling with methanol and, for purification, dissolved in an amount of methanolic caustic soda solution required for neutralization, filtered with charcoal, and precipitated with dilute hydrochloric acid. Yield: 82.3 g, MP 306° to 308°C (with decomposition).

References

Merck Index 4890
Kleeman and Engel p. 16

I.N. p. 46
REM p. 1265
Priewe, H. and Rutkowski, R.; US Patent 2,776,241;January 1,1957;assigned to Schering AG, Germany

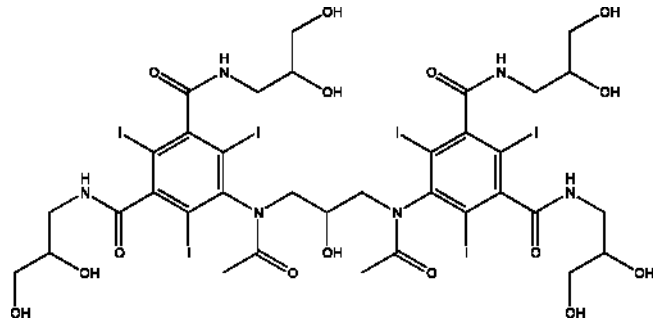
IODIXANOL

Therapeutic Function: Diagnostic aid

Chemical Name: 1,3-Benzenedicarboxamide, 5,5'-((2-hydroxy-1,3-propanediyl)bis(acetylimino))bis(N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-

Common Name: Iodixanol

Structural Formula:



Chemical Abstracts Registry No.: 92339-11-2

Trade Name	Manufacturer	Country	Year Introduced
OptiPrep	Nycomed Pharma	Norway	-
OptiPrep	Axis-Shield PoC AS	Norway	-
Visipaque	Nycomed Ireland	Ireland	-

Raw Materials

Hydrochloric acid
$NaICl_2$
Sulfuric acid
2-Methoxyethanol
Epichlorohydrin
Dimethyl 5-nitroisophthalate
1-Amino-2,3-propandiol
Sodium hydroxide
Acetic anhydride

Manufacturing Process

Dimethyl 5-nitroisophthalate (215 g) and 1-amino-2,3-propandiol (196 g)

were refluxed in methanol (500 ml). After twenty hours the solution was cooled and stored in a refrigerator overnight. The product 5-nitro-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide was filtered and washed with methanol. Yield: 270 g (84%). M.p. 128-132°C.

5-Nitro-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide (18.1 g) was suspended in water (250 ml), conc. hydrochloric acid (4.2 ml) and 10% PdO/charcoal (0.5 g) were added, and the mixture hydrogenated in a Parr apparatus for one day. After filtration the filtrate was heated at 80-90°C and 3.88 M $NaICl_2$ (42.5 ml) was added through a dropping funnel over 1 hour. The solution was heated for 2.5 hours. After cooling to 20°C 5-amino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide crystallized out.

5-Amino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide (110 g) was suspended in acetic anhydride (480 ml) and heated to 50°C. Concentrated sulfuric acid (3 ml) was then added. The starting material was dissolved after a few minutes, and the reaction mixture was heated at 60°C for 75 min. After cooling the residue dissolved in methanol (300 ml) with water (150 ml) the solution was heated to 50°C and the pH adjusted to about 10.5 by 10 N sodium hydroxide. After 4-5 hours the pH didn't decrease, and the hydrolysis was complete. The reaction mixture was cooled to 20°C and neutralized by adding hydrochloric acid. After stirring overnight 5-Acetamido-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide was filtered and washed with water. Yield: 94 g (80%). Melting point 275°C, dec.

2-Methoxyethanol (300 ml) and sodium hydroxide (20 g) was added to the reactor at 50°C, and 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophtalamide (304 g) was added after two hours of stirring. All solids were allowed to dissolve overnight before cooling to 30°C and adjustment to pH 12 with diluted hydrochloric acid. Epichlorohydrin (11 g) was added to the solution after further cooling to 15°C, and the reaction was allowed to proceed for 51 hours. As a result 1,3-bis(acetamido)-N,N'-bis[3,5-bis(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-2-hydroxypropane was obtained.

References

Nordal V., Holtermann H.; US Patent No. 4,250,113; Feb. 10, 1981; Assigned to Nyegaard and Co. A/S, Oslo, Norway

Malthe-Sorenssen D., et al.; US Patent No. 6,232,499 B1; May 15, 2001; Assigned to Nycomed Imaging AS, Oslo (NO)

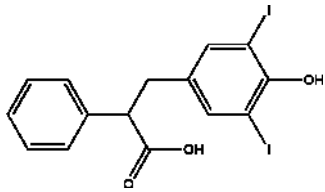
IODOALPHIONIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 4-Hydroxy-3,5-diiodo-α-phenylbenzenepropanoic acid

Common Name: Pheniodol

Structural Formula:



Chemical Abstracts Registry No.: 577-91-3

Trade Name	Manufacturer	Country	Year Introduced
Priodax	Schering	US	1943
Perfectochol	Lafayette	US	1952
Bilopsyl	Labaz	-	-
Choletrast	Burroughs-Wellcome	-	-

Raw Materials

Dextro-β-(4-hydroxyphenyl)-α-phenylpropionic acid
Iodine
Dimethylaminoethanol
Acetic acid

Manufacturing Process

Dextro-β-(4-hydroxyphenyl)-α-phenylpropionic acid (24 g) was dissolved in 630 ml of water containing 8.0 g of sodium hydroxide, and, with good stirring at 25°C, 51 g of iodine and 51 g of potassium iodide dissolved in 240 ml of water was added dropwise over a period of 30 minutes. During this period another 8 g of sodium hydroxide dissolved in 60 ml of water was added in order to keep the reaction mixture alkaline to phenolphthalein. Stirring was continued for 15 minutes longer. The resulting solution was made acid to Congo red with concentrated hydrochloric acid, and about 5 g of sodium bisulfite was added to partially decolorize the resulting slurry. The solid was collected by filtration and washed well with water.

The crude iodinated acid was then dissolved in 500 ml of 95% alcohol, 10 g of dimethylaminoethanol was added, the solution was decolorized with activated charcoal and filtered at 70°C. After keeping the filtrate for several hours at 5°C. the heavy crystalline precipitate which formed was collected by filtration and washed with acetone. The mother liquors were concentrated to 150 ml and cooled to give a second crop which was further purified by recrystallization from 50 ml of 95% alcohol. In this way a total of 36.0 g of dimethylaminoethanol salt of dextro-β-(3,5-diiodo-4-hydroxy)-α-phenylpropionic acid, MP 151° to 153°C, was obtained. The melting point of the dimethylaminoethanol salt of unresolved β-(3,5-diiodo-4-hydroxy)-α-phenylpropionic acid was 142° to 144°C.

The pure dimethylaminoethanol salt was dissolved in 400 ml of 50% acetic acid at 90°C and then cooled to 5°C. The solid which precipitated was

collected by filtration, washed with water, cold 50% acetic acid and finally with low-boiling petroleum ether. After drying in vacuo there was obtained 24 g of hydrated dextro-β-(3,5-diiodo-4-hydroxy)-α-phenylpropionic acid, MP 80° to 85°C.

References

Merck Index 4893
I.N. p. 756
Tullar, B.F. and Hoppe, J.O.; US Patent 2,552,696; May 15, 1951; assigned to Sterling Drug Inc.

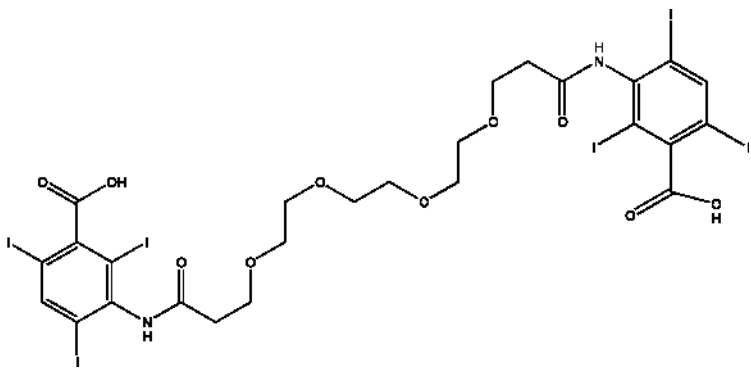
IODOXAMIC ACID

Therapeutic Function: Diagnostic aid

Chemical Name: Benzoic acid, 3,3'-((1,16-dioxo-4,7,10,13-tetraoxahexadecane-1,16-diyl)diimino)bis(2,4,6-triiodo-

Common Name: Acide iodoxamique, Acidum iodoxamicum, Iodoxamic acid

Structural Formula:



Chemical Abstracts Registry No.: 31127-82-9

Trade Name	Manufacturer	Country	Year Introduced
Endobil	Bracco	-	-
Endobil	Krka	-	-

Raw Materials

4,7,10,13-Tetraoxahexadecane-1,16-dinitrile

Thionyl chloride
3-Amino-2,4,6-triiodobenzoic acid
Dimethylacetamide

Manufacturing Process

148.5 g 4,7,10,13-tetraoxahexadecane-1,16-dinitrile (U.S. Patent No. 2,401,607) was added to a solution of 232 g (2.45 mol) concentrate sulfuric acid in 290 ml absolute ethanol at 15°C. The mixture was heated at reflux for 15 hours, cooled and poured into 1000 g ice and 250 g ammonium sulfate. It was extracted with methylene chloride, dried and a solvent was removed in vacuum. The residue was distilled to give 4,7,10,13-tetraoxahexadecane-1,16-dicarbonic acid dimethyl ester; BP: 190°-195°C/0.005 mm Hg.

1 mol above prepared diester was saponificated with equivalent of NaOH in water. The reaction mixture was heated for 90 minutes. On cooling it was extracted with ether and the water layer was evaporated to dryness. The residue was washed with acetone. The obtained disodium salt of 4,7,10,13-tetraoxahexadecane-1,16-dicarbonic acid (yield 100%; MP: 102°-104°C) was acidified with calculated quantity of HCl to give the dicarbonic acid. The solvent was evaporated to dryness. Acetone was added to the residue for removing a by-product (sodium chloride) by filtration. Acetone was evaporated and the residue was extracted with ether, dried and evaporated. The residual liquid was 4,7,10,13-tetraoxahexadecane-1,16-dicarbonic acid.

100 ml thionyl chloride was cautious added to 56 g above prepared diacid and heated at 40°-50°C and excess thionyl chloride was distilled in vacuum. The residue was the 4,7,10,13-tetraoxahexadecane-1,16-dicarbonic acid dichloride. The desired iodoxamic acid was prepared from above dichloride and 3-amino-2,4,6-trijode benzoic acid, in dimethylacetamide.

References

Felder and Pitre; D.B. Patent No. 1,937,211; July 22 1969; Milan, Italy

IOGLYCAMIC ACID

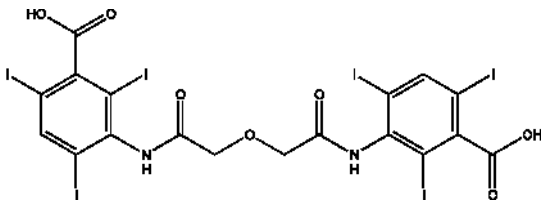
Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3,3'-[Oxybis[(1-oxo-2,1-ethanediyl)imino]]bis[2,3,6-triiodobenzoic acid]

Common Name: -

Chemical Abstracts Registry No.: 2618-25-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Biligram	Schering	W. Germany	1971
Biligram	Schering	UK	1972
Biligram	S.E.P.P.S.	France	1974
Bilivistan	Schering	Italy	-
Rayvist	Schering	W. Germany	-

Raw Materials

2,4,6-Triiodo-aminobenzoic acid
Diglycolic acid dichloride

Manufacturing Process

910 g of dry 2,4,6-triiodo amino benzoic acid are dissolved with stirring in 4,800 cc of dry, boiling chlorobenzene. A solution of 151.7 g diglycolic acid dichloride in 100 cc of dry chlorobenzene is slowly added to this solution and the mixture is further heated for 4 to 5 hours under reflux until development of hydrogen chloride has ceased. The resulting precipitate is filtered from the warm solution with suction and washed with chlorobenzene and then with ether. The microcrystalline, almost colorless crude product, 942 g, consists of the a-modification of diglycolic acid di-(3-carboxy-2,4,6-triiodo anilide).

The crude product is suspended, while stirring, in 2.5 liters of pure methanol and a solution of 73 g of pure sodium hydroxide in the same weight of water, diluted with 675 cc methanol, is slowly added to this suspension until the acid is dissolved and the pH of this solution reaches 9.0. The solution is allowed to stand at this pH for 15 minutes. The pH is then brought to 4.0 by addition of 10% acetic acid and 17 g of charcoal are stirred in. After 15 minutes the coal is filtered off and the clear filtrate is slowly added to a stirred solution of 415 cc of pure, concentrated hydrochloric acid in 4.15 liters of 50% methanol. After ½ hour of stirring and decanting after 1 hour, the precipitate is easily filtered off with suction, washed with little methanol and thoroughly with water, until the thixotropic residue is free of hydrochloric acid. In order to obtain a product of highest purity, this treatment is repeated two times. The resulting pure product, after drying in vacuo at 50°C still containing one molecule of methanol per two molecules of the acid (plus 4 molecules of water), must be suspended in boiling water and steamed out. The hot suspension is filtered with suction, the white microcrystalline residue is dried in vacuo at 50°C to give 860 g (83.5% of the theoretical yield) of the pure dihydrate of the diglycolic acid di-(3-carboxy-2,4,6-triiodo anilide), β-modification.

References

Merck Index 4912
Kleeman and Engel p. 494
I.N. p. 28
Priewe, H. and Rutkowski, R.; US Patent 2,853,424; September 23, 1958; assigned to Schering A.G. (W. Germany)

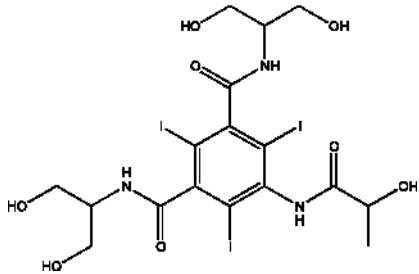
IOPAMIDOL

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 5-(α-Hydroxypropionylamino)-2,4,6-triiodoisophthalic acid di-(1,3-dihydroxyisopropylamide)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 60166-93-0

Trade Name	Manufacturer	Country	Year Introduced
Iopamiro	Bracco	Italy	1981
Solutrast	Byk Gulden	W. Germany	1981
Niopam	Merck	UK	1982
Iopamiro	Astra	Sweden	1983
Isovue	Squibb	-	-

Raw Materials

5-Amino-2,4,6-triiodo-isophthalic acid
Thionyl chloride
DL-2-Acetoxypropionyl chloride
2-Amino-1,3-propanediol

Manufacturing Process

400 g (0.72 mol) 5-amino-2,4,6-triiodo-isophthalic acid was added to 200 ml thionyl chloride, the mixture was stirred at a boil for 6 hours, and the resulting solution was evaporated. The residue was dissolved in anhydrous ethyl acetate, and the solution was again evaporated to dryness. The solid material was dissolved in 4,000 ml ethyl acetate, and the solution was stirred into an ice-cold solution of 500 g sodium chloride and 200 g sodium bicarbonate in 2.5 liters water. The organic phase was separated from the aqueous solution, washed with aqueous sodium solution, dried by contact with anhydrous calcium chloride, and evaporated to dryness.

The residue of 420 g 5-amino-2,4,6-triiodo-isophthalyl chloride (97.5% yield) had a melting point above 300°C when recrystallized from toluene.

300 g (0.503 mol) 5-amino-2,4,6-triiodo-isophthalyl chloride was dissolved in 1,200 ml dimethylacetamide, and 187 g (126 mol) DL-2-acetoxypropionyl chloride was added dropwise to the solution with agitation. The mixture was permitted to stand overnight at ambient temperature and was then evaporated in a vacuum to approximately 400 ml. The oily residue was stirred into ice water to precipitate 353 g crystalline DL-5-(α-acetoxypropionylamino)-2,4,6-triiodo-isophthalyl chloride (98% yield) which was purified by suspension in warm chloroform free alcohol.

The purified intermediate melted at 210°C. 70.9 g (0.10 mol) of the intermediate was dissolved in 150 ml dimethylacetamide, and 15 g (0.08 mol) tributylamine was added. The mixture was heated to 50°C, and 56.6 g (0.62 mol) 1,3-dihydroxyisopropylamine (2-amino-1,3-propanediol) dissolved in 80 ml dimethylacetamide was added drop by drop. The reaction went to completion within a few hours, and the reaction mixture was evaporated to dryness in a vacuum. The oily residue was added to 350 ml methylene chloride with vigorous agitation, and the resulting precipitate was filtered off and purified by repeated suspension of warm methylene chloride.

Work-up of the reaction mixture yielded 56.5 g (73.5%) DL-5-α-hydroxypropionylamino-2,4,6-triiodo-isophthalic acid di-(1,3-dihydroxyisopropylamide) which was recrystallized from aqueous ethanol and melted with decomposition above 300°C.

References

Merck Index 4915
DFU 4 (12) 876 (1979)
I.N. p. 524
Felder, E., Vitale, R.S. and Pitre, D.E.; US Patent 4,001,323; January 4, 1977; assigned to Savac AG

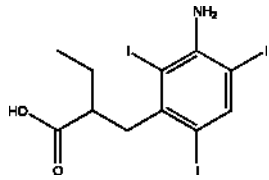
IOPANOIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3-Amino-α-ethyl-2,4,6-triiodobenzenepropanoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 96-83-3

Trade Name	Manufacturer	Country	Year Introduced
Telepaque	Winthrop	US	1952
Telepaque	Winthrop	France	1955
Ace-Line	Maruishi	Japan	-
Biliopaco	Rovi	Spain	-
Chole-Contrast	Orion	Finland	-
Cistobil	Bracco	Italy	-
Colegraf	Estedi	Spain	-
Holevid	Krka	Yugoslavia	-
Leabar	Toyo	Japan	-
Molpaque	Tokyo Tanabe	Japan	-
Neocontrast	Bama-Geve	Spain	-
Polognost	Polfa	Poland	-
Teletrast	Astra	-	-

Raw Materials

m-Nitrobenzaldehyde
Butyric anhydride
Hydrogen
Iodine monochloride

Manufacturing Process

(A) Preparation of α-Ethyl-m-Nitrocinnamic Acid: This acid is prepared from 100 g of m-nitrobenzaldehyde, 210 g of butyric anhydride and 73 g of sodium butyrate. The crude α-ethyl-m-nitrocinnamicacid is crystallized from ethanol giving about 105 g, MP 140° to 142°C. From the filtrates there may be isolated a small amount of a stereoisomer, which when pure melts at 105° to 106°C.

(B) Preparation of m-Amino-α-Ethylhydrocinnamic Acid: A mixture of 50 g of α-ethyl-m-nitrocinnamic acid, 9.1 g of sodium hydroxide, 600 cc of water and 5 teaspoons of Raney nickel catalyst is shaken at 32°C in an atmosphere of

hydrogen at an initial pressure of 450 psi until the calculated amount of hydrogen is absorbed. The filtered solution is acidified with hydrochloric acid, made basic with ammonium hydroxide and again acidified with acetic acid. Upon concentration of this solution, an oil separates which crystallizes upon standing, giving about 20 g, MP 60° to 68°C. Complete evaporation of the filtrate and extraction of the residue of inorganic salts with ether gives about 20 g of additional material, MP 54° to 59°C. Recrystallization of the combined product from benzene petroleum ether gives about 35 g of m-amino-α-ethylhydrocinnamic acid, MP 67° to 70°C.

(C) Preparation of β-(3-Amino-2,4,6-Triiodophenyll-α-Ethylpropionic Acid: A solution of 5.0 g of m-amino-α-ethylhydrocinnamic acid in 100 cc of water containing 5 cc of concentrated hydrochloric acid is added over a period of ½ hour to a stirred solution of 3.2 cc of iodine monochloride in 25 cc of water and 25 cc of concentrated hydrochloric acid heated to 60°C. After addition is complete, the heating is continued for one hour longer at 60° to 70°C. A black oil separates which gradually solidifies.

The mixture is then cooled and sodium bisulfite added to decolorize. Recrystallization of the product from methanol gives about 8 g, MP 147° to 150°C. The β-(3-amino-2,4,6-triiodophenyl)-α-ethylpropionic acid may be purified further by precipitation of the morpholine salt from ether solution and regeneration of the free amino acid by treatment of a methanol solution of the morpholine salt with sulfur dioxide. The pure amino acid has the MP 155° to 156.5°C.

References

Merck Index 4916
Kleeman and Engel p. 495
DOT 15 (7) 310 (1979)
I.N. p. 28
REM p. 1266
Archer, S.;US Patent 2,705,726; April 5, 1955; assigned to Sterling Drug Inc.

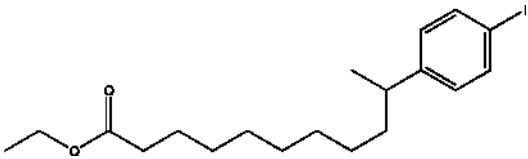
IOPHENDYLATE

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: Ethyl 10-(p-iodophenyl)undecylate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 99-79-6

Trade Name	Manufacturer	Country	Year Introduced
Pantopaque	Lafayette	US	1944
Ethiodan	Allen and Hanburys	UK	-

Raw Materials

Ethyl undecylenate
Iodobenzene

Manufacturing Process

60 volumes of ethyl undecylenate is introduced gradually at 7° to 8°C during 35 minutes to a well-cooled mixture of 52.5 parts of aluminum chloride and 150 volumes of iodobenzene. The mixture is decomposed with cracked ice and dilute hydrochloric acid. The iodobenzene layer is washed with sodium bisulfite solution and with water, and then distilled. The composition of matter having the probable formula, ethyl 4-iodophenyl-undecylate, is a colorless liquid boiling at 196° to 198°C/1 mm, and of specific gravity of 1.26/20°C.

References

Merck Index 4917
Kleeman and Engel p. 494
REM p. 1267
Strain, W.H., Plati, J.T. and Warren, S.L.;US Patent 2,348,231; May 9, 1944; assigned to Noned Corporation and Eastman Kodak Company

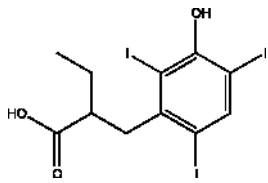
IOPHENOIC ACID

Therapeutic Function: Diagnostic aid

Chemical Name: α-Ethyl-3-hydroxy-2,4,6-triiodobenzenepropanoic acid

Common Name: Iophenoxic acid; Teridax

Structural Formula:



Chemical Abstracts Registry No.: 96-84-4

Trade Name	Manufacturer	Country	Year Introduced
Teridax	Schering	-	-

Raw Materials

Sodium propionate
Propionic anhydride
Potassium hydroxide
Sodium amalgam
m-Hydroxybenzaldehyde
Hydrochloric acid
Acetic acid
Iodine monochloride

Manufacturing Process

A mixture of m-hydroxy-benzaldehyde, fused sodium propionate and of butyric anhydride was stirred and refluxed at heating.

The mixture was then poured into water and acidified with hydrochloric acid. The organic material was extracted with chloroform, the chloroform was exaporated, and the residue stirred for one and 1.5 h with dilute potassium hydroxide solution. Acetic acid was added to make the solution almost neutral, but still slightly basic, the mixture was stirred with activated charcoal for about 15 min, filtered, and the filtrate acidified to Congo red with hydrochloric acid. A crystalline product was obtained upon cooling for several hours, and this was collected by filtration and recrystallized from water giving α-ethyl-m-hydroxycinnamic acid.

A solution of α-ethyl-m-hydroxycinnamic acid and potassium hydroxide in water was added to 3% sodium amalgam, and the mixture was stirred while heating on a steam bath for several hours. The mixture was then cooled, the mercury separated, and the reaction mixture was acidified and extracted with ether. The ether extracts were concentrated giving a residue containing α-ethyl-β-(m-hydroxyphenyl)propionic acid.

α-Ethyl-β-(m-hydroxyphenyl)propionic acid was dissolved in acetic acid. The solution was warmed on a steam bath, and water was added followed iodine monochloride. The mixture was stirred and heated for several hours, and water was then added to cause precipitation of the product. The semi-solid precipitate was triturated with a small amount of 95% alcohol, collected by filtration and washed with low boiling petroleum ether. Recrystallization from dilute alcohol, using charcoal for decolorization, gave α-ethyl-β-(2,4,6-triiodo-3-hydroxyphenyl)propionic acid.

References

Albany S.A.; US Patent No. 2,931,830; April 5, 1960; Assigned: Sterling Drug Inc., New York, N.Y, a corporation of Delaware

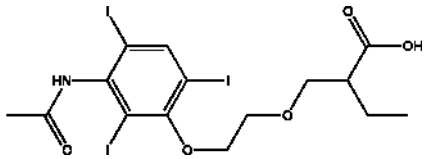
IOPRONIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 2-[[2-[3-(Acetylamino)-2,4,6-triiodophen-oxy]ethoxy] methyl]-butanoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 37723-78-7

Trade Name	Manufacturer	Country	Year Introduced
Bilimiru	Bracco	Italy	1974
Bilimiro	Byk Gulden	W. Germany	1980

Raw Materials

Sodium
Sodium hydroxide
3-(2-Iodoethoxy)-2-ethylpropionic acid ethyl ester
3-Acetylamino-2,4,6-triiodophenol
Hydrogen chloride

Manufacturing Process

A solution of 192 g 3-acetylamino-2,4,6-triiodophenol, sodium (0.35 mol) in 350 ml dimethylacetamide, was mixed with 107.5 g 3-(2-iodoethoxy)-2-ethylpropionic acid ethyl ester (0.35 mol) at 90°C with stirring over a period of about 20 to 30 minutes. Stirring was continued while the mixture was held at 95°C to 100°C for 16 hours. The solvent was then removed by distillation in a vacuum, and the residue was poured into 4,000 ml water. The solid precipitate formed was recovered and washed with water, dilute sodium carbonate solution, dilute sodium bisulfite solution, and again with much water. The ethyl ester was obtained in a yield of 220 g (90%). When recrystallized from 75% aqueous ethanol, it melted at 80°C to 86°C.

The ester (70 g, 0.1 mol) was saponified in a boiling mixture of 250 ml methanol and 250 ml water to which 100 ml N sodium hydroxide solution was added in small batches with stirring. The methanol was distilled from the saponification mixture, the residue was mixed with water and extracted with ethyl acetate. The aqueous phase was acidified with hydrochloric acid in the presence of sodium bisulfite.

The free acid gradually crystallized from the acidified solution in the amount of

42.4 g (63% yield). When recrystallized from 50% ethanol and from ethyl acetate, it melted at 130°C.

References

Merck Index 4919
I.N. p. 29
Felder, E. and Pitre, D.; US Patent 3,842,124; October 15, 1974;assigned to Bracco Industria Chimica, Societa per Azioni (Italy)

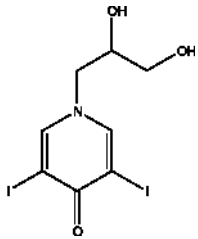
IOPYDOL

Therapeutic Function: Diagnostic aid

Chemical Name: 4(1H)-Pyridinone, 1-(2,3-dihydroxypropyl)-3,5-diiodo-

Common Name: Iopydol; Jopydolum

Structural Formula:



Chemical Abstracts Registry No.: 5579-92-0

Trade Name	Manufacturer	Country	Year Introduced
Hytrast Vial.	Guerbet	-	-
Hytrast	Byk Gulden	-	-

Raw Materials

4-Pyridone
Chloroiodide

Manufacturing Process

50 g 4-pyridone was dissolved in 300 ml 20% hydrochloric acid and slowly mixed with 180 g of chloroiodide in 200 ml 20% hydrochloric acid. Then the obtained dark solution was strong alkalized with sodium hydroxide. The solvent was removed to dryness and sodium salt diiod-4-pyridone was

obtained. It was dissolved in water, filtered and equivalent quantity of glacial acetic acid or hydrochloric acid was added to give 3,5-diiod-4-pyridone as a powder. 34.5 g 3,5-diiod-pyridone was dissolved in 100 ml 1 N NaOH by heating on a water bath and added to a 15 g of monochlorohydrine added. The mixture was heated on water bath before a dense pasty mass obtained. It was filtered off and treated with 1 N NaOH. The obtained 1-(2,3-dihydroxypropyl)-3,5-diiodo-4(1H)-pyridinone was recrystallized from diluted hydrochloric acid. MP: 161°C.

References

D.R. Patent No. 579,224; Dec. 30, 1930; I.G.Farbenindustrie Akt.-Ges. in Frankfurt a. M.

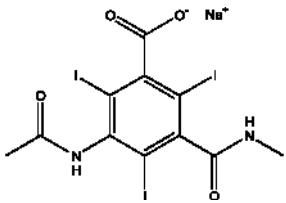
IOTHALAMATE SODIUM

Therapeutic Function: Diagnostic aid

Chemical Name: Benzoic acid, 3-(acetylamino)-2,4,6-triiodo-5-((methylamino)carbonyl)-, monosodium salt

Common Name: Iothalamate sodium; Jodtalaminatrium; Sodium isothalamate

Structural Formula:



Chemical Abstracts Registry No.: 1225-20-3

Trade Name	Manufacturer	Country	Year Introduced
Angio-Conray	Mallinckrodt Inc.	USA	-
Iothalamate Sodium	Mallinckrodt Inc.	USA	-
Vascoray	Mallinckrodt Inc.	USA	-
Vascoray	Tyco Healthcare	Canada	-

Raw Materials

Methylamine
Palladium on charcoal
5-Nitroisophthalic acid, dimethyl ester
Iodine monochloride

Manufacturing Process

Normal aqueous sodium hydroxide (0.02 eq) was added at room temperature with rapid swirling to a solution of 5-nitroisophthalic acid, dimethyl ester, (4.8 g, 0.02 mole) in acetone-methanol (100 ml each). The clear solution immediately assumed a deep red-purple color which gradually lightened to a brown color over a 25-minute period. On standing overnight the solution lightened in color to a pale pink.

The solvent was evaporated, and the residue extracted with warm water (50 ml). The residue of unsaponified diester (0.23 g), 4.2%; m.p. 115°-117°C was filtered off, and the filtrate was acidified toprecipitate the crude monomethyl ester of 5-nitroisoftalic acid. Yield 3.4 g (75%). M.p. 170.5°-175.5°C.

The preparation was repeated on a larger scale with certain variations. Methanolic potassium hydroxide was substituted for the aqueous sodium hydroxide, and acetone was used as the solvent for the 5-nitroisophthalic acid, dimethyl ester. Yield, 78%. M.P. 175°-179°C (corrected).

Crude 5-nitroisophthalic acid, monomethyl ester (46.3 g, 0.21 mole) was dissolved in 35% aqueous methylamine solution (500 ml). On standing, the orange solution became blood red. The reaction mixture was evaporated overnight on the steam bath, the cool residue was treated with 50 ml of water and the solution was acidified with hydrochloric acid. A yellow precipitate of crude N-methyl-5-nitroisophthalamic acid was separated and dried (yield 41.5 g). This acid was redissolved in dilute ammonia solution and the resulting solution (pH 5.2) was treated with charcoal. Acidification of the treated solution yield a pale yellow product of neutral equivalent 213. A small portion (10 g) was recrystaliized from 1:1 water-ethanol (300 ml) to yield orange N-methyl-5-nitroisophthalamic acid. M.p. 251°-252.5°C.

Crude N-methyl-5-nitrosophthalamic acid (11.2 g, 0.05 mole) was reduced with hydrogen in a low pressure hydrogenator. The solvent was anhydrous methanol (250 ml) and the catalyst was 5% palladium on charcoal slurried in 10 ml of water. After the theoretical quantity of hydrogen for reduction of the nitro group had been absorbed the solution was filtered to remove the catalyst and the solvent was evaporated under reduced pressure, leaving a white residue of crude 5-amino-N-methylisophthaIamic acid. M.p. 227°-230°C (corrected).

The crude 5-amino-N-methylisophthalamic acid was dissolved in hydrochloric acid (100 ml concentrated acid and 100 ml of water) and this solution was diluted to 1 liter with water. Iodine monochloride (27.4 g of 95% ICI, 0.16 mole) in concentrated hydrochloric acid (30 ml) was added in one portion to the stirred solution maintained at 54°C. The solution was heated on a steam bath. After 2 hours the solution was diluted to 1.5 liters and after 3 hours titration of an aliquot indicated that 50% of the iodine monochloride had been consumed. Precipitation of a solid began after 33/4 hours of reaction (75°C). Intermittent heating and stirring was continued for 4 days, 10 g of 95% iodine monochloride was added during the third day. After 4 days, titration of an aliquot indicated that 96% of the theoretical quantity of iodine monochloride had been consumed. The precipitated solid was filtered off, washed with water and dried at 75°C under reduced pressure. Yield of 5-amino-2,4,6-triiodo-N-

methylisophthalamic acid 20.6 g. M.p. 266-268°C (dec.).

1.95 molar $KICl_2$ a solution (1144 ml, 2.22 moles) was added during 0.5 hour to a stirred suspension of 5-amino-N-methylisophthalamic acid (196 g, 1.01 moles) in 2.5 liters of water. After three hours of additional stirring, a solution of sodium hydroxide (88 g, 2.2 moles of NaOH in 200 ml of water) was added. Then, additional 1.95 molar $KICl_2$ solution (522 ml, 1.01 mole) was added during 0.5 hour. The reaction mixture was stirred overnight after which the crude product was collected and purified by conversion first to the ammonium salt, then to the free acid. Yield of 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, 310 g (53.6%).

Acetyl chloride (17 ml, 0.24 mole) was added in portions during 10 minutes to a stirred slurry of 5-amino-2,4,6-triiodo-N-methylisophthalamic acid (57.2 g, 0.1 mole) in dimethylacetamide (120 ml). Solution occurred in 0.5-1 hour and after a total of 1.5 hours 20 ml of water was added and the reaction mixture was evaporated to a thick slurry. The product was purified by twice dissolving it as a sodium salt and precipitating the free acid by the addition of mineral acid. The resulting nearly colorless 5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid decomposed at about 285°C but did not melt below 300°C. Yield, 47 g (76.5%).

5-Acetamido-2,4,6-triiodo-N-methylisophthalamic acid was slurried in water and dissolved by the addition of an equivalent quantity of sodium hydroxide. The solution was evaporated to dryness to yield the sodium salt of 5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid. Its solubility in water at 25°C is approximately 85 g per 100 ml of solution. The acute intravenous LD_{50} of this salt in male albino mice is approximately 19.2 g/kg.

References

Hoey G.B. et al.; US Patent No. 3,145,197; Aug. 18, 1964

IOTHALMATE MEGLUMINE

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3-(Acetylamino)-2,4,6-triiodo-5-[(methylamino)carbonyl]-benzoic acid

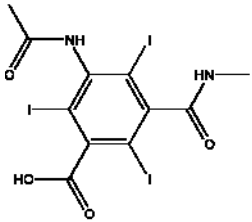
Common Name: -

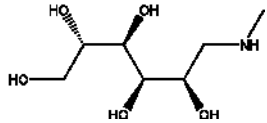
Chemical Abstracts Registry No.: 13087-53-1; 2276-90-6 (Acid)

Raw Materials

5-Amino-2,4,6-triiodo-N-methylisophthalamic acid
Acetic anhydride
N-Methyl glucamine

Structural Formula:





Trade Name	Manufacturer	Country	Year Introduced
Conray	Mallinckrodt Inc.	US	1962
Conray	Byk Gulden	W. Germany	1964
Contrix	Guerbet	France	1965
Angio-Conray	Daiichi	Japan	-
Cysto-Conray	Mallinckrodt Inc.	US	-
Gastro-Conray	May and Baker	UK	-
Sombril	Rovi	Spain	-
Vascoray	Mallinckrodt Inc.	US	-
Vascoray	Astra	Sweden	-

Manufacturing Process

Crude 5-amino-2,4,6-triiodo-N-methylisophthalamic acid (21.0 g) was dissolved in warm dimethylacetamide (40 ml) and acetic anhydride (30 ml) and concentrated sulfuric acid (2 drops) were added. This solution was heated on the steam bath for 2 hours, then heated at 110°C for 5 minutes, then cooled. Water and ammonium hydroxide were added to destroy the excess acetic anhydride, after which the mixture was evaporated to a volume of 50 ml. The cooled solution was acidified with concentrated hydrochloric acid and a tan solid was collected. The crude product was dissolved in 100 ml of water containing a slight excess of sodium hydroxide. The pH was adjusted to 4.5 with acetic acid, and the solution was treated with charcoal. The colorless solution was acidified with concentrated hydrochloric acid and cooled, and the precipitate was filtered off and dried under reduced pressure. The resulting 5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid decomposes about 285°C and does not melt below 300°C.

5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid was slurried in water and dissolved by the addition of an equivalent quantity of N-methylglucamine. The solution was evaporated to dryness to yield the meglumate salt of 5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid.

References

Merck Index 4922
Kleeman and Engel p. 496
I.N. p. 29
REM p. 1269

Hoey, G.B.; US Patent 3,145,197; August 18,1964; assigned to Mallinckrodt Chemical Works

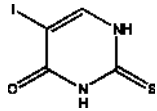
IOTHIOURACIL

Therapeutic Function: Thyroid inhibitor

Chemical Name: 2,3-Dihydro-5-iodo-2-thioxo-4(1H)-pyrimidinone

Common Name: Iodothiouracil

Structural Formula:



Chemical Abstracts Registry No.: 5984-97-4

Trade Name	Manufacturer	Country	Year Introduced
Itrumil	Ciba	US	1951

Raw Materials

5-Iodo-2-benzyl thiouracil
Acetic anhydride

Manufacturing Process

As an illustrative example 64.4 g of 5-iodo-2-benzyl thiouracil were deposited in the reaction vessel and dissolved by adding 400 cc of glacial acetic acid containing 10 cc of acetic anhydride and the reaction vessel was connected tightly with the reflux condenser. The second vessel or generator was charged with 95 cc of acetic anhydride and the vessel connected to a vessel such as a dropping funnel or equivalent containing 75 cc of a 50% solution of hydroiodic acid which was added slowly, as by dropwise addition, to the acetic anhydride in the generator. The mixture in the generator soon became hot and the hydrogen iodide which evolved passed continuously through the connecting conduit into the reaction flask just above the level of liquid therein. As the hydrogen iodide contacted the solution of the 2 benzyl derivative,a ring of the debenzylated product formed under the inlet conduct. This operation was continued until all of the hydroidic acid was added to the generator vessel. The hydrogen iodide remaining in the generator was driven over into the reaction vessel by heating the generator. It was ascertained that the reaction is complete when no more precipitate forms in the main reaction vessel. During the reaction vapors evolved were condensed in the condenser and returned to the reaction vessel as reflux. The upper end of the reflux is

preferably connected with a vent leading to a drying chamber.

The reaction vessel was cooled and the precipitate separated by pouring or decanting off the supernatant liquor. The precipitate of the 5-iodo-2-thiouracil was then thoroughly washed, as, for example, on a Buchner funnel. The precipitate was then extracted twice with hot glacial acetic acid to remove unreacted material and then washed thoroughly by alternate washes with alcohol and water. The product was then further purified by dissolving it in warm dilute sodium hydroxide and after cooling was reprecipitated by careful acidulation with acetic acid. Utilizing this procedure 37 g of purified 5-iodo-2-thiouracil were obtained.

The supernatant liquid separated from the precipitate was concentrated in vacuo and 7.4 g of the unreacted 5-iodo-2-benzyl thiouracil were recovered. This obviously may be utilized for further debenzylation.

As pointed out previously, the 5-iodo-2-thiouracil is carefully dried, preferably in a vacuum over P_2O_5.

References

Merck Index 4924
OCDS Vol. 1 p. 265 (1977)
I.N. p. 573
Barrett, H.W.; US Patent 2,585,615; February 12, 1952; assigned to The Chemical Foundation

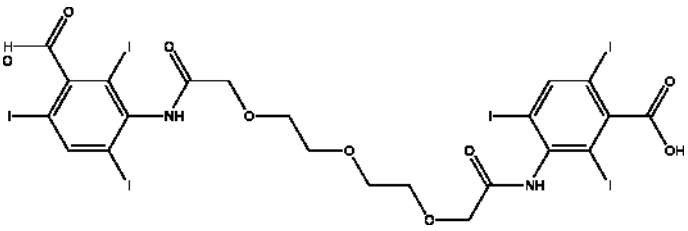
IOTROXIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3,3'-[Oxybis(ethyleneoxymethylenecarbonylimino)]bis-[2,4,6-triiodo-benzoic acid]

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 51022-74-3

Trade Name	Manufacturer	Country	Year Introduced
Biliscopin	Schering	W. Germany	1978
Biliscopin	Schering	Switz.	1981
Biliscopin	Nippon Schering	Japan	1982
Chologram	Schering	Italy	1982

Raw Materials

3-Amino-2,4,6-triiodobenzoic acid
3,6,9-Trioxaundecane diacid dichloride

Manufacturing Process

(a) Condensation in dimethylacetamide: To a suspension of 51.5 g of anhydrous 3-amino-2,4,6-triiodo-benzoic acid (0.1 mol) in 100 ml of dimethylacetamide were slowly added dropwise, while stirring, 15.5 g of 3,6,9-trioxaundecanediacid dichloride (0.06 mol), during which the temperature gradually rose to about 50°C and the whole passed into solution. After being stirred overnight, the solution was added dropwise to 1 liter of a 0.28 N solution of sodium hydroxide, and then 200 ml of 2 N hydrochloric acid were cautiously added. The precipitate was filtered off with suction, washed with water and dried. The yield was practically quantitative.

(b) Condensation in dioxan: 15.5 g of 3,6,9-trioxaundecane diacid dichloride were added dropwise at about 95°C to a solution of 51.5 g of anhydrous 3-amino-2,4,6-triiodo-benzoic acid in 52 ml of anhydrous dioxan. After further stirring and heating for 3 hours, the solution was cooled, stirred dropwise into 500 ml of a 0.4 N solution of sodium hydroxide, and further worked up as described in paragraph (a). The yield was practically quantitative.

(c) Purification: To the crude product obtained as described under paragraph (a) or (b) in 300 ml of methanol was slowly added a quantity (about 15 ml) of a 12 N solution of sodium hydroxide such that a test portion diluted with water had a pH-value of 8 to 9. After stirring the mixture overnight, the sodium salt of 3,6,9-trioxaundecane-1,11-dioyl-bis-(3-carboxy-2,4,6-triodo-anilide) which crystallized out was filtered off with suction, was hed with methanol and dried. Yield: 92 g (90% of the theoretical yield).

A solution of the salt in 900 ml of water was treated with active carbon, and concentrated hydrochloric acid was added until the pH-value was 1. The precipitate was filtered off with suction, washed with water, and dried at 50°C.

The yield of pure 3,6,9-trioxaundecane-1,11-dioyl-bis-(3-carboxy-2,4,6-triiodo-anilide) was 80 g (80% of the theoretical yield). The substance melted at 175°C with sintering.

References

Kleeman and Engel p. 497
DOT 15 (1) 48 (1979)
I.N. p. 30
Schering, A.G.; British Patent 1,501,507; February 15, 1978

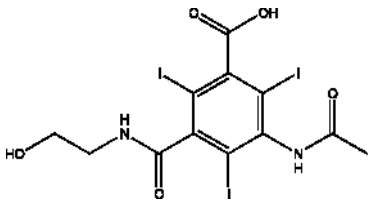
IOXITALAMIC ACID

Therapeutic Function: Diagnostic aid

Chemical Name: 3-(Acetylamino)-5-(((2-hydroxyethyl)amino)carbonyl)-2,4,6-triiodobenzoic acid

Common Name: Acide ioxitalamique; Acidum ioxitalamicum; Acidum joxitalamicum; Ioxitalamic acid

Structural Formula:



Chemical Abstracts Registry No.: 28179-44-4

Trade Name	Manufacturer	Country	Year Introduced
Oxilan	Cook Imaging Corporation	-	-
Telebrix	Laboratory Guerbet	-	-

Raw Materials

Acetic acid	3-Methoxycarboxyl-5-nitrobenzoic acid
Hydrochloric acid	Ammonium chloride
$NaICl_2$	Palladium oxide on charcoal
Thionyl chloride	Sodium bicarbonate
Sodium hydroxide	Acetic anhydride
Sulfuric acid	Ethanolamine
Triethylamine	Ammonia

Manufacturing Process

3-Methoxycarboxyl-5-nitrobenzoic acid (25 g) was hydrogenated in methanol (500 ml) using palladium oxide on charcoal (2.5 g 10%) at atmospheric pressure. When the exothermic reaction was completed the catalyst was fluttered off. After cooling the solution at -20°C for 2.5 h, 12.7 g of 3-amino-5-methoxycarbonylbenzoic acid was isolated. An additional 6.5 g of it was isolated by concentrating the mother liquor.

The 3-amino-5-methoxycarbonylbenzoic acid (12.0 g) was suspended in water (280 ml), dissolved by addition of concentrated hydrochloric acid (7.1 ml) and glacial acetic acid (28.5 ml). At 60°-70°C $NaICl_2$ solution (73 ml, 58.7 g ICl/100 ml) was added dropwise while stirring in the course of about 3 h. The reaction mixture was heated at 80°-90°C for additional 3 h while stirring.

After cooling to room temperature the mother liquor was decanted and the residue dissolved as ammonium salt in water (80 ml). The ammonium salt was precipitated by adding ammonium chloride (2.4 g) and cooling to 0°C. The ammonium salt was filtered off and dissolved in water (140 ml), charcoaled twice at 80°C and the acid was precipitated at room temperature by addition of hydrochloric acid and was filtered off. The crude product was dissolved in ethyl acetate (100 ml) and the solution was washed 3 times with hydrochloric acid (2 N). By evaporating the solvent, 19 g of 3-amino-5-methoxycarbonyl-2,4,6-triiodobenzoic acid was isolated. Melting point 170°-176°C.

A mixture of 3-amino-5-methoxycarbonyl-2,4,6-triiodobenzoic acid (198 g) and thionyl chloride (400 ml) was heated while stirring at 70°C for 16 h. The solid material dissolved slowly. Thionyl chloride was evaporated in vacuo, the residue dissolved in chloroform (1000 ml), the solution washed with water (80 ml each), twice with saturated sodium bicarbonate, then 5 times with 2 N sodium hydroxide solution and finally with water to neutral. The solution was dried with $CaCl_2$ filtered and evaporated to dryness. The 3-amino-5-methoxycarbonyl-2,4,6-triiodobenzoyl chloride was dried at 50°C in vacuo. Yield: 203.0 g. Melting point 55°-60°C.

To the 3-amino-5-methoxycarbonyl-2,4,6-triiodobenzoyl chloride (53.0 g) was added acetic anhydride (106 ml). After stirring at room temperature for 20 min then insoluble material was filtered off (3-4 g). To the filtrate was added concentrated sulfuric acid (0.3 ml) whereby a yellowish product started to precipitate. The temperature reached about 50°C. The 3-acetamido-5-methoxycarbonyl-2,4,6-triiodobenzoyl chloride was isolated after storing in refrigerator overnight. Yield: 39.0 g. Melting point 210°-215°C.

The 3-acetamido-5-methoxycarbonyl-2,4,6-triiodobenzoyl chloride was dissolved in a mixture of dioxan and dimethylformamide. In the course of 2 h this solution was added dropwise to a solution of ethanolamine and triethylamine in dioxan. The stirring was continued. A sticky precipitate was filtered off. The filtrate was evaporated to dryness in vacuo. The residue was triturated with aqueous sodium bicarbonate, filtered off and mixed with first fraction. The combined solids were then suspended in aqueous sodium bicarbonate filtered off washed with water and dried in vacuo to give methyl 5-acetamido-2,4,6-triiodo-(N-β-hydroxyethyl)-isophthalamate.

The methyl 5-acetamido-2,4,6-triiodo-(N-β-hydroxyethyl)-isophthalamate was mixed with fresh distilled ethanolamine and stirred. The excess ethanolamine was removed in vacuo at 50°-60°C. The residue was dissolved in water, and charcoaled at pH 5.5. The crude product was precipitated with hydrochloric acid (pH 0.5) and filtered after stirring at 0°C. 5-Acetamido-2,4,6-triiodo-(N-β-hydroxyethyl)isophthalamic acid was suspended in ethanol and dissolved by addition of concentrated ammonia. The ammonium salt started to precipitate in the course and was isolated after stirring. The salt was dissolved in water, filtered and the acid was precipitated with hydrochloric acid (pH 0.5). After stirring the product was filtered off and dried in vacuo.

References

Savesen S. et al.; US Patent No. 3,702,866; Nov. 14, 1972; Assigned: Nyegaard and Co.A/S, Nycoveien, Norway

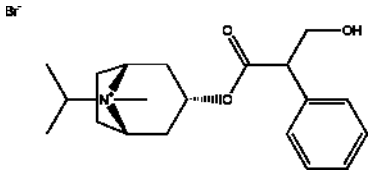
IPRATROPIUM BROMIDE

Therapeutic Function: Bronchodilator

Chemical Name: 3-(3-Hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 22254-24-6

Trade Name	Manufacturer	Country	Year Introduced
Atrovent	Boehringer Ingelheim	W. Germany	1975
Atrovent	Boehringer Ingelheim	UK	1977
Atrovent	De Angeli	Italy	1980
Breva	Valeas	Italy	1980
Atrovent	Teijin	Japan	1981
Atrovent	Boehringer Ingelheim	Canada	1982
Atem	Chiesi	Italy	-
Itrop	Boehringer Ingelheim	-	-
Vagos	Valeas	Italy	-

Raw Materials

N-Isopropyl-noratropine
Methyl bromide

Manufacturing Process

21 1.5 g (0.667 mol) of N-isopropyl-noratropine were dissolved at 60°C in 2.11 liters of absolute toluene in a 3-liter glass pressure tube. While the solution was still warm, 95 g (1 mol) of ice-cold methylbromide were added, and the pressure tube was sealed immediately thereafter. The reaction mixture was kept at 60°C for four days. After one hour of standing, the formation of crystals began. At the end of four days the crystals were separated by vacuum filtration at 60°C, washed with 600 cc of toluene at 60°C, and dried in vacuo in a drying cabinet at 100°C. Raw yield: 263.7 g (95.8% of theory). MP: 224°C to 225°C (decomp.). The raw product was refluxed with 2.5 liters of chloroform for 30 minutes, vacuum filtered while

hot, washed with 200 cc of chloroform, and dried in a vacuum drying cabinet at 100°C. Yield: 249 g (90.6% of theory). MP: 226°C to 228°C (decomp.). The purified product was recrystallized from 1.2 liters of n-propanol, washed with 200cc of n-propanol and dried in a vacuum drying cabinet at 100°C. Yield: 237 g (86.15% of theory). MP: 230°C to 232°C (decomp.). By evaporation of the mother liquor to 100 cc another 6.0 g of the pure product, MP 230°C to 231.5°C (decomp.), were obtained.

References

Merck Index 4929
Kleeman and Engel p. 498
OCDS Vol.3 p.160 (1984)
DOT 11 (12) 461 (1975) and 17 (7) 299 (1981)
I.N. p. 525
REM p.916 Zeile, K., Schulz, W., Banholzer, R. and Wick, H.; US Patent 3,505,337; April 7, 1970; assigned to Boehringer Ingelheim G.m.b.H. (W. Germany)

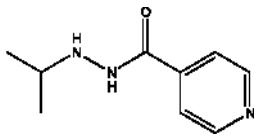
IPRONIAZID

Therapeutic Function: Antidepressant, Monoamine oxidase inhibitor

Chemical Name: 4-Pyridinecarboxylic acid 2-(1-methylethyl)hydrazide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54-92-2

Trade Name	Manufacturer	Country	Year Introduced
Marsilid	Roche	US	1952
Marsilid	Roche	France	1960
Ellepibina	L.P.B.	Italy	-
Ipronid	A.F.I.	Norway	-
Rivivol	Zambeletti	Italy	-

Raw Materials

Isonicotinyl hydrazide
Acetone
Hydrogen

Manufacturing Process

A mixture of 40 g of isonicotinyl hydrazine and 600 cc of acetone was heated on a steam bath until solution was complete. Upon cooling the reaction mixture, 1-isonicotinyl-2-isopropylidene hydrazine precipitated in the form of white needles; MP 161°C to 161.5°C.

A solution of 20 g of 1-isonicotinyl-2-isopropylidene hydrazine in 150 cc of methanol was reduced with hydrogen at room temperature and 50 psi using 300 mg of platinum black as a catalyst.

References

Merck Index 4934
Kleeman and Engel p. 499
OCDS Vol. 1 p. 254 (1977)
I.N. p. 525
Fox, H.H.; US Patent 2,685,585; August 3, 1954; assigned to Hoffmann-La Roche, Inc.

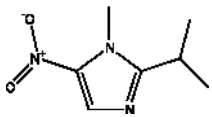
IPRONIDAZOLE

Therapeutic Function: Antiprotozoal

Chemical Name: 1-Methyl-2-(1-methylethyl)-5-nitro-1H-imidazole

Common Name: 2-Isopropyl-1-methyl-5-nitroimidazole

Structural Formula:



Chemical Abstracts Registry No.: 14885-29-1

Trade Name	Manufacturer	Country	Year Introduced
Ipropran	Roche	W. Germany	1981

Raw Materials

2-Isopropyl-4-nitroimidazole
Dimethyl sulfate

Manufacturing Process

2-Isopropyl-4 (or 5-nitroimidazole) (31 g = 0.2 mol), dioxane (70 g) and dimethylsulfate (28 g = 0.22 mol) were heated on a steam bath under reflux for 45 minutes. The solvent was removed in vacuo on a steam bath, the residue dissolved in 20 ml of water and the product precipitated by the gradual addition of 80 g of 25% sodium hydroxide solution at 0°C. A small additional amount was obtained by extraction of the mother liquor with methylene chloride. The product melted at 60°C.

The product was purified as follows. 60 g of product was dissolved in 3N aqueous hydrochloric acid, the solution was treated with charcoal and filtered. The filtrate was neutralized by the gradual addition of aqueous concentrated ammonia at 0°C to 5°C under stirring whereupon the product precipitated in white plates as the neutralization proceeded. The precipitate was filtered by suction, washed on the filter with 50 ml of ice cold water and dried at room temperature, MP 60°C.

The hydrochloride salt was formed by reacting the product, dissolved in isopropanol, with 25% ethanolic hydrochloric acid, whereupon the salt precipitated and was isolated. It has a melting point of 177°C to 182°C (dec). Similarly, the bisulfate salt was formed using 96% sulfuric acid. It has a MP of 151.5°C to 152.5°C.

References

Merck Index 4934
OCDS Vol. 2 p. 244 (1980)
I.N. p. 525
Hoffer, M. and Mitrovic, M.; US Patent 3,502,776; March 24, 1970; assigned to Hoffmann-La Roche Inc.

IRBESARTAN

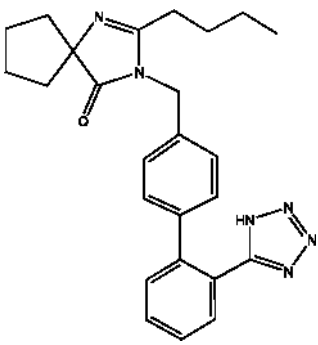
Therapeutic Function: Antihypertensive

Chemical Name: 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-((2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)-

Common Name: Irbesartan

Chemical Abstracts Registry No.: 138402-11-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Aprovel	Sanofi-Winthrop Industrie	France	-
Irbesartan	Bristol-Myers Squibb	-	-
Irbest	Biochem Pharma Industries	-	-
Irovel-H	Sun Pharmaceuticals Industries Ltd.	India	-
Irovel	Sun Pharmaceuticals Industries Ltd.	India	-
Xarb	Nicholas Piramal India Ltd. (Npil)	India	-
Xarb-H	Nicholas Piramal India Ltd. (Npil)	India	-

Raw Materials

Ethyl valerimidate	1-Aminocyclopentanecarboxylic acid
Sodium cyanide	Cyclopentanone
Triethylamine	Oxalic acid dihydrate
Valeryl chloride	4-Bromomethyl-2'-cyanobiphenyl
Tributyltin azide	Trityl chloride

Manufacturing Process

1. Synthesis of 2-n-Butyl-4-spirocyclopentane-2-imidazolin-5-one

Method 1:

The ethyl ester of 1-aminocyclopentanecarboxylic acid is prepared according to Adkins and Billica (J. Amer. Chem. Soc., 1948, 70, 3121).

Ethyl valerimidate hydrochloride is prepared according to Mac Elvain (J. Amer. Chem. Soc., 1942, 64, 1825-1827) and then freed from its hydrochloride by reaction with potassium carbonate and extraction with CH_2Cl_2.

The ethyl ester of 1-aminocyclopentanecarboxylic acid (1.57 g) and ethyl valerimidate (1.56 g) are dissolved in 12 ml of xylene containing 6 drops of acetic acid. After refluxing for 6.5 h, the reaction medium is concentrated under vacuum, the residue is chromatographed on silica gel using a chloroform/methanol/acetic acid mixture (94/4/2; v/v/v) as the eluent. The fraction containing the expected product is evaporated several times in the presence of xylene and then benzene in order to remove the acetic acid. 1.91 g of 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one are obtained in the form of a thick oil.

Method 2:

1.97 g of sodium cyanide are dissolved in 3.9 ml of water in a round-bottomed flask and a solution containing 2.33 g of ammonium chloride in 5.9 ml of water and 3.5 ml of 20% aqueous ammonia is added; finally, 3 g of cyclopentanone in 3.8 ml of methanol are added to the flask. After stirring for 1.5 h, the mixture is heated at 60°C for 45 min, heating is then stopped, stirring is continued for 45 min and the mixture is then cooled to 25°C. It is extracted several times with methylene chloride.

The 1-aminocyclopentanenitrile obtained is dissolved in 300 ml of acetone, and a solution of 2.25 g of oxalic acid dihydrate in 200 ml of acetone is added, with stirring. The precipitate of 1-aminocyclopentanenitrile formed is filtered off.

5.1 g of the oxalate obtained in the previous step are treated with 7.65 ml of concentrated sulfuric acid (d = 1.84) over 45 min, with stirring. The evolution of a gas is observed and the temperature rises to 100°C. The mixture is cooled to about 35°C and poured into a mixture of ice and concentrated aqueous ammonia (10 g/2.8 ml). The suspension formed is extracted with chloroform containing 5% of methanol. The 1-aminocyclopentanecarboxamide was obtained.

3 g of the compound prepared in the previous step are placed in 70 ml of anhydrous THF and 3.3 ml of triethylamine, and 3 ml of valeryl chloride in 10 ml of anhydrous THF are added, with stirring. A white suspension is formed. The intermediate which is formed, but not isolated, is 1-(N-valeryl)aminocyclopentanecarboxamide. 6 g of potassium hydroxide pellets, 7 ml of water and 16 ml of methanol are added. The mixture is refluxed for 2.5 h and 9 g of ammonium chloride are then added. After stirring for 15 min, the mixture is concentrated under vacuum. The residue of the 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one obtained is taken up in water and extracted with ethyl acetate.

2. Synthesis of 2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)-methyl]-2-imidazolin-5-one

A mixture containing 250 mg of sodium hydride (as an 80% dispersion in mineral oil) and 5 ml of DMF is prepared under a nitrogen atmosphere and a solution containing 0.97 g of 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one in 10 ml of DMF is added dropwise. The mixture is stirred for 30 min at 20°C and a solution of 1.5 g of 4-bromomethyl-2'-cyanobiphenyl in 10 ml of DMF is then added. After stirring for 1 h at 20°C, the DMF is evaporated off under reduced pressure, the residue is then taken up with ethyl acetate,

filtered and evaporated. The residue of 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one is purefied by chromatography.

1.56 g of the previous product, 2.6 g of tributyltin azide and 30 ml of xylene are refluxed for 66 h. The xylene is then evaporated off and the residue is dissolved in 20 ml of CH_2Cl_2 and 5 ml of THF with the addition of 0.8 ml of 10 N sodium hydroxide solution and, after stirring for 30 min, 2.5 g of trityl chloride, and the mixture is stirred for 26 h. After evaporation of the solvents, the residue is taken up in ethyl acetate in ethyl acetate, washed with water and then with a 3% solution of potassium bisulfate and water. It is dried and evaporated. The residue is chromatographed on alumina using a hexane/ethyl acetate mixture (9/1; v/v) as the eluent to give 1.97 g of the 2-n-butyl-4-spirocyclopentane-1-[(2'-(triphenylmethyltetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one. Melting point 150-152°C.

1.96 g of the product prepared in the previous step are dissolved in 10 ml of methanol and 10 ml of THF. After the reaction medium has been cooled to 5°C, 1.5 ml of 4 N hydrochloric acid are added and the mixture is stirred for 3 h at 20°C and 1 h at 30°C. After evaporation of the solvents, the residue is taken up in water and the pH is brought to 12 by the addition of 10 N sodium hydroxide solution. The aqueous phase is extracted with ether, toluene and ether again. The aqueous phase is acidified to pH 2 by the addition of 1 N hydrochloric acid and then extracted with ethyl acetate and the extract is evaporated. The aqueous phase is acidified to pH 2 by the addition of 1 N hydrochloric acid and then extracted with ethyl acetate and the extract is dried and evaporated. The white solid obtained is dried at 50°C under 0.05 mm of mercury to give 840 mg of the 2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one. Melting point 180-181°C.

References

Bernhart C. et al.; US Patent No. 5,270,317; Dec. 14, 1993; Assigned to Elf Sanofi, Paris, France

IRINOTECAN HYDROCHLORIDE

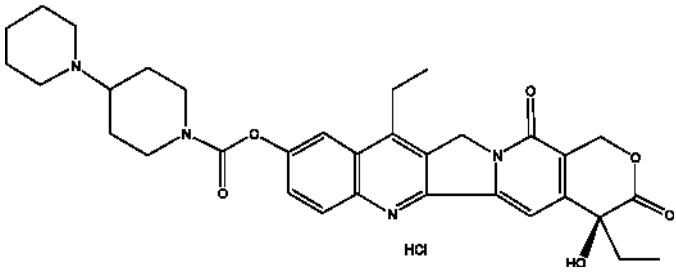
Therapeutic Function: Antineoplastic

Chemical Name: (1,4'-Bipiperidine)-1'-carboxylic acid, (4S)-3,4,12,14-tetrahydro-4,11-diethyl-4-hydroxy-3,4-dioxo-1H-pyrano(3',4':6,7) indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride

Common Name: Camptetin hydrochloride; Irinotecan hydrochloride

Chemical Abstracts Registry No.: 100286-90-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Campto	Rhone-Poulenc Rorer	France	-
Camptosar	Pharmacia Canada Inc.	Canada	-
Irinotecan hydrochloride	Ohua Pharmaceutical Technology Co., Ltd.	China	-
Irinotel Inj.	Dabur Pharmaceuticals Ltd.	India	-

Raw Materials

Triethylamine 7-Ethyl-10-hydroxycamptothecin
Phosgene dimer 1-Chlorocarbonyl-4-piperidinopiperidine
4-Piperidinopiperidine

Manufacturing Process

7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin was synthesized by 2 methods.

Method 1.

7-Ethyl-10-hydroxycamptothecin (500 mg, 1.27 mmol) was suspended in dry dioxane (400 ml) and dissolved therein by adding triethylamine (2 ml) to the suspension under warming. This solution was stirred at room temperature while introducing thereinto phosgene prepared toties quoties by decomposing phosgene dimer (trichloromethoxychloroformate, 400 ml) in the presence of an active carbon catalyst. After 0.5 hours, consumption of the starting materials was confirmed and insoluble 10-chlorocarbonyloxy-7-ethylcamptothecin was removed by filtration.

10-Chlorocarbonyloxy-7-ethylcamptothecin (300 mg, 0.66 mmol) is suspended in dry dioxane (50 ml). To this suspension is added 4-piperidinopiperidine (330 mg, 1.96 mmol) as the amine, the reaction followed by the after-treatment was carried out whereby the 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin title compound (154 mg, 39.8%) was obtained.

Method 2.

7-Ethyl-10-hydroxycamptothecin (790 mg, 2.01 mmol) and 1-chlorocarbonyl-4-piperidinopiperidine (910 mg, 3.95 mmol) were dissolved in anhydrous pyridine (50 ml), and the mixture was stirred for 1 hour at 20°C. The reaction mixture was evaporated to dryness in vacuo, the residue was dissolved in $CHCl_3$ (200 ml). The solution was washed successively with a 7% aqueous solution of $NaHCO_3$ (200 ml), a saturated aqueous solution NaCl, and the $CHCl_3$ layer was filtered, and evaporated in vacuo. The residual material was decolorized by passing it through a short silica gel column. 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin was obtained as a pale yellow mass, which was recrystallized from ethanol (ca. 60 ml) to give colorless needles (750 mg, 63.5% in yield).

To an ice-cooled suspension in distilled water (15 ml) of 7-ethyl-10-[1-(4-piperidino)piperidino]carbonyloxycamptothecin (1.00 g, 1.7 mmol) was added 0.1 N HCl (15.3 ml, 1.53 mmol), and the suspension was stirred vigorously for 5 minutes under cooling in an ice bath and filtered off. 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin hydrochloride was obtained in yield 96%.

References

Miyasaka T. et al.; US Patent No. 4,604,463; August 5, 1986; Assigned to Kabushiki Kaisha Yakult Honsha, Tokyo, Japan

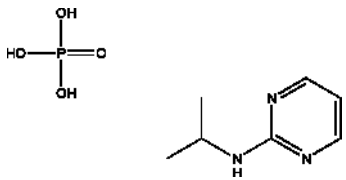
ISAXONINE PHOSPHATE

Therapeutic Function: Neurotropic

Chemical Name: N-(1-Methylethyl)-2-pyrimidinamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4214-72-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nerfactor	Ipsen	France	1981

Raw Materials

2-Isopropylamino pyrimidine
Phosphoric acid

Manufacturing Process

6 liters of ethanol and 685 g (5 mold of 2-isopropylamino pyrimidine were added to a 10 liter reactor and stirred. To the solution were added 600 g (5.2 mols) of phosphoric acid and the mixture was boiled under reflux for one hour. There was obtained a dark green solution which was treated with 30 g of carbon black. After separation and crystallization while stirring overnight, the crystallized product was separated, washed with ethanol and dried at 50°C. There was obtained 1,027 g (87% yield) of a white powder melting at 125°C. The analysis of the compound showed a good correspondence with the formula $C_7H_{14}O_4N_3P$.

References

Merck Index 4953
DFU 1 (5) 315 (1982)
Esanu, A.; US Patent 4,073,895; February 14, 1978; assigned to Societe D'Etudes de Produits Chimiques (France)

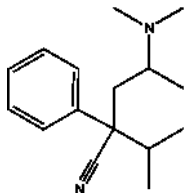
ISOAMINILE

Therapeutic Function: Antitussive

Chemical Name: α-[2-(Dimethylamino)propyl]-α-(1-methylethyl) benzeneacetonitrile

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 77-51-0

Trade Name	Manufacturer	Country	Year Introduced
Peracon	Toyo Jozo	Japan	1969
Dimyril	Fisons	UK	-

Trade Name	Manufacturer	Country	Year Introduced
Mucalan	Delagrange	France	-
Sedotosse	Panthox and Burck	Italy	-

Raw Materials

α-Isopropyl phenyl acetonitrile
Sodium amide
2-Dimethylamino-1-chloropropane

Manufacturing Process

140 cc of benzene and 24 g of α-isopropyl phenyl acetonitrile are added to 7.5 g of sodium amide. The mixture is stirred and refluxed for one hour. After cooling, 25 g of 2-dimethylamino-1-chloropropane, dissolved in 20 cc of benzene, are added and stirring and refluxing of the mixture is continued for 4 hours. After the reaction is completed, water is added to the reaction mixture. The benzene layer is separated from the aqueous layer and is extracted by means of 4N hydrochloric acid. The acid solution is rendered alkaline.

The separated oil is taken up in ether. After drying the ethereal solution over sodium sulfate and distilling off the ether, the resulting crude α-isopropyl-α-(β'-dimethylamino propyl) phenyl acetonitrile is purified by distillation in a vacuum. The compound boils at 138° to 146°C/3 mm, according to US Patent 2,934,557.

References

Merck Index 4956
Kleeman and Engel p. 499
OCDS Vol. 1 p.82 (1977)
I.N. p. 527
Stuhmer, W. and Funke, S.; US Patent 2,934,557; April 26, 1960; assigned to Kali-Chemie AG, Germany
Dickinson, H.M.N.; US Patent 3,074,996; January 22, 1963; assigned to Abbott Labs.

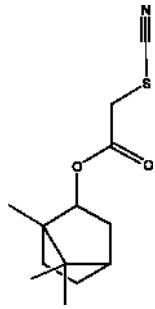
ISOBORNYL THIOCYANOACETATE

Therapeutic Function: Pediculicide

Chemical Name: Thiocyanatoacetic acid 1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 115-31-1

Trade Name	Manufacturer	Country	Year Introduced
Bornate	Wyeth	US	1946

Raw Materials

Camphene
Chloroacetic acid
Potassium thiocyanate

Manufacturing Process

200 g of camphene and 150 g of chloroacetic acid were heated 16 hours at 125°C, cooled to room temperature and the resulting product washed with water. In this way, 177 g of isobornyl monochloroacetate, analyzing 12.8%, by weight, chlorine was recovered. 174 g of the isobornyl monochloroacetate was dissolved in 300 cc of ethyl alcohol, 100 g of potassium thiocyanate added to this solution and the mixture refluxed for a period of 8 hours. 276 g of a product was recovered, which analyzed as follows: chlorine, 0.2% by wt. and sulfur, 10.9% by wt. This analysis shows the product to be principally isobornyl thiocyanoacetate.

References

Merck Index 4976
I.N. p. 527
Borglin, J.N.; US Patent 2,217,611; October 8, 1940; assigned to Hercules Powder Co.

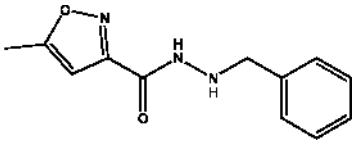
ISOCARBOXAZIDE

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	US	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 lbenzylidene-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 mi. 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 and Engel p. 500

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

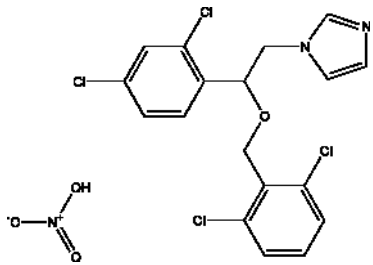
ISOCONAZOLE NITRATE

Therapeutic Function: Antibacterial, Antifungal

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

Common Name: -

Structural Formula:



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	UK	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-Dichlorotenzyl 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-b-(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-b-(2,6-dichlorobenzyloxy)phenethyl]imidazole nitrate; melting point 179°C.

References

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

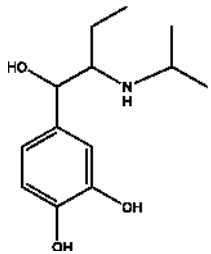
ISOETHARINE

Therapeutic Function: Sympathomimetic, Bronchodilator

Chemical Name: 2-Benzenediol, 4-(1-hydroxy-2-((1-methylethyl)amino) butyl)-

Common Name: Etyprenalinum; Isoetharine

Structural Formula:



Chemical Abstracts Registry No.: 530-08-5

Trade Name	Manufacturer	Country	Year Introduced
Dilabron	Sterling Winthrop	-	-
Isoetharine	Shanghai Lansheng Corporation	-	-

Raw Materials

3,4-Dibenzyl-hydroxy-butyrophenone
Bromine
Isopropylamine
Palladium on carbon

Manufacturing Process

36 g 3,4dibenzyl-hydroxy-butyrophenone was dissolved in 125 ml methylene chloride and 16 g bromine was added dropwise after 15 g calcium carbonate. An obtained precipitate was filtered off. The filtrate was distilled to dryness to give 1-(3,4-dibenzyloxy-phenyl)-2-bromo-butan-1-one. It was dissolved in a portion of ethanol and 15 g of isopropylamine was added. The mixture had stood for night at room temperature and thereafter ether was added. The isopropylamine hydrobromide had fallen. It was filtered off, the filtrate was shook with 200 ml of diluted hydrochloric acid. At that 4-(1-hydroxy-2-isopropylamino-butyl)-benzene-1,2-diol chlorohydrate was separated as an oil. The oil was diluted with the 5 volumes of ethanol and the calculated quantity hydrogen was passed through in a presence of palladium on coal catalyst. The catalyst was filtered off and a solvent was removed to dryness, the residue had crystallized by grinding with acetone. The obtained 4-(1-hydroxy-2-isopropylamino-butyl)-benzene-1,2-diol chlorohydrate was recrystallized from methanol. MP: 212°-213°C. Chlorohydrate may be changed into isoetharine with the calculated quantity of any base.

References

D.R. Patent No. 638,650; June 8, 1934; I.G.Farbenindustrie Akt.-Ges. in Frankfurt a.M.

ISOFLUPREDONE

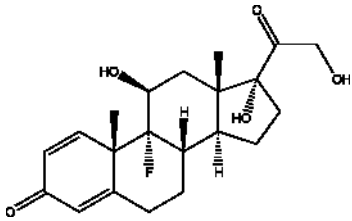
Therapeutic Function: Glucocorticoid

Chemical Name: Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-, (11β)-

Common Name: Deltafludrocortisone, 9-Fluorprednisolone, Isoflupredone

Chemical Abstracts Registry No.: 338-95-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Isoflupredon	Farmabios	-	-
Abicorten	Fatro	-	-

Raw Materials

Potassium dihydrogen phosphate
Disodium hydrogen phosphate
Corynebacterium simplex
9α-Fluoro-4-pregnen-11β,17α,21-triol-3,20-diene

Manufacturing Process

A 100 ml broth culture containing a 0.1% yeast extract concentration, 9.0 ml of 0.2 M KH_2PO_4 and 9.0 ml of 0.2 M Na_2HPO_4 contained in a 300 ml Erlenmeyer flask, is seeded with 1 ml of a 24-h broth culture of Corynehacierium simplex (A. T, C. C. 6946). The flask is incubated at 28°C for 24 h. A second 300 ml Erlenmeyer flask containing 150 mg of sterile 9α-fluoro-4-pregnen-11β,17α,21-triol-3,20-diene in 5.0 ml acetone is inoculated with the 24 h culture of *Corynebacterium simplex* (A. T. C. C. 6946). The culture-containing steroid solution is incubated for 48 h at 28° to 30°C.

The product is extracted with chloroform and isolated by evaporation to dryness. Recrytstallizstion of the residue affords 9α-fluoro-$\delta^{1,4}$-pregnadiene-11β,17α,21-triol-3.20-dione as a solid.

References

Belleville A.N.; US Patent No. 2,837,464; June 3, 1958; Assigned: Schering Corporation, Bloomfield, N.J., a corporation of New Jersey

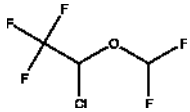
ISOFLURANE

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	US	1980
Aerrane	Ohio Medical	Switz.	1983
Aerrane	Ohio Medical	UK	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 $SbCl_5 \cdot HF$ 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.; US Patent 3,535,388; October 20, 1970; assigned to Air Reduction Co., Inc.

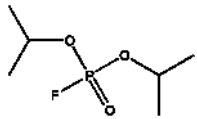
ISOFLUROPHATE

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	US	1949
D.F.P.	Sumitomo	Japan	-
D.F.P.	Boots	UK	-
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 and Engel p. 501
PDR p. 1179
I.N.p. 437
REM p. 899
Hardy, E.E. and Kosolapoff, G.M.; US Patent 2,409,039; October 8, 1946; assigned to Monsanto Chemical Company

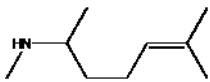
ISOMETHEPTENE

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	US	1948
Cesal	Dainippon	Japan	-
Midrin	Camrick	US	-
Migralam	Bart	US	-

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

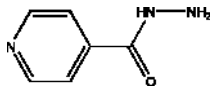
ISONIAZID

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	US	1952
Niconyl	Parke Davis	US	1952
INH	Lilly	US	1952
Tisin	U.S.V. Pharm.	US	1952
Pyrizidin	Warner Lambert	US	1952
Cotinazin	Pfizer	US	1952
Tyvid	Merrell National	US	1952
Ditubin	Schering	US	1952

Trade Name	Manufacturer	Country	Year Introduced
Rimafon	Roche	US	1952
Armazide	Armour	US	1952
Anteben	Dainippon	Japan	-
Cedin	Lyssia	W. Germany	-
Cernidon	Gayoso Wellcome	Spain	-
Cin Vis	Vis	Italy	-
Dardex	Llorente	Spain	-
Diazid	Nippon Shinyaku	Japan	-
Dinacrin	Winthrop-Stearns	Philippines	-
Dow-Isoniazid	Dow	US	-
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 Inc.	US	-
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	US	-
Niazid	Sankyo	Japan	-
Nicazide	Wassermann	Italy	-
Niconyl	Parke Davis	US	-
Nicotibina	Zambeletti	Italy	-
Nicotbine	Abic	Israel	-
Nicotubin	Leiras	Finland	-
Nicozid	Piam	Italy	-
Nicozide	Premo	US	-
Niplen	Tanabe	Japan	-
Panazid	Panray	US	-
Pycazide	Smith and Nephew	UK	-
Pyrizidin	Nepera	US	-
Rifamate	Merrell Dow	US	-

Trade Name	Manufacturer	Country	Year Introduced
Rimifon	Roche	France	-
Sumifon	Sumitomo	Japan	-
TB-Phlogin	Heyl	W. Germany	-
Tebesium	Hefa-Frenon	W. Germany	-
Tebilon	Kwizda	Austria	-
Tibinide	Ferrosan	Denmark	-
Tibizina	Farmochimica	Italy	-
Tubanox	Morgens	Spain	-
Tuberon	Shionogi	Japan	-
Tubilysin	Orion	Finland	-
Zidaf imia	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 and Engel p. 503
PDR pp. 798, 830, 1237
OCDS Vol. 1 p. 254 (1977) and 2,266 (1980)
I.N. p. 529
REM p. 1214
Gasson, E.J.; US Patent 2,830,994; April 15, 1958; assigned to The Distillers Company Limited, Scotland
Fox, H.H.; US Patent 2,596,069; May 6, 1952; assigned to Hoffmann-La Roche Inc.

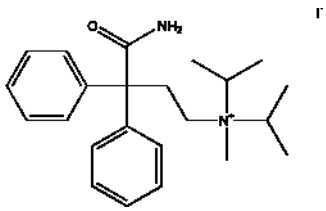
ISOPROPAMIDE IODIDE

Therapeutic Function: Spasmolytic

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

Common Name: Diisopropylaminodiphenylbutyramide methiodide

Structural Formula:



Chemical Abstracts Registry No.: 71-81-8

Trade Name	Manufacturer	Country	Year Introduced
Darbid	SKF	US	1957
Priamide	Delalande	France	1959
Combid	SKF	US	-
Dipramid	Valeas	Italy	-
Marygin M	Sumitomo	Japan	-
Ornade	SKF	US	-
Prochlor-Iso	Schein	US	-
Pro-Iso	Zenith	US	-
Tyrimide	SKF	UK	-

Raw Materials

γ-Diisopropylamino-α,α-iphenylbutyronitrile
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 3% 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 and Engel p. 504
PDR pp. 1606, 1706, 1711, 1999
I.N. p. 531
REM p. 916
Speeter, M.E.; US Patent 2,823,233; February 11, 1956; assigned to Bristol Laboratories Inc.

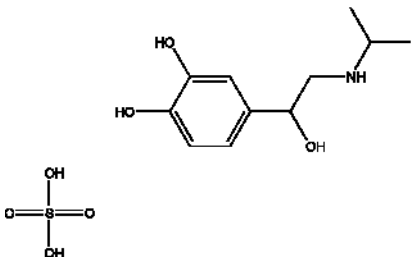
ISOPROTERENOL SULFATE

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:



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

Trade Name	Manufacturer	Country	Year Introduced
Isonorin	Smith, Miller and Patch	US	1949
Norisodrine	Abbott	US	1950
Medihaler-Iso	Riker	US	1956
Luf-Iso	Mallinckrodt Inc.	US	1974
Aleudrin	Lewis	UK	-
Aludrin	Boehringer Ingelheim	W. Germany	-
Asmadren	A.F.I.	Norway	-
Asthpul	Nippon Shoji	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Dyspnoesan	Noury Pharma	Netherlands	-
Ingelan	Boehringer Ingelheim	W. Germany	-
Isomenyl	Kaken	Japan	-
Meterdos-Iso	West-Silten	UK	-
Nebair	Warner-Chilcott	US	-
Novodrin	VEB Berlin Chemie	E. Germany	-
Prenomiser	Fisons	UK	-
Propynalin	Ferrosan	Denmark	-
Proternol	Nikken	Japan	-
Sedansol "Iso"	Nippon Zoki	Japan	-
Vapo-N-Iso	Fisons	US	-

Raw Materials

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

Manufacturing Process

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

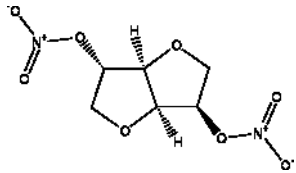
ISOSORBIDE DINITRATE

Therapeutic Function: Coronary vasodilator

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	US	1959
Sorbitrate	Stuart	US	1968
Isordil	Ayerst	UK	1971
Sorquad	Tutag	US	1972
ISDN	Cooper	US	1975
Iso-Bid	Geriatric	US	1975
Isomotic	Alcon	US	1980
Dilatrate	Reed Carnrick	US	1981
Cardio-10	Nicholas	W. Germany	-
Cardis	Iwaki	Japan	-
Carvanil	Banyu	Japan	-
Cardopax	Erco	Denmark	-
Carvasin	Ayerst	Italy	-
Cedocard	Tillotts	UK	-
Cordil	Disco	Israel	-
Cornilat	Galenika	Yugoslavia	-
Corovliss	Boehringer Mannheim	W. Germany	-
Difutrat	Srbolek	Yugoslavia	-
Dilatrate	Reed Carnrick	US	-
Diretan	Ono	Japan	-
Duranitrate	Durachemie	W. Germany	-
Isobid	Geriatric	US	-
Isocardide	Sam-On	Israel	-
ISO-D	Dunhall	US	-
Isoket	Gebro	Austria	-
Isomack	Mack	W. Germany	-
Isopuren	Klinge	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Isordil	Wyeth	US	-
Isotrate	Hauck	US	-
Laserdil	Laser	US	-
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	UK	-
Sorbangil	Kabi Vitrum	Sweden	-
Sorbid	I.E. Kimya Evi	Turkey	-
Tinidil	Pliva	Yugoslavia	-
Vascardin	Nicholas	UK	-

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 and 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.; US Patent 4,156,736; May 29, 1979; assigned to Sanol Schwarz-Monheim G.m.b.H. (W. Germany)

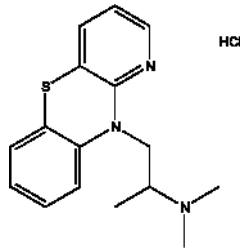
ISOTHIPENDYL HYDROCHLORIDE

Therapeutic Function: Antihistaminic

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

Common Name: -

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Theruhistin	Ayerst	US	1957
Andantol	Gerda	France	1957
Aczen NS	Kanebo, Ltd.	Japan	-
Adantol	Imidas	Brazil	-
Andanton	Lacer	Spain	-
Nilergex	I.C.I.	UK	-
Thiodantol	Teva	Israel	-

Raw Materials

Sulfur
Sodium amide
Hydrogen chloride
Phenylpyridylamine
Dimethylaminoisopropyl 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 1% 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 and Engel p. 505
OCDS Vol. 1 p.430 (1977)
I.N.p. 534
Schuler, W.A. and Klebe, H.; US Patent 2,974,139; March 7, 1961; assigned to Degussa (W. Germany)

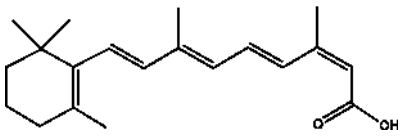
ISOTRETINOIN

Therapeutic Function: Antiacne, Keratolytic

Chemical Name: Retinoic acid, 13-cis-

Common Name: cis-Retinoic acid; Isotretinoin

Structural Formula:



Chemical Abstracts Registry No.: 4759-48-2

Trade Name	Manufacturer	Country	Year Introduced
Accutane	Roche	-	-
Amnesteem	Bertek	-	-
Amnesteem	Mylan Laboratories Inc.	-	-
Amnesteem	Genpharm Inc.	-	-
Claravis	BARR	-	-
Isotrex	Stiefel	-	-

Trade Name	Manufacturer	Country	Year Introduced
Oratane	Douglas	-	-
Roaccutane	R.P. Scherer GmbH and Co. KG	Germany	-
Sotret	Ranbaxy	India	-
Tasmar	Hoffmann - La Roche Inc.	-	-

Raw Materials

Butyl lithium
Diisopropylamine
Methyl 3,3-dimethyl acrylate
β-Ionylidene acetaldehyde

Manufacturing Process

Under an atmosphere of nitrogen, a solution of n-butyl lithium in hexane (321 ml, 15%) was added to a solution of diisopropylamine (48.6 g, 0.48 mole) in tetrahydrofuran (1000 ml) at -30°C and the mixture was stirred for one hour. The reaction mixture was then cooled to -72°C and methyl 3,3-dimethyl acrylate (55 g, 0.48 mole) was added to it. Stirring was continued at -65° to -75°C for 30 min. To the resulting mixture, a solution of β-ionylidene acetaldehyde (100 g, 0.458 mole, 9-trans content: 80%) was added and the reaction mixture was stirred at -65° to -75°C for 1 h. The reaction mixture was then warmed to 40°C and stirred at this temperature for 3 h. Solvent was removed under vacuum and the reaction mixture was diluted with water (700 ml) and methanol (300 ml). Activated charcoal (4 g) was then added and the mixture was refluxed for 30 min. The heterogeneous mixture was filtered through hyflo and the hyflo bed was washed with methanol (300 ml) and water (150 ml). The aqueous methanolic layer was then extracted with hexanes (2 x 500 ml) and acidified with 10% sulfuric acid to pH 2.80.5. The desired product was then extracted with dichloromethane (2 x 500 ml). The combined dichloromethane layer was washed with water (2 x 300 ml) and concentrated in vacuo to afford the desired isotretinoin. Crystallization from methanol (200 ml) afforded isotretinoin (44 g) in greater than 99% HPLC purity.

References

Salman M., et al.; US Patent No. 6,441,226 B1; August 27, 2001; Assigned: Ranbaxy Laboratories Limited, New Delhi (IN)

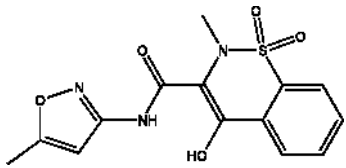
ISOXICAM

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) and 19 (7) 414 (1983)
I.N. p. 534
Zinnes, H., Schwartz, M.L. and Shavel, J. Jr.; US Patent 3,787,324; January 22, 1974; assigned to Warner-Lambert Co.

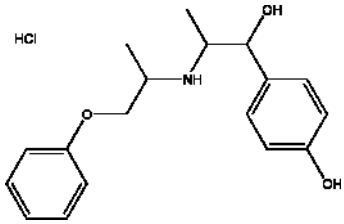
ISOXSUPRINE HYDROCHLORIDE

Therapeutic Function: Vasodilator

Chemical Name: 4-Hydroxy-α-[1-[(1-methyl-2-phenoxyethyl)amipo]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	US	1959
Cardilan	Ferrosan	Denmark	-
Defencin	Bristol	UK	-
Isokulin	Toho Iyaku	Japan	-
Isolait	Elder	US	-
Largiven	Bristol	Italy	-
Suprilent	Duphar	Belgium	-
Synzedrin	Teisan	Japan	-
Trophodilan	Duphar	France	-
Vahodilan	Morita	Japan	-
Vaxoprin	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 and 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.; US Patent 3)256,836; October 2,1962;assigned to North American Philips Company

ITRACONAZOLE

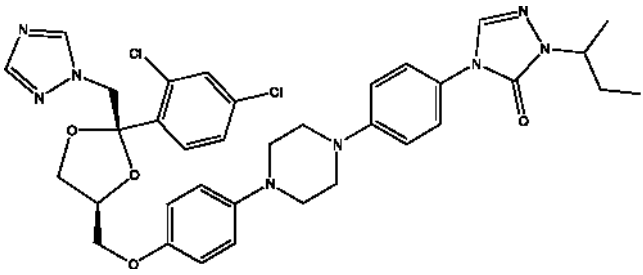
Therapeutic Function: Antifungal

Chemical Name: 3H-1,2,4-Triazol-3-one, 4-(4-(4-(4-((2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl) methoxy)phenyl)-1-piperazinyl)phenyl)-2,4-dihydro-2-(1-methylpropyl)-

Common Name: Itraconazole

Chemical Abstracts Registry No.: 84625-61-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Canadiol	Esteve	-	-
Canditral	Glenmark Pharmaceuticals Ltd.	India	-
Funit	Nobel	-	-
Itaspor	Intas Pharmaceuticals Pvt. Ltd.	India	-
Itraconazole	Janssen Pharmaceutica Inc.	USA	-
Itraconazole pellets	Chemo Iberica	Spain	-
Kanazol	Slaviamed	Yugoslavia	-
Micoral	Sintyal	-	-
Orungal	Janssen Pharmaceutica N.V.	Belgium	-
Sporacid	Dexa Medica	-	-
Sporanox	Farmasa/Neo Quimica	-	-
Sporanox	Janssen Pharmaceutica Inc.	Belgium	-
Sporanox	Ortho Biotech. Inc.	USA	-
Sporanox	Johnson and Johnson	India	-
Sporex	Toprak	-	-

Raw Materials

Hydrogen
Hydrobromic acid
Sodium hydride
1-(4-Methoxyphenyl)piperazine dihydrochloride
cis-[2-(2,4-Dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl]methanesulfonate
4-Methyl-2-pentanone
1-Chloro-4-nitrobenzene
Potassium carbonate

Manufacturing Process

Synthesis of cis-4-{4-[4-{4-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl}-1-piperazinyl]phenyl}-2,4-dihydro-2-(methylpropyl)-3H-1,2,4-triazol-3-one is showed by the same procedure as for cis-4-{4-[4-{4-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3- dioxolan-4-ylmethoxy]phenyl}-1-piperazinyl]phenyl}-2,4-

dihydro-2-propyl-3H-1,2,4-triazol-3-one described in the patent.

A mixture of 13.4 parts of 1-(4-methoxyphenyl)piperazine dihydrochloride, 7.9 parts of 1-chloro-4-nitrobenzene, 10 parts of potassium carbonate and 90 parts of N,N-dimethylformamide is stirred and refluxed overnight. The reaction mixture is diluted with water and the product is extracted twice with trichloromethane. The residue is triturated in 4-methyl-2-pentanone. The product is filtered off and crystallized from 1,4-dioxane, yielding 10.5 parts (67%) of 1-(4-methoxyphenyl)-4-(4-nitrophenyl)piperazine; melting point 195.1°C.

A mixture of 12 parts of 1-(4-methoxyphenyl)-4-(4-nitrophenyl)piperazine, 200 parts of methanol and 225 parts of tetrahydrofuran is hydrogenated at normal pressure and at 20°C with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and washed with N,N-dimethylacetamide. Product is filtered off and crystallized from 1-butanol, yielding 8 parts (74%) of 4-[4-(4-methoxyphenyl)-1-piperazinyl]benzenamine; melting point 191.8°C.

A mixture of 30 parts of 4-[4-(4-methoxyphenyl)-1-piperazinyl]benzenamine and 300 parts of a hydrobromic acid solution 48% in water is stirred and refluxed for 10 days. The reaction mixture is evaporated and the residue is alkalized with sodium hydroxide. The mixture is filtered and the filtrate is acidified with acetic acid. The precipitated product is filtered off and crystallized from 1,4-dioxane, yielding 12 parts (44%) of 2,4-dihydro-4-{4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl}-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one.

To a stirred solution of 2,4-dihydro-4-{4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl}-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one in 100 parts of dimethyl sulfoxide are added 0.3 parts of sodium hydride dispersion 78% and the whole is stirred at 50°C till foaming has ceased. Then there are added 3.7 parts of cis-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl]methanesulfonate and stirring is continued for 3 hours at 100°C. The reaction mixture is cooled and poured onto water. The product is extracted with dichloromethane. The extracts are washed with a diluted sodium hydroxide solution and filtered. The residue is crystallized from 1-butanol. The product yield 4.3 parts (75%) of cis-4-{4-[4-{4-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl}-1-piperazinyl]phenyl}-2,4-dihydro-2-(methylpropyl)-3H-1,2,4-triazol-3-one.

References

Heeres, J., Backx, L.J.J.; US Patent No. 4,267,179; May 12,1981; Assigned to Janssen Pharmaceutica, N.V., Beerse, Belgium

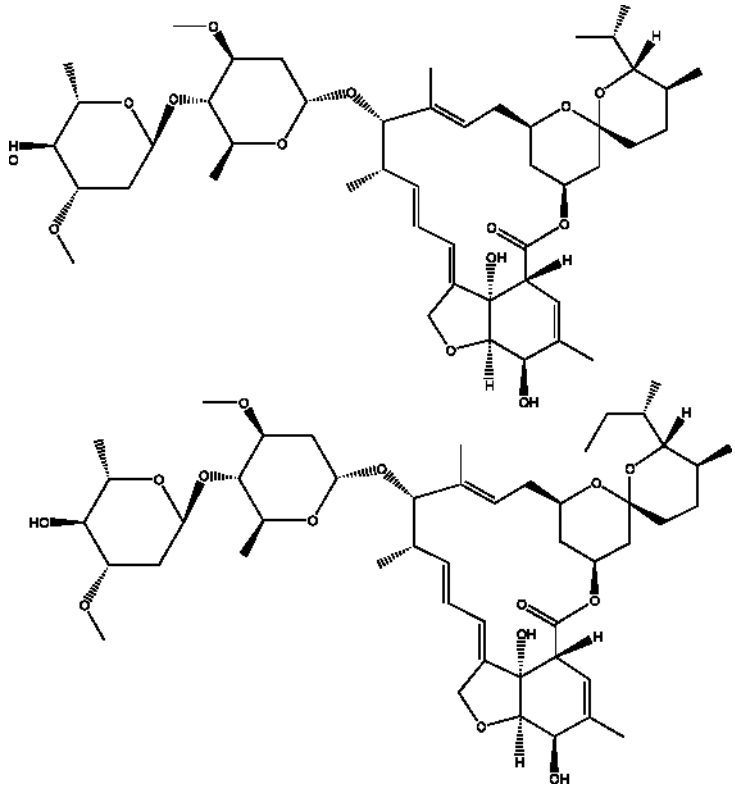
IVERMECTIN

Therapeutic Function: Antiprotozoal

Chemical Name: A mixture of Ivermectin component B_{1a} and Ivermectin component B_{1b}

Common Name: Hyvermectin; Ivermectin

Structural Formula:



Chemical Abstracts Registry No.: 70288-86-7; 74564-75-3

Trade Name	Manufacturer	Country	Year Introduced
Equimectrin Paste	Merial Limited	USA	-
Eqvalan	Merial	UK	-
Heartgard	Merial Limited	USA	-
Iverhart	Virbac Corporation	-	-
Ivermectol	Ochoa Laboratories (P) Ltd.	-	-
Ivomec	Merial Limited	USA	-
Jetamec	Merial Limited	USA	-
Mectizan	Merck Sharp and Dohme	-	-
Merial	Merial Limited	USA	-

Trade Name	Manufacturer	Country	Year Introduced
Panomec	Merial Limited for Canada	USA	-
Paramax MCS	Coopers	-	-
Qualimec	Janssen	-	-
Stromectol	Merck and Company, Inc.	-	-
Stromectol, Mectizan Generic	Sintofarma/Cifarma	-	-
Zimecterin	Merial	-	-

Raw Materials

Avermectin B_1	Rhodium trichloride trihydrate
Hydrogen	Triphenylphosphine
Hydrazine hydrate	tris-(Hexylphenyl)-phosphine

Manufacturing Process

Avermectin is produced by biotechnological methods with the aid of Streptomyces avermitilis.

Preparation of Catalyst I

Rhodium trichloride trihydrate (1.00 g, 3.80 mmol) was dissolved in water (5.0 ml) with heating (70°C). A solution of triphenylphosphine (1.95 g, 7.43 mmol) in acetone (25.0 ml) was then added under a nitrogen atmosphere in the course of 20 min. After 10 min hydrazine hydrate (1.90 ml; 39.09 mmol) was added with stirring and the mixture was heated at reflux temperature for 3 hours, then kept at 45°C for a further 1 hour. The crystalline solid was filtered off under nitrogen and washed with a little acetone and then with diethyl ether. 1.05 g of an orange-coloured solid were obtained.

Hydrogenation with catalyst I

The catalyst (10 mg) was dissolved in toluene (25 ml) and added under argon to the solution of a mixture (1.1 g) of avermectin B_{1a} (96%) and avermectin B_{1b} (4%) and of 100 mg of triphenylphosphine in toluene (25 ml) in a stainless steel autoclave. This starting material was then hydrogenated at 88°C under a hydrogen pressure of 20 bar with stirring of the solution. After 10 hours, HPLC analysis revealed a content of 86% dihydro-avermectin B_{1a} and of 4 % dihydroavermectin B_{1b}, and also of 3% tetrahydroavermectin B_{1a}.

Preparation of Catalyst II

Under an atmosphere of argon, a mixture of 7.5 mg of rhodium trichloride, 30.0 mg of tris-(hexylphenyl)-phosphine, 3 ml of acetone and 15 ml of hydrazine hydrate is heated with stirring and reflux cooling for 4 hours.

Hydrogenation with catalyst II

The catalyst is added to a solution of 4.3 g of avermectin (B_{1a} and B_{1b} mixture) in 25 ml of a mixture of acetone and cyclohexane in a ratio of 2:1. After addition of 51.4 mg of tris-(mexylphenyl)phosphine, the hydrogenation is carried out in a steel autoclave at a hydrogen pressure 5 bar and at 88°C. After a hydrogenation time of 4 hours, 8.9% of starting material, 89.9% of ivermectin (B_{1a} and B_{1b} mixture), tetrahydroavermectin content <0.1% was obtained (according to HPLC analysis).

Removing of the catalyst system

The crude product after distillative removal of the solvent mixture, dissolved in a mixture of 35 ml of methanol and 20 ml of water and this solution is extracted with 25 ml of cyclohexane in a separating funnel. The phases are separated and concentrated under reduced pressure. The extraction is repeated twice in the same manner.

Result:

The crude product of the hydrogenation

690 ppm of Rh

The resulting product contains

after the 1st extraction	39 ppm of Rh
after the 2nd extraction	29 ppm of Rh
after the 3rd extraction	22 ppm of Rh

References

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