I

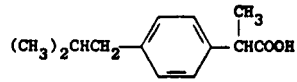
IBUPROFEN

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	U.K.	1969
Brufen	Kakenyaku Kako	Japan	1971
Brufen	Labaz	W. Germany	1971
Brufen	Formenti	Italy	1972
Brufen	Dacour	France	1972
Motrin	Upjohn	U.S.	1974
Rufen	Boots	U.S.	1981
Advil	Whitehall	U.S.	–
Algofen	Ibirn	Italy	–
Andran	Takata	Japan	–
Anflagen	Ohta	Japan	–
Artofen	Ikapharm	Israel	–
Artril	Eczacibasi	Turkey	–
Artril 300	Farmasa	Brazil	–
Bluton	Morishita	Japan	–
Brufamic	Teigo	Japan	–
Buburone	Towa Yakuhin	Japan	–
Butylenin	Sanken	Japan	–
Daiprophen	Daito	Japan	–
Donjust-B	Horita	Japan	–
Ebufac	D.D.S.A.	U.K.	–
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	U.K.	–

Trade Name	Manufacturer	Country	Year Introduced
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	Japan	–
Nurofen	Crookes	U.K.	–
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

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

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 2½ 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)propionic acid MP 75° to 77.5°C. (The procedure was reported in U.S. Patent 3,228,831.)

References

Merck Index 4797
Kleeman & Engel p. 482
PDR pp. 687, 728, 830, 1854, 1897
OCDS Vol. 1 p. 86 (1977) & 2, 218, 356 (1980)
DOT 5 (3) 101 (1969)
I.N. p. 510
REM p. 1117
Nicholson, J.S. and Adams, S.S.; U.S. Patent 3,228,831; January 11, 1966; assigned to Boots Pure Drug Company Limited, England
Nicholson, J.S. and Adams, S.S.; U.S. Patent 3,385,886; May 28, 1968; assigned to Boots Pure Drug Company Limited, England

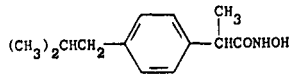
IBUPROXAM

Therapeutic Function: Antiinflammatory

Chemical Name: N-Hydroxy-α-methyl-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 dur-

ing 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 1.25 N 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 50 g 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.; U.S. Patent 4,082,707; April 4, 1978; assigned to Societa Italo-Britannica L. Manetti-H. Roberts & Co. (Italy)

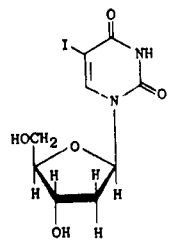
IDOXURIDINE

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	U.S.	1963
Stoxil	SKF	U.S.	1963
Herplex	Allergan	U.S.	1963
Idoxene	Spodefell	U.K.	1963
Idoviran	Chauvin Blache	France	1963
Herpetil	Farmila	Italy	1963
Spectanefran	Pharm-Allergan	W. Germany	1964
Cheratil	Francia	Italy	–
Colircusi Virucida	Cusi	Spain	–

Trade Name	Manufacturer	Country	Year Introduced
Dendrit	Smith & Nephew	U.K.	–
Gel "V"	P.O. S.	France	–
Herpid	W.B. Pharm.	U.K.	–
Herpidu	Dispersa	Switz.	–
IDU	Pliva	Yugoslavia	–
IDU Ophthalmic	Sumitomo	Japan	–
Iducher	Farmigea	Italy	–
Iduridin	Ferring	Sweden	–
Idustatin	Isnardi	Italy	–
Kerecid	SKF	U.K.	–
Oftan-Idurin	Star	Finland	–
Ophthalmadine	S.A.S.Sci.	U.K.	–
Synmiol	Winzer	W. Germany	–
Virexin	Vinas	Spain	–
Virunguent	Hermal	W. Germany	–
Virusan	Ikapharm	Israel	–
Vistaspectran	Allergan	W. Germany	–
Zostrum	W.B. Pharm.	U.K.	–

Raw Materials

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

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 4½ 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-uracil are added. A white precipitate is soon formed. The reaction mixture is kept under reflux for ½ 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-uridine are 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 & Engel p. 483
DOT 7 (5) 191 (1971) & 10 (10) 268 (1974)
I.N. p. 512
REM p. 1232
Roussel-Uclaf; British Patent 1,024,156; March 30, 1966

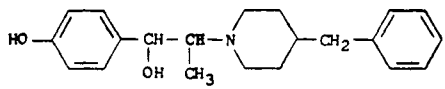
IFENPRODIL TARTRATE

Therapeutic Function: Vasodilator

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

Common Name: –

Structural Formula:



(base)

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 & 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 & 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.; U.S. Patent 3,509,164; April 28, 1970; assigned to Societe Anonyme des Laboratoires Robert et Carriere, France

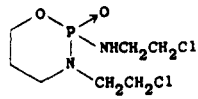
IFOSFAMIDE

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	U.K.	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 60 cc 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 & Engel p. 485
OCDS Vol. 3 p. 151 (1984)
DOT 12 (11) 450 (1976) & 16 (5) 171 (1980)
I.N. p. 513
REM p. 1155
Arnold, H., Brock, N., Bourseaux, F. and Bekel, H.; U.S. Patent 3,732,340; May 8, 1973; assigned to Asta-Werke A.G. Chemische Fabrik (W. Germany)

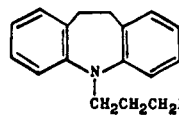
IMIPRAMINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

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

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	U.S.	1959
Presamine	USV Pharm	U.S.	1971
SK-Pramine	SKF	U.S.	1974
Janimine	Abbott	U.S.	1975
WDD Tab	Tutag	U.S.	1979
Berkomine	Berk	U.K.	–
Censtim	Ohio Medical	U.S.	–
Chemipramine	Chemo-Drug	Canada	–
Chemoreptin	Toho Iyaku	Japan	–
Chrytemin	Fujinaga	Japan	–
Depress	Toho	Japan	–
Deprinol	Dumex	Denmark	–
Dimipressin	Drugs	U.K.	–
Dynaprin	Monico	Italy	–
Eupramin	Pliva	Yugoslavia	–
Feinalmin	Sanko	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
I.A.-Pram	Inter-Alia Pharm	U.K.	–
Imavate	Robins	U.S.	–
Imidol	Yoshitomi	Japan	–
Imilanyle	Takata	Japan	–
Imipramine	Lederle	U.S.	–
Imipranil	Medica	Finland	–
Imiprin	Protea	Australia	–
Impranil	Barlow Cote	Canada	–
Impril	I.C.N.	–	–
Intalpran	Inter-Alia Pharm.	U.K.	–
Iprogen	Genethic	U.K.	–
Iramil	Knoll	W. Germany	–
Melipramin	Egyt	Hungary	–
Meripramin	Kanebo	Japan	–
Norpramine	Norton	U.K.	–
Novopramine	Novopharm	Canada	–
Primonil	Ikapharm	Israel	–
Prodepress	Medac	Australia	–
Pryleugan	Arzneimittelwerk Dresden	E. Germany	–
Psychoforin	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-dimethylamino propyl)-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 & Engel p. 485
PDR pp. 527, 673, 901, 993, 1569, 1606, 1723
OCDS Vol. 1 p. 401 (1977); 2, 420 (1980) & 3, 32 (1984)
I.N. p. 514
REM p. 1095
Haefliger, F. and Schindler, W.; U.S. Patent 2,554,736; May 29, 1951; assigned to J.R. Geigy AG, Switzerland

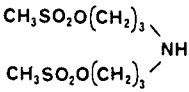
IMPROSULFAN TOSYLATE

Therapeutic Function: Antitumor

Chemical Name: Bis-(3-methanesulfonyloxypropyl)amine

Common Name: –

Structural Formula:



(base)

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
p-Toluenesulfonic acid

Manufacturing Process

A solution of 5 g of bis(3-methylsulfonyloxypropyl)amine hydrochloride in 20 ml of ice water is neutralized with 1 N 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

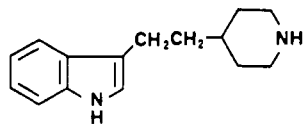
INDALPINE

Therapeutic Function: Antidepressant

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

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-2-ethoxy)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.; U.S. Patent 4,064,255; December 20, 1977; assigned to Mar-Pha Societe D'Etudes et D'Exploitation De Marques

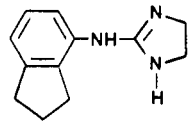
INDANAZOLINE

Therapeutic Function: Vasoconstrictive agent (nasal spray)

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 2½ 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.

33.4 g (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 2 N 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.; U.S. Patent 3,882,229; May 6, 1975; assigned to Nordmark-Werke GmbH

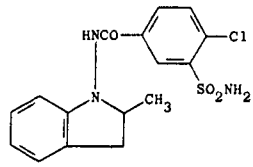
INDAPAMIDE

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	U.K.	1978
Natrilix	Servier	Australia	1983
Lozol	Revlon	U.S.	1983
Arifon	Servier	France	–
Bajaten	Volpino	Argentina	–
Idamix	Gentili	Italy	–
Lozide	Servier	France	–

Trade Name	Manufacturer	Country	Year Introduced
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-benzoyl chloride 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 chlorhydrate 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 & Engel p. 487
PDR p. 1816
OCDS Vol. 2 p. 349 (1980)
DOT 12 (8) 313 (1976) & 13 (1) 41 (1977)
I.N. p. 516
REM p. 944
Beregl, L., Hugon, P., Laubie, M.; U.S. Patent 3,565,911; February 23, 1971; assigned to Science Union et Cie, Societe Francaise de Recherche Medicale, France

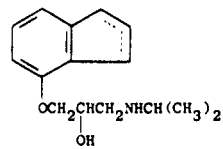
INDENOLOL

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

Trade Name	Manufacturer	Country	Year Introduced
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.

(b) 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 & Engel p. 487
DOT 16 (1) 24 (1980)
I.N. p. 516
Murakami, M., Murase, K., Niigata, K., Tachikawa, S. and Takenaka, T.; U.S. Patent 4,045,482; August 30, 1977; assigned to Yamanouchi Pharmaceutical Co., Ltd. (Japan)

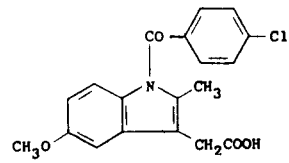
INDOMETHACIN

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	U.S.	1965
Amuno	MSD	W. Germany	1965
Indocid	MSD-Chibret	France	1966
Indocid	MSD	U.K.	1966
Mefacen	Chiesi	Italy	1967
Algometacin	Biagini	Italy	—
Argun	Merckle	W. Germany	—
Arthrexin	Lennon	S. Africa	—
Artracin	D.D.S.A.	U.K.	—
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	U.K.	—
Imet	Firma	Italy	—
Indacin	Merck-Banyu	Japan	—
Inderapollon	Kaigai	Japan	—
Indetrit	Medica	Finland	—
Indium	Pharma Williams	Italy	—
Indo	Arcana	Austria	—
Indodur	Medica	Finland	—
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	U.S.	—
Novomethacin	Novopharm	Canada	—

Trade Name	Manufacturer	Country	Year Introduced
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	U.K.	–
Zalbico	Toyo	Japan	–

Raw Materials

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

Manufacturing Process

(A) 2-Methyl-5-Methoxy-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 B. The residual oily anhydride is used without purification in the next step.

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

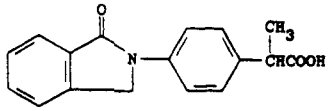
INDOPROFEN

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

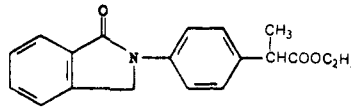
Trade Name	Manufacturer	Country	Year Introduced
Flosint	Carlo Erba	Italy	1976
Flosin	Carlo Erba	W. Germany	1982
Flosin	Carlo Erba	Switz.	1982
Flosint	Carlo Erba	U.K.	1982
Fenint	Montedison	W. Germany	–
Praxis	Lisapharma	Italy	–

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 evapo-

rated 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 U.S. Patent 3,767,805.)

References

Merck Index 4853
DFU 1 (5) 242 (1976)
Kleeman & 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.; U.S. 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

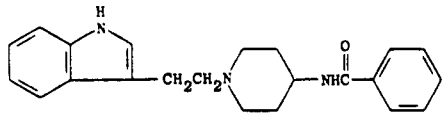
INDORAMIN

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	U.K.	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 2 N 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.; U.S. Patent 3,527,761; September 8, 1970; assigned to John Wyeth & Brother, Ltd. (U.K.)

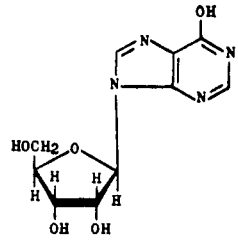
INOSINE

Therapeutic Function: Cardiotonic

Chemical Name: 9-β-D-ribofuranosylhypoxanthine

Common Name: Hypoxanthine riboside

Structural Formula:



Chemical Abstracts Registry No.: 58-63-9

Trade Name	Manufacturer	Country	Year Introduced
Foreart	Guarnieri	Italy	1970
Oxiamin	Made	Spain	–
Ribonosine	Toyo Jozo	Japan	–
Salinite	Shinshin	Japan	–
Tebertin	Berenguer-Beneyto	Spain	–
Trophicardyl	Innothera	France	–
Virusina	Dukron	Italy	–

Raw Materials

Adenosine
Barium nitrite
Sulfuric acid

Manufacturing Process

As described in U.S. 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 U.S. 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^{++} (2 ppm), 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.; U.S. Patent 3,049,536; August 14, 1962; assigned to Zellstoff Fabrik Waldhof, Germany

Motozaki, S., Tsunoda, T., Aoki, R., Okumura, S., Kondo, Y., Muramatsu, N., Momose, H. and Tamagawa, Y.; U.S. Patent 3,111,459; November 19, 1963; assigned to Ajinomoto KK, Japan

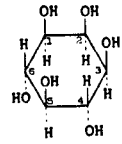
INOSITOL

Therapeutic Function: Vitamin B complex; lipotropic

Chemical Name: Myo-Inositol

Common Name: Hexahydroxycyclohexane; cyclohexitol

Structural Formula:



Chemical Abstracts Registry No.: 87-89-8

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

Raw Materials

Starch factory steep water
Calcium hydroxide

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 i-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.; U.S. Patent 2,112,553; March 29, 1938
Elkin, M. and Meadows, C.M.; U.S. Patent 2,414,365; January 14, 1947; assigned to American Cyanamid Co.

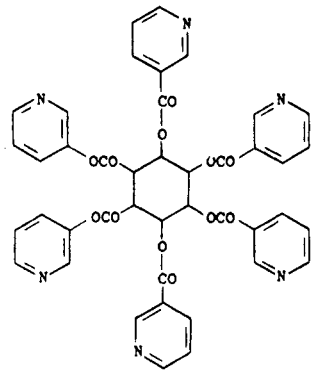
INOSITOL NIACINATE

Therapeutic Function: Vasodilator (peripheral)

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	U.S.	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	—

Trade Name	Manufacturer	Country	Year Introduced
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 & Engel p. 490
I.N. p. 519
A.B. Bofors; British Patent 1,053,689; January 4, 1967

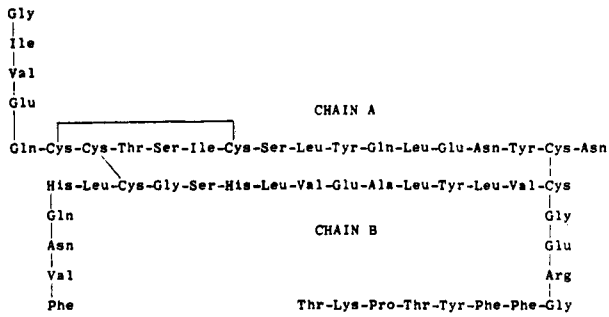
INSULIN

Therapeutic Function: Antidiabetic

Chemical Name: Complex polypeptide hormone with molecular weight over 6,000; see Structural Formula

Common Name: –

Structural Formula:



HUMAN INSULIN

Chemical Abstracts Registry No.: 9004-10-8

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

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 & (5) 262 (1983)
REM p. 973
Maxwell, L.C. and Hinkel, W.P.; U.S. Patent 2,695,861; November 30, 1954; assigned to Armour & Co.

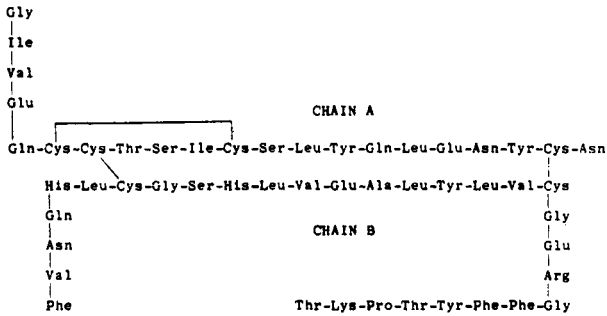
INSULIN ISOPHANE

Therapeutic Function: Hypoglycemic

Chemical Name: Isophane insulin

Common Name: Isophane insulin injection

Structural Formula:



Chemical Abstracts Registry No.: —

Trade Name	Manufacturer	Country	Year Introduced
NPH-Iletin	Lilly	U.S.	1950
Protaphane	Novo	U.S.	1981
Humulin-I	Lilly	U.K.	1982
Insulatard	Leo	Switz.	1983
Novolin N	Squibb-Novo	U.S.	—

Raw Materials

Zinc insulin
Salmiridine 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.; U.S. Patent 2,538,018; January 16, 1951; assigned to Nordisk Insulinlaboratorium, Denmark

INSULIN ZINC SUSPENSION

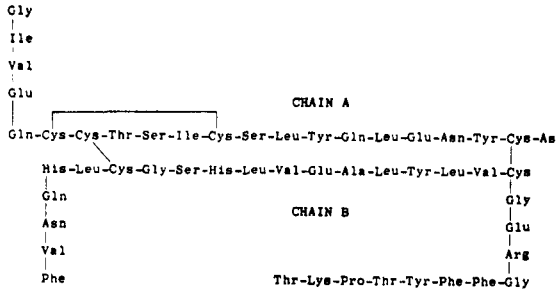
Therapeutic Function: Hypoglycemic

Chemical Name: Insulin zinc suspension

Common Name: –

Structural Formula:

(base)



Chemical Abstracts Registry No.: 8049-62-5

Trade Name	Manufacturer	Country	Year Introduced
Lente Insulin	Squibb	U.S.	1971
Iletin I	Lilly	U.S.	–
Protamine	Lilly	U.S.	–
Semilente	Squibb-Novo	U.S.	–
Ultralente	Squibb-Novo	U.S.	–

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 Hallas-Moller, K.; U.S. 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: Complex protein; structure not precisely defined

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 cell-containing 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 0.3 N 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 0.3 N 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. The dried 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. (U.K.)

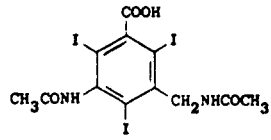
IODAMIDE

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 & Engel p. 493
I.N. p. 521
REM p. 1269
Felder, E. and Pitre, D.; U.S. Patent 3,360,436; December 26, 1967; assigned to Eprova Ltd. (Switz.)

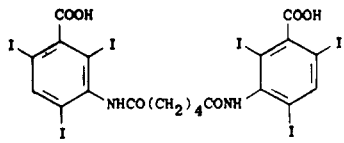
IODIPAMIDE

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 (2618-26-0 = No Salt; 3521-84-4 = Meglumate)

Trade Name	Manufacturer	Country	Year Introduced
Cholografin	Squibb	U.S.	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 & Engel p. 16
I.N. p. 46
REM p. 1265
Priewe, H. and Rutkowski, R.; U.S. Patent 2,776,241; January 1, 1957; assigned to Schering AG, Germany

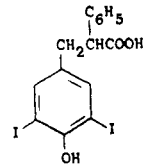
IODOALPHIONIC ACID

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	U.S.	1943
Perfectochol	Lafayette	U.S.	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.; U.S. Patent 2,552,696; May 15, 1951; assigned to Sterling Drug Inc.

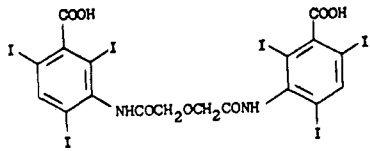
IOGLYCAMIC ACID

Therapeutic Function: Diagnostic air (radiopaque medium)

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 2618-25-9

Trade Name	Manufacturer	Country	Year Introduced
Meglumine Salt:			
Biligram	Schering	W. Germany	1971
Biligram	Schering	U.K.	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 α-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 & Engel p. 494
I.N. p. 28
Priewe, H. and Rutkowski, R.; U.S. Patent 2,853,424; September 23, 1958; assigned to Schering A.G. (W. Germany)

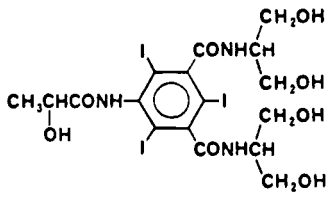
IOPAMIDOL

Therapeutic Function: Radiopaque contrast 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

Trade Name	Manufacturer	Country	Year Introduced
Niopam	Merck	U.K.	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 (1.26 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.; U.S. Patent 4,001,323; January 4, 1977; assigned to Savac AG

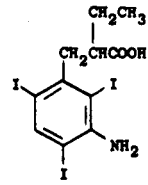
IOPANOIC ACID

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	U.S.	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-nitrocinnamic acid 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-Triiodophenyl)-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 & Engel p. 495
DOT 15 (7) 310 (1979)
I.N. p. 28
REM p. 1266
Archer, S.; U.S. Patent 2,705,726; April 5, 1955; assigned to Sterling Drug Inc.

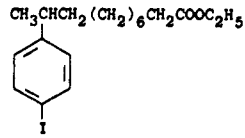
IOPHENDYLATE

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	U.S.	1944
Ethiodan	Allen & Hanburys	U.K.	–

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

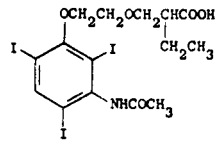
IOPRONIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 2-[[2-[3-(Acetylamino)-2,4,6-triiodophenoxy] 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

3-Acetylamino-2,4,6-triiodophenol
Sodium
3-(2-Iodoethoxy)-2-ethylpropionic acid ethyl ester
Sodium hydroxide
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.; U.S. Patent 3,842,124; October 15, 1974; assigned to Bracco Industria Chimica, Societa per Azioni (Italy)

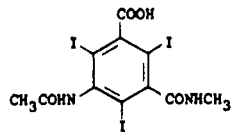
IOTHALMATE MEGLUMINE

Therapeutic Function: Diagnostic aid (radiopaque medium)

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

Common Name: –

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Conray	Mallinckrodt	U.S.	1962
Conray	Byk Gulden	W. Germany	1964
Contrix	Guerbet	France	1965
Angio-Conray	Daiichi	Japan	–
Cysto-Conray	Mallinckrodt	U.S.	–
Gastro-Conray	May & Baker	U.K.	–
Sombril	Rovi	Spain	–
Vascoray	Mallinckrodt	U.S.	–
Vascoray	Astra	Sweden	–

Raw Materials

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

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 & Engel p. 496
I.N. p. 29
REM p. 1269
Hoey, G.B.; U.S. Patent 3,145,197; August 18, 1964; assigned to Mallinckrodt Chemical Works

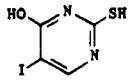
IOTHIOURACIL

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	U.S.	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 hydriodic 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 hydriodic 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.; U.S. Patent 2,585,615; February 12, 1952; assigned to The Chemical Foundation

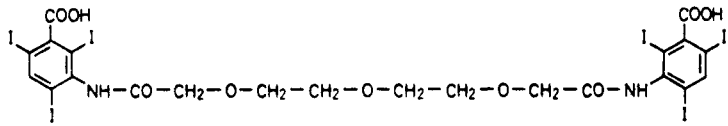
IOTROXIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3,3'-[Oxybis(ethyleneoxymethylenecarbonylimino)] bis-[2,4,6-triiodobenzoic 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-trioxaundecane diacid 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, washed 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 & Engel p. 497
DOT 15 (1) 48 (1979)
I.N. p. 30
Schering, A.G.; British Patent 1,501,507; February 15, 1978

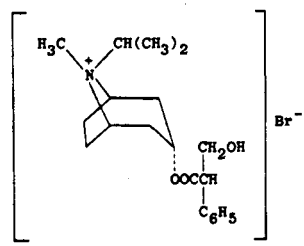
IPRATROPIUM BROMIDE

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	Boehr. Ingel.	W. Germany	1975
Atrovent	Boehr. Ingel.	U.K.	1977
Atrovent	De Angeli	Italy	1980
Breva	Valeas	Italy	1980
Atrovent	Teijin	Japan	1981
Atrovent	Boehr. Ingel.	Canada	1982
Atem	Chiesi	Italy	–
Itrop	Boehr. Ingel.	–	–
Vagos	Valeas	Italy	–

Raw Materials

N-Isopropyl-noratropine
Methyl bromide

Manufacturing Process

211.5 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 200 cc 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 & Engel p. 498
OCDS Vol. 3 p. 160 (1984)
DOT 11 (12) 461 (1975) & 17 (7) 299 (1981)
I.N. p. 525
REM p. 916
Zeile, K., Schulz, W., Banholzer, R. and Wick, H.; U.S. Patent 3,505,337; April 7, 1970; assigned to Boehringer Ingelheim G.m.b.H. (W. Germany)

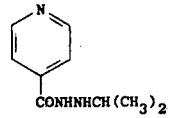
IPRONIAZID

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	U.S.	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 & Engel p. 499
OCDS Vol. 1 p. 254 (1977)
I.N. p. 525
Fox, H.H.; U.S. Patent 2,685,585; August 3, 1954; assigned to Hoffmann-La Roche, Inc.

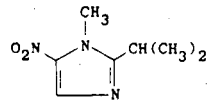
IPRONIDAZOLE

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 3 N 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.; U.S. Patent 3,502,776; March 24, 1970; assigned to Hoffmann-La Roche Inc.

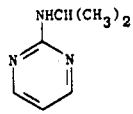
ISAXONINE PHOSPHATE

Therapeutic Function: Peripheral neuropathy treatment

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

Common Name: –

Structural Formula:



(base)

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 mols) 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.; U.S. Patent 4,073,895; February 14, 1978; assigned to Societe D'Etudes de Produits Chimiques (France)

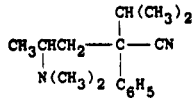
ISOAMINILE

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	U.K.	–
Mucalan	Delagrange	France	–
Sedotosse	Panthox & 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 4 N 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 U.S. Patent 2,934,557.

References

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

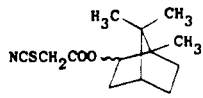
ISOBORNYL THIOCYANOACETATE

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	U.S.	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.; U.S. Patent 2,217,611; October 8, 1940; assigned to Hercules Powder Co.