X

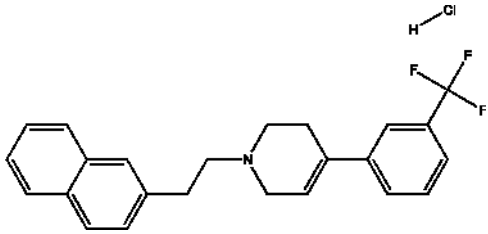
XALIPRODEN HYDROCHLORIDE

Therapeutic Function: Serotonin antagonist, Nootropic

Chemical Name: Pyridine, 1,2,3,6-tetrahydro-1-(2-(2-naphthalenyl)ethyl)-4-(3-(trifluoromethyl)phenyl)- hydrochloride

Common Name: Xaliproden hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 90494-79-4

Trade Name	Manufacturer	Country	Year Introduced
Xaliproden hydrochloride	Sanofi (Sanofi-Aventis)	-	-

Raw Materials

2-Naphthylacetic acid
Lithium aluminum hydride
Sodium hydroxide
Hydrobromic acid
4-(3-Trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride

Manufacturing Process

A solution of 27.8 kg of 2-naphthylacetic acid in 95 L of tetrahydrofuran is added, at a temperature below 20°C to a mixture of 27.5 L of tetrahydrofuran and 10.0 kg of lithium aluminum hydride. The mixture is cooled to 0°C and the following are then added slowly: firstly 10 L of water, then a solution of 1.5 kg of sodium hydroxide in 10 L of water, and finally 30 L of water. The salts which separate out are washed with 160 L of tetrahydrofuran and then

filtered off. The combined tetrahydrofuran solutions are evaporated and the 24.5 kg of 2-(2-naphthyl)ethanol are obtained.

The 2-(2-naphthyl)ethanol is treated with 138 L of concentrated hydrobromic acid. The mixture is refluxed for 5 h and allowed to return to room temperature, with stirring, and the product obtained is then filtered off and washed with water. The moist product is dissolved in 147 L of isopropanol under reflux, about 75 L of solvent are removed by distillation and the mixture is allowed to cool overnight. The product which has crystallized is filtered off, washed with previously cooled isopropanol and dried under vacuum at 40°C. So the 2-(2-bromoethyl)naphthalene is obtained (yield: 81%, calculated relative to the starting naphthylacetic acid).

A mixture of 12.5 g of 2-(2-bromoethyl)naphthalene, 14.0 g of 4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride, 4.34 g of sodium hydroxide, 135 ml of water and 95 ml of 95% ethanol is refluxed for 5 h, the reaction mixture is subsequently allowed to cool to room temperature overnight and then filtered and the product isolated in this way is washed with water and dried under vacuum at 50°C to give 1-[2-(2-naphthyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine (yield of 90%, calculated relative to the starting 4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride).

References

Buj M., Filhol R.; US Patent No. 6,118,006; September 12, 2000; Assigned: Sanofi-Synthelabo, Paris, France

XAMOTEROL FUMARATE

Therapeutic Function: Beta-adrenergic blocker, Cardiac stimulant

Chemical Name: 4-Morpholinecarboxamide, N-(2-((2-hydroxy-3-(4-hydroxyphenoxy)propyl)amino)ethyl)-, (+-)-, fumarate (2:1)

Common Name: Carwin, Sepan, Xamoterol fumarate

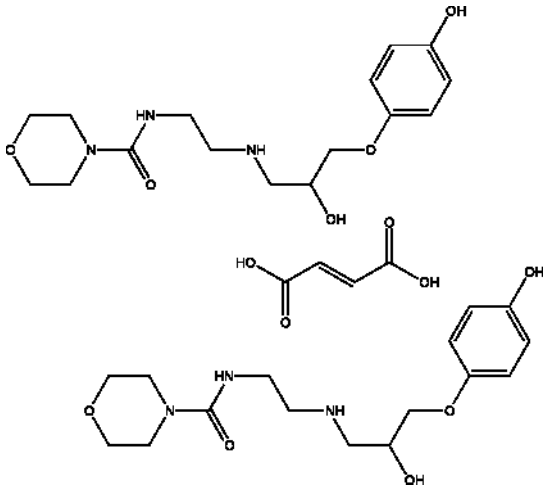
Chemical Abstracts Registry No.: 81801-12-9 (Base); 90730-93-1

Trade Name	Manufacturer	Country	Year Introduced
Sepan	Yamanouchi	-	-
Xamoterol fumarate	ICI (AstraZeneca)	-	-

Raw Materials

Potassium hydroxide
Hydrogen chloride
Palladium on charcoal
Morpholine
Sodium hydroxide
1-p-Benzyloxyphenoxy-2,3-epoxypropane
Acetic acid
Hydrogen
Phenyl chloroformate

Structural Formula:



Manufacturing Process

A suspension of 1-p-benzyloxyphenoxy-2,3-epoxypropane (11.5 g) in isopropanol (6 ml) is added to a stirred mixture of 4-(N-beta-aminoethylcarbamoyl) morpholine hydrogen sulphate (12.7 g), potassium hydroxide (7.0 g) and isopropanol (10 ml) and the mixture is stirred at 45°C for 1 hour and then evaporated to dryness under reduced pressure. The residual oil is stirred with water, the mixture is filtered and the solid residue is dissolved in acetone. A 30% solution of hydrogen chloride in propanol is added until the pH of the mixture is less than 2, and the mixture is filtered. The solid residue is crystallised from water and there is thus obtained 1-p-benzyloxyphenoxy-3-(beta-morpholinocarbonamidoethyl)amino-2-propanol hydrochloride (4.9 g).

A solution of the above compound in a mixture of ethanol (20 ml) and acetic acid (20 ml) is shaken with a 30% palladium-on-charcoal catalyst (0.1 g) in an atmosphere of hydrogen at laboratory temperature and pressure until 250 ml of hydrogen is absorbed. The mixture is filtered, the filtrate is evaporated to dryness under reduced pressure and to the residue is added a hot solution of fumaric acid (1.25 g) in ethanol (15 ml). The mixture is kept at 5°C for 12 hours and is then filtered, and the solid residue is washed with hot ethanol and then dried. There is thus obtained 1-p-hydroxyphenoxy-3-beta-(morpholinocarbonamido)ethyl-amino-2-propanol hydrogen fumarate, m.p. 168-169°C (with decomposition).

The 4-(N-beta-aminoethylcarbamoyl)morpholine hydrogen sulphate used as starting material may be obtained as follows:

Morpholine (4.35 g) and phenyl chloroformate (6.35 g) are separately and simultaneously added dropwise during 20 min to a stirred mixture of toluene (10 ml), water (5 ml) and sodium hydroxide (2 g) which is maintained at 0°C. The mixture is stirred for a further 2 hours whilst the temperature is allowed to rise to 20°C. The toluene solution is separated, the aqueous solution is

extracted twice with toluene and the combined toluene solutions are washed with water, dried and evaporated to dryness under reduced pressure. The residue is crystallised from petroleum ether (boiling point 60-80°C) and there is thus obtained N-phenoxycarbonylmorpholine, melting point 46.5-47.5°C.

A mixture of the above compound (11 g) and ethylenediamine (27.8 g) is stirred at laboratory temperature for 3 days and the excess of ethylene diamine is removed by evaporation under reduced pressure. The residue is dissolved in methanol, the solution is cooled to 5°C and concentrated sulfuric acid is added until the pH of the solution is 2. A filter-aid (Celite, 10 g) is added and the mixture is stirred for 1 hour and then filtered. The filtrate is evaporated to dryness under reduced pressure and the residue is stirred with ethyl acetate. The mixture is filtered and there is thus obtained as solid residue 4-(N-beta-aminoethylcarbamoyl)morpholine hydrogen sulphate, melting point 168-169°C.

References

Main Brian G, Barlow Jeffrey J.; US Patent No. 4,143,140; March 6, 1979; Assigned to Imperial Chemical Industries Limited (London, GB2)

XANTHINOL NIACINATE

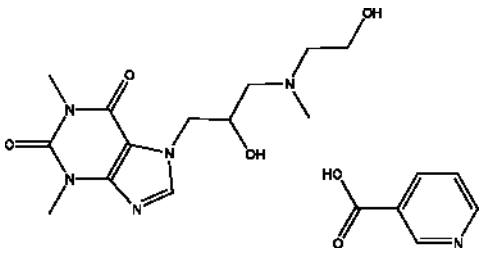
Therapeutic Function: Vasodilator

Chemical Name: 3-Pyridine carboxylic acid compounded with 3,7-dihydro-7-[2-hydroxy-3-[(2-hydroxymethyl)methylamino]propyl]-1,3-dimethyl-1H-purine-2,6-dione (1:1)

Common Name: -

Chemical Abstracts Registry No.: 437-74-1

Structural Formula:



Raw Materials

Epichlorohydrin	Theophylline
Methylaminoethanol	Nicotinic acid

Trade Name	Manufacturer	Country	Year Introduced
Complamex	Calder	UK	1971
Adrogeron	Adroka	Switz.	-
Angioamin	Dompe	Italy	-
Circulan	Unipharm	Israel	-
Complamin	Riker	US	-
Digi-Complamin	Beecham-Wulfing	W. Germany	-
Emodinamin	Sigurta	Italy	-
Jupal	Arzneimittelwerk Dresden	E. Germany	-
Landrina	Landerlan	Spain	-
Niconicol	Farmos	Finland	-
Retilian	Kwizda	Austria	-
Sadamin	Polfa	Poland	-
Teonicol	Farmos	Finland	-
Vasoprin	Alfa	Italy	-
Vedrin	Polifarma	Italy	-
Xanidil	Spofa	Czechoslovakia	-
Xavin	Chinoin	Hungary	-

Manufacturing Process

To a well-stirred solution of 740 parts by weight of epichlorohydrin in 200 parts by volume of isopropyl alcohol are added 600 parts by weight of methylaminoethanol during about 3 hours at 15°C to 20°C. The heat generated by the condensation is removed by means of a cooling bath. After the addition of the total quantity of methylaminoethanol, stirring is continued for 1 hour at 25°C. The condensation reaction is completed when development of heat reaction can no longer be observed. The solution thus produced of the raw 1-chloro-3-(methylhydroxyethylamino)-propanol-2 in isopropyl alcohol is a colorless viscous liquid which is used without further purification for the subsequent condensation with theophylline.

320 parts by weight of caustic soda are dissolved in 200 parts by weight of water and diluted with 6,000 parts by weight of isopropyl alcohol. 1,584 parts by weight of theophylline-hydrate are added to the well-stirred alcoholic caustic soda solution having a temperature between 50°C to 60°C. As a result, most of the theophylline sodium salt is precipitated and a doughy or pasty white reaction product is formed. While being stirred and heated to the boiling point of alcohol, the solution of the afore-described 1-chloro-3-(methylhydroxyethylamino)-propanol-2 is added dropwise into the reaction vessel during about 3 hours. After further cooking for 2 hours, the alcoholic solution of deposited sodium chloride is filtered off. By vaporizing the alcohol, the 3-(methylhydroxyethylamino)-2-hydroxypropyltheophylline can be obtained as a very viscous oil which contains impurities in the form of by-products.

For purpose of purification, the hot alcoholic solution is mixed with 975 parts by weight of nicotinic acid while being stirred and heated until the nicotinic acid is completely dissolved.

The 3-(methylhydroxyethylamino)-2-hydroxypropyltheophylline-nicotinate

separates, while still being warm, in the form of shiny, thin, small sheets. After cooling, the crystallization product is sucked off from the mother liquor and recrystallized from 85% isopropyl alcohol.

The melting point of the pure nicotinic acid salt is 180°C and the yield is 75% to 80% related to the used theophylline. The substance has a nearly neutral reaction and is very readily soluble in water.

References

Merck Index 9871
Kleeman and Engel p. 951
I.N. p. 1018
Bestian, A.H.W.; US Patent 2,924,598; February 9, 1960: assigned to Firma Johann A. Wulfiny (Germany)

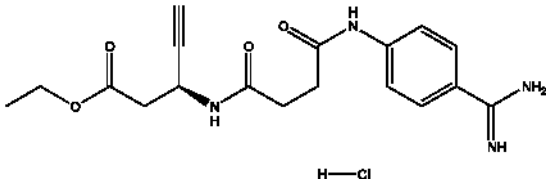
XANTHIOL HYDROCHLORIDE

Therapeutic Function: Antiemetic, Sedative

Chemical Name: 4-[3-(2-Chloro-9H-thioxanthen-9-yl)propyl]-1-piperazinepropanol dihydrochloride

Common Name: Xanthiol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 17162-32-2

Trade Name	Manufacturer	Country	Year Introduced
Xemilofiban hydrochloride	Searle (Pharmacia)	-	-

Raw Materials

o-Mercaptobenzoic acid
Phosphorus
Hydroiodic acid
Butyl bromide
Hydrochloric acid
1-(3-Hydroxypropyl)piperazine
Sulfuric acid
Acetic anhydride
Lithium
1,3-Dibromopropane
Potassium carbonate

Manufacturing Process

A stirred mixture of 50.0 g (0.32 mole) of commercial o-mercaptobenzoic acid, 200 ml of chlorobenzene and 500 ml of 96 % sulfuric acid was stirred at approximately 70°C for 6 h. After the mixture had remained overnight at 25°C, the layers were separated.

Ice cubes were added to the sulfuric acid layer and the water formed was allowed to diffuse slowly into the sulfuric acid. The finely divided solid was collected on a filter, washed with water by trituration, and refiltered. The filter cake was digested in 300 ml of hot isopropyl alcohol, filtered, and the 3: 10-(2-chloro)thiaxanthenone, melting point 151-152°C (recrystallized from hot dimethylformamide) was obtained. Yield, 32.0 g (41 %).

As a structure proof, the compound was prepared by an alternate route: 5-chloroanthranilic acid, prepared by the chlorination of anthranilic acid, according to J. Am. Chem.Soc. 68, 1303 (1946) was converted into 5-chloro-2-mercaptobenzoic acid by the method described in J. Org. Chem., 18, 1380 (1953), and the latter was condensed with benzene by means of sulfuric acid to yield 10-(2-chloro)thiaxanthenone, identical with that obtained by the first method.

A stirred mixture of 20.0 g (0.081 mole) of 10-(2-chloro) thiaxanthenone, 20.0 g of red phosphorus and 125 ml of acetic anhydride was treated dropwise with 125 ml of hydroiodic acid (D=1.5). The reaction was extremely exothermic, and after the addition, the mixture was stirred and refluxed for 6 h. It was then cooled somewhat and poured into ice-water. The mixture was filtered and the filter cake was treated with boiling methanol and filteredhot. The pale yellow filtrate was concentrated, cooled, and the 4: 2-chlorothiaxanthene, melting point 102-103°C (recrystallization from ethanol) was isolated. Yield, 11.0 g (59 %).

This compound was also prepared by alternate procedure: 10-(2-chloro)thiaxanthenone was reduced to10-(2-chloro)thiaxanthenol with sodium amalgam in methanol according to the procedure described for 10-thiaxanthenone to 10-thiaxanthenol in J. Am. Chem. Soc., 72, 5332 (1950). The 10-(2-chloro)thiaxanthenol, so obtained, melted at 128-129 °C centigrade and was disproportionated into a mixture of 10-(2-chloro)thiaxanthenone and 2-chlorothiaxanthene by reflexing in glacial acetic acid for 2 h. The mixture was separated by fractional crystallization from methanol in which the 2-chlorothiaxanthene is the more soluble.

To a solution of butyl lithium, prepared from 1.2 g (0.17 g) of lithium, 10 ml of butyl bromide and 200 ml of dry ether according to J. Am. Chem.Soc. 71, 1499 (1949), washdded 3.1 g (0.035 mole) of 2-chlorothiaxanthene and the mixture was stirred under reflux for 3 h under an atmosphere of dry nitrogen. The dark red mixture was then siphoned, in portions, by means of nitrogen pressure into a stirred solution of 80.0 g (0.4 mole) of 1,3-dibromopropane in 300 ml of dry ether. During the addition, which was over a period of 15 min, the deep red color of the organo-metallic solution was immediately discharged and a white precipitate formed. The mixture was stirred and refiuxed for 1 h, filtered, and the filtrate was washed with water, then with dilute hydrochloric acid and dried over magnesium sulfate. Fractional distillation yielded, in addition to the unreacted 1,3-dibromopropane, 4.7 g (52%) of 2-chloro-10-

(3-bromopropyl)thiaxanthene as a viscous oil, boiling point 190-204°C (0.7 millimeters).

A mixture of 7.6 g of 2-chloro-10-(3-bromopropyl)thiaxanthene, 5.8 g of 1-(3-hydroxypropyl)piperazine, 6.0 g of anhydrous potassium carbonate and 50 ml of toluene was refluxed for 16 h. Water was added to the cooled mixture and the layers were separated. The toluene solution was extracted with dilute hydrochloric acid, the acidic aqueous solution was made alkaline with sodium hydroxide, and the oil was extracted with ether. The ether solution was washed with water, dried and the 2-chloro-10-{3-[1-(3-hydroxypropyl)-4-piperazinyl]propyl}thiaxanthene was obtained.

References

GB Patent No. 863,699; May 29, 1958; Assigned: Chas Pfizer and Co., Inc, a corporation organized under the laws of the State of Delaware, USA, of 11, Barlett Street, Brooklyn, State of New York, USA

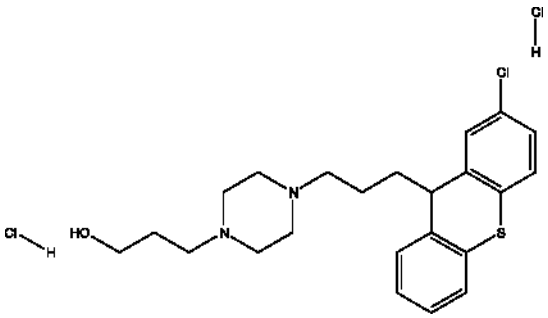
XEMILOFIBAN HYDROCHLORIDE

Therapeutic Function: Fibrinogen receptor antagonist

Chemical Name: (3S)-3-[[4-[[4-(Aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoic acid ethyl ester monohydrochloride

Common Name: Xemilofiban hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 156586-91-3

Trade Name	Manufacturer	Country	Year Introduced
Complamin	Doetsch Grether AG	-	-

Raw Materials

Succinic anhydride

4-Aminobenzamidine dihydrochloride

Dimethylaminopyridine	Hydrogen chloride
N-Methylmorpholine	Isobutyl chloroformate
Diisopropylethylamine	Ethyl 3-amino-4-pentynoate
Dimethylaminopyridine	

Manufacturing Process

4-Aminobenzamidine dihydrochloride (25.0 g, 120 mmol), was added to dry DMF (100 ml). To this solution dry pyridine (100 ml) and succinic anhydride (12.0 g, 120 mmol) followed by dimethylaminopyridine (DMAP 1.5 g 0.012 mmol) were added. The product precipitated after heating for 0.5 h at 100°C, then was filtered, washed with water, acetonitrile and ether. The light solid was suspended in dioxane, 4 N HCl in dioxane (100 ml) was added and the suspension was stirred for 1 h, filtered and dried in a desiccator to give 28.0 g, 88% of 4-[[4-(aminoiminomethyl)phenyl]amino]-4-oxo-butanoic acid hydrochloride as a white yellow solid, melting point 270-290°C (dec.).

4-[[4-(Aminoiminomethyl)phenyl]amino]-4-oxo-butanoic acid hydrochloride was added to dry DMF followed by N-methylmorpholine and isobutyl chloroformate at 25°C. The mixture was stirred for 5 min. Ethyl 3-amino-4-pentynoate was added followed by di-iso-propylethylamine and a catalytic amount of dimethylaminopyridine. After 1 h, the solvent was removed under reduced pressure and the product was purified by reverse phase chromatography (0.05% TFA water/acetonitrile) and lyophilized to give ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate.

By division of stereo-isomers of the ethyl 3-[[4-[[4-(aminoiminomethyl) phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate on column chromatography the ethyl (3S)-3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate may be obtained.

References

Bovy Ph.R., et al.; US Patent No. 5,344,957; September 6, 1994; Assigned: G.D. Searle and Co., Chicago, III.; Monsanto Company, St. Louiss, Mo.

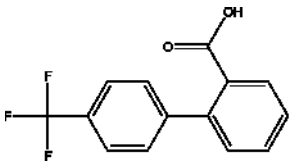
XENALIPIN

Therapeutic Function: Antihyperlipidemic

Chemical Name: (1,1'-Biphenyl)-2-carboxylic acid, 4'-(trifluoromethyl)-

Common Name: Xenalipin

Structural Formula:



Chemical Abstracts Registry No.: 84392-17-6

Trade Name	Manufacturer	Country	Year Introduced
Xenalipin	Wellcome (GSK)	-	-

Raw Materials

Magnesium
Iodine
2-(2-Methoxyphenyl)-4,4-dimethyl-2-oxazoline
Dibromethane p-bromo trifluoromethylbenzene

Manufacturing Process

a). Preparation of 2-(4,4-dimethyl-2-oxazolin-2-yl)-4'-trifluoromethylbiphenyl:

A mechanically stirred solution of magnesium turnings (5.1 g, 0.21 mole) Mallinckrodt, for Grignards reaction, and 2-(2-methoxyphenyl)-4,4-dimethyl-2-oxazoline (41 g, 0.2 mole) in 50 mL dry tetrahydrofuran under nitrogen was prepared. To this was added a crystal of iodine, 1 mL of dibromethane and 2 mL of neat p-bromotrifluoromethylbenzene to initiate the Grignard reaction. Following initiation of the reaction, the remainder of the p-bromotrifluoromethylbenzene (50 g, 0.22 mole total) in 100mL dry tetrahydrofuran was added dropwise at a rate sufficient to maintain the reaction at gentle reflux. The addition took 1 hour. At the end of the addition period, the reaction mixture was heated to reflux for 3 hours. The reaction mixture was then cooled to room temperature and 10 mL water was added dropwise to coagulate the salts. The tetrahydrofuran was decanted and the remaining solids were slurried twice with 300 mL ethyl ether and twice with 300 mL dichloromethane. Each organic extract was decanted from the solids in turn and combined and evaporated under reduced pressure to an oil.

This oil was redissolved in 300 mL dichloromethane, washed once with 100 mL water and once with 10 mL saturated sodium chloride solution, dried and concentrated under reduced pressure. The resulting residue was distilled under reduced pressure (0.040 mm, 95.degree.) to yield 2-(4,4-dimethyl-2-oxazoline-2-yl)-4'-trifluoromethylbiphenyl, yield 33%. A sample was recrystallized from 30-60°C petroleum ether (melting point 50-51°C).

b). Preparation of 4'-(trifluoromethyl)-2-biphenylcarboxylic acid:

A solution of 2-(4,4-dimethyl-2-oxazolin-2-yl)-4'-trifluoromethylbiphenyl (3.5 g, 0.011 mole) in 60 mL 6 N hydrochloric acid was stirred at vigorous reflux for 2 hr. The reaction mixture was then cooled to room temperature and extracted with methylene chloride. The organic extracts were dried and concentrated under reduced pressure to yield a solid. Recrystallisation from ethyl ether/pentane afforded 4'-(trifluoromethyl)-2-biphenyl carboxylic acid, yield 86% (melting point 167-169°C).

References

Eaddy John F.; US Patent No. 4,578,522; March 25, 1986

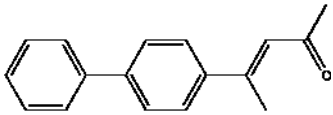
XENIPENTONE

Therapeutic Function: Antiinflammatory

Chemical Name: (E)-4-[1,1'-Biphenyl]-4-yl-3-penten-2-one

Common Name: Xenipentone

Structural Formula:



Chemical Abstracts Registry No.: 55845-78-8

Trade Name	Manufacturer	Country	Year Introduced
Xenipentone	ZYF Pharm Chemical	-	-

Raw Materials

Zinc	4-Acetylbiphenyl
Trimethyl borate	Ethyl bromoacetate
Thionyl chloride	Methyl magnesium bromide

Manufacturing Process

a). 3-(4-Biphenylyl)-2-butenoic acid ethyl ester:

6.45 g (0.1 mole) of activated zinc metal (20 mesh) is placed in a flask fitted with a septum inlet and a magnetic stirrer. The system is maintained under a nitrogen atmosphere and kept at a temperature of 25°C. A solution of 19.6 g (0.1 mole) of 4-acetylbiphenyl in 75 ml of dry tetrahydrofuran and 75 ml of trimethyl borate (distilled from calcium hydride) is injected and the mixture stirred. 11.1 ml (0.1 mole) of freshly distilled ethyl bromoacetate is injected in one shot and the mixture stirred at 25°C for 12 hours. A mixture of 25 ml of concentrated ammonium hydroxide and 75 ml of glycerin is added, and the aqueous phase is separated and extracted thrice with 25 ml portions of diethyl ether. The combined organic extracts are dried over anhydrous magnesium sulphate and the diethylether removed on a rotary evaporator, the residue is vacuum distilled and the fraction distilling at 0.125 mm at 171-172°C is collected. Recrystallisation of 3-(4-biphenylyl)-2-butenoic acid ethyl ester from petroleum ether yields the heading compound, substantially in trans form.

b). 3-(4-Biphenylyl)-2-butenoic acid:

The 3-(4-biphenylyl)-2-butenoic acid ethyl ester is mixed with 6 g of 85% potassium hydroxide in 100 ml of aqueous ethanol and the resulting mixture heated on a steam bath for 30 min. The mixture is then cooled, poured into ice and extracted twice with 25 ml portions of diethylether. The aqueous phase is filtered over Celite and the filtrate acidified with 2 N hydrochloric acid

to pH 4 and cooled. The resulting precipitate is filtered, washed with ether, air dried with suction and then dried under high vacuum at 50°C to yield the 3-(4-biphenylyl)-2-butenoic acid substantially in trans form.

c). 3-(4-Biphenylyl)-2-butenoic acid chloride:

The crude 3-(4-biphenylyl)-2-butenoic acid is dissolved in 200 ml of dry tetrahydrofuran and 4 ml (0.055 mole) of thionyl chloride is added. The solution is refluxed under a nitrogen atmosphere for 3 hours and the solvent and excess thionyl chloride then distilled off. The resulting residue is flash distilled in a microdistillation apparatus at 145-153°C/0.075 mm to yield the 3-(4-biphenylyl)-2-butenoic acid chloride, substantially in trans form.

d). 2-(p-Biphenylyl-2-pentene-4-one: 10.0 g. (0.039 mole) of crude 3-(4-biphenylyl)-2-butenoic acid chloride, is dissolved in 200 ml of dry tetrahydrofuran. The solution placed in a 500 ml round bottom flask fitted with a septum inlet and magnetic stirrer, and held under a nitrogen atmosphere. The solution is cooled to -30°C in a dry ice/isopropanol bath and 19.5 ml (0.039 mole) of a commercial 2 M methyl magnesium bromide solution in dry toluene is added, dropwise, over 30 min. After the addition is complete, the mixture is allowed to warm to room temperature and then stirred for 1 hour. The reaction is quenched by the addition of 20 ml of saturated ammonium chloride solution and the organic layer is separated. The aqueous layer is extracted twice with 20 ml portions of ether and the combined organic extracts are then dried over anhydrous magnesium sulphate and evaporated to yield the heading compound, m.p. 130° to 133°C, after recrystallization from petroleum ether.

References

Anderson Paul L., Brittain Darryl A.; US Patent No. 4,081,476; March 28, 1978; Assigned to Sandoz, Inc. (E. Hanover, NJ)

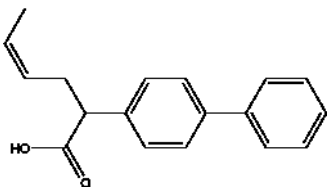
XENYHEXENIC ACID

Therapeutic Function: Lipid metabolism regulator

Chemical Name: (1,1'-Biphenyl)-4-acetic acid, α-2-butenyl-

Common Name: Acidum xenyhexenicum, Diphenesenic acid, Xenyhexenic acid

Structural Formula:



Chemical Abstracts Registry No.: 964-82-9

Trade Name	Manufacturer	Country	Year Introduced
Xenyhexenic acid	ZYF Pharm Chemical	-	-

Raw Materials

Aluminum chloride
Biphenyl
Sulfur
Hydrogen chloride
Ethanol
Sodium hydride
Potassium hydroxide
Acetyl chloride
Morpholine
Acetic acid
Sodium hydoxide
Sulfuric acid
Crotyl bromide

Manufacturing Process

In a flask were placed 1,2-dichloroethane, $AlCl_3$ and acetyl chloride. The reaction mixture is cooled to 10°C. Then biphenyl are loaded in little charge during 3 h, avoiding to arise temperature over 20°C. The mixture is slowly heated to 50°C and kept at this temperature for 4 h.

The obtained solution is then poured in a mixture of ice and of HCl 37%, under stirring. Thereafter the mixture is let to stay for 12 h and phases decantation occurs. Aqueous phase is extracted with dichloroethane. Organic phases collected together are washed with H_2O. Organic phase is dried on $CaCl_2$ and then evaporated under vacuum till dryness. Solid residue is warm dissolved in acetone, then is cooled and kept under stirring 1 night. Thereafter it is let to stay 2 h in refrigerator and then the mixture is filtered, the solid is washed with acetone and then with petroleum ether. The product is dried under vacuum at 40°C to obtained the 4-phenyl-acetophenone.

The 4-phenyl-acetophenone was placed in a flask together with morpholine and sulfur and the mixture heated under reflux for 5 h and a dark red solution was obtained. After cooling to 50°C and addition of CH_3OH a solid precipitated. The mixture is kept under stirring at 50°C for 1 h, and then let to stay 1 night in a refrigerator. Solid product is filtered and washed with CH_3OH and then dried under vacuum at 50°C to give the 4,4'-biphenylyl-aceto-thiomorpholinamide.

The 4,4'-biphenylyl-aceto-thiomorpholinamide was placed together with H_2O, CH_3COOH and HCl 37% in a flask. The mixture is heated under reflux for 8 h and then poured in H_2O. The mixture is cooled to 10°C and then filtered, the solid product is pressed and washed with H_2O. The solid product is dispersed in H_2O and NaOH 30% is added to the solution till pH value arises to 9.

Sulfur is then separated through filtration and the filtered solution is heated to 60°C, decolorized with active carbon, acidified to pH 2 with HCl 10%. The solid product then separated is filtered, washed with H_2O till pH neutral. The product is then dried under vacuum at 60°C to give the 4,4'-biphenylyl-acetic acid.

In a flask there were placed anhydrous ethanol, concentrated H_2SO_4 and the 4,4'-biphenylyl-acetic acid. The mixture is heated under reflux for 3 h. The reaction mixture is then poured in a solution of $NaHCO_3$ in of frozen water, under stirring. Ester derivative precipitates and is filtered after 3 h stirring. Solid product is washed with H_2O till washing liquid is neutral. Drying is carried out at 35°C under vacuum to give the ethyl 4,4'-biphenyl-acetate.

In a flask there are charged sodium hydride titre 80% and benzene. Keeping temperature 20-30°C a solution of ethyl 4,4'-biphenylacetate and of crotyl bromide in dimethylformamide is dropped during 30 min in the flask. Then the reaction mixture is heated under reflux for 2 h, and subsequently cooled to 10°C. Thereafter H_2O are charged and mixture stirred 15 min. Two phases separate. Organic phase is washed with H_2O and dried. The dried solution is concentrated under vacuum till an oily residue consisting of ethyl ester of diphenesenic acid.

The ethyl ester of diphenesenic acid residue is dissolved in ethanol. H_2O and KOH are then added and the mixture is heated under reflux for 2 h. The alcohol is evaporated under vacuum. The residue is dissolved in H_2O. Aqueous solution is washed with petroleum ether. The solution is then decolorized with active carbon and acidified slowly with HCl 10% till pH 2.1. After stirring at room temperature for 4 h the solid product is filtered, washed with H_2O till washing liquid is neutral. The solution is then dried under vacuum at 50°C. So the 2-[4-biphenylyl]-4-hexenoic acid (diphenesenic acid), melting point 118-119°C (crystallized from cyclohexane), boiling point 182-183°C is obtained.

References

Vecchio A.D., Sestini G.; US Patent No. 4,562,287; December 31, 1985; Assigned: Scharper S.p.A. per l'Industria Farmaceutica, Milan, Italy

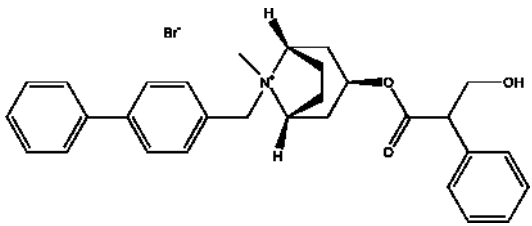
XENYTROPIUM BROMIDE

Therapeutic Function: Antimuscarinic, Spasmolytic

Chemical Name: Atropinium, 8-(p-phenylbenzyl)-, bromide

Common Name: Fentropilium, Phenylbenzylatropinium bromide, Xenytropium bromide, Xenytroponi bromidum

Structural Formula:



Chemical Abstracts Registry No.: 511-55-7

Trade Name	Manufacturer	Country	Year Introduced
Xenytropium bromide	Licencia Budapest	-	-

Raw Materials

4-Diphenyl-methyl-bromide
DL-Tropic acid ester of the tropine
trans-Tropanol
O-Acetyl-DL-tropic acid bromide

Manufacturing Process

2 methods of preparation of endo-(+/-)-8-([1,1'-biphenyl]-4-ylmethyl)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-azoniabicyclo[3.2.1]octane bromide.

1). 28.9 g of dl-tropic acid ester of the tropine is dissolved in 300 ml of luke-warm acetone and to the solution are added 25.0 g of 4-diphenyl-methyl-bromide, dissolved in 75 ml of acetone. The solution is kept for 1 h at room temperature, thereafter during 6 h at 40-60°C. The separated quaternary salt is filtered off, washed with acetone and dried at gentle heat. The endo-(+/-)-8-([1,1'-biphenyl]-4-ylmethyl)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-azoniabicyclo[3.2.1]octane as snow-white microcrystalline powder, melting point 220-222°C (dec., recystallizing from ethyl alcohol) is obtained (yield 35.0-39.0 g).

2). 14.1 g of trans-tropanol are dissolved in 150 ml of acetone and the solution mixed with 24.7 g of 4-diphenyl-methyl-bromide dissolved in a little acetone. The solution is kept for some hours at about 50°C and therefater the separated 4-diphenyl-methyl-trans-tropinium-bromide is isolated in the usual manner. Yield about 90%. After recrystallising in ethyl alcohol the compound melts at about 230°C (dec.).

19.4 g of the quarternary aminoalcohol obtained in the above manner is mixed with 13.5 g of O-acetyl-dl-tropic acid bromide, in a vessel provided with a tube containing calcium chloride, and the mixture is warmed in an oil bath at 120-130°C until no more development of hydrogen bromide gas (approx. 3 h) takes place. For the purpose of splitting of the acetyl-residue the resulting ester is boiled for 0.5 h with 50 ml of 10% hydrobromic acid and the resulting solution evaporated to dryness in vacuo. On the endo-(+/-)-8-([1,1'-biphenyl]-4-ylmethyl)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-azoniabicyclo[3.2.1]octane, melting point 221°C (dec., recrystallization from alcohol) is obtained.

References

Nador K., Gyermek L.; US Patent No. 2,833,773; May 6, 1958; Assigned: 'Licencia' Talalmanyokat Ertekesito Vallalat, Budapest, Hungary

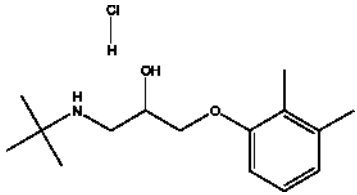
XIBENOLOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 2-Propanol, 1-((1,1-dimethylethyl)amino)-3-(2,3-dimethylphenoxy)- hydrochloride

Common Name: Xibenolol, Selapin

Structural Formula:



Chemical Abstracts Registry No.: 81584-06-7 (Base); 59708-57-5

Trade Name	Manufacturer	Country	Year Introduced
Xibenolol hydrochloride	Teikoku Hormone	-	-
Xibenolol hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

t-Butylamine
(2,3-Dimethylphenyl)glycidic ether

Manufacturing Process

A mixture of (2,3-dimethylphenyl)glycidic ether and t-butylamine in ethanol is heated at reflux for 6 h. The solvent is removed, the residue is washed with water and then extracted with benzene. The dried extract is evaporated to give 1-t-butylamino-1-(2,3-dimethylphenoxy)-2-propanol, melting point 71-72°C (crystallized from isopropanol).

References

Kunz W. et al.; US Patent No. 3,309,406; March 14, 1967

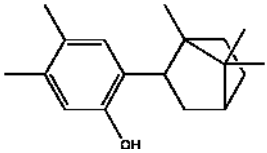
XIBORNOL

Therapeutic Function: Antibacterial

Chemical Name: 6-Isobornyl-3,4-xylenol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13741-18-9

Trade Name	Manufacturer	Country	Year Introduced
Nanbacine	Fournier	France	1976
Xibol	Reig Jofre	Spain	-

Raw Materials

3,4-Xylenol
Camphene

Manufacturing Process

100 g of 3,4-xylenol and 150 g of camphene are melted in a two-necked flask equipped with a reflux condenser and a thermometer. 10 g of stannic chloride are added in small quantities; the temperature is kept between 70°C and 80°C for 4 hours. The mass is then allowed to cool and 300 ml of benzene and 300 ml of water are added. The aqueous layer is decanted off, and the supernatant organic layer is washed, first with 1,200 ml of 10% potassium hydroxide and then with water until neutral. The benzene is driven off and the mass is distilled. The fraction which passes between 203°C and 223°C/200 mm Hg is collected and recrystallized in petroleum ether.

100 mg of the recrystallized product is dissolved in 10 ml of hexane.

This solution is then slowly passed through a chromatographic alumina column, 20 cm in length and 16 mm in diameter, containing 20 g of alumina (Prolabo).

The column is then eluted with benzene and 2 ml fractions of the eluent are collected as soon as the product appears in the eluent. The presence of the product is detected by means of the color change in the collected eluent after adding 1 drop of 2% ferric chloride and 2 drops of 5% potassium ferricyanide solution.

18 ml of a first fraction are collected, the next 2 ml of eluent are discarded and then a second fraction of 20 ml is collected. Removal of the solvent from the first fraction by distillation leaves a product having a melting point of between 94°C and 96°C and removal of the solvent from the second fraction leaves a product having a melting point between 86°C and 88°C.

The product remaining from the first fraction is 6-isobornyl-3,4-xylenol while that from the second fraction is its isomer 6-exo-isocamphenyl-3,4-xylenol.

References

Merck Index 9887
Kleeman and Engel p. 952
DOT 8 (6) 235 (1972)
I.N. p. 1019
Mar-Pha, Societe d'Etude et d'Exploitation de Marques; British Patent 1,206,774; Sept. 30, 1970

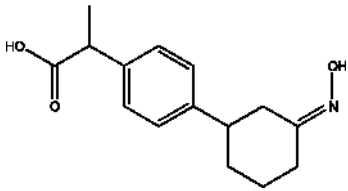
XIMOPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: Benzeneacetic acid, 4-(3-(hydroxyimino)cyclohexyl)-α-methyl-

Common Name: Ximoprofen, Xifam

Structural Formula:



Chemical Abstracts Registry No.: 56187-89-4

Trade Name	Manufacturer	Country	Year Introduced
Ximoprofen	Logeais	-	-

Raw Materials

Sodium hydroxide
2-[4-(3'-Oxo-cyclohexyl)phenyl]propionic acid
Hydroxylamine hydrochloride

Manufacturing Process

2-[4-(3'-Oxocyclohexyl)phenyl]propionic acid (4.0 g; 16.2 mmoles) is dissolved in 1 N sodium hydroxide (55 ml) and treated with hydroxylamine hydrochloride (2.22 g; 32 mmoles) during 24 h at room temperature. The gummy precipitate formed on acidification is converted to the sodium salt in aqueous solution which is then evaporated to dryness. The residue is dissolved in methanol or ethanol to remove an insoluble. After evaporating off the alcool, the sodium salt is again dissolved in water and converted to the acid which is crystallized from water-methanol (1:1), to give 3.0 g (yield 70%) of 2-[4-(3'-hydroxyimino-cyclohexyl)phenyl]propionic acid, melting point

178°C.

References

Maillard J.G.; US Patent No. 3,935,255; January 27, 1976; Assigned: Laboratoires Jacques Logeais, Issy-les-Moulineaux, France

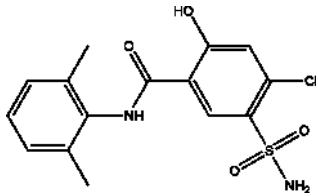
XIPAMID

Therapeutic Function: Diuretic, Antihypertensive

Chemical Name: 4-Chloro-5-sulfamoyl-2',6'-salicyloxylidide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 14293-44-8

Trade Name	Manufacturer	Country	Year Introduced
Aquaphor	Beiersdorf	W. Germany	1971
Diurexan	Merck	UK	1979
Aquaphor	Farmades	Italy	1980
Aquaphoril	Homburg	W. Germany	-
Diurex	Lacer	Spain	-

Raw Materials

4-Chlorosalicylic acid
Ammonia
Phosphorus trichloride
Chlorosulfonic acid
2,6-Dimethylaniline

Manufacturing Process

The 4-chloro-5-sulfamyl salicylic acid used as starting point was prepared in the following way:

(a) 4-Chloro-5-Chlorosulfonyl Salicylic Acid: 100 grams 4-chloro salicylic acid was added portionwise with stirring at about -5°C to 275 ml chlorosulfonic acid. The temperature was not allowed to rise above +3°C. At the end of the addition, the solution formed was stirred for 1 hour in an ice bath, then for 1

hour at 20°C and finally for 2 1/2 hours at 80°C oil bath temperature. Then the dark brown solution, after ensuing slow cooling with vigorous stirring, was poured onto ice; the precipitate was vacuum filtered, washed with water and dried. After recrystallization from toluene the compound formed had a melting point of 181° to 183°C.

(b) 4-Chloro-5-Sulfamyl Salicylic Acid: 40 grams 4-chloro-5-chlorosulfonyl salicylic acid obtained from (a) was added portionwise with stirring to 250 ml liquid ammonia. This was allowed to stand for 2 hours, then the precipitate was vacuum filtered and dissolved in 500 ml water. The solution was filtered and the filtrate was treated with 2 N hydrochloric acid until no more precipitation occurred. The 4-chloro-5-sulfamyl salicylic acid obtained as the precipitate was filtered off and finally recrystallized from water, MP 258° to 260°C.

5.0 grams 4-chloro-5-sulfamyl salicylic acid was suspended in 100 ml water-free chlorobenzene and then 2.44 grams of 2,6-dimethylaniline and 0.9 ml phosphorus trichloride were added to the suspension in turn. The reaction mixture was heated under reflux for 5 hours. After cooling, the chlorobenzene was separated from the precipitate by decantation. The latter was finally collected on a filter and washed, first with chlorobenzene and, after drying, with 2 N hydrochloric acid and water. The compound obtained by recrystallization from methanol had a melting point of 256°C.

References

Merck Index 9888
Kleeman and Engel p. 952
OCDS Vol. 2 p. 93 (1980)
DOT 7 (6) 227 (1971)
I.N. p. 1019
Liebenow, W.; US Patent 3,567,777; March 2, 1971; assigned to P. Beiersdorf and Co., AG, Germany

XIPRANOLOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker, Antiarrhythmic

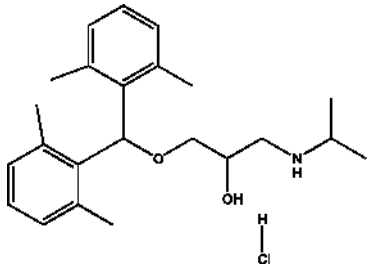
Chemical Name: 2-Propanol, 1-(bis(2,6-dimethylphenyl)methoxy)-3-((1-methylethyl)amino)- hydrochloride

Common Name: Xipranolol hydrochloride

Chemical Abstracts Registry No.: 19179-88-5

Trade Name	Manufacturer	Country	Year Introduced
Xipranolol hydrochloride	ZYF Pharm Chemical	-	-

Structural Formula:



Raw Materials

Thionyl chloride	2,6,2',6'-Tetramethylbenzylhydrol
Glycidol	Sodium carbonate
Ammonia	Hydrogen chloride
Platinum	Hydrogen

Manufacturing Process

To a solution of 65.2 g of 2,6,2',6'-tetramethylbenzylhydrol in 170 ml of anhydrous benzene and 33.0 g of dry magnesium sulfate 20 ml of freshly distilled thionyl chloride are added drop-wise with stirring. Stirring is continued for another hour after completion of the addition and, after filtration, the solvent is removed under reduced pressure. The 70.0 g of 2,6,2'6'-tetramethylbenzhydryl chloride, is obtained and then used without previous purification for the next reaction step.

A solution of 31.0 g (0.42 mol) of glycidol in 85 ml of anhydrous benzene and 46.0 g of sodium carbonate is heated to reflux. At this temperature and under a nitrogen atmosphere a solution of 70.0 g (0.27 mol) of crude 2,6,2',6'-tetramethylbenzhydryl chloride in 120 ml of anhydrous benzene is added drop-wise. After completion of the addition, the mixture is kept refluxing for another 8 h. After filtration and removal of the solvent under reduced pressure, the yellow coloured residue is subjected to distillation under reduced pressure. There are obtained 64.0 g (80% of the theoretical yield) of a fraction boiling at 175-195°C/1 mm Hg, which slowly solidifies. This distillate, consisting of crude 1,2-epoxy-3-[di-(2,6-xylyl)-methoxy]propane, is used for the next reaction step without purification.

In an autoclave a mixture of 10.0 g of crude 1,2-epoxy-3-[di-(2,6-xylyl)-methoxy]propane and 100 ml of 25% ammonia in 300 ml of methanol is heated at 80°C for 5 h with shaking. The solvent is removed by evaporation and the residue (about 12.0 g) is dissolved in 10 ml of ethanol and the solution passed through a column filled with silica gel, which affords separation of the main fraction from the by-product. The solvent is removed by evaporation and the residue is crystallised from petroleum ether (boiling range 60-80°C). 5.7 g of the desired 1-amino-3-[di-(2,6-xylyl)-methoxy]propan-2-ol are obtained in the form of colourless crystals, melting point 105-106°C.

A mixture consisting of 1.0 g of 1-amino-3-[di-(2,6-xylyl)-methoxy]propan-2-

ol, 200 ml of acetone and 20 ml of methanol is subjected to reducing conditions by adding an adequate supply of platinum catalyst and calculated amounts of hydrogen. A further quantity of 50 ml of acetone is added after 2.5 h and the reaction continued for another 3 h. The mixture is left standing overnight. The solvents are removed by evaporation and dryed to give the 1-[di-(2,6-xylyl)-methoxy]-3-(isopropylamino)propan-2-ol, melting point 189-191°C.

References

GB Patent No. 1,266,454; March 8, 1972; Assigned: N.V. Koninklijke Pharmaceutische Fabriken v/h Brocades-Stheeman and Pharmacia, a Dutch Body Corporate of Stationsweg, 33, Mepel, Holand

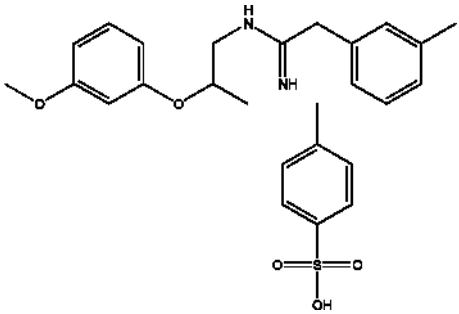
XYLAMIDINE TOSYLATE

Therapeutic Function: Serotonin antagonist

Chemical Name: Acetamidine, N-(2-(m-methoxyphenoxy)propyl)-2-(m-tolyl)-, mono-p-toluenesulfonate

Common Name: Xylamidine tosilate

Structural Formula:



Chemical Abstracts Registry No.: 6443-40-9

Trade Name	Manufacturer	Country	Year Introduced
Xylamidine tosylate	Wellcome Research Laboratories	-	-
Xylamidine tosylate	Wellcome Foundation	-	-

Raw Materials

3-Methylphenylacetonitrile
Ammonia
Sodium p-toluene-sulfonate
Hydrogen chloride
Methyl phenolate
Potassium carbonate

2-Chloropropionitrile	Potassium iodide
Lithium aluminum hydride	Sodium hydroxide

Manufacturing Process

A mixture of 3-methylphenylacetonitrile and dry ethanol was cooled in an ice-bath and dry hydrogen chloride was passed. The mixture was allowed to stand at room temperature for 3 days and then treated portionwise, with vigorous shaking and occasional cooling, with a saturated solution of ammonia in dry ethanol. Addition was continued until a smell of ammonia persisted. The mixture was allowed to stand at room temperature for 2 days and then filtered. The fitltrate was treated with a saturated aqueous solution of 1.1 equivalents of sodium p-toluene-sulfonate and diluted with water. The crystalline precipitate was removed and 3-methylphenylacetamidine p-toluenesulphonate (recrystallised from ethanol) was obtained.

A mixture of methyl phenolate and anhydrous potassium carbonate in dry ethyl methyl ketone was stirred and heated to reflux, during the dropwise addition of a solution of 2-chloropropionitrile in dry ethyl methyl ketone containing finely-powdered potassium iodide. The addition took 20 min. Stirring and heating were continued for a total of 2 h after which the mixture was cooled, poured into water and extracted with ether. The combined ether extract was washed several times with 2 N sodium hydroxide to remove phenol, dried over anhydrous sodium sulfate, and evaporated. The residue was distilled under water-pump vacuum to give pure 2-(3-methoxy-phenoxy)-propionitrile, boiling point 152-154°C/13 mm.

A solution of 2-(3-methoxy-phenoxy)-propionitrile in dry ether was added dropwise to a stirred suspension of lithium aluminium hydride in dry ether. The mixture was then heated to reflux for 3 h, cooled and treated cautiously (vigorous stirring) with water, then with 15% aqueous sodium hydroxide and finally with water. The mixture was stirred for 20 min and filtered. The filtrate was dried over anhydrous potassium carbonate and evaporated. The residue was distilled under water-pump vacuum to give pure 2-(3-methoxy-phenoxy)-propylamine, boiling point 148-152°C/13 mm.

2-(3-Methoxy-phenoxy)-propylamine was added to a suspension of 3-methylphenylacetamidine ρ-toluenesulphonate in absolute ethanol. The mixture was heated to reflux for 4 h by which time the initially vigorous evolution or ammonia had practically ceased. The resulting solution was cooled somewhat and diluted with ether to give an oil which rapidly crystallised on scratching. The solid was filtered and recrystallised from a mixture of ethanol and water to give N-[2-(3-methoxyphenoxy)-propyl]-3-methylbenzeneethanimidamide ρ-toluenesulphonate, melting point 93-96°C (crystallized from water).

References

GB Patent No. 1,094,985; Oct. 29, 1964; Assigned: The Wellcome Foundation Limited, a Company incorporated in England, of 183-193, Euston Road, London

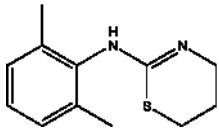
XYLAZINE

Therapeutic Function: Analgesic, Anesthetic

Chemical Name: 4H-1,3-Thiazine-2-amine, N-(2,6-dimethylphenyl)-5,6-dihydro-

Common Name: Xylazine, Sedazine

Structural Formula:



Chemical Abstracts Registry No.: 7361-61-7

Trade Name	Manufacturer	Country	Year Introduced
Xylazine	Bayer	-	-
Xylazine	Bachem AG	-	-
Xylazine	CMS Chemicals Limited	-	-

Raw Materials

2,6-Dimethylaniline
3-Aminopropanol-1
Sodium hydroxide
Thiophosgene
Hydrochloric acid

Manufacturing Process

2,6-Dimethylphenyl isothiocyanate, 31.0 g (0.2 mole), prepared from 2,6-dimethylaniline with thiophosgene, were added dropwise during 15 min to a well-stirred suspension of 15.0 g (0.2 mole) of 3-aminopropanol-1 in 100 ml of ether. The ether started to boil. Stirring under reflux was continued for 30 min, and the ether was then distilled off. The residue was treated with 100 ml of concentrated hydrochloric acid and boiled under reflux for 30 min. After cooling, it was diluted with water, filtered free from impurities, and the base was precipitated by the addition of concentrated sodium hydroxide solution. When recrystallized from benzene-ligroin, the resulting compound 2-(2,6-dimethyl-phenylamino)-4H-5,6-dihydro-1,3-thiazine, melting point 140-142°C (yield 90% of the theoretical).

References

Behner O. et al.; US Patent No. 3,235,550; Feb. 15, 1966; Assigned: Farbenfabriken Bayer Aktiengesellschaft, Leverkusen, Germany, a corporation of Germany

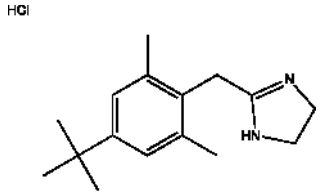
XYLOMETAZOLINE HYDROCHLORIDE

Therapeutic Function: Adrenergic (vasopressor)

Chemical Name: 2-[[4-(1,1-Dimethylethyl)-2,6-dimethylphenyl]methyl]-4,5-dihydro-1H-imidazole hydrochloride

Common Name:-

Structural Formula:



Chemical Abstracts Registry No.: 1218-35-5; 526-36-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Otrivin	Geigy	US	1959
Coryzin	Star	Finland	-
Hidropid	Pliva	Yugoslavia	-
Ilvanol	Siegfried	W. Germany	-
Novorin	Polfa	Poland	-
Olynth	Goedecke	W. Germany	-
Servilaryn	Servipharm	Switz.	-
Sinutab	Parke Davis	US	-

Raw Materials

p-tert-Butyl-o,o'-dimethylphenylacetonitrile
Ethylenediamine
Hydrogen chloride

Manufacturing Process

62 grams of para-tertiany-butyl-ortho,ortho'-dimethyl-phenyl-acetonitrile [obtainable, for example, by the method of Buu-Hoi and P. Cagniant, Bulletin de la Societe Chimique de France, volume 9, page 891 (1942)], 20.6 grams of ethylenediamine of 96% purity and 1.55 cc of carbon disulfide are heated together in a distillation flask with the exclusion of moisture for 48 hours on a boiling water bath. Ammonia is evolved. Upon cooling the reaction product solidifies and is then dissolved in benzene, the solution is filtered while hot with the addition of animal charcoal and petroleum ether is added. The mixture is filtered to remove the impurities that are first precipitated and by the further addition of petroleum ether 2-(para-tertiary-butyl-ortho,ortho'-dimethyl-phenyl-methyl)-imidazoline is caused to crystallize out.

The product melts at 131° to 133°C after being recrystallized from a mixture

of benzene and petroleum ether. It can be converted into its hydrochloride as follows:

189 grams of 2-(para-tertiary-butyl-ortho,ortho'-dimethyl-phenyl-methyl)-imidazoline are dissolved in 400 cc of absolute ethanol, the solution is rendered acid by the addition of 104 cc of an ethanolic solution of hydrochloric acid of 30% strength, the mixture is filtered with the addition of animal charcoal, and dry ethyl acetate and absolute ether are added until crystallization sets in. After cooling the mixture, the salt is filtered off with suction and crystallized several times from absolute ethanol with the use of animal charcoal and the addition of dry mixture of ethyl acetate and ether. The hydrochloride so obtained melts at 327° to 329°C (with decomposition).

References

Merck Index 9895
Kleeman and Engel p. 953
PDR p. 898
OCDS Vol. 1 p. 242 (1977)
I.N. p. 1020
REM p. 891
Hueni, A.; US Patent 2,868,802; January 13,1959; assigned to Ciba Pharmaceutical Products Inc.